Spring 2025 – Epigenetics and Systems Biology
Lecture Outline (Epigenetics and Evolution)
Michael K. Skinner – Biol 476/576
Weeks 15 and 16 (April 15 & 22)

Epigenetics and Evolution

- Darwinian Evolution
- Lamarck's Environment and Evolutionary Biology
- History Environment and Evolutionary Biology
- Waddington Environment and Evolutionary Biology
- Molecular and Genetic Aspects of Evolutionary Biology
- Hopeful Monsters and Evolutionary Biology
- Epigenetics and Evolutionary Biology
- Sociobiology and Evolutionary Biology
- Sexual Selection and Evolutionary Biology
- Epigenetic Transgenerational Inheritance and Evolutionary Biology
- Summary Epigenetics and Evolutionary Biology

Required Reading

Laland, et al. (2014) Does evolutionary theory need a rethink? Nature 54:161-4

Skinner MK (2015) Environmental Epigenetics and a Unified Theory of the Molecular Aspects of Evolution: A Neo-Lamarckian Concept that Facilitates Neo-Darwinian Evolution. Genome Biol Evol. 26;7(5):1296-302

Skinner MK, Nilsson EE. (2021) Role of environmentally induced epigenetic transgenerational inheritance in evolutionary biology: Unified Evolution Theory. Environ Epigenet. 7(1):dvab012.

Books

Jablonka, E. & Lamb, M.J. (2014). Evolution in Four Dimensions: Genetic, Epigenetic, Behavioral and Symbolic Variation in the History of Life. MIT Press, Cambridge.

Literature

Gems D, Virk RS, de Magalhães JP. Epigenetic clocks and programmatic aging. Ageing Res Rev. 2024 Nov:101:102546.

Yi SV. Epigenetics Research in Evolutionary Biology: Perspectives on Timescales and Mechanisms. Mol Biol Evol. 2024 Sep 3;41(9):msae170.

Baduel P, Sammarco I, Barrett R, et al. The evolutionary consequences of interactions between the epigenome, the genome and the environment. Evol Appl. 2024 Jul 23;17(7):e13730.

Korolenko A, Skinner MK. Generational stability of epigenetic transgenerational inheritance facilitates adaptation and evolution. Epigenetics. 2024 Dec;19(1):2380929.
Schuff M, Strong AD, Welborn LK, Ziermann-Canabarro JM. Imprinting as Basis for Complex Evolutionary Novelties in Eutherians. Biology (Basel). 2024 Aug 31;13(9):682.
Fukuda K. The role of transposable elements in human evolution and methods for their functional analysis: current status and future perspectives. Genes Genet Syst. 2024 10;98(6):289-304.
Skinner MK, Nilsson EE. Role of environmentally induced epigenetic transgenerational inheritance in evolutionary biology: Unified Evolution Theory. Environ Epigenet. 2021 Oct 30;7(1):dvab012.
Sadler KC. Epigenetics across the evolutionary tree: New paradigms from non-model animals. Bioessays. 2022 Nov 20:e2200036.
Fanter C, Madelaire C, Genereux DP, van Breukelen F, Levesque D, Hindle A. Epigenomics as a paradigm to understand the nuances of phenotypes. J Exp Biol. 2022 Mar 8;225(Suppl_1):jeb243411.
Fischer S, Weber LM, Liefke R. Evolutionary adaptation of the Polycomb repressive complex 2. Epigenetics Chromatin. 2022 Feb 22;15(1):7.
Brand CL, Levine MT. Functional Diversification of Chromatin on Rapid Evolutionary Timescales. Annu Rev Genet. 2021 Nov 23;55:401-425.
Fouché S, Oggenfuss U, Chanclud E, Croll D. A devil's bargain with transposable elements in plant pathogens. Trends Genet. 2022 Mar;38(3):222-230.
Vigneau J, Borg M. The epigenetic origin of life history transitions in plants and algae. Plant Reprod. 2021 Dec;34(4):267-285.
Brodie ED, Gregory B, Lisch D, Riddle NC. The Epigenome and Beyond: How Does Non-genetic Inheritance Change Our View of Evolution? Integr Comp Biol. 2022 Feb 5;61(6):2199-2207.
Sammarco I, Pieters J, Salony S, Toman I, et al. Epigenetic targeting of transposon relics: beating the dead horses of the genome? Epigenetics. 2022 Nov;17(11):1331-1344.
Mina M, Iyer A, Ciriello G. Epistasis and evolutionary dependencies in human cancers. Curr Opin Genet Dev. 2022 Sep 28;77:101989.
Shimizu KK. Robustness and the generalist niche of polyploid species: Genome shock or gradual evolution? Curr Opin Plant Biol. 2022 Oct;69:102292.
Klein SP, Anderson SN. The evolution and function of transposons in epigenetic regulation in response to the environment. Curr Opin Plant Biol. 2022 Oct;69:102277.
Lucibelli F, Valoroso MC, Aceto S. Plant DNA Methylation: An Epigenetic Mark in Development, Environmental Interactions, and Evolution. Int J Mol Sci. 2022 Jul 27;23(15):8299.
Laine VN, Sepers B, Lindner M, Gawehns F, Ruuskanen S, van Oers K. An ecologist's guide for studying DNA methylation variation in wild vertebrates. Mol Ecol Resour. 2022 Apr 25.
Foroozani M, Holder DH, Deal RB. Histone Variants in the Specialization of Plant Chromatin. Annu Rev Plant Biol. 2022 May 20;73:149-172.
Brand CL, Levine MT. Functional Diversification of Chromatin on Rapid Evolutionary Timescales. Annu Rev Genet. 2021 Nov 23;55:401-425.
Fouché S, Oggenfuss U, Chanclud E, Croll D. A devil's bargain with transposable elements in plant pathogens. Trends Genet. 2022 Mar;38(3):222-230.
Vigneau J, Borg M. The epigenetic origin of life history transitions in plants and algae. Plant Reprod. 2021 Dec;34(4):267-285.
Han B, Wei Q, Amiri E, Hu H, Meng L, Strand MK, Tarpy DR, Xu S, Li J, Rueppell O. The molecular basis of socially induced egg size plasticity in honey bees. Elife. 2022 Nov 8;11:e80499

Galanti D, Ramos-Cruz D, Nunn A, Rodríguez-Arévalo I, Scheepens JF, Becker C, Bossdorf O. Genetic and environmental drivers of large-scale epigenetic variation in Thlaspi arvense. PLoS Genet. 2022 Oct 12;18(10):e1010452.
Patalano S, Alsina A, Gregorio-Rodríguez C, Bachman M, Dreier S, Hernando-Herraez I, Nana P, Balasubramanian S, Sumner S, Reik W, Rulands S. Self-organization of plasticity and specialization in a primitively social insect. Cell Syst. 2022 Sep 21;13(9):768-779.e4.
Klein SP, Anderson SN. The evolution and function of transposons in epigenetic regulation in response to the environment. Curr Opin Plant Biol. 2022 Oct;69:102277.
Chandana BS, Mahto RK, Singh RK, Ford R, Vaghefi N, Gupta SK, Yadav HK, Manohar M, Kumar R. Epigenomics as Potential Tools for Enhancing Magnitude of Breeding Approaches for Developing Climate Resilient Chickpea. Front Genet. 2022 Jul 22;13:900253.
Sato T, Sassone-Corsi P. Nutrition, metabolism, and epigenetics: pathways of circadian reprogramming. EMBO Rep. 2022 May 4;23(5):e52412.
Colonna Romano N, Fanti L. Transposable Elements: Major Players in Shaping Genomic and Evolutionary Patterns. Cells. 2022 Mar 19;11(6):1048.
Pinho GM, Martin JGA, Farrell C, Haghani A, Zoller JA, Zhang J, Snir S, Pellegrini M, Wayne RK, Blumstein DT, Horvath S. Hibernation slows epigenetic ageing in yellow-bellied marmots. Nat Ecol Evol. 2022 Apr;6(4):418-426.
Niiranen L, Leciej D, Edlund H, Bernhardsson C, Fraser M, Quinto FS, Herzig KH, Jakobsson M, Walkowiak J, Thalmann O. Epigenomic Modifications in Modern and Ancient Genomes. Genes (Basel). 2022 Jan 20;13(2):178.
de Miranda JR, Brettell LE, Chejanovsky N, et al. Cold case: The disappearance of Egypt bee virus, a fourth distinct master strain of deformed wing virus linked to honeybee mortality in 1970's Egypt. Virol J. 2022 Jan 15;19(1):12.
Nizam A, Meera SP, Kumar A. Genetic and molecular mechanisms underlying mangrove adaptations to intertidal environments. iScience. 2021 Nov 30;25(1):103547.
Viviani A, Ventimiglia M, Fambrini M, Vangelisti A, Mascagni F, Pugliesi C, Usai G. Impact of transposable elements on the evolution of complex living systems and their epigenetic control. Biosystems. 2021 Dec;210:104566.
Wong JM, Eirin-Lopez JM. Evolution of Methyltransferase-Like (METTL) Proteins in Metazoa: A Complex Gene Family Involved in Epitranscriptomic Regulation and Other Epigenetic Processes. Mol Biol Evol. 2021 Dec 9;38(12):5309-5327.
Hotzy C, Fowler E, Kiehl B, Francis R, Mason J, Moxon S, Rostant W, Chapman T, Immler S. Evolutionary history of sexual selection affects microRNA profiles in Drosophila sperm. Evolution. 2022 Feb;76(2):310-319.
Veronica CS, Ivan GM, Francisco GG. Evolutionary consequences of pesticide exposure include transgenerational plasticity and potential terminal investment transgenerational effects. Evolution. 2022 Sep 18. Online ahead of print.
Feiner N, Radersma R, Vasquez L, Ringnér M, Nystedt B, Raine A, Tobi EW, Heijmans BT, Uller T. Environmentally induced DNA methylation is inherited across generations in an aquatic keystone species. iScience. 2022 Apr 25;25(5):104303.
Harney E, Paterson S, Collin H, Chan BHK, Bennett D, Plaistow SJ. Pollution induces epigenetic effects that are stably transmitted across multiple generations. Evol Lett. 2022 6(2):118-135.
Drews F, Boenigk J, Simon M. Paramecium epigenetics in development and proliferation. J Eukaryot Microbiol. 2022 Sep;69(5):e12914.
Kulkarni P, Mohanty A, Salgia R, Uversky VN. Intrinsically disordered BMP4 morphogen and the beak of the finch: Co-option of an ancient axial patterning system. Int J Biol Macromol. 2022 Oct 31;219:366-373.

Nilsson EE, Ben Maamar M, Skinner MK. Environmentally Induced Epigenetic Transgenerational Inheritance and the Weismann Barrier: The Dawn of Neo-Lamarckian Theory. J Dev Biol. 2020 Dec 4;8(4):28.
Adrian-Kalchhauser I, Sultan SE, Shama LNS, et al. Understanding 'Non-genetic' Inheritance: Insights from Molecular-Evolutionary Crosstalk. Trends Ecol Evol. 2020 Dec;35(12):1078-1089.
Kent C, Agrawal P. Regulation of Social Stress and Neural Degeneration by Activity-Regulated Genes and Epigenetic Mechanisms in Dopaminergic Neurons. Mol Neurobiol. 2020 Nov;57(11):4500-4510.
Choi JY, Lee YCG. Double-edged sword: The evolutionary consequences of the epigenetic silencing of transposable elements. PLoS Genet. 2020 Jul 16;16(7):e1008872.
Wambui Mbichi R, Wang Q-F, Wan T. RNA directed DNA methylation and seed plant genome evolution. Plant Cell Rep. 2020 Aug;39(8):983-996.
Trefflich S, Dalmolin RJS, Ortega JM, Castro MAA. Which came first, the transcriptional regulator or its target genes? An evolutionary perspective into the construction of eukaryotic regulons. Biochim Biophys Acta Gene Regul Mech. 2020 Jun;1863(6):194472.
Tikhodeyev ON. Heredity determined by the environment: Lamarckian ideas in modern molecular biology. Sci Total Environ. 2020 Mar 25;710:135521.
de Mendoza A, Lister R, Bogdanovic O. Evolution of DNA Methylome Diversity in Eukaryotes. J Mol Biol. 2019 Nov 11;S0022-2836(19)30659-X.
Fallet M, Luquet E, David P, Cosseau C. Epigenetic inheritance and intergenerational effects in mollusks. Gene. 2020 Mar 1;729:144166.
Aristizabal MJ, Anreiter I, Halldorsdottir T, et al. Biological embedding of experience: A primer on epigenetics. Proc Natl Acad Sci U S A. 2020 Sep 22;117(38):23261-23269.
Drinnenberg IA, Berger F, Elsässer SJ, et al. EvoChromo: towards a synthesis of chromatin biology and evolution. Development. 2019 Sep 26;146(19):dev178962.
Srikant T, Drost H-G. How Stress Facilitates Phenotypic Innovation Through Epigenetic Diversity. Front Plant Sci. 2021 Jan 15;11:606800.
Watson H, Powell D, Salmón P, et al. Urbanization is associated with modifications in DNA methylation in a small passerine bird. Evol Appl. 2020 Nov 13;14(1):85-98.
Luo X, Song R, Moreno DF, et al. Epigenetic Mechanisms Contribute to Evolutionary Adaptation of Gene Network Activity under Environmental Selection. Cell Rep. 2020 Oct 27;33(4):108306.
Baugh LR, Day T. Nongenetic inheritance and multigenerational plasticity in the nematode C. elegans. Elife. 2020 Aug 25;9:e58498.
Ewe CK, Torres Cleuren YN, Flowers SE, et al. Natural cryptic variation in epigenetic modulation of an embryonic gene regulatory network. Proc Natl Acad Sci U S A. 2020 Jun 16;117(24):13637-13646.
Heckwolf MJ, Meyer BS, Häsler R, et al. Two different epigenetic information channels in wild three-spined sticklebacks are involved in salinity adaptation. Sci Adv. 2020 Mar 20;6(12):eaaz1138.
Venney CJ, Love OP, Drown EJ, Heath DD. DNA Methylation Profiles Suggest Intergenerational Transfer of Maternal Effects. Mol Biol Evol. 2020 Feb 1;37(2):540-548.
Adrian-Kalchhauser I, Blomberg A, Larsson T, et al. The round goby genome provides insights into mechanisms that may facilitate biological invasions. BMC Biol. 2020 Jan 28;18(1):11.
Tikhodeyev ON. Heredity determined by the environment: Lamarckian ideas in modern molecular biology. Sci Total Environ. 2020 Mar 25;710:135521.

Collens A, Kelley E, Katz LA. The concept of the hologenome, an epigenetic phenomenon, challenges aspects of the modern evolutionary synthesis. J Exp Zool B Mol Dev Evol. 2019 Dec;332(8):349-355.
Green DA 2nd , Kronforst MR. Monarch butterflies use an environmentally sensitive, internal timer to control overwintering dynamics. Mol Ecol. 2019 Aug;28(16):3642-3655.
Srikulnath K, Singchat W, Laopichienpong N, et al. Overview of the betta fish genome regarding species radiation, parental care, behavioral aggression, and pigmentation model relevant to humans. Genes Genomics. 2021 Jan 29. doi: 10.1007/s13258-020-01027-2.
Camacho MP. What's all the fuss about? The inheritance of acquired traits is compatible with the Central Dogma. Hist Philos Life Sci. 2020 Jul 20;42(3):32.
Johnson LM, Smith OJ, Hahn DA. Baer CF. Short-term heritable variation overwhelms 200 generations of mutational variance for metabolic traits in Caenorhabditis elegans. Evolution. 2020 Nov;74(11):2451-2464.
Sarkies P. Molecular mechanisms of epigenetic inheritance: Possible evolutionary implications. Semin Cell Dev Biol. 2020 Jan;97:106-115.
Minow MAA, Colasanti J. Does variable epigenetic inheritance fuel plant evolution? Genome. 2020 May;63(5):253-262.
Tikhodeyev ON. Heredity determined by the environment: Lamarckian ideas in modern molecular biology. Sci Total Environ. 2020 Mar 25;710:135521.
Adrian-Kalchhauser I, Sultan SE, Shama LNS, Spence-Jones H, Tiso S, Keller Valsecchi CI, Weissing FJ. Understanding 'Non-genetic' Inheritance: Insights from Molecular-Evolutionary Crosstalk. Trends Ecol Evol. 2020 Dec;35(12):1078-1089.
Biwer C, Kawam B, Chapelle V, Silvestre F. The Role of Stochasticity in the Origin of Epigenetic Variation in Animal Populations. Integr Comp Biol. 2020 Dec 16;60(6):1544-1557.
Zoonomia Consortium. A comparative genomics multitool for scientific discovery and conservation. Nature. 2020 Nov;587(7833):240-245.
Feng S, Stiller J, Deng Y, et al. Dense sampling of bird diversity increases power of comparative genomics. Nature. 2020 Nov;587(7833):252-257.
Galupa R, Nora EP, Worsley-Hunt R, et al. A Conserved Noncoding Locus Regulates Random Monoallelic Xist Expression across a Topological Boundary. Mol Cell. 2020 77(2):352-367.e8.
Bogutz AB, Brind'Amour J, Kobayashi H, Jensen KN, Nakabayashi K, Imai H, Lorincz MC, Lefebvre L. Evolution of imprinting via lineage-specific insertion of retroviral promoters. Nat Commun. 2019 Dec 12;10(1):5674.
Luo X, Song R, Moreno DF, Ryu HY, Hochstrasser M, Acar M. Epigenetic Mechanisms Contribute to Evolutionary Adaptation of Gene Network Activity under Environmental Selection. Cell Rep. 2020 Oct 27;33(4):108306.
Höglund A, Henriksen R, Fogelholm J, Churcher AM, Guerrero-Bosagna CM, Martinez-Barrio A, Johnsson M, Jensen P, Wright D. The methylation landscape and its role in domestication and gene regulation in the chicken. Nat Ecol Evol. 2020 Dec;4(12):1713-1724.
McCaw BA, Stevenson TJ, Lancaster LT. Epigenetic Responses to Temperature and Climate. Integr Comp Biol. 2020 Dec 16;60(6):1469-1480.
Steele EJ, Gorczynski RM, Lindley RA, Liu Y, Temple R, Tokoro G, Wickramasinghe DT, Wickramasinghe NC. Lamarck and Panspermia - On the Efficient Spread of Living Systems Throughout the Cosmos. Prog Biophys Mol Biol. 2019 Dec;149:10-32.
Guerrero TP, Fickel J, Benhaiem S, Weyrich A. Epigenomics and gene regulation in mammalian social systems. Curr Zool. 2020 Jun;66(3):307-319.

Bar-Sadeh B, Rudnizky S, Pnueli L, Bentley GR, Stöger R, Kaplan A, Melamed P. Unravelling the role of epigenetics in reproductive adaptations to early-life environment. Nat Rev Endocrinol. 2020 Sep;16(9):519-533.
Choi JY, Lee YCG. Double-edged sword: The evolutionary consequences of the epigenetic silencing of transposable elements. PLoS Genet. 2020 Jul 16;16(7):e1008872.
Verzijden M. Leapfrog to speciation boosted by mother's influence. Nature. 2019 Oct;574(7776):38-39.
Glémin S, François CM, Nicolas Galtier N. Genome Evolution in Outcrossing vs. Selfing vs. Asexual Species. Methods Mol Biol. 2019;1910:331-369.
Liehr T. From Human Cytogenetics to Human Chromosomics. Int J Mol Sci. 2019 Feb 14;20(4).
Suesdek L. Microevolution of medically important mosquitoes - A review. Acta Trop. 2019 Mar;191:162-171.
Banta JA, Richards CL. Quantitative epigenetics and evolution. Heredity (Edinb). 2018 Sep;121(3):210-224.
Bartlett AA, Hunter RG. Transposons, stress and the functions of the deep genome. Front Neuroendocrinol. 2018 Apr;49:170-174.
Larsen PA, Hunnicutt KE, Larsen RJ, Yoder AD, Saunders AM. Warning SINEs: Alu elements, evolution of the human brain, and the spectrum of neurological disease. Chromosome Res. 2018 Mar;26(1-2):93-111.
Deakin JE. Chromosome Evolution in Marsupials. Genes (Basel). 2018 Feb 6;9(2).
Laubach ZM, Perng W, Dolinoy DC, Faulk CD, Holekamp KE, Getty T. Epigenetics and the maintenance of developmental plasticity: extending the signalling theory framework. Biol Rev Camb Philos Soc. 2018 Aug;93(3):1323-1338.
Weinhold A. Transgenerational stress-adaption: an opportunity for ecological epigenetics. Plant Cell Rep. 2018 Jan;37(1):3-9.
Lee YCG, Levine MT. Germline Genome Protection on an Evolutionary Treadmill. Dev Cell. 2017 Oct 9;43(1):1-3.
Manjrekar J. Epigenetic inheritance, prions and evolution. J Genet. 2017 Jul;96(3):445-456.
Vaiserman AM, Koliada AK, Jirtle RL. Non-genomic transmission of longevity between generations: potential mechanisms and evidence across species. Epigenetics Chromatin. 2017 Jul 27;10(1):38.
Nishinakamura R, Takasato M. Human development, heredity and evolution. Development. 2017 Jun 15;144(12):2099-2103.
Hu J, Barrett RDH. Epigenetics in natural animal populations. J Evol Biol. 2017 Sep;30(9):1612-1632.
Auge GA, Leverett LD, Edwards BR, Donohue K. Adjusting phenotypes via within- and across-generational plasticity. New Phytol. 2017 Oct;216(2):343-349.
Lacal I, Ventura R. Epigenetic Inheritance: Concepts, Mechanisms and Perspectives. Front Mol Neurosci. 2018 Sep 28;11:292.
Palumbo D, Affinito O, Monticelli A, Cocozza S. DNA Methylation variability among individuals is related to CpGs cluster density and evolutionary signatures. BMC Genomics. 2018 Apr 2;19(1):229.
Colwell M, Drown M, Showel K, Drown C, Palowski A, Faulk C. Evolutionary conservation of DNA methylation in CpG sites within ultraconserved noncoding elements. Epigenetics. 2018;13(1):49-60.
Spadafora C. The "evolutionary field" hypothesis. Non-Mendelian transgenerational inheritance mediates diversification and evolution. Prog Biophys Mol Biol. 2018 May;134:27-37.

Jiang F, Liu Q, Liu X, Wang XH, Kang L. Genomic data reveal high conservation but divergent evolutionary pattern of Polycomb/Trithorax group genes in arthropods. Insect Sci. 2019 Feb;26(1):20-34.
Yung PYK, Elsässer SJ. Evolution of epigenetic chromatin states. Curr Opin Chem Biol. 2017 Dec;41:36-42.
Skoglund P, Thompson JC, Prendergast ME, et al. Reconstructing Prehistoric African Population Structure. Cell. 2017 Sep 21;171(1):59-71.e21.
Medina Munoz M, Pollio AR, White HL, Rio RVM. Into the Wild: Parallel Transcriptomics of the Tsetse-Wigglesworthia Mutualism within Kenyan Populations. Genome Biol Evol. 2017 Sep 1;9(9):2276-2291.
Bolzán AD. Interstitial telomeric sequences in vertebrate chromosomes: Origin, function, instability and evolution. Mutat Res. 2017 Jul;773:51-65.
Yan H, Opachaloemphan C, Mancini G, et al. An Engineered orco Mutation Produces Aberrant Social Behavior and Defective Neural Development in Ants. Cell. 2017 Aug 10;170(4):736-747.e9.
Fukuda K, Inoguchi Y, Ichiyanagi K, et al. Evolution of the sperm methylome of primates is associated with retrotransposon insertions and genome instability. Hum Mol Genet. 2017 Sep 15;26(18):3508-3519.
Nishinakamura R, Takasato M. Human development, heredity and evolution. Development. 2017 Jun 15;144(12):2099-2103.
Kronholm I, Bassett A, Baulcombe D, Collins S. Epigenetic and Genetic Contributions to Adaptation in Chlamydomonas. Mol Biol Evol. 2017 Sep 1;34(9):2285-2306.
Turbil C. In between mental evolution and unconscious memory: Lamarckism, Darwinism, and professionalism in late Victorian Britain. J Hist Behav Sci. 2017 Sep;53(4):347-363.
Burkhardt RW Jr. Lamarck, evolution, and the inheritance of acquired characters. Genetics. 2013 Aug;194(4):793-805.
Penny D. Epigenetics, Darwin, and Lamarck. Genome Biol Evol. 2015 May 29;7(6):1758-60.
Liu Y. Natural Selection and Pangenesis: The Darwinian Synthesis of Evolution and Genetics. Adv Genet. 2018;102:121-142.
Wang Y, Liu H, Sun Z. Lamarck rises from his grave: parental environment-induced epigenetic inheritance in model organisms and humans. Biol Rev Camb Philos Soc. 2017 Nov;92(4):2084-2111.
Tanghe KB. A Historical Taxonomy of Origin of Species Problems and Its Relevance to the Historiography of Evolutionary Thought. J Hist Biol. 2017 Nov;50(4):927-987.
Merlin C, Liedvogel M. The genetics and epigenetics of animal migration and orientation: birds, butterflies and beyond. J Exp Biol. 2019 Feb 6;222(Pt Suppl 1).
Banta JA, Richards CL. Quantitative epigenetics and evolution. Heredity (Edinb). 2018 Sep;121(3):210-224.
St-Cyr S, McGowan PO. Adaptation or pathology? The role of prenatal stressor type and intensity in the developmental programing of adult phenotype. Neurotoxicol Teratol. 2018 Mar - Apr;66:113-124.
Artemov AV, Mugue NS, Rastorguev SM, et al. Genome-Wide DNA Methylation Profiling Reveals Epigenetic Adaptation of Stickleback to Marine and Freshwater Conditions. Mol Biol Evol. 2017 Sep 1;34(9):2203-2213.
McNew SM, Beck D, Sadler-Riggleman I, Knutie SA, Koop JAH, Clayton DH, Skinner MK. Epigenetic variation between urban and rural populations of Darwin's finches. BMC Evol Biol. 2017 Aug 24;17(1):183.

De Tiège A, Van de Peer Y, Braeckman J, Tanghe KB. The sociobiology of genes: the gene's eye view as a unifying behavioural-ecological framework for biological evolution. Hist Philos Life Sci. 2017 Nov 22;40(1):6.
Boomsma JJ, Gawne R. Superorganismality and caste differentiation as points of no return: how the major evolutionary transitions were lost in translation. Biol Rev Camb Philos Soc. 2018 Feb;93(1):28-54.
Andreou D, Eizaguirre C, Boehm T, Milinski M. Mate choice in sticklebacks reveals that immunogenes can drive ecological speciation. Behav Ecol. 2017 Jul-Aug;28(4):953-961.
Jones B1, Robinson GE. Genetic accommodation and the role of ancestral plasticity in the evolution of insect eusociality. J Exp Biol. 2018 Nov 26;221(Pt 23). pii: jeb153163.
Schmid MW, Heichinger C, Coman Schmid D, et al. Contribution of epigenetic variation to adaptation in Arabidopsis. Nat Commun. 2018 Oct 25;9(1):4446. doi: 10.1038/s41467-018-06932-5.
Jeremias G, Barbosa J, Marques SM, Asselman J, Gonçalves FJM, Pereira JL. Synthesizing the role of epigenetics in the response and adaptation of species to climate change in freshwater ecosystems. Mol Ecol. 2018 Jul;27(13):2790-2806.
Toth AL, Rehan SM. Molecular Evolution of Insect Sociality: An Eco-Evo-Devo Perspective. Annu Rev Entomol. 2017 Jan 31;62:419-442.
Bewick AJ, Ji L, Niederhuth CE, et al. On the origin and evolutionary consequences of gene body DNA methylation. Proc Natl Acad Sci U S A. 2016 Aug 9;113(32):9111-6
Horst NA, Reski R. Alternation of generations - unravelling the underlying molecular mechanism of a 165-year-old botanical observation. Plant Biol (Stuttg). 2016 Jul;18(4):549-51.
Rehan SM, Glastad KM, Lawson SP, Hunt BG. The Genome and Methylome of a Subsocial Small Carpenter Bee, Ceratina calcarata. Genome Biol Evol. 2016 May 13;8(5):1401-10.
Hernando-Herraez I, Garcia-Perez R1, Sharp AJ, Marques-Bonet T. DNA Methylation: Insights into Human Evolution. PLoS Genet. 2015 Dec 10;11(12):e1005661.
Cunningham CB, Ji L, Wiberg RA, et al. The Genome and Methylome of a Beetle with Complex Social Behavior, Nicrophorus vespilloides (Coleoptera: Silphidae). Genome Biol Evol. 2015 Oct 9;7(12):3383-96.
Cui J, You C, Chen X. The evolution of microRNAs in plants. Curr Opin Plant Biol. 2017 Feb;35:61-67.
Félix MA. Phenotypic Evolution With and Beyond Genome Evolution. Curr Top Dev Biol. 2016;119:291-347.
Lowdon RF, Jang HS, Wang T. Evolution of Epigenetic Regulation in Vertebrate Genomes. Trends Genet. 2016 May;32(5):269-83.
Rodrigues JA, Zilberman D. Evolution and function of genomic imprinting in plants. Genes Dev. 2015 Dec 15;29(24):2517-31.
Fagny M, Patin E, MacIsaac JL, et al. The epigenomic landscape of African rainforest hunter-gatherers and farmers. Nat Commun. 2015 Nov 30;6:10047.
Vogt G. Stochastic developmental variation, an epigenetic source of phenotypic diversity with far-reaching biological consequences. J Biosci. 2015 Mar;40(1):159-204.
Fagny M, Patin E, MacIsaac JL, et al. The epigenomic landscape of African rainforest hunter-gatherers and farmers. Nat Commun. 2015 Nov 30;6:10047.
Vogt G. Stochastic developmental variation, an epigenetic source of phenotypic diversity with far-reaching biological consequences. J Biosci. 2015 Mar;40(1):159-204.
Chen DH, Huang Y, Ruan Y, Shen WH. The evolutionary landscape of PRC1 core components in green lineage. Planta. 2016 Apr;243(4):825-46.

Orlando L, Gilbert MT, Willerslev E. Reconstructing ancient genomes and epigenomes. Nat Rev Genet. 2015 Jul;16(7):395-408
Lowdon RF, Jang HS, Wang T. Evolution of Epigenetic Regulation in Vertebrate Genomes. Trends Genet. 2016 May;32(5):269-83.
Lin Q, Fan S, Zhang Y, et al. The seahorse genome and the evolution of its specialized morphology. Nature. 2016 Dec 14;540(7633):395-399.
Field Y, Boyle EA, Telis N, et al. Detection of human adaptation during the past 2000 years. Science. 2016 Nov 11;354(6313):760-764.
Reid NM, Proestou DA, Clark BW, et al. The genomic landscape of rapid repeated evolutionary adaptation to toxic pollution in wild fish. Science. 2016 Dec 9;354(6317):1305-1308.
Vargas AO, Krabichler Q, Guerrero-Bosagna C. An Epigenetic Perspective on the Midwife Toad Experiments of Paul Kammerer (1880-1926). J Exp Zool B Mol Dev Evol. 2017 Jan;328(1-2):179-192.
Kuijper B, Hoyle RB. When to rely on maternal effects and when on phenotypic plasticity? Evolution. 2015 Mar 24. doi: 10.1111/evo.12635. [Epub ahead of print]
Giuliani C, Bacalini MG, et al. The epigenetic side of human adaptation: hypotheses, evidences and theories. Ann Hum Biol. 2015 Jan;42(1):1-9.
Kratochwil CF, Meyer A. Closing the genotype-phenotype gap: emerging technologies for evolutionary genetics in ecological model vertebrate systems. Bioessays. 2015 Feb;37(2):213-26.
Skinner MK1, Guerrero-Bosagna C, Haque MM, Nilsson EE, Koop JA, Knutie SA, Clayton DH. Epigenetics and the evolution of Darwin's Finches. Genome Biol Evol. 2014 Jul 24;6(8):1972-89.
Skinner MK, Savenkova MI, Zhang B, Gore AC, Crews D. Gene bionetworks involved in the epigenetic transgenerational inheritance of altered mate preference: environmental epigenetics and evolutionary biology. BMC Genomics. 2014 May 16;15:377.
Mendizabal I, Keller TE, Zeng J, Yi SV. Epigenetics and evolution. Integr Comp Biol. 2014 Jul;54(1):31-42.
Burggren WW. Epigenetics as a source of variation in comparative animal physiology - or - Lamarck is lookin' pretty good these days. J Exp Biol. 2014 Mar 1;217(Pt 5):682-9.
Diez CM, Roessler K, Gaut BS. Epigenetics and plant genome evolution. Curr Opin Plant Biol. 2014 Apr;18:1-8.
Castonguay E, Angers B. The key role of epigenetics in the persistence of asexual lineages. Genet Res Int. 2012;2012:534289.
Bonduriansky R, Crean AJ, Day T. The implications of nongenetic inheritance for evolution in changing environments. Evol Appl. 2012 Feb;5(2):192-201.
Kuzawa CW, Thayer ZM. Timescales of human adaptation: the role of epigenetic processes. Epigenomics. 2011 Apr;3(2):221-34.
Skinner MK. Environmental epigenetic transgenerational inheritance and somatic epigenetic mitotic stability. Epigenetics. 2011 Jul;6(7):838-42.
Gluckman PD, Low FM, Buklijas T, Hanson MA, Beedle AS. How evolutionary principles improve the understanding of human health and disease. Evol Appl. 2011 Mar;4(2):249-63.
Goldschmidt EE. Plant grafting: new mechanisms, evolutionary implications. Front Plant Sci. 2014 Dec 17;5:727.
Boffelli D, Martin DI. Epigenetic inheritance: a contributor to species differentiation? DNA Cell Biol. 2012 Oct;31 Suppl 1:S11-6.

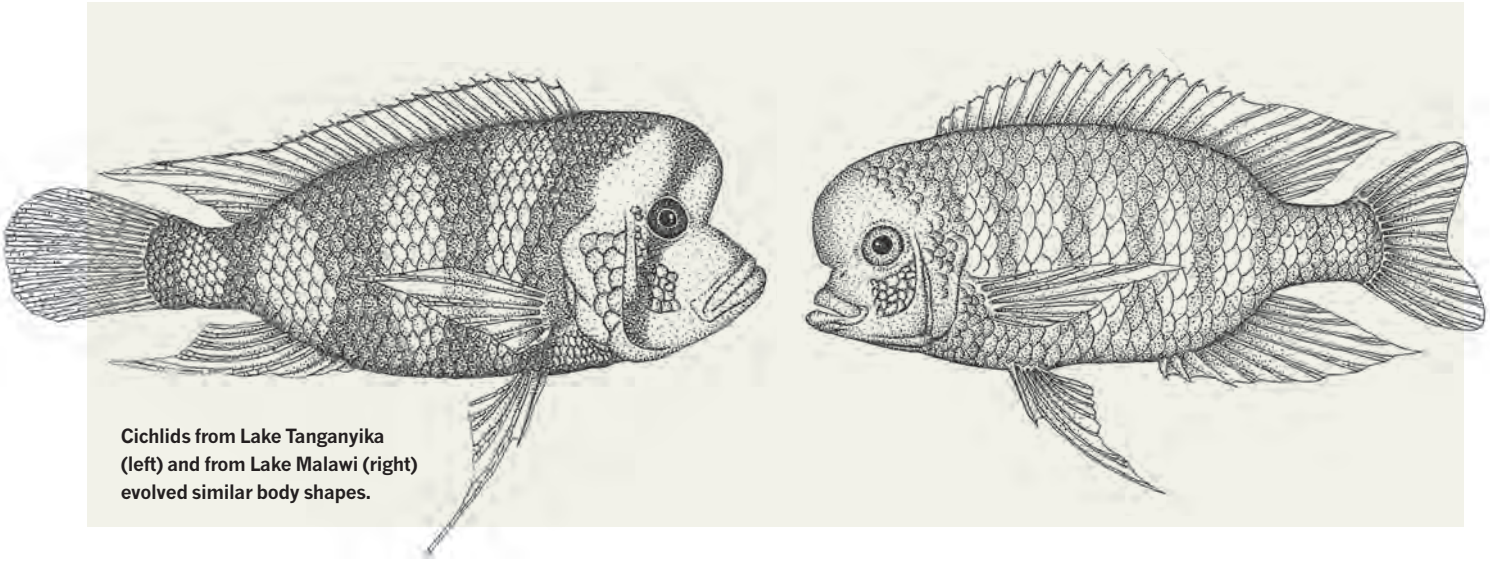
Flatscher R, Frajman B, Schönswetter P, Paun O. Environmental heterogeneity and phenotypic divergence: can heritable epigenetic variation aid speciation? Genet Res Int. 2012;2012:698421.
Qi B, Huang W, Zhu B, Zhong X, et al. Global transgenerational gene expression dynamics in two newly synthesized allohexaploid wheat (Triticum aestivum) lines. BMC Biol. 2012 Jan 26;10:3.
Rebollo R, Horard B, Hubert B, Vieira C. Jumping genes and epigenetics: Towards new species. Gene. 2010 Apr 1;454(1-2):1-7.
Zhang H, Bian Y, Gou X, Dong Y, Rustgi S, et al. Intrinsic karyotype stability and gene copy number variations may have laid the foundation for tetraploid wheat formation. Proc Natl Acad Sci U S A. 2013 Nov 26;110(48):19466-71.
Soubry A. Epigenetic inheritance and evolution: A paternal perspective on dietary influences. Prog Biophys Mol Biol. 2015 Mar 10. pii: S0079-6107(15)00033-4.
Ruden DM, Cingolani PE, Sen A, et al. Epigenetics as an answer to Darwin's "special difficulty," Part 2: natural selection of metastable epialleles in honeybee castes. Front Genet. 2015 Feb 24;6:60.
Rodríguez-Mega E1, Piñeyro-Nelson A, Gutierrez C, et al. The role of transcriptional regulation in the evolution of plant phenotype: A dynamic systems approach. Dev Dyn. 2015 Mar 2.
Ermini L, Der Sarkissian C, Willerslev E, Orlando L. Major transitions in human evolution revisited: a tribute to ancient DNA. J Hum Evol. 2015 Feb;79:4-20.
Stanyon R, Bigoni F. Sexual selection and the evolution of behavior, morphology, neuroanatomy and genes in humans and other primates. Neurosci Biobehav Rev. 2014 Oct 14;46P4:579-590.
Crews D, Gillette R, Miller-Crews I, Gore AC, Skinner MK. Nature, nurture and epigenetics. Mol Cell Endocrinol. 2014 Dec;398(1-2):42-52.
Bateson P. Evolution, epigenetics and cooperation. J Biosci. 2014 Apr;39(2):191-200.
Duncan EJ, Gluckman PD, Dearden PK. Epigenetics, plasticity, and evolution: How do we link epigenetic change to phenotype? J Exp Zool B Mol Dev Evol. 2014 Jun;322(4):208-20.
Varriale A. DNA methylation, epigenetics, and evolution in vertebrates: facts and challenges. Int J Evol Biol. 2014;2014:475981.
Walker SI, Callahan BJ, Arya G, et al. Evolutionary dynamics and information hierarchies in biological systems. Ann N Y Acad Sci. 2013 Dec;1305:1-17.
Stringer JM, Barrand S, Western P. Fine-tuning evolution: germ-line epigenetics and inheritance. Reproduction. 2013 Jun 14;146(1):R37-48.
Jablonka E. Epigenetic variations in heredity and evolution. Clin Pharmacol Ther. 2012 Dec;92(6):683-8.
Weigel D, Colot V. Epialleles in plant evolution. Genome Biol. 2012 Oct 11;13(10):249.
Mihola O, Trachtulec Z, Vlcek C, Schimenti JC, Forejt J. (2009) A mouse speciation gene encodes a meiotic histone H3 methyltransferase. Science. 16;323(5912):373-5.
Rapp RA, Wendel JF. (2005) Epigenetics and plant evolution. New Phytol. 168(1):81-91.
Feinberg AP, Irizarry RA. (2010) Evolution in health and medicine Sackler colloquium: Stochastic epigenetic variation as a driving force of development, evolutionary adaptation, and disease. Proc Natl Acad Sci U S A. 2010 Jan 26;107 Suppl 1:1757-64.
Blanchette M, Green ED, Miller W, Haussler D. (2004) Reconstructing large regions of an ancestral mammalian genome in silico. Genome Res. 14(12):2412-23.
Murphy BF, Thompson MB. (2011) A review of the evolution of viviparity in squamate reptiles: the past, present and future role of molecular biology and genomics. J Comp Physiol B. Jul;181(5):575-94.
Galliot B, Quiquand M. (2011) A two-step process in the emergence of neurogenesis. Eur J Neurosci. 34(6):847-62.

Olson-Manning CF, Wagner MR, Mitchell-Olds T. (2012) Adaptive evolution: evaluating empirical support for theoretical predictions. Nat Rev Genet. 13(12):867-77.
Bard JB. (2011) The next evolutionary synthesis: from Lamarck and Darwin to genomic variation and systems biology. Cell Commun Signal. 3;9(1):30. doi: 10.1186/1478-811X-9-30.
Frankel N, Erezyilmaz DF, McGregor AP, Wang S, Payre F, Stern DL. (2011) Morphological evolution caused by many subtle-effect substitutions in regulatory DNA. Nature. 29;474(7353):598-603.
Kuzawa CW, Thayer ZM. (2011) Timescales of human adaptation: the role of epigenetic processes. Epigenomics. ;3(2):221-34.
Wagner A. (2011) The molecular origins of evolutionary innovations. Trends Genet. 27(10):397-410.
Papp B, Notebaart RA, Pál C. (2011) Systems-biology approaches for predicting genomic evolution. Nat Rev Genet. 2;12(9):591-602.
Fedoroff NV. (2012) Presidential address. Transposable elements, epigenetics, and genome evolution. Science. 9;338(6108):758-67.
Escamilla-Del-Arenal M, da Rocha ST, Heard E. (2011) Evolutionary diversity and developmental regulation of X-chromosome inactivation. Hum Genet. 130(2):307-27.
Okamoto I, et al. (2011) Eutherian mammals use diverse strategies to initiate X-chromosome inactivation during development. Nature. 21;472(7343):370-4.
Barry G, Mattick JS. (2012) The role of regulatory RNA in cognitive evolution. Trends Cogn Sci. 16(10):497-503.
Damiani G. (2007) The Yin and Yang of anti-Darwinian epigenetics and Darwinian genetics. Riv Biol. 100(3):361-402.
Van Speybroeck L. (2002) From epigenesis to epigenetics: the case of C. H. Waddington. Ann N Y Acad Sci. 981:61-81.
Varmuza S. (2003) Epigenetics and the renaissance of heresy. Genome. 46(6):963-7; discussion 968-73.
Flatscher R, Frajman B, Schönswetter P, Paun O. (2012) Environmental heterogeneity and phenotypic divergence: can heritable epigenetic variation aid speciation? Genet Res Int. 2012:698421.
Rebollo R, Horard B, Hubert B, Vieira C. (2010) Jumping genes and epigenetics: Towards new species. Gene. 1;454(1-2):1-7.
Choi JK, Kim YJ. (2009) Implications of the nucleosome code in regulatory variation, adaptation and evolution. Epigenetics. 1;4(5):291-5.
Handel AE, Ramagopalan SV. (2010) Is Lamarckian evolution relevant to medicine? BMC Med Genet. 13;11:73.
Bräutigam K, et al. (2013) Epigenetic regulation of adaptive responses of forest tree species to the environment. Ecol Evol. 3(2):399-415.
Houle D, Govindaraju DR, Omholt S. (2010) Phenomics: the next challenge. Nat Rev Genet. (12):855-66.
Kaneko K. (2011) Proportionality between variances in gene expression induced by noise and mutation: consequence of evolutionary robustness. BMC Evol Biol. 26;11:27.
Davidson LA, Baum B. (2012) Making waves: the rise and fall and rise of quantitative developmental biology. Development. 139(17):3065-9.
Furusawa C, Kaneko K. (2012) A dynamical-systems view of stem cell biology. Science. 12;338(6104):215-7.
Kicheva A, Cohen M, Briscoe J. (2012) Developmental pattern formation: insights from physics and biology. Science. 12;338(6104):210-2.

Goldbeter A, Gérard C, Gonze D, Leloup JC, Dupont G. (2012) Systems biology of cellular rhythms. FEBS Lett. 31;586(18):2955-65.
Jobe EM, McQuate AL, Zhao X. (2012) Crosstalk among Epigenetic Pathways Regulates Neurogenesis. Front Neurosci. 6:59.
Kasinski AL, Slack FJ. (2011) Epigenetics and genetics. MicroRNAs en route to the clinic: progress in validating and targeting microRNAs for cancer therapy. Nat Rev Cancer. 24;11(12):849-64.
Huang S. (2011) Systems biology of stem cells: three useful perspectives to help overcome the paradigm of linear pathways. Philos Trans R Soc Lond B Biol Sci. 12;366(1575):2247-59.
Galliot B, Quiquand M. (2011) A two-step process in the emergence of neurogenesis. Eur J Neurosci. 34(6):847-62.
Jeltsch A. (2010) Molecular biology. Phylogeny of methylomes. Science. 14;328(5980):837-8.
Lamarck on use and disuse. http//www.ucl.ac.uk/taxome/jim/Mim/lamarck6.html
Handel AE, Ramagopalan SV. Is Lamarckian evolution relevant to medicine? BMC Med Genet. 2010 May 13;11:73.
Waddington CH. Selection of the Genetic Basis for an Acquired Character. 1952 Nature 169: 278
Waddington CH. The Epigenotype. 1942 Endeavour (18-20).
Waddington CH. Assimilation of an Acquired Character. 1953 Evolution Vol. 7, No. 2, pp. 118-126.
Jollos V. Inherited Changes Produced by Heat-Treatment in Drosophila Melanogaster. 1934 (477-494).
Waddington CH. Canalization of the Development and the Inheritance of Acquired Characters. 1942 Nature, Vol. 150, No. 3811 (563-565)
Crews D. Epigenetics and its implications for behavioral neuroendocrinology. Front Neuroendocrinol. 2008 Jun;29(3):344-57.
Jeltsch A. Molecular biology. Phylogeny of methylomes. Science. 2010 May 14;328(5980):837-8.
Ryba T, Hiratani I, Lu J, Itoh M, Kulik M, Zhang J, Schulz TC, Robins AJ, Dalton S, Gilbert DM. Evolutionarily conserved replication timing profiles predict long-range chromatin interactions and distinguish closely related cell types. Genome Res. 2010 Jun;20(6):761-70.
Lupski JR. Retrotransposition and structural variation in the human genome. Cell. 2010 Jun 25;141(7):1110-2.
van Doorn GS, Edelaar P, Weissing FJ. On the origin of species by natural and sexual selection. Science. 2009 Dec 18;326(5960):1704-7.
Theissen G. Saltational evolution: hopeful monsters are here to stay. Theory Biosci. 2009 Mar;128(1):43-51.
Theissen G. The proper place of hopeful monsters in evolutionary biology. Theory Biosci. 2006 Mar;124(3-4):349-69.
Niswander L, Anderson KV. Hopeful monsters and morphogens at the beach. Nat Cell Biol. 2002 Nov;4(11):E259-62.
Erwin DH, Valentine JW. "Hopeful monsters," transposons, and Metazoan radiation. Proc Natl Acad Sci U S A. 1984 Sep;81(17):5482-3.
Feinberg AP, Irizarry RA. Evolution in health and medicine Sackler colloquium: Stochastic epigenetic variation as a driving force of development, evolutionary adaptation, and disease. Proc Natl Acad Sci U S A. 2010 Jan 26;107 Suppl 1:1757-64
Ching TT, Maunakea AK, Jun P, Hong C, Zardo G, Pinkel D, Albertson DG, Fridlyand J, Mao JH, Shchors K, Weiss WA, Costello JF. Epigenome analyses using BAC microarrays identify evolutionary conservation of tissue-specific methylation of SHANK3. Nat Genet. 2005 Jun;37(6):645-51.
Loakes D, Holliger P. Darwinian chemistry: towards the synthesis of a simple cell. Mol Biosyst. 2009 Jul;5(7):686-94.

O'Connell LA, Hofmann HA. Genes, hormones, and circuits: An integrative approach to study the evolution of social behavior. Front Neuroendocrinol. 2010 Dec 14. [Epub ahead of print]
Bull JJ, Wang IN. Optimality models in the age of experimental evolution and genomics. J Evol Biol. 2010 Sep 1;23(9):1820-38.
Foster KR. A defense of sociobiology. Cold Spring Harb Symp Quant Biol. 2009;74:403-18.
Medina M, Sachs JL. Symbiont genomics, our new tangled bank. Genomics. 2010 95(3):129-37.
Saito H, Inoue T. Synthetic biology with RNA motifs. Int J Biochem Cell Biol. 2009 41(2):398-404.
Palumbi SR. Speciation and the evolution of gamete recognition genes: pattern and process. Heredity. 2009 Jan;102(1):66-76.
Nakamoto T. Evolution and the universality of the mechanism of initiation of protein synthesis. Gene. 2009 Mar 1;432(1-2):1-6.
Shapiro BJ, David LA, Friedman J, Alm EJ. Looking for Darwin's footprints in the microbial world. Trends Microbiol. 2009 May;17(5):196-204.
Van de Peer Y, Maere S, Meyer A. The evolutionary significance of ancient genome duplications. Nat Rev Genet. 2009 Oct;10(10):725-32.
Charlesworth D, Willis JH. The genetics of inbreeding depression. Nat Rev Genet. 2009 Nov;10(11):783-96.
Williams TM, Carroll SB. Genetic and molecular insights into the development and evolution of sexual dimorphism. Nat Rev Genet. 2009 Nov;10(11):797-804.
Moura GR, Carreto LC, Santos MA. Genetic code ambiguity: an unexpected source of proteome innovation and phenotypic diversity. Curr Opin Microbiol. 2009 Dec;12(6):631-7.
Yi SV, Goodisman MA. Computational approaches for understanding the evolution of DNA methylation in animals. Epigenetics. 2009 Nov 16;4(8):551-6.

COMMENT



Cichlids from Lake Tanganyika (left) and from Lake Malawi (right) evolved similar body shapes.

Does evolutionary theory need a rethink?

Researchers are divided over what processes should be considered fundamental.

POINT

Yes, urgently

Without an extended evolutionary framework, the theory neglects key processes, say Kevin Laland *and colleagues.*

Charles Darwin conceived of evolution by natural selection without knowing that genes exist. Now mainstream evolutionary theory has come to focus almost exclusively on genetic inheritance and processes that change gene frequencies.

Yet new data pouring out of adjacent fields are starting to undermine this narrow stance. An alternative vision of evolution is beginning to crystallize, in which the processes by which organisms grow and develop are recognized as causes of evolution.

Some of us first met to discuss these advances six years ago. In the time since, as members of an interdisciplinary team, we have worked intensively to develop a broader framework, termed the extended evolutionary synthesis[1] (EES), and to flesh out its structure, assumptions and predictions. In essence, this synthesis maintains that important drivers of evolution, ones that cannot be reduced to genes, must be woven into the very fabric of evolutionary theory.

We believe that the EES will shed new light on how **PAGE 162** ▶

COUNTERPOINT

No, all is well

Theory accommodates evidence through relentless synthesis, say Gregory A. Wray, Hopi E. Hoekstra *and colleagues.*

In October 1881, just six months before he died, Charles Darwin published his final book. *The Formation of Vegetable Mould, Through the Actions of Worms*[11] sold briskly: Darwin's earlier publications had secured his reputation. He devoted an entire book to these humble creatures in part because they exemplify an interesting feedback process: earthworms are adapted to thrive in an environment that they modify through their own activities.

Darwin learned about earthworms from conversations with gardeners and his own simple experiments. He had a genius for distilling penetrating insights about evolutionary processes — often after amassing years of observational and experimental data — and he drew on such disparate topics as agriculture, geology, embryology and behaviour. Evolutionary thinking ever since has followed Darwin's lead in its emphasis on evidence and in synthesizing information from other fields.

A profound shift in evolutionary thinking began **PAGE 163** ▶

ILLUSTRATION BY R. CRAIG ALBERTSON

POINT: YES, URGENTLY ▶ evolution works. We hold that organisms are constructed in development, not simply 'programmed' to develop by genes. Living things do not evolve to fit into pre-existing environments, but co-construct and coevolve with their environments, in the process changing the structure of ecosystems.

The number of biologists calling for change in how evolution is conceptualized is growing rapidly. Strong support comes from allied disciplines, particularly developmental biology, but also genomics, epigenetics, ecology and social science[1,2]. We contend that evolutionary biology needs revision if it is to benefit fully from these other disciplines. The data supporting our position gets stronger every day.

Yet the mere mention of the EES often evokes an emotional, even hostile, reaction among evolutionary biologists. Too often, vital discussions descend into acrimony, with accusations of muddle or misrepresentation. Perhaps haunted by the spectre of intelligent design, evolutionary biologists wish to show a united front to those hostile to science. Some might fear that they will receive less funding and recognition if outsiders — such as physiologists or developmental biologists — flood into their field.

However, another factor is more important: many conventional evolutionary biologists study the processes that we claim are neglected, but they comprehend them very differently (see 'No, all is well'). This is no storm in an academic tearoom, it is a struggle for the very soul of the discipline.

Here we articulate the logic of the EES in the hope of taking some heat out of this debate and encouraging open discussion of the fundamental causes of evolutionary change (see Supplementary Information; go.nature.com/boffk7).

Plasticity: commodore butterflies emerge with different colours in dry (left) and wet seasons.

ORANGE: PETER CHADWICK/SPL; BLUE: LAWRENCE LAWRY/SPL

CORE VALUES

The core of current evolutionary theory was forged in the 1930s and 1940s. It combined natural selection, genetics and other fields into a consensus about how evolution occurs. This 'modern synthesis' allowed the evolutionary process to be described mathematically as frequencies of genetic variants in a population change over time — as, for instance, in the spread of genetic resistance to the myxoma virus in rabbits.

In the decades since, evolutionary biology has incorporated developments consistent with the tenets of the modern synthesis. One such is 'neutral theory', which emphasizes random events in evolution. However, standard evolutionary theory (SET) largely retains the same assumptions as the original modern synthesis, which continues to channel how people think about evolution.

The story that SET tells is simple: new variation arises through random genetic mutation; inheritance occurs through DNA; and natural selection is the sole cause of adaptation, the process by which organisms become well-suited to their environments. In this view, the complexity of biological development — the changes that occur as an organism grows and ages — are of secondary, even minor, importance.

In our view, this 'gene-centric' focus fails to capture the full gamut of processes that direct evolution. Missing pieces include how physical development influences the generation of variation (developmental bias); how the environment directly shapes organisms' traits (plasticity); how organisms modify environments (niche construction); and how organisms transmit more than genes across generations (extra-genetic inheritance). For SET, these phenomena are just outcomes of evolution. For the EES, they are also causes.

Valuable insight into the causes of adaptation and the appearance of new traits comes from the field of evolutionary developmental biology ('evo-devo'). Some of its experimental findings are proving tricky to assimilate into SET. Particularly thorny is the observation that much variation is not random because developmental processes generate certain forms more readily than others[3]. For example, among one group of centipedes, each of the more than 1,000 species has an odd number of leg-bearing segments, because of the mechanisms of segment development[3].

In our view, this concept — developmental bias — helps to explain how organisms adapt to their environments and diversify into many different species. For example, cichlid fishes in Lake Malawi are more closely related to other cichlids in Lake Malawi than to those in Lake Tanganyika, but species in both lakes have strikingly similar body shapes[4]. In each case, some fish have large fleshy lips, others protruding foreheads, and still others short, robust lower jaws.

SET explains such parallels as convergent evolution: similar environmental conditions select for random genetic variation with equivalent results. This account requires extraordinary coincidence to explain the multiple parallel forms that evolved independently in each lake. A more succinct hypothesis is that developmental bias and natural selection work together[4,5]. Rather than selection being free to traverse across any physical possibility, it is guided along specific routes opened up by the processes of development[5,6].

Another kind of developmental bias occurs when individuals respond to their environment by changing their form — a phenomenon called plasticity. For instance, leaf shape changes with soil water and chemistry. SET views this plasticity as merely fine-tuning, or even noise. The EES sees it as a plausible first step in adaptive evolution. The key finding here is that plasticity not only allows organisms to cope in new environmental conditions but to generate traits that are well-suited to them. If selection preserves genetic variants that respond effectively when conditions change, then adaptation largely occurs by accumulation of genetic variations that stabilize a trait after its first appearance[5,6]. In other words, often it is the trait that comes first; genes that cement it follow, sometimes several generations later[5].

Studies of fish, birds, amphibians and insects suggest that adaptations that were, initially, environmentally induced may promote colonization of new environments and facilitate speciation[5,6]. Some of the best-studied examples of this are in fishes, such as sticklebacks and Arctic char. Differences in the diets and conditions of fish living at the bottom and in open water have induced distinct body forms, which seem to be evolving reproductive isolation, a stage in forming new species. The number of species in a lineage does not depend solely on how random genetic variation is winnowed through different environmental sieves. It also hangs on developmental properties that contribute to the lineage's 'evolvability'.

In essence, SET treats the environment as a 'background condition', which may trigger or modify selection, but is not itself part of the evolutionary process. It does not differentiate between how termites become adapted to mounds that they construct and, say, how organisms adapt to volcanic eruptions. We view these cases as fundamentally different[7].

Volcanic eruptions are idiosyncratic events, independent of organisms' actions. By contrast, termites construct and regulate their homes in a repeatable, directional manner that is shaped by past selection and that instigates future selection. Similarly, mammals, birds and insects defend, maintain and improve their nests — adaptive responses to nest building that have evolved again and again[7]. This 'niche construction', like developmental bias, means that organisms co-direct their own evolution by systematically changing environments and thereby biasing selection[7].

INHERITANCE BEYOND GENES

SET has long regarded inheritance mechanisms outside genes as special cases; human culture being the prime example. The EES explicitly recognizes that parent–offspring similarities result in part from parents reconstructing their own developmental environments for their offspring. 'Extra-genetic inheritance' includes PAGE 164 ▶

COUNTERPOINT: NO, ALL IS WELL ▶ during the 1920s, when a handful of statisticians and geneticists began quietly laying the foundations for a dramatic transformation. Their work between 1936 and 1947 culminated in the 'modern synthesis', which united Darwin's concept of natural selection with the nascent field of genetics and, to a lesser extent, palaeontology and systematics. Most importantly, it laid the theoretical foundations for a quantitative and rigorous understanding of adaptation and speciation, two of the most fundamental evolutionary processes.

In the decades since, generations of evolutionary biologists have modified, corrected and extended the framework of the modern synthesis in countless ways. Like Darwin, they have drawn heavily from other fields. When molecular biologists identified DNA as the material basis for heredity and trait variation, for instance, their discoveries catalysed fundamental extensions to evolutionary theory. For example, the realization that many genetic changes have no fitness consequences led to major theoretical advances in population genetics. The discovery of 'selfish' DNA prompted discussions about selection at the level of genes rather than traits. Kin selection theory, which describes how traits affecting relatives are selected, represents another extension[12].

Nonetheless there are evolutionary biologists (see 'Yes, urgently') who argue that theory has since ossified around genetic concepts. More specifically, they contend that four phenomena are important evolutionary processes: phenotypic plasticity, niche construction, inclusive inheritance and developmental bias. We could not agree more. We study them ourselves.

But we do not think that these processes deserve such special attention as to merit a new name such as 'extended evolutionary synthesis'. Below we outline three reasons why we believe that these topics already receive their due in current evolutionary theory.

NEW WORDS, OLD CONCEPTS

The evolutionary phenomena championed by Laland and colleagues are already well integrated into evolutionary biology, where they have long provided useful insights. Indeed, all of these concepts date back to Darwin himself, as exemplified by his analysis of the feedback that occurred as earthworms became adapted to their life in soil.

Today we call such a process niche construction, but the new name does not alter the fact that evolutionary biologists have been studying feedback between organisms and the environment for well over a century[13]. Stunning adaptations such as termite mounds, beaver dams, and bowerbird displays have long been a staple of evolutionary studies. No less spectacular are cases that can only be appreciated at the microscopic or molecular scale, such as viruses that hijack host cells to reproduce and 'quorum sensing', a sort of group think by bacteria.

Another process, phenotypic plasticity, has drawn considerable attention from evolutionary biologists. Countless cases in which the environment influences trait variation have been documented — from the jaws of cichlid fishes that change shape when food sources alter, to leaf-mimicking insects that are brown if born in the dry season and green in the wet. Technological advances in the past decade have revealed an incredible degree of plasticity in gene expression in response to diverse environmental conditions, opening the door to understanding its material basis. Much discussed, too, was a book[5] by behavioural scientist Mary Jane West-Eberhard that explored how plasticity might precede genetic changes during adaptation.

So, none of the phenomena championed by Laland and colleagues are neglected in evolutionary biology. Like all ideas, however, they need to prove their value in the marketplace of rigorous theory, empirical results and critical discussion. The prominence that these four phenomena command in the discourse of contemporary evolutionary theory reflects their proven explanatory power, not a lack of attention.

MODERN EXPANSION

Furthermore, the phenomena that interest Laland and colleagues are just four among many that offer promise for future advances in evolutionary biology. Most evolutionary biologists have a list of topics that they would like to see given more attention. Some would argue that epistasis — complex interactions among genetic variants — has long been under-appreciated. Others would advocate for cryptic genetic variation (mutations that affect only traits under specific genetic or environmental conditions). Still others would stress the importance of extinction, or adaptation to climate change, or the evolution of behaviour. The list goes on.

We could stop and argue about whether 'enough' attention is being paid to any of these. Or we could roll up our sleeves, get to work, and find out by laying the theoretical foundations and building a solid casebook of empirical studies. Advocacy can take an idea only so far.

What Laland and colleagues term the standard evolutionary theory is a caricature that views the field as static and monolithic. They see today's evolutionary biologists as unwilling to consider ideas that challenge convention.

We see a very different world. We consider ourselves fortunate to live and work in the most exciting, inclusive and progressive period of evolutionary research since the modern synthesis. Far from being stuck in the past, current evolutionary theory is vibrantly creative and rapidly growing in scope. Evolutionary biologists today draw inspiration from fields as diverse as genomics, medicine, ecology, artificial intelligence and robotics. We think Darwin would approve.

GENES ARE CENTRAL

Finally, diluting what Laland and colleagues deride as a 'gene-centric' view would de-emphasize the most powerfully predictive, broadly applicable and empirically validated component of evolutionary theory. Changes in the hereditary material are an essential part of adaptation and speciation. The precise genetic basis for countless adaptations has been documented in detail, ranging from antibiotic resistance in bacteria to camouflage coloration in deer mice, to lactose tolerance in humans.

Although genetic changes are required for adaptation, non-genetic processes can sometimes play a part in how organisms evolve. Laland and colleagues are correct that phenotypic plasticity, for instance, may contribute to the adaptedness of an individual. A seedling might bend towards brighter light, growing into a tree with a different shape from its siblings'. Many studies have shown that this kind of plasticity is beneficial, and that it can readily evolve if there PAGE 164 ▶

JOHN VAN WYHE/DARWIN-ONLINE.ORG.UK

A worm cast pictured in Charles Darwin's final book.

POINT: YES, URGENTLY ▶ the transmission of epigenetic marks (chemical changes that alter DNA expression but not the underlying sequence) that influence fertility, longevity and disease resistance across taxa[8]. In addition, extra-genetic inheritance includes socially transmitted behaviour in animals, such as nut cracking in chimpanzees or the migratory patterns of reef fishes[8,9]. It also encompasses those structures and altered conditions that organisms leave to their descendants through their niche construction — from beavers' dams to worm-processed soils[7,10]. Research over the past decade has established such inheritance to be so widespread that it should be part of general theory.

Mathematical models of evolutionary dynamics that incorporate extra-genetic inheritance make different predictions from those that do not[7–9]. Inclusive models help to explain a wide range of puzzling phenomena, such as the rapid colonization of North America by the house finch, the adaptive potential of invasive plants with low genetic diversity, and how reproductive isolation is established.

"There is more to inheritance than genes."

Such legacies can even generate macro-evolutionary patterns. For instance, evidence suggests that sponges oxygenated the ocean and by doing so created opportunities for other organisms to live on the seabed[10]. Accumulating fossil data indicate that inherited modifications of the environment by species has repeatedly facilitated, sometimes after millions of years, the evolution of new species and ecosystems[10].

BETTER TOGETHER

The above insights derive from different fields, but fit together with surprising coherence. They show that variation is not random, that there is more to inheritance than genes, and that there are multiple routes to the fit between organisms and environments. Importantly, they demonstrate that development is a direct cause of why and how adaptation and speciation occur, and of the rates and patterns of evolutionary change.

SET consistently frames these phenomena in a way that undermines their significance. For instance, developmental bias is generally taken to impose 'constraints' on what selection can achieve — a hindrance that explains only the absence of adaptation. By contrast, the EES recognizes developmental processes as a creative element, demarcating which forms and features evolve, and hence accounting for why organisms possess the characters that they do.

Researchers in fields from physiology and ecology to anthropology are running up against the limiting assumptions of the standard evolutionary framework without realizing that others are doing the same. We believe that a plurality of perspectives in science encourages development of alternative hypotheses, and stimulates empirical work. No longer a protest movement, the EES is now a credible framework inspiring useful work by bringing diverse researchers under one theoretical roof to effect conceptual change in evolutionary biology. ■

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1. Pigliucci, M. & Müller, G. B. *Evolution: The Extended Synthesis* (MIT Press, 2010).
2. Noble, D. *et al. J. Physiol.* **592,** 2237–2244 (2014).
3. Arthur, W. *Biased Embryos and Evolution* (Cambridge Univ. Press, 2004).
4. Brakefield, P. M. *Trends Ecol. Evol.* **21,** 362–368 (2006).
5. West-Eberhard, M. J. *Developmental Plasticity and Evolution* (Oxford Univ. Press, 2003).
6. Pfennig D. W. *et al. Trends Ecol. Evol.* **25,** 459–467 (2010).
7. Odling-Smee, F. J., Laland, K. N. & Feldman, M. W. *Niche Construction: The Neglected Process in Evolution* (Princeton Univ. Press, 2003).
8. Jablonka, E. & Lamb, M. *Evolution in Four Dimensions: Genetic, Epigenetic, Behavioral, and Symbolic Variation in the History of Life* (MIT Press, 2014).
9. Hoppitt, W. & Laland, K. N. *Social Learning: An Introduction to Mechanisms, Methods, and Models* (Princeton Univ. Press, 2013)
10. Erwin, D. H. & Valentine J. W. *The Cambrian Explosion: The Construction of Animal Biodiversity* (Roberts, 2013).

COUNTERPOINT: NO, ALL IS WELL ▶ is genetic variation in the response[14]. This role for plasticity in evolutionary change is so well documented that there is no need for special advocacy.

Much less clear is whether plasticity can 'lead' genetic variation during adaptation. More than half a century ago, developmental biologist Conrad Waddington described a process that he called genetic assimilation[15]. Here, new mutations can sometimes convert a plastic trait into one that develops even without the specific environmental condition that originally induced it. Few cases have been documented outside of the laboratory, however. Whether this is owing to a lack of serious attention or whether it reflects a genuine rarity in nature can be answered only by further study.

Lack of evidence also makes it difficult to evaluate the role that developmental bias may have in the evolution (or lack of evolution) of adaptive traits. Developmental processes, based on features of the genome that may be specific to a particular group of organisms, certainly can influence the range of traits that natural selection can act on. However, what matters ultimately is not the extent of trait variation, nor even its precise mechanistic causes. What matters is the heritable differences in traits, especially those that bestow some selective advantage. Likewise, there is little evidence for the role of inherited epigenetic modification (part of what was termed 'inclusive inheritance') in adaptation: we know of no case in which a new trait has been shown to have a strictly epigenetic basis divorced from gene sequence. On both topics, further research will be valuable.

All four phenomena that Laland and colleagues promote are 'add-ons' to the basic processes that produce evolutionary change: natural selection, drift, mutation, recombination and gene flow. None of these additions is essential for evolution, but they can alter the process under certain circumstances. For this reason they are eminently worthy of study.

"What matters is the heritable differences in traits, especially those that bestow some selective advantage."

We invite Laland and colleagues to join us in a more expansive extension, rather than imagining divisions that do not exist. We appreciate their ideas as an important part of what evolutionary theory might become in the future. We, too, want an extended evolutionary synthesis, but for us, these words are lowercase because this is how our field has always advanced[16].

The best way to elevate the prominence of genuinely interesting phenomena such as phenotypic plasticity, inclusive inheritance, niche construction and developmental bias (and many, many others) is to strengthen the evidence for their importance.

Before claiming that earthworms "have played a more important part in the history of the world than most persons would at first suppose"[11], Darwin collected more than 40 years of data. Even then, he published only for fear that he would soon be "joining them"[17]. ■

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11. Darwin, C. *The Formation of Vegetable Mould, Through the Actions of Worms* (John Murray, 1881).
12. Alcock, J. *The Triumph of Sociobiology* (Oxford Univ. Press, 2001).
13. Bailey, N. W. *Trends Ecol. Evol.* **27,** 561–569 (2012).
14. Wada, H. & Sewall, K. B. *Integ. Comp. Biol.* http://dx.doi.org/10.1093/icb/icu097 (2014).
15. Waddington, C. H. *Nature* **150,** 563–565 (1942).
16. Callebaut, W. in *Evolution: The Extended Synthesis* (Pigliucci, M. & Müller, G. B. eds) 443–482 (MIT Press, 2010).
17. Browne, J. *Charles Darwin: The Power of Place* Vol. II 479 (Jonathan Cape, 2003).

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Environmental Epigenetics and a Unified Theory of the Molecular Aspects of Evolution: A Neo-Lamarckian Concept that Facilitates Neo-Darwinian Evolution

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Abstract

Environment has a critical role in the natural selection process for Darwinian evolution. The primary molecular component currently considered for neo-Darwinian evolution involves genetic alterations and random mutations that generate the phenotypic variation required for natural selection to act. The vast majority of environmental factors cannot directly alter DNA sequence. Epigenetic mechanisms directly regulate genetic processes and can be dramatically altered by environmental factors. Therefore, environmental epigenetics provides a molecular mechanism to directly alter phenotypic variation generationally. Lamarck proposed in 1802 the concept that environment can directly alter phenotype in a heritable manner. Environmental epigenetics and epigenetic transgenerational inheritance provide molecular mechanisms for this process. Therefore, environment can on a molecular level influence the phenotypic variation directly. The ability of environmental epigenetics to alter phenotypic and genotypic variation directly can significantly impact natural selection. Neo-Lamarckian concept can facilitate neo-Darwinian evolution. A unified theory of evolution is presented to describe the integration of environmental epigenetic and genetic aspects of evolution.

Key words: epigenetics, Lamarck, Darwin, natural selection, environment, review.

Introduction

Charles Darwin's concept of evolution by natural selection is the unifying theme for much of modern biology (Darwin 1859). Remarkably, Darwin had no understanding of the molecular mechanisms involved in this process. Integration of Darwin's thinking with advances in genetic and molecular sciences over the past century facilitated the development of a well supported neo-Darwinian theory of evolution (Olson-Manning et al. 2012). The current primary concept for the molecular basis of evolution involves genetics and mutations, such that random DNA sequence and chromosomal alterations create a genetic variation that directly impacts phenotype and phenotypic variation. The majority of models in evolutionary biology involves DNA sequence mutations as the primary molecular mechanism underlying heritable phenotypic variation (Laland et al. 2014). A conundrum in evolutionary theory is that the frequency of potentially advantageous genetic mutations is extremely low (Jablonka and Raz 2009; Day and Bonduriansky 2011; Kuzawa and Thayer 2011; Nei and Nozawa 2011; Laland et al. 2014). Although recent studies with organisms such as microbes demonstrate genotypic variation are sufficient (Levy and Siegal 2008; Avelar et al. 2013; Ho and Zhang 2014) and additional mechanisms such as random genetic drift, genetic assimilation, directed mutations and epistasis also play important roles, genetic theory alone has difficulty explaining some aspects of evolution (Laland et al. 2014). For example, phenotypic mutation rates and genotypic mutation rates are dramatically different and genetics has been the primary molecular mechanism considered (Burger et al. 2006), but the inclusion of an additional mechanism such as epigenetics can help explain this discordance. Understanding the origins of genotypic variation and rapid evolutionary phenomenon under environmental pressure is difficult to explain with only classic genetics considered. Opposing groups of evolutionary biologists are now debating the need to "rethink" the theory (Laland et al. 2014). Genetics is the primary molecular mechanism considered in classic neo-Darwinian evolution theory (Olson-Manning et al. 2012) (table 1 and fig. 1).

In addition to evolution considerations, a large number of biological phenomena have been observed that cannot be

Table 1
Evolution Theory Components

Neo-Lamarckian concept
Environment directly alters phenotype generationally
Darwinian evolution theory
Natural selection acts on phenotypic variation
Neo-Darwinian evolution theory
Genetic mutations promote phenotypic variation on which natural selection acts
Unified evolution theory
Environmental epigenetic alterations promote genetic mutations to alter genotypic variation Environmental epigenetics and genetic mutations both promote phenotypic variation on which natural selection acts

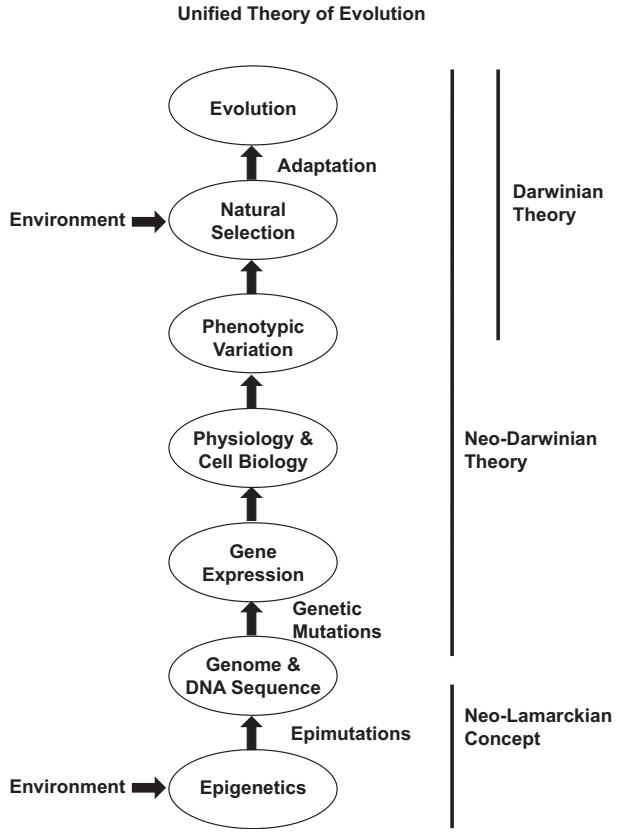

Fig. 1.—Schematic of the unified theory of evolution. No dominance is suggested by the appearance of specific circles (e.g., epimutations vs. genetics) such that all are equally important components.

easily explained by genetics alone. These include the fact that identical twins with similar genetics generally have discordant disease (Zwijnenburg et al. 2010; Kratz et al. 2014; Tan et al. 2015), or the fact that generally only a small percentage of a disease population has been found to have a correlated genetic mutation, or the fact that many diseases have increased in frequency an order of magnitude in only a couple decades, or the fact that hundreds of environmental contaminants not able to alter DNA sequence have been shown to alter disease or phenotype later in life (Skinner 2014a). Many biological observations do not follow normal Mendelian genetic rules and are difficult to explain with classic genetic processes or mechanisms (McClintock 1984). An example in evolution is that the rates of molecular and morphological evolution are largely decoupled and these patterns of phenotypic divergence are regulatory and not classic genetic mutations (Janecka et al. 2012). Epigenetic resolution of the "curse of complexity" in adaptive evolution of complex traits has been suggested (Badyaev 2014).

Recently documented molecular mechanisms that can dramatically influence genome activity and contribute to phenotypic variation involve epigenetics (Skinner et al. 2010). Many of the above phenomenon when epigenetics is considered as an additional molecular mechanism can be more easily understood, such as the discordance of identical twins (Zwijnenburg et al. 2010; Kratz et al. 2014; Tan et al. 2015). Waddington (1953) coined the term epigenetics and the classic epigenetic definitions of Waddington (1953) and others (Skinner 2011) are descriptive, without an understanding of the molecular elements (Skinner 2011). Considering our current molecular understanding, epigenetics is defined as "molecular processes around DNA that regulate genome activity independent of DNA sequence and are mitotically stable" (Skinner et al. 2010). These epigenetic mechanisms include DNA methylation, histone modifications, chromatin structure, and selected noncoding RNA (ncRNA) (Skinner 2014a). Epigenetic processes such as DNA methylation can become programmed (e.g., imprinted) and be inherited over generations (Skinner 2014a). Environmental factors have been shown to promote the epigenetic transgenerational inheritance of phenotypic variation. Several examples of environmentally induced epigenetic transgenerational inheritance of phenotypic change have been shown to be inherited for hundreds of generations (Cubas et al. 1999). Therefore, like genetic changes, epigenetic changes can have an important role in short-term microevolution (Day and Bonduriansky 2011) and contribute to macroevolutionary (i.e., at or above the level of species) processes, such as speciation and adaptive radiation (Rebollo et al. 2010; Flatscher et al. 2012). A number of insightful reviews have proposed a role for epigenetics in evolution, primarily as a responsive molecular mechanism in natural selection (Jablonka et al. 1998; Pigliucci 2007; Laland et al. 2014).

Environment and Evolution

A variety of environmental factors can influence evolution and general biology. These range from ecological parameters such as temperature and light to nutritional parameters such as caloric restriction or high fat diets. A host of environmental chemicals from phytochemicals to toxicants can also influence

phenotype and health (Skinner 2014a). Environment has a critical role in natural selection and Darwinian evolution (Darwin 1859). Natural selection is a process in which environmental factors influence the survival or reproductive success of individuals bearing different phenotypes. The current paradigm in evolutionary biology holds that changes in DNA sequence underlie the variation that can evolve in response to natural selection (Laland et al. 2014) (table 1). Although James Baldwin in 1896 suggested environment through sociobiology type mechanisms (i.e., behavior) could alter phenotypic variation, these are thought to be due to genetic changes and considered a neo-Darwinian process (Baldwin 1896; Paenke et al. 2007). Therefore, in neo-Darwinian evolution the primary link between the environment and evolution is to mediate the natural selection process (Olson-Manning et al. 2012; Laland et al. 2014).

In contrast, Lamarck proposed one of the early evolutionary theories in 1802 in that environment promotes the phenotypic alterations associated with evolution (Lamarck 1802; Calabi 2001). This is distinct to the role of environment providing selective pressure in natural selection, such that environment directly alters the phenotype to influence evolution. This theory was seen as conflicting with Darwin's natural selection evolutionary theory and so was discounted and today is not seriously considered in modern evolutionary theory or neo-Darwinian evolution (Day and Bonduriansky 2011). However, if there was a molecular mechanism that generationally could facilitate the ability of the environment to alter genotypic and phenotypic variation, such a neo-Lamarckian concept may facilitate evolution (table 1 and fig. 1).

Interestingly, Darwin (1868) himself was a strong proponent of the inheritance of acquired characteristics. The blending of inheritance and evolution by natural selection appeared to be a fundamentally flawed concept that would require an untenably high mutation rate in order to maintain the trait variation required for selection (Jenkins 1867). To address this, Darwin (1868) proposed pangenesis, a complex theory of environmentally responsive somatic cell transmittance to offspring. Therefore, Darwin conceptually supported Lamarck's theory of the inheritance of acquired characteristics, but until the last 30 years the potential molecular mechanism was unclear.

Environmental Epigenetics

Epigenetics provides molecular mechanisms for the environment to directly alter phenotypic variation and its subsequent inheritance (Crews et al. 2007; Skinner, Gurerrero-Bosagna, Haque, et al. 2014). A variety of epigenetic mechanisms have been identified including DNA methylation, histone modifications, chromatin structure, and selected ncRNA. All these mechanisms have the ability to program and alter gene expression and have been shown to have a critical role in normal development and biological processes (Skinner et al. 2010; Skinner 2014a). For example, the ability to generate an embryonic stem cell requires the erasure of DNA methylation such that the cell becomes pluripotent (Seisenberger et al. 2013). Although the vast majority of environmental factors cannot alter DNA sequence, epigenetic processes can be dramatically altered in response to environmental factors from nutrition to temperature (Skinner 2014a). All organisms that have been investigated contain highly conserved epigenetic processes (e.g., DNA methylation) that can be environmentally modified (Skinner 2014a). Epigenetics provides an additional molecular mechanism, integrated with genetics, to regulate biology.

The ability of environment to directly alter the development and function of cells and tissues is critical for the health and phenotype of the individual. This direct environmental epigenetic effect on the individual would likely have a limited impact on evolution, unless the epigenetic changes could be transmitted between generations. A large number of environmental factors from nutrition to toxicants have been shown to induce the epigenetic transgenerational inheritance of disease and phenotypic variation (Skinner 2014a). Epigenetic transgenerational inheritance is defined as the germline transmission of epigenetic information between generations in the absence of direct exposure (Skinner et al. 2010). Environmental exposures during a critical period of germline development, fetal gonadal sex determination or gametogenesis, have been shown to permanently program epigenetic marks such as DNA methylation (Skinner 2014a). Nutrition (Pembrey et al. 2006; Burdge et al. 2011), temperature (Song et al. 2013), stress (Skinner 2014b), and toxicants (Anway et al. 2005; Skinner 2014a) have all been shown to promote the epigenetic transgenerational inheritance of phenotypic variation (Skinner 2014a). The phenomenon has been observed in plants, insects, fish, rodents, pigs, and humans (Skinner 2014a). In mammals the altered transgenerational phenotypes have been observed for generations (Skinner 2014a), with environmentally induced epigenetic transgenerational inheritance of phenotypic variation in plants being transmitted for hundreds of generations (Cubas et al. 1999). Therefore, environment can promote the epigenetic transgenerational inheritance of phenotypic variation. The ability of environment to alter phenotype and alter phenotypic variation, independent of genetics, through this epigenetic mechanism is proposed to be important for evolution (Anway et al. 2005; Jablonka and Raz 2009; Day and Bonduriansky 2011; Kuzawa and Thayer 2011; Skinner 2014a).

Darwin proposed that one of the critical determinants of evolution was sexual selection (Darwin 1859). A previous study investigated the ability of an environmental factor (toxicant) to promote the epigenetic transgenerational inheritance of an alteration in mate preference associated with sexual selection (Crews et al. 2007). An F0 generation gestating female rat was exposed to the agricultural fungicide vinclozolin transiently and then the F3 generation animals

(great-grand-offspring) were obtained to assess alterations in mate preference behavior (Anway et al. 2005). A dramatic alteration in mate preference was observed (Crews et al. 2007) along with epigenetic alterations (termed epimutations) in the germline (sperm) (Guerrero-Bosagna et al. 2010). Transgenerational transcriptome changes in the brain regions correlated with the alterations in mate preference behavior (Skinner et al. 2008). Therefore, an environmental factor that altered sexual selection was found to promote a permanent alteration in the sperm epigenome in an imprinted-like manner that was inherited for multiple generations (Crews et al. 2007; Skinner et al. 2010). These studies suggest that environmental epigenetics may play an important role in evolutionary change. The role of epigenetics in mate choice and evolution has been further discussed (Zeh JA and Zeh DW 2008; Bonduriansky and Day 2013). Indeed, several recent reviews have suggested a role for epigenetics in microevolution and macroevolution (Jablonka and Raz 2009; Rebollo et al. 2010; Skinner et al. 2010; Day and Bonduriansky 2011; Kuzawa and Thayer 2011; Flatscher et al. 2012; Klironomos et al. 2013; Badyaev 2014; Jaeger and Monk 2014; Skinner 2014a).

Unified Theory

Environmental epigenetics and epigenetic transgenerational inheritance provide a molecular mechanism for the neo-Lamarckian concept that environmental factors directly alter phenotype (table 1). The ability of environmental epigenetics to alter phenotypic variation provides an initial element for evolution where environment can directly establish the variation and phenotype in a population (fig. 1). Although aspects of the original Lamarckian evolution theory were not accurate (Lamarck 1802), such as having "directed" phenotypes within a generation (Koonin and Wolf 2009; Koonin 2014), the concept that environment can directly impact phenotype is supported by environmental and transgenerational epigenetic studies (Crews et al. 2007; Koonin and Wolf 2009; Koonin 2014; Skinner, Gurerrero-Bosagna, Haque, et al. 2014). Therefore, the first aspect of the unified theory involves the ability of environment to impact epigenetic programming generationally to alter phenotypic variation (fig. 1).

The well-established aspect of Darwinian evolution is the ability of environment through natural selection to act on phenotypic variation within an evolutionary event (Darwin 1859; Olson-Manning et al. 2012). The classic neo-Darwinian view is that genetic mutations and genetic variation are the primary molecular mechanism involved in generating the phenotypic variation (Nei and Nozawa 2011; Olson-Manning et al. 2012) (table 1). Although epigenetics can also have a critical role in the establishment and maintenance of phenotypic variation, the genetic mutations and genotype of the phenotype will be critical. This neo-Darwinian natural selection event for evolution is the other component of the unified theory (fig. 1).

A combination of environmental epigenetic impacts on phenotypic variation and the ability of environment to mediate natural selection will both be important for evolution. Therefore, this neo-Lamarckian concept facilitates neo-Darwinian evolution (fig. 1). This unified theory provides an expanded understanding of the molecular aspects of evolution and solutions for issues such as the mechanisms for rapid evolutionary phenomenon. The mechanisms that environment can impact evolution are also expanded. An integration of epigenetics and genetics will be essential to consider in our future understanding of the molecular aspects of evolution (Jablonka and Raz 2009; Day and Bonduriansky 2011; Laland et al. 2014; Skinner 2014a).

An additional important consideration involves the ability of epigenetic processes to promote genetic mutations (table 1). In cancer biology, altered epigenetics has been shown to promote genome instability and formation of genetic mutations (Feinberg 2004). Nearly all genetic mutations can be directly influenced by epigenetic processes. The most frequent point mutation (single nucleotide polymorphism) is a C to T conversion that is facilitated by CpG DNA methylation (Jones et al. 1992). Repeat elements in the genome when expanded create copy number variations (CNV) that are controlled by hypermethylation of DNA (Liu et al. 2012). Transposable elements are also silenced by hypermethylation of DNA (Yagi et al. 2012). Translocation events and inversions are also influenced by histone modifications, DNA methylation, and ncRNA (Solary et al. 2014). Therefore, epigenetics can directly influence genetic mutations and the origin of genotypic variation is influenced by environmental epigenetic alterations (table 1). In contrast, genetic mutations have been shown to influence epigenetics (Furey and Sethupathy 2013). Recently, we have found that environmentally induced epigenetic transgenerational inheritance of disease and phenotypic variation can promote genetic mutations (i.e., CNV) in later generations (Skinner MK, Guerrero-Bosagna C, Haque MM, unpublished data). Therefore, environmental epigenetics may not only promote increased phenotypic variation, but epigenetics can also drive genetic change and increase genotypic variation. This also needs to be considered in the unified evolution theory (fig. 1).

Discussion

Environmental epigenetics and epigenetic transgenerational inheritance alter phenotypic variation which can be acted on by natural selection. Therefore, environmental epigenetics can directly influence phenotype and this neo-Lamarckian concept can facilitate natural selection and neo-Darwinian evolution. These different aspects of evolution should not be seen as conflicting, but instead can form a unified theory for evolution (fig. 1). This expanded understanding of the molecular aspects of evolution provides novel insights into the mechanism for

rapid evolutionary events. An expanded understanding of how environment impacts evolution is also provided. The unified theory provides novel considerations that environment can both act to directly influence phenotypic variation and directly facilitate natural selection (fig. 1). Previous evolutionary models have primarily considered genetics and mutations as the primary molecular driver for evolution (Nei and Nozawa 2011; Olson-Manning et al. 2012; Laland et al. 2014). More recently, a number of models have started to consider epigenetics in these evolution models as well (Rebollo et al. 2010; Skinner et al. 2010; Day and Bonduriansky 2011; Kuzawa and Thayer 2011; Flatscher et al. 2012; Klironomos et al. 2013; Badyaev 2014; Jablonka and Lamb 2014; Jaeger and Monk 2014). For example, consideration of epigenetics as an additional molecular mechanism has assisted in the understanding of genetic drift (Gordon et al. 2012), genetic assimilation (Zuckerkandl and Cavalli 2007), and directed mutation (Jablonka and Lamb 2007; Kryazhimskiy et al. 2014). The consideration of epigenetics can also be used to better understand neutral evolution (Kimura 1989) through mechanisms, such as robustness (Ohta 2011). The unified theory suggests additional variables that should be considered are the multiple roles of environment and the integration of epigenetics into future evolution models.

Epigenetic transgenerational inheritance of phenotypic variation will have an important role in microevolutionary and macroevolutionary changes, including speciation. A recent study was designed to investigate the epigenetic changes associated with phylogenetic distance in Darwin's finches (Skinner, Gurerrero-Bosagna, Haque, et al. 2014), a well-known example of adaptive radiation (Darwin 1859; Lack 1947; Burns et al. 2002; Grant and Grant 2008; Huber et al. 2010; Donohue 2011). Erythrocyte DNA was obtained from five species of sympatric Darwin's finches that vary in phylogenetic relatedness. Genome-wide alterations in genetic mutations, using CNV, were compared with epigenetic alterations associated with differential DNA methylation regions (epimutations) (Skinner, Gurerrero-Bosagna, Haque, et al. 2014). A greater number of epimutations than genetic mutations were observed among the different species, with the number of epimutations increasing with phylogenetic distance. The number, chromosomal locations, regional clustering, and overlap of epimutations suggest that epigenetic change has likely had a role in the speciation and evolution of Darwin's finches (Skinner, Gurerrero-Bosagna, Haque, et al. 2014). A number of additional observations also support a role of epigenetics and speciation. Using *Drosophila* and maternally inherited ncRNA silencing of transposons a role for epigenetics and speciation was discussed (Brennecke et al. 2008). The role of epigenetics and a punctuated equilibrium in the mobilization of transposable elements was also suggested (Zeh et al. 2009). An interesting study comparing Neanderthal and human DNA methylation maps also supports a role for epigenetics in speciation (Gokhman et al. 2014) and evolution.

Although the causal role of epimutations was not established in the Darwin's finch adaptive radiation (Skinner, Gurerrero-Bosagna, Haque, et al. 2014) or other models (Brennecke et al. 2008; Zeh et al. 2009; Gokhman et al. 2014), the causal role of genome-wide genetic mutations has also not been established (Laland et al. 2011). Future studies need to focus on the causal relationship of epigenetic alterations in relation to phenotypic variation that is acted on by natural selection. Genetics and genetic mutations are critical for evolution, but they are not the only molecular factors to consider. Although the major paradigm in the biological sciences is genetic determinism, this paradigm is limited in its ability to explain biological phenomenon ranging from the molecular basis of disease etiology (Skinner 2014a) to certain aspects of evolution by natural selection (Skinner et al. 2010; Day and Bonduriansky 2011; Longo et al. 2012). As Thomas Kuhn suggested during a scientific revolution when the current paradigm reveals anomalies then new science needs to be considered (Kuhn 1962). This type of challenge to current paradigms is also supported by other scientific philosophy, such as Popper (Rieppel 2008) and Macintyre (MacIntyre 1977). A paradigm shift is required to explain how genetics and epigenetics integrate to regulate genome activity and evolution, and these advances will need to be incorporated into future evolutionary biology modeling (Rebollo et al. 2010; Skinner et al. 2010; Day and Bonduriansky 2011; Kuzawa and Thayer 2011; Flatscher et al. 2012; Klironomos et al. 2013; Badyaev 2014; Jablonka and Lamb 2014; Jaeger and Monk 2014; Skinner 2014a) and theory.

Summary

The integration of environmental epigenetics into the molecular aspects of evolution theory suggests a neo-Lamarckian concept that facilitates neo-Darwinian evolution. Several of the novel factors to be considered are summarized below. In regards to the neo-Lamarckian concept:

1. Environmental epigenetics provides a molecular mechanism for Lamarck's proposal that environment can directly alter phenotype in a heritable manner.
2. Environmental exposures at critical developmental windows promote the epigenetic transgenerational inheritance of germline (e.g., sperm) epimutations that alter phenotypic variation.
3. Direct environmental exposures of developing somatic tissue can alter somatic epigenomes and phenotype in the individual exposed, but this will not be heritable and the phenotypes will often be distinct to transgenerational phenotypes.
4. In regards to novel aspects of neo-Darwinian evolution:
5. Transgenerational germline epimutations alter genome stability to promote genetic mutations and genotypic variation in subsequent generations.

6. Phenotypic variation is derived from a combination of integrated genetic and epigenetic processes on which natural selection acts.
7. Environment has a critical role in natural selection, as well as in the induction of heritable adaptive phenotypic variation.

As shown in figure 1, these concepts and components contribute to a unified theory that integrates environmental epigenetics into the molecular aspects of evolution. It is important to note that there is not a dominance of genetics or epigenetics, but the two molecular processes integrate to regulate biology.

Previously, an environmental exposure was found to promote the epigenetic transgenerational inheritance of phenotypic traits such as mate preference, which can play an important role in evolution (Crews et al. 2007; Skinner 2014a). Several reviews have subsequently suggested a role for epigenetics in evolution (Jablonka and Raz 2009; Rebollo et al. 2010; Skinner et al. 2010; Day and Bonduriansky 2011; Kuzawa and Thayer 2011; Flatscher et al. 2012) and experimental models have shown the importance of epigenetic associated genes (Mihola et al. 2009) and molecular elements (Long et al. 2013; Skinner, Gurerrero-Bosagna, Haque, et al. 2014) in evolution. The current report extends these studies to present a unified theory that combines both neo-Lamarckian and neo-Darwinian aspects and expands our understanding of how environment impacts evolution. The integration of epigenetics and genetics will be critical for all areas of biology including evolution.

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Literature Cited

Anway MD, Cupp AS, Uzumcu M, Skinner MK. 2005. Epigenetic transgenerational actions of endocrine disruptors and male fertility. Science 308:1466–1469.

Avelar AT, Perfeito L, Gordo I, Ferreira MG. 2013. Genome architecture is a selectable trait that can be maintained by antagonistic pleiotropy. Nat Commun. 4:2235.

Badyaev AV. 2014. Epigenetic resolution of the "curse of complexity" in adaptive evolution of complex traits. J Physiol. 592:2251–2260.

Baldwin J. 1896. A new factor in evolution. Am Nat. 30:441–451.

Bonduriansky R, Day T. 2013. Nongenetic inheritance and the evolution of costly female preference. J Evol Biol. 26:76–87.

Brennecke J, et al. 2008. An epigenetic role for maternally inherited piRNAs in transposon silencing. Science 322:1387–1392.

Burdge GC, et al. 2011. Progressive, transgenerational changes in offspring phenotype and epigenotype following nutritional transition. PLoS One 6:e28282.

Burger R, Willensdorfer M, Nowak MA. 2006. Why are phenotypic mutation rates much higher than genotypic mutation rates? Genetics 172:197–206.

Burns KJ, Hackett SJ, Klein NK. 2002. Phylogenetic relationships and morphological diversity in Darwin's finches and their relatives. Evolution 56:1240–1252.

Calabi L. 2001. On Darwin's "metaphysical notebooks." I: Teleology and the project of a theory. Riv Biol. 94:123–159.

Crews D, et al. 2007. Transgenerational epigenetic imprints on mate preference. Proc Natl Acad Sci U S A. 104:5942–5946.

Cubas P, Vincent C, Coen E. 1999. An epigenetic mutation responsible for natural variation in floral symmetry. Nature 401:157–161.

Darwin C. 1859. On the origin of species. London: John Murray.

Darwin C. 1868. The variation of animals and plants under domestication. London: John Murray.

Day T, Bonduriansky R. 2011. A unified approach to the evolutionary consequences of genetic and nongenetic inheritance. Am Nat. 178: E18–E36.

Donohue K. 2011. Darwin's finches: readings in the evolution of a scientific paradigm. Chicago (IL): University of Chicago Press.

Feinberg AP. 2004. The epigenetics of cancer etiology. Semin Cancer Biol. 14:427–432.

Flatscher R, Frajman B, Schonswetter P, Paun O. 2012. Environmental heterogeneity and phenotypic divergence: can heritable epigenetic variation aid speciation? Genet Res Int. 2012: 698421.

Furey TS, Sethupathy P. 2013. Genetics. Genetics driving epigenetics. Science 342:705–706.

Gokhman D, et al. 2014. Reconstructing the DNA methylation maps of the Neandertal and the Denisovan. Science 344:523–527.

Gordon L, et al. 2012. Neonatal DNA methylation profile in human twins is specified by a complex interplay between intrauterine environmental and genetic factors, subject to tissue-specific influence. Genome Res. 22:1395–1406.

Grant P, Grant R. 2008. How and why species multiply: the radiation of Darwin's finches. Princeton (NJ): Princeton University Press.

Guerrero-Bosagna C, Settles M, Lucker B, Skinner M. 2010. Epigenetic transgenerational actions of vinclozolin on promoter regions of the sperm epigenome. PLoS One 5:e13100.

Ho WC, Zhang J. 2014. The genotype-phenotype map of yeast complex traits: basic parameters and the role of natural selection. Mol Biol Evol. 31:1568–1580.

Huber SK, et al. 2010. Ecoimmunity in Darwin's finches: invasive parasites trigger acquired immunity in the medium ground finch (*Geospiza fortis*). PLoS One 5:e8605.

Jablonka E, Lamb MJ. 2007. Precis of evolution in four dimensions. Behav Brain Sci. 30:353–365; discussion: 365–389.

Jablonka E, Lamb MJ. 2014. Evolution in four dimensions, revised edition. Cambridge: MIT Press.

Jablonka E, Lamb MJ, Avital E. 1998. "Lamarckian" mechanisms in darwinian evolution. Trends Ecol Evol. 13:206–210.

Jablonka E, Raz G. 2009. Transgenerational epigenetic inheritance: prevalence, mechanisms, and implications for the study of heredity and evolution. Q Rev Biol. 84:131–176.

Jaeger J, Monk N. 2014. Bioattractors: dynamical systems theory and the evolution of regulatory processes. J Physiol. 592:2267–2281.

Janecka J, Chowdhary B, Murphy W. 2012. Exploring the correlations between sequence evolution rate and phenotypic divergence across the Mammalian tree provides insights into adaptive evolution. J Biosci. 37:897–909.

Jenkins F. 1867. The origins of species. North Br Rev. 46:277–318.

Jones PA, Rideout WM 3rd, Shen JC, Spruck CH, Tsai YC. 1992. Methylation, mutation and cancer. Bioessays 14:33–36.
Kimura M. 1989. The neutral theory of molecular evolution and the world view of the neutralists. Genome 31:24–31.
Klironomos FD, Berg J, Collins S. 2013. How epigenetic mutations can affect genetic evolution: model and mechanism. Bioessays 35: 571–578.
Koonin EV. 2014. Calorie restriction a Lamarck. Cell 158:237–238.
Koonin EV, Wolf YI. 2009. Is evolution Darwinian or/and Lamarckian? Biol Direct. 4–42.
Kratz CP, Edelman DC, Wang Y, Meltzer PS, Greene MH. 2014. Genetic and epigenetic analysis of monozygotic twins discordant for testicular cancer. Int J Mol Epidemiol Genet. 5:135–139.
Kryazhimskiy S, Rice DP, Jerison ER, Desai MM. 2014. Microbial evolution. Global epistasis makes adaptation predictable despite sequence-level stochasticity. Science 344:1519–1522.
Kuhn TS. 1962. The structure of scientific revolutions. Chicago (IL): University of Chicago Press.
Kuzawa CW, Thayer ZM. 2011. Timescales of human adaptation: the role of epigenetic processes. Epigenomics 3:221–234.
Lack D. 1947. Darwin's finches. New York: Cambridge University Press.
Laland K, et al. 2014. Does evolutionary theory need a rethink? Nature 514:161–164.
Laland KN, Sterelny K, Odling-Smee J, Hoppitt W, Uller T. 2011. Cause and effect in biology revisited: is Mayr's proximate-ultimate dichotomy still useful? Science 334:1512–1516.
Lamarck J. 1802. Recherches sur l'organisation des corps vivans. Paris: Chez L'auteur, Maillard.
Levy SF, Siegal ML. 2008. Network hubs buffer environmental variation in *Saccharomyces cerevisiae*. PLoS Biol. 6:e264.
Liu MM, Chan CC, Tuo J. 2012. Genetic mechanisms and age-related macular degeneration: common variants, rare variants, copy number variations, epigenetics, and mitochondrial genetics. Hum Genomics. 6: 13.
Long HK, et al. 2013. Epigenetic conservation at gene regulatory elements revealed by non-methylated DNA profiling in seven vertebrates. Elife 2: e00348.
Longo G, Miquel PA, Sonnenschein C, Soto AM. 2012. Is information a proper observable for biological organization? Prog Biophys Mol Biol. 109:108–114.
MacIntyre A. 1977. Epistemological crises, dramatic narrative and the philosophy of science. Monist 60:453–472.
McClintock B. 1984. The significance of responses of the genome to challenge. Science 226:792–801.
Mihola O, Trachtulec Z, Vlcek C, Schimenti JC, Forejt J. 2009. A mouse speciation gene encodes a meiotic histone H3 methyltransferase. Science 323:373–375.
Nei M, Nozawa M. 2011. Roles of mutation and selection in speciation: from Hugo de Vries to the modern genomic era. Genome Biol Evol. 3: 812–829.
Ohta T. 2011. Near-neutrality, robustness, and epigenetics. Genome Biol Evol. 3:1034–1038.
Olson-Manning CF, Wagner MR, Mitchell-Olds T. 2012. Adaptive evolution: evaluating empirical support for theoretical predictions. Nat Rev Genet. 13:867–877.
Paenke I, Sendhoff B, Kawecki TJ. 2007. Influence of plasticity and learning on evolution under directional selection. Am Nat. 170:E47–E58.
Pembrey ME, et al. 2006. ALSPAC Study Team. 2006. Sex-specific, male-line transgenerational responses in humans. Eur J Hum Genet. 14: 159–166.
Pigliucci M. 2007. Do we need an extended evolutionary synthesis? Evolution 61:2743–2749.
Rebollo R, Horard B, Hubert B, Vieira C. 2010. Jumping genes and epigenetics: towards new species. Gene 454:1–7.
Rieppel O. 2008. Re-writing Popper's philosophy of science for systematics. Hist Philos Life Sci. 30:293–316.
Seisenberger S, Peat JR, Reik W. 2013. Conceptual links between DNA methylation reprogramming in the early embryo and primordial germ cells. Curr Opin Cell Biol. 25:281–288.
Skinner MK. 2011. Environmental epigenetic transgenerational inheritance and somatic epigenetic mitotic stability. Epigenetics 6:838–842.
Skinner MK. 2014a. Endocrine disruptor induction of epigenetic transgenerational inheritance of disease. Mol Cell Endocrinol. 398: 4–12.
Skinner MK. 2014b. Environmental stress and epigenetic transgenerational inheritance. BMC Med. 12–153.
Skinner MK, Anway MD, Savenkova MI, Gore AC, Crews D. 2008. Transgenerational epigenetic programming of the brain transcriptome and anxiety behavior. PLoS One 3:e3745.
Skinner MK, Gurerrero-Bosagna C, Haque MM, Nilsson EE, et al. 2014. Epigenetics and the evolution of Darwin's finches. Genome Biol Evol. 6:1972–1989.
Skinner MK, Manikkam M, Guerrero-Bosagna C. 2015. Epigenetic transgenerational actions of environmental factors in disease etiology. Trends Endocrinol Metab. 21:214–222.
Solary E, Bernard OA, Tefferi A, Fuks F, Vainchenker W. 2014. The Ten-Eleven Translocation-2 (TET2) gene in hematopoiesis and hematopoietic diseases. Leukemia 28:485–496.
Song J, Irwin J, Dean C. 2013. Remembering the prolonged cold of winter. Curr Biol. 23:R807–R811.
Tan Q, Christiansen L, von Bornemann Hjelmborg J, Christensen K. 2015. Twin methodology in epigenetic studies. J Exp Biol. 218:134–139.
Waddington CH. 1953. Epigenetics and evolution. Symp Soc Exp Biol. 7: 186–199.
Yagi S, Hirosawa M, Shiota K. 2012. DNA methylation profile: a composer-, conductor-, and player-orchestrated Mammalian genome consisting of genes and transposable genetic elements. J Reprod Dev. 58:265–273.
Zeh DW, Zeh JA, Ishida Y. 2009. Transposable elements and an epigenetic basis for punctuated equilibria. Bioessays 31:715–726.
Zeh JA, Zeh DW. 2008. Maternal inheritance, epigenetics and the evolution of polyandry. Genetica 134:45–54.
Zuckerkandl E, Cavalli G. 2007. Combinatorial epigenetics, "junk DNA," and the evolution of complex organisms. Gene 390:232–242.
Zwijnenburg PJ, Meijers-Heijboer H, Boomsma DI. 2010. Identical but not the same: the value of discordant monozygotic twins in genetic research. Am J Med Genet B Neuropsychiatr Genet. 153B:1134–1149.

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Review Article

Role of environmentally induced epigenetic transgenerational inheritance in evolutionary biology: Unified Evolution Theory

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Abstract

The current evolutionary biology theory primarily involves genetic alterations and random DNA sequence mutations to generate the phenotypic variation required for Darwinian natural selection to act. This neo-Darwinian evolution is termed the Modern Evolution Synthesis and has been the primary paradigm for nearly 100 years. Although environmental factors have a role in neo-Darwinian natural selection, Modern Evolution Synthesis does not consider environment to impact the basic molecular processes involved in evolution. An Extended Evolutionary Synthesis has recently developed that extends the modern synthesis to consider non-genetic processes. Over the past few decades, environmental epigenetics research has been demonstrated to regulate genetic processes and directly generate phenotypic variation independent of genetic sequence alterations. Therefore, the environment can on a molecular level through non-genetic (i.e. epigenetic) mechanisms directly influence phenotypic variation, genetic variation, inheritance and adaptation. This direct action of the environment to alter phenotype that is heritable is a neo-Lamarckian concept that can facilitate neo-Darwinian (i.e. Modern Synthesis) evolution. The integration of genetics, epigenetics, Darwinian theory, Lamarckian concepts, environment, and epigenetic inheritance provides a paradigm shift in evolution theory. The role of environmental-induced epigenetic transgenerational inheritance in evolution is presented to describe a more unified theory of evolutionary biology.

Key words: review; evolution; epigenetic; transgenerational; inheritance; genetics; adaptation; phenotype; Darwin; Lamarck; molecular

Current Evolution Paradigm

Charles Darwin's theory of evolution through natural selection provides the basis for our current concepts of evolutionary biology [1]. Adaptive evolution occurs with four biological processes: (i) variation within a population; (ii) variation is heritable; (iii) competition occurs between offspring for limited resources; and (iv) the survival and reproduction of the offspring are not random, but are associated with heritable variation [1, 2]. These concepts of evolution through natural selection developed in the late 1800s and were then advanced in the early 1900s with the rediscovery of Mendelian genetics and the identification of DNA (deoxyribonucleic acid) and RNA (ribonucleic acid) as the molecular mechanism involved in phenotypic variation and inheritance. Adaptation of the classic Darwinian theory with molecular genetics led to the concept of the "Modern Evolutionary Synthesis" proposed in the mid-1900s by Huxley [3]. Subsequently, the role of genetics in phenotypic variation, inheritance and adaptation was established in large part by the field of population genetics. This neo-Darwinian (i.e. Modern Evolution Synthesis) theory of evolution has developed over the past century and is the current paradigm in evolutionary biology [2, 4, 5].

The advances in molecular genetics, genome-wide DNA sequence mutation analysis and understanding of genetic variation are inadequate in considering the complexities of phenotypic variation observed and in rapid evolutionary events for the current evolutionary biology theory (i.e. Modern Synthesis). This is in large part due to the low frequency of associated genetic mutations [4–10]. Phenotypic mutation rates and genetic mutation rates are dramatically different [10]. Understanding the origins of genetic variation and environmental pressure induced evolutionary phenomena are difficult to explain with the Modern Evolution Synthesis theory [4, 11]. Over the past 50 years, molecular technology has been used to investigate evolutionary biology, but many examples of finding no correlated genetic mutations or a low frequency of DNA sequence mutations suggest that additional mechanisms are also involved. Phenotypic plasticity is a very good example of how physiological change can facilitate adaptation, but most phenotypic plasticity has not been related to genetic

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DNA sequence alterations [2, 4, 5, 11, 12]. Darwin proposed a critical role for environmental impacts to mediate natural selection, but genetic changes alone cannot explain these phenomena well. This has led to the debate that a reevaluation of the current evolution paradigm is needed [2, 4, 5, 11, 12].

Recently an Extended Evolutionary Synthesis (EES) has been developed to expand the Modern Synthesis concepts and include non-classical genetic concepts [13]. This EES incorporates non-genetic processes and non-genetic inheritance and expands on classic genetic considerations, but does not fully develop the molecular processes or elements that integrate with the genetic mechanism [13]. This demonstrates an appreciation that the Modern Synthesis, in considering our current molecular biology, falls short of effectively explaining all mechanisms of evolution. Other aspects of EES not well developed include a lack of detail on how environment can directly impact developmental and biological processes independent of classic genetics. The current review discusses the role of environmental epigenetics and epigenetic transgenerational inheritance as a major molecular component to integrate classic evolution concepts of Lamarck, Darwin and Modern Synthesis and the more recent EES to develop a more unified theory.

Environment and Evolution

Environment has a critical role in Darwinian Evolution [1] as one of the primary factors to facilitate natural selection processes. These environmental factors act on the survival and reproductive fitness of individuals having different phenotypes. The current paradigm in evolutionary biology is that DNA sequence alterations promote this phenotypic variation that responds to the environmental pressure through natural selection [4, 11]. In addition to evolutionary biology, a large number of biological phenomena suggest major impacts of the environment. Ecological parameters such as chemical exposures, temperature, and limited nutrition all impact an individual's physiology and phenotypes, but do not have the ability to alter DNA sequence. Identical twins have essentially the same genetics, but generally develop discordant disease as they age [1, 2, 4–6, 14–25]. Only a low frequency (generally 1% or less) of individuals that have a specific disease have a correlated genetic mutation, and the dramatic increase in disease frequency in the population cannot be explained with genetics alone [26]. Many phenomena such as regional disease frequency or the fact that environmental toxicant exposures can promote disease, but do not generally have the ability to alter DNA sequence, cannot be easily explained with genetic mutations alone [27]. Therefore, many biological phenomena do not follow normal Mendelian genetic rules and are difficult to explain with classic genetic processes or mechanisms alone [17].

One of the first evolutionary biology theories proposed in 1802 by Jean Baptiste Lamarck suggested that environment promotes the phenotypic alterations associated with evolution [20, 21]. This Lamarckian concept was that environment directly promotes phenotypic variation, which becomes heritable for subsequent generations. This is distinct from the role of environmental factors providing a selection pressure in Darwin's natural selection theory. This Lamarckian concept was interpreted as conflicting with Darwin's natural selection evolutionary theory, so was discounted and not considered in the Modern Synthesis (i.e. neo-Darwinian) evolution theory [6]. As will be discussed, a molecular mechanism that could promote direct alterations in phenotype generationally, independent of DNA sequence, and alter genome activity would support this Lamarckian concept [11].

Environment and Phenotypic Variation

A number of evolutionary biology observations suggest that the rates of molecular and morphological evolution are largely decoupled [18]. One of the first observations that environment directly promotes phenotypic variation was the report of *Daphnia magna* to respond to the presence of predators in the environment [19]. This morphological phenotype induced by the environment was termed the Baldwin effect and later thought to be due to genetics and considered a neo-Darwinian phenomenon [28]. However, this phenomenon does not follow normal Mendelian genetics and is a good example of environmentally induced phenotypic variation. In the early 1900s Paul Kammerer demonstrated in the midwife toad an environmentally induced parent-of-origin non-genetic acquired reproductive trait with arid or aquatic environments [23]. One of the more significant series of studies was pioneered by Conrad Waddington in the 1940s and 1950s [24]. Several generations of *Drosophila* (i.e. fruit fly) following heat shock exposure promoted a wing structure change that was transmitted for sixteen generations, so was inherited. This adaptive wing shape became "canalized" in the population. This non-genetic phenomenon that became inherited was referred to as "epigenetics" [24]. Although the specific molecular aspects of the epigenetic process were not known or proposed, epigenetics was, by definition, a non-genetic process that did not follow normal Mendelian genetic rules. As will be discussed, the molecular mechanisms have now been characterized and provide a new science to help explain this and other non-genetic (i.e. independent of DNA sequence) processes and inheritance.

The initial genetic terminology used to describe phenotypic variation effects such as those observed by Baldwin, Kammerer, and Waddington was genetic accommodation [22]. These non-genetic heritable changes occur in response to novel environmental pressure. Although these early observations were critical phenomena, interest waned in favor of strictly genetic inheritance of traits in the absence of any known non-genetic mechanisms. When the Modern Synthesis (i.e. neo-Darwinian) theory was formalized, Ernst Mayr described these non-genetic (soft) forms of inheritance as "gradual change of genetic material itself, either by use or disuse, or by some internal presence of tendencies, or through a direct effect of the environment" [25]. Therefore, environmental impacts on phenotypic variation and non-genetic inheritance were strictly left out of the Modern Evolution Synthesis without a specific mechanism to be considered [2]. In contrast, environmental impacts on genetic processes such as horizontal gene transfer in bacteria in adaptation to extreme environments [29], generational maternal effects in both plants and animals [30, 31], and generational prion protein transmission [32, 33] are processes acceptable for inclusion in the Modern Synthesis and EES theories. These processes are examples of multigenerational direct exposure (i.e. intergenerational) phenomena. Therefore, the current Modern Evolution Synthesis involves a genetic determinism focus that cannot explain the environmental impacts on phenotypic variation or non-genetic forms of inheritance. The "curse of complexity" in adaptive evolution of complex traits has been suggested to be resolved by the non-genetic molecular mechanisms of epigenetics [34]. To address these issues, an EES does consider non-genetic components [13], but does not effectively consider a direct environmental impact on phenotypic variation, adaptation, and evolution.

Epigenetics

As discussed, the term epigenetics was coined by Conrad Waddington in the 1940s [24]. Studies in embryology and development were known as "epigenesis," which was a concept from Aristotle's time. The integration of epigenesis and genetics provided the origins for the term epigenetics [24, 35]. As discussed, Waddington's experiments with drosophila demonstrated that a heat induced wing structure developed and was inherited for multiple generations, which was termed "epigenetics." The definition of epigenetics has changed with greater understanding of the molecular mechanisms. The initial definition of Waddington focused on gene–environment interactions but had no molecular insights [24, 36, 37]. As our molecular understanding has developed, the definition has evolved [27], the current definition of epigenetics is "molecular factors and processes around DNA that regulate genome activity independent of DNA sequence, and are mitotically stable" [38]. The genome activity not only involves gene expression, but also genome stability components such as silencing repeat regions and transposable elements to maintain genome integrity [38]. The mitotic stability of the epigenome is critical to maintain cell specificity and differentiation following cell proliferation [38]. Therefore, as a cell undergoes mitosis, the DNA sequence is replicated, as well as the epigenome is replicated to allow cells and tissues to maintain the normal state of differentiation and development acquired [38]. The history of epigenetics is summarized in Table 1 and involved the initial definition of the term in the 1940s, discovery of DNA methylation in the 1970s by Holliday and Pugh, and Riggs [39, 40], demonstration of the role of DNA methylation in X-inactivation in the late 1980s [41], role in imprinted genes for allelic gene expression in the 1990s [42], role of histone modifications in the 1990s [43], role of non-coding RNA (ncRNA) in 2000s [44], epigenome mapping in 2005 [45], and the identification of epigenetic transgenerational inheritance in 2005 [27] (Table 1).

The currently known molecular epigenetic factors include DNA methylation, histone modifications, changes to chromatin structure, expression of non-coding RNA, and RNA methylation [46] (Fig. 1). All these epigenetic factors can directly regulate gene expression independent of DNA sequence. The first factor identified was DNA methylation that occurs at a cytosine residue adjacent to a guanine residue (CpG) sites to form 5-methylcytosine [47]. Although other DNA modifications exist, such as 5-hydroxymethyctyosine or methyl adenine, they are far less frequent and their potential roles in mechanisms of non-genetic adaptation have not been identified. Histone modifications can also act as an epigenetic factor to regulate gene expression independent of DNA sequence (Fig. 1). The chemical modification of histone proteins with methylation or acetylation can modify the gene expression of the associated DNA [48–50]. These histone modifications also effect chromatin structure, impact regulatory protein (e.g. transcription factor) binding, and promote heterochromatin or euchromatin regions of the genome. Histone variants can also alter chromatin structure and gene regulation [51]. In the male germline histone retention is impacted by histone modifications and alters early embryonic development [52]. Non-coding RNAs are another critical epigenetic factor that regulates gene expression independent of DNA sequence (Fig. 1). A number of different classes of ncRNA exist that are not translated into protein, but can regulate gene expression by binding to DNA or proteins involved in gene expression [53, 54]. The small and large ncRNA act as epigenetic regulatory factors to alter gene expression [55]. RNA methylation at N6-methyl adenine is also an epigenetic factor that can regulate the ncRNA secondary structure to influence protein or DNA binding, and regulates gene expression [56, 57] (Fig. 1). The different epigenetic factors do not only act independently, but integrate with each other to provide a level of epigenetic complexity to accommodate the needs of cellular development and differentiation. For example, ncRNA can facilitate DNA methylation processes [58] (Fig. 1). The DNA methylation can modify histone modifications and chromatin structure [59] (Fig. 1). Therefore, the complexity of the epigenome with its various epigenetic factors can accommodate the requirements for the cellular, organ and phenotypic variation observed. The integration of all these epigenetic processes has been shown to be critical for epigenetic inheritance in response to environmental factors [60]. These epigenetic molecular factors and processes provide the ability for environmental factors to alter gene expression independent of DNA sequence. Therefore, gene expression and genome activity require a precursor epigenetic process to occur, which allows classic genetic processes to function.

Environmental epigenetics is the primary molecular mechanism in any organism that is used to promote physiological and phenotypic alterations [2, 14–16, 34, 38, 47–57, 61–71]. Factors such as nutrition, temperature, light, toxicants, exposures, stress, or trauma [27, 46] directly alter epigenetics to promote the cellular response and environmental phenotypic variation. The actions of environmental factors early in development can permanently program the cellular molecular function, which then impacts later life disease or phenotypes [27, 46]. Since cellular identity and function is determined by the epigenetics which regulates the transcriptome, environmental epigenetics is the molecular factor that essentially controls cellular phenotypic variation. Mary

Table 1: History of epigenetics

1940s	Conrad Waddington defined epigenetics as environment–gene interactions that induce developmental phenotypes
1975	Holliday and Pugh, and Riggs identify DNA methylation
1988	X-chromosome inactivation and DNA methylation
1990s	Imprinted genes, allelic expression, and DNA methylation
1995	Histone modifications and chromatin structure
2000s	Non-coding RNAs
2005	Epigenome mapping
2005	Epigenetic transgenerational inheritance

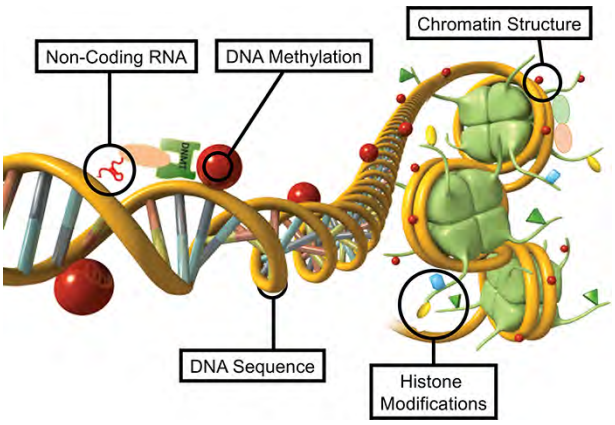

Figure 1: Representation of the primary epigenetic factors and processes schematic of non-coding RNA, DNA methylation, chromatin structure, histone modifications, and DNA structure presented. Modified from Nilsson *et al.* [46]

Jane West-Eberhard proposed that environmental pressures result in selection of novel phenotypic traits, which results in genetic alterations, and ultimately speciation [68]. This theory has been coined "genes as followers" and was suggested to be a genetic phenomenon. However, environmental epigenetics has now been suggested to provide the molecular mechanism involved, not genetics [2, 14–16, 34, 38, 47–57, 61–71]. Therefore, the current epigenetic science developed over the past decades indicates environmental epigenetics is the primary molecular mechanism promoting phenotypic variation that is associated with adaptation processes [11]. A large number of studies and literature supports a direct role for non-genetic processes (i.e. epimutations) in phenotypic variation (Table 2). The role of epigenetics in regulating this phenotypic variation to impact evolution is the content of this literature.

The current neo-Darwinian (i.e. Modern Synthesis) suggests that genetic variation is essential for evolution and drives phenotypic variation and adaptation. Interestingly, genetic mutations most often require an epigenetic precursor [11]. This includes the most predominant point mutation of C to T conversion being promoted by DNA methylation, or DNA methylation regulation of copy number variation, or histone modifications and DNA methylation altering translocation sites, or DNA methylation regulating transposable element activity [11]. The environmental induction of epigenetic transgenerational inheritance has been shown to increase the frequency of point mutations and copy number mutations generationally [11, 71]. Therefore, environmental epigenetics and epigenetic inheritance promote genetic variation that may facilitate adaptive phenotypic variation [71]. The frequency of epigenetic alterations is five orders of magnitude higher than genetic mutation frequency [72, 73]. As will be discussed, the ability of environmental epigenetics to be a primary driver of phenotypic and genetic variation needs to be integrated into a unified evolutionary biology theory.

Epigenetic Transgenerational Inheritance and Evolution

Environmentally induced epigenetic transgenerational inheritance was first described on a molecular level with a toxicant exposure in a rat model [74] and later with a stress exposure in a mouse model [75]. This is a non-genetic form of inheritance mediated through epigenetic alterations in the germline (sperm or egg) that transmit altered phenotypes to subsequent generations [46, 76]. The phenomenon has been extensively demonstrated in hundreds of laboratories in all organisms investigated from plants to humans. In plants, worms, and flies transgenerational inheritance has been transmitted hundreds of generations [46, 77]. Environmental exposures include industrial toxicants, nutrition, smoking, alcohol, and stress or trauma. The direct environmental exposure of an individual impacts the exposed individual and the germline within that individual that will generate the next generation, so this is referred to as a multigenerational exposure (i.e. intergenerational phenomenon) (Fig. 2). The first transgenerational generation not involving direct exposure is the grand-offspring F2 generation. For a gestating female, the F0 generation mother, F1 generation fetus, and germline within the fetus that will generate the F2 generation grand-offspring are all directly exposed, such that the first transgenerational generation is the F3 generation great grand-offspring (Fig. 2). The repeated demonstration of epigenetic transgenerational inheritance of altered phenotypes suggests that this molecular mechanism plays a significant role in ecology and medicine and should be integrated into evolutionary biology theory [4, 6, 11, 12, 16, 77–92]. Environmentally induced epigenetic transgenerational inheritance has also been observed in a number of field populations responding to natural selection [11, 88, 89, 92]. A number of these studies are summarized below and have been reviewed in regard to a role for epigenetics in evolution [1, 2, 4, 7, 8, 12, 16, 29, 33, 46, 74, 76, 77, 82, 93–101].

This non-genetic form of inheritance is induced early in development to reprogram the epigenetics of the sperm or egg to allow transmission to the next generation. The next generation will have its embryonic stem cell epigenome and transcriptome altered, which will impact all the somatic cells derived from the stem cells epigenetics and transcriptomes [46]. Those cells sensitive to the epigenetic alterations will have an increased susceptibility to develop disease later in life, such that the generational physiology and phenotype of the individual will be modified. A large number of different transgenerational pathologies develop, and the toxicant exposures result in generational toxicology [46]. Since the impacts are transgenerationally inherited, they have the potential to impact evolution [11]. The origins of the transgenerational germline epigenetic alterations have been shown to be throughout gametogenesis from the primordial germ cells to the mature gametes [52]. Therefore, like genetic changes, epigenetic changes can have an important role in short-term microevolution [6] and contribute to macroevolutionary (i.e. at or above the level of species) processes, such as speciation and adaptive radiation [2, 4, 12, 79, 80] (Table 3).

Examples of epigenetics and epigenetic transgenerational inheritance impacts on evolution (e.g. natural population) are provided below for natural populations and laboratory models (Table 4). Empirical tests of the potential role of environmental epigenetic mechanisms in environmental adaptation and evolution have been described [102]. A role for environmentally induced epigenetic variation and inheritance in plants has been observed [77, 97–100]. The high level of developmental plasticity in changing environments is proposed to be due to environmental epigenetics facilitating adaptation and evolution in plants [103, 104]. Plant models of reproduction lack sequestered germ cells [105], so have adaptive epigenetics and phenotypes. Specific examples include *Taraxacum officinale* [106, 107] and *Arabidopsis* [108, 109]. The *Caenorhabditis elegans* is a model worm with high epigenetic variation and epigenetic transgenerational inheritance [110–112]. Epigenetic inheritance of histone modifications and ncRNA can alter adaptive responses in *C. elegans* [113]. The house sparrow (*Passer domesticus*) demonstrates high levels of epigenetic variation facilitating rapid phenotypic change and adaptive evolution [102, 114]. The invasive house sparrow exhibits phenotypic and epigenetic variation in subpopulations in the Middle East [115] and Australia [116]. Clonal lineages of animals that are not reliant on genetic variation also have been used to investigate environmentally induced epigenetic variation. The asexual snail *Potamopyrgus antipodarum* is a widespread invasive species in North America. Alteration of environmental conditions (i.e. water flow) was found to associate with adaptive phenotypic variation that correlated with epigenetic alterations [117, 118]. *Chrosomus eos-neogaeus* is a hybrid clonal fish that inhabits lakes and intermittent stream environments that has epigenetic variation in the divergent environments [119, 120]. Another fish example is *Poecilia*, a fish that survives in fresh water and sulfur environments, having distinct generational epigenetic changes in the distinct environments [121]. Combined observations support a role for environmentally induced epigenetic variation and inheritance to promote adaptive phenotypic variation.

Table 2: Non-genetic (epigenetic) association with phenotypic variation references

Reference title		
Recherches sur l'organisation des corps vivans	Lamarck J. 1802	[21]
A New Factor in Evolution	Baldwin J. 1896	[19]
Organisers and Genes	Waddington CH. 1940	[24]
An epigenetic mutation responsible for natural variation in floral symmetry	Cubas P. 1999	[77]
Developmental plasticity and evolution	West-Eberhard MJ. 2003	[68]
The Baldwin effect and genetic assimilation: revisiting two mechanisms of evolutionary change mediated by phenotypic plasticity	Crispo E. 2007	[22]
Transgenerational epigenetic imprints on mate preference	Crews D. 2007	[82]
Transgenerational epigenetic programming of the brain transcriptome and anxiety behavior	Skinner MK. 2008	[93]
Identical but not the same: the value of discordant monozygotic twins in genetic research	Zwijnenburg PJ. 2010	[15]
Progressive, Transgenerational Changes in Offspring Phenotype and Epigenotype following Nutritional Transition	Burdge GC. 2011	[84]
Exploring the correlations between sequence evolution rate and phenotypic divergence across the Mammalian tree provides insights into adaptive evolution	Janecka J. 2012	[18]
Adaptive evolution: evaluating empirical support for theoretical predictions	Olson-Manning CF. 2012	[5]
Environmental heterogeneity and phenotypic divergence: can heritable epigenetic variation aid speciation?	Flatscher R. 2012	[79]
Epigenetic variation, inheritance, and selection in plant populations	Hirsch S. 2012	[97]
Epigenetic variation: origin and transgenerational inheritance	Becker C. 2012	[100]
General-purpose genotype or how epigenetics extend the flexibility of a genotype	Massicotte R. 2012	[119]
Epigenetics and the evolution of Darwin's finches	Skinner MK. 2014	[122]
How stable "should" epigenetic modifications be? Insights from adaptive plasticity and bet hedging	Herman JJ. 2014	[91]
Environmentally responsive genome-wide accumulation of de novo Arabidopsis thaliana mutations and epimutations	Jiang C. 2014	[72]
Genetic and epigenetic analysis of monozygotic twins discordant for testicular cancer	Kratz CP. 2014	[14]
Stochastic developmental variation, an epigenetic source of phenotypic diversity with far-reaching biological consequences	Vogt G. 2015	[89]
Environmental Epigenetics and a Unified Theory of the Molecular Aspects of Evolution: A Neo-Lamarckian Concept that Facilitates Neo-Darwinian Evolution	Skinner MK. 2015	[11]
Landscape of natural epigenetic variation in humans	Chatterjee A. 2015 Heyn H. 2013	[140, 141]
Facing environmental predictability with different sources of epigenetic variation	Leung C. 2016	[120]
Epigenetic programming alterations in alligators from environmentally contaminated lakes	Guillette LJ, Jr, 2016	[125]
Epigenetics in natural animal populations	Hu J. 2017	[92]
Epigenetic and chromatin-based mechanisms in environmental stress adaptation and stress memory in plants	Lamke J. 2017	[132]
Epigenetic variation between urban and rural populations of Darwin's finches	McNew SM. 2017	[123]
Natural epigenetic variation within and among six subspecies of the house sparrow, Passer domesticus	Riyahi S. 2017	[115]
Epigenetics and adaptive phenotypic variation between habitats in an asexual snail	Thorson JLM. 2017	[117]
Facilitation of environmental adaptation and evolution by epigenetic phenotype variation: insights from clonal, invasive, polyploid, and domesticated animals	Vogt G. 2017	[102]
An Epigenetic Perspective on the Midwife Toad Experiments of Paul Kammerer (1880–1926)	Vargas AO. 2017	[23]
Epigenetic and genetic variation among three separate introductions of the house sparrow (Passer domesticus) into Australia	Sheldon EL. 2018	[116]
Contribution of epigenetic variation to adaptation in Arabidopsis	Schmid MW. 2018	[108]
Regional epigenetic variation in asexual snail populations among urban and rural lakes	Thorson JLM. 2019	[118]
Sources of epigenetic variation and their applications in natural populations	Angers B. 2020	[90]
Understanding natural epigenetic variation	Richards CL. 2010	[99]
Rapid Epigenetic Adaptation in Animals and Its Role in Invasiveness	Carneiro VC. 2020	[114]
Epigenetic regulation in plant abiotic stress responses	Chang YN. 2020	[133]
Epimutations Define a Fast-Ticking Molecular Clock in Plants	Yao N. 2021	[73]
Epigenetic variation in animal populations: Sources, extent, phenotypic implications, and ecological and evolutionary relevance	Vogt G. 2021	[70]
Epigenetic inheritance of DNA methylation changes in fish living in hydrogen sulfide-rich springs	Kelley JL. 2021	[121]
Differential DNA Methylation in Somatic and Sperm cells of Hatchery versus Wild (Natural-Origin) Steelhead Trout Populations	Nilsson E. 2021	[124]

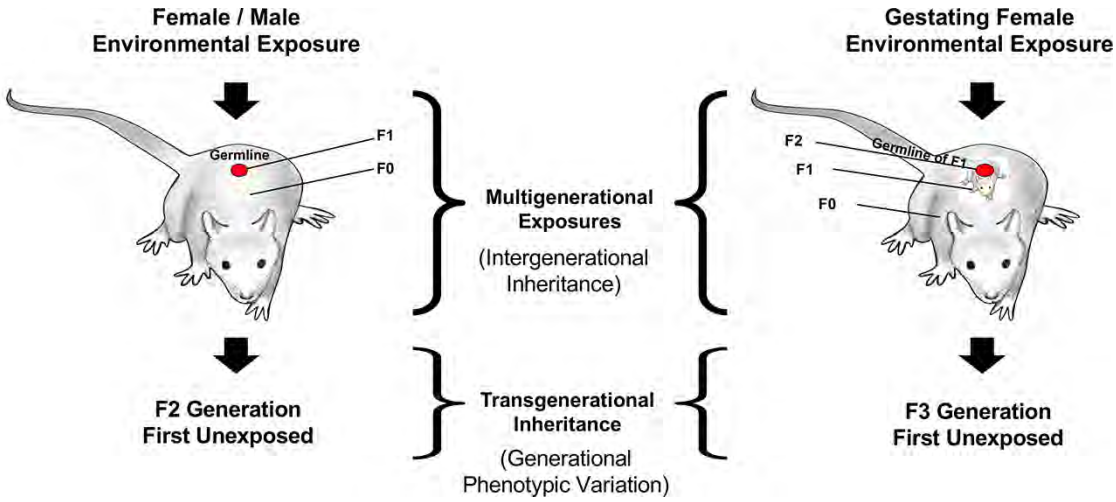

Figure 2: Environmentally induced transgenerational epigenetic inheritance: schematic of environmental exposure and affected generations for both gestating female and adult male or female. The multigenerational direct exposures are indicated in contrast to the transgenerational generation without direct exposure. Modified from Nilsson *et al.* [46]

Table 3: Non-genetic (epigenetic) association with evolution references

Reference title		
The significance of responses of the genome to challenge	McClintock B. 1984	[17]
Maternal Effects as Adaptations	Mousseau TA, 1998	[31]
Epigenetic transgenerational actions of endocrine disruptors and male fertility	Anway MD, 2005	[74]
Environmental epigenomics and disease susceptibility	Jirtle RL, 2007	[76]
Chromatin structure and the inheritance of epigenetic information	Margueron R, 2010	[51]
Epigenetic transgenerational actions of environmental factors in disease etiology	Skinner MK, 2010	[27]
A unified approach to the evolutionary consequences of genetic and nongenetic inheritance	Day T, 2011	[6]
Transgenerational inheritance of an acquired small RNA-based antiviral response in C. elegans	Rechavi O, 2011	[110]
Transgenerational epigenetic inheritance of longevity in Caenorhabditis elegans	Greer EL, 2011	[111]
Transgenerational epigenetic inheritance in plants	Hauser MT, 2011	[131]
Remembering the prolonged cold of winter	Song J, 2013	[86]
Nongenetic inheritance and the evolution of costly female preference	Bonduriansky R, 2013	[129]
Transgenerational developmental programming	Aiken CE, 2014	[101]
Implication of sperm RNAs in transgenerational inheritance of the effects of early trauma in mice	Gapp K, 2014	[75]
Potential roles of noncoding RNAs in environmental epigenetic transgenerational inheritance	Yan W. 2014	[44]
Does evolutionary theory need a rethink?	Laland K. 2014	[4]
Transgenerational epigenetic inheritance in mammals: how good is the evidence?	van Otterdijk SD, 2016	[135]
The evolutionary implications of epigenetic inheritance	Jablonka E. 2017	[2]
Transgenerational epigenetics: Integrating soma to germline communication with gametic inheritance	Sharma A. 2017	[66]
Principles of Transgenerational Small RNA Inheritance in Caenorhabditis elegans	Rechavi O, 2017	[113]
Lamarck rises from his grave: parental environment-induced epigenetic inheritance in model organisms and humans	Wang Y, 2017	[137]
Functions and mechanisms of epigenetic inheritance in animals	Skvortsova K, 2018	[134]
Plant epigenetic mechanisms: role in abiotic stress and their generational heritability	Sudan J, Raina M, Singh R. 2018	[103]
Quantitative epigenetics and evolution	Banta JA, 2018	[69]
Environmentally Induced Epigenetic Transgenerational Inheritance of Disease	Nilsson E, 2018	[46]
Protein-Based Inheritance: Epigenetics beyond the Chromosome	Harvey ZH, 2018	[32]
Histone Methylation and Memory of Environmental Stress	Fabrizio P, 2019	[112]
Maternal transmission of the epigenetic "memory of winter cold" in Arabidopsis	Luo X, 2020	[109]
Molecular mechanisms of epigenetic inheritance: Possible evolutionary implications	Sarkies P. 2020	[88]

Adaptive radiations also provide additional examples of epigenetically mediated evolutionary change. One of the first examples of this used five species of Darwin's finches in the Galapagos islands to assess genetic and epigenetic relatedness [122]. The epigenetic variation observed statistically correlated with the phylogenic relatedness of the different species, in contrast with the genetic variation, which did not correlate, and was at a higher frequency than the genetic alterations [122]. Observations were extended in the Darwin's finches with a comparison of epigenetic variation between two Darwin finch species having distinct urban and rural populations with phenotypic variation [123]. Finches in the urban environment with altered nutrition were found to have epigenetic variation, but no genetic variation [123]. Another example of human-mediated alterations in phenotypic variation

Table 4: Examples of epigenetic transgenerational inheritance impacts on evolution

Organism		Reference
Plant	(*Taraxacum officinale*, Arabidopsis)	[77, 97–100, 103–109]
Worm	(*Caenorhabditis elegans*)	[110–113]
Bird	(House sparrow, *Passer domesticus*)	[102, 114–116]
Asexual snail	(*Potamopyrgus antipodarum*)	[117, 118]
Hybrid clonal fish	(*Chrosomus eos-neogaeus*)	[119, 120]
Fish	(*Poecilia mexicana*)	[121]
Bird	(Darwin finch, *Geospiza fortis*)	[122, 123]
Fish	(Steelhead trout, *Oncorhynchus mykiss*)	[124]
Alligator	(*Alligator mississippiensis*)	[125]
Mouse	(*Mus musculus*)	[46, 75]
Rat	(*Rattus norvegicus*)	[46, 74, 82, 93]

and epigenetic variation used the steelhead trout (*Oncorhynchus mykiss*) [124]. The hatchery and wild populations of steelhead trout have significant phenotypic variation in growth, maturation rates, and subsequent fitness and survival. Epigenetic differences between the fish populations were dramatic in somatic and germ cells, with minimal genetic alterations, between the hatchery and wild populations [124]. A similar observation was made with the American alligator (*Alligator mississippiensis*) in Florida USA, where animals in a pristine uncontaminated environment had dramatic epigenetic alterations when compared to alligators in contaminated environments, associated with corresponding reproductive pathologies and phenotypic variation [125]. Observations demonstrate that invaders, founder populations, clonal lineages, and adaptive radiations involve environmental epigenetics and epigenetic inheritance for adaptive phenotypic variation and evolution [102] (Table 4).

Observations in a growing number of mammalian species also support a role for environmentally induced epigenetic transgenerational inheritance in adaptation and evolution [126] (Table 4). The first studies to investigate the role of environmental epigenetics and epigenetic transgenerational inheritance used ancestral toxicant or stress exposure types of experimental design [74, 75]. Darwin proposed that one of the critical determinants of evolution was sexual selection [1]. A study was designed to investigate the environmental impacts of a toxicant exposure on the epigenetic transgenerational inheritance of altered mate preference associated with sexual selection [82]. An F0 generation female gestating rat was exposed to the agricultural fungicide vinclozolin transiently during gonadal sex determination and then subsequent F3 generation animals (great grand-offspring) were obtained to assess mate preference behavior alterations and epigenetic alterations. A significant mate preference alteration was identified along with epigenetic alterations in the germline [82]. Transgenerational brain transcriptome changes associated with the mate preference behaviors were observed [93]. Therefore, environmentally induced epigenetic transgenerational inheritance of mate preference, known to be critical for evolution, was observed [27, 82, 93]. A number of reviews have suggested a role for epigenetics in both microevolution and macroevolution [6–8, 16, 34, 79, 80, 127–130], Table 3.

The current Modern Synthesis and EES theories support the role of genetics as being the primary molecular factor involved in adaptation and evolution. Genetic variation was thought to be the driver for phenotypic variation in the Modern Synthesis, while the EES suggests epigenetics can facilitate phenotypic variation as well. The above examples demonstrate that epigenetics and epigenetic inheritance are stable and could independently impact evolution alongside genetics. The environmentally induced epigenetic transgenerational inheritance of phenotypic variation needs to be considered an equally important molecular mechanism. The promotion of adaptive or maladaptive traits through epigenetic variation is orders of magnitudes more frequent than genetic induced adaptive or maladaptive traits. The distinction is that environment can readily promote the epigenetic variation that becomes inherited to facilitate the natural selection and evolutionary process. Since epigenetic alterations also facilitate formation of genetic mutations and genetic variation, indirectly environmental epigenetics can facilitate and drive genetic variation. These advances in our understanding of molecular biology, physiology and inheritance need to be incorporated into a more unified evolutionary theory.

Integration of Epigenetic Transgenerational Inheritance and Unified Theory of Evolution

The advances in epigenetics over the last three decades have demonstrated that epigenetics is equally important as genetics in the regulation of gene expression, phenotypic variation, and adaptation (Table 2). Epigenetics is the precursor for all genomic activity (i.e. gene expression) and genetic stability (e.g. transposable element mobilization or copy number variation). Therefore, all biological processes from evolution to disease etiology will require the incorporation of epigenetics and genetics. The evidence for a functional role of environmental epigenetics and epigenetic transgenerational inheritance in the phenotypic variation and adaptation in plants [131–133] and animals [46, 134–136] is now compelling. This new science demonstrates a role for the environment to directly promote phenotypic variation that is heritable. This provides significant support for the previously discarded ideas of "soft inheritance" (i.e. epigenetic inheritance) from the late 1800s and early 1900s [11]. This neo-Lamarckian concept provides a redemption for some of the ideas of Jean Baptiste Lamarck [21], who first described the inheritance of acquired characteristics [11, 137, 138] (Fig. 3). Since the neo-Darwinian theory (i.e. Modern Synthesis) did not include direct environmental impacts to promote phenotypic (i.e. non-genetic) variation, the integration of epigenetics, environmental epigenetics and epigenetic transgenerational inheritance need to be integrated in a Unified Theory of Evolution (Table 4 and Fig. 3). The EES supports this concept and promotes a role for non-genetic phenomenon such as epigenetics and epigenetic inheritance [13]. This is also supported by computational modeling of evolution [6, 139]. However, the direct actions of the environment to promote heritable phenotypic variation independent of DNA sequence mutations and genetics are not a major component of the EES. Therefore, there is a consensus that the current concepts need to be integrated and incorporated into our understanding of evolutionary biology [11, 13] (Table 3).

The integration of epigenetic transgenerational inheritance expands the role of epigenetics beyond the short-term impacts of gene expression to also promote phenotypic variation within a population permanently. Therefore, environmentally induced epigenetic transgenerational inheritance has macroevolution impacts equally as important as genetics and genetic mutations [11] (Table 3). Due to the molecular frequency of epigenetic

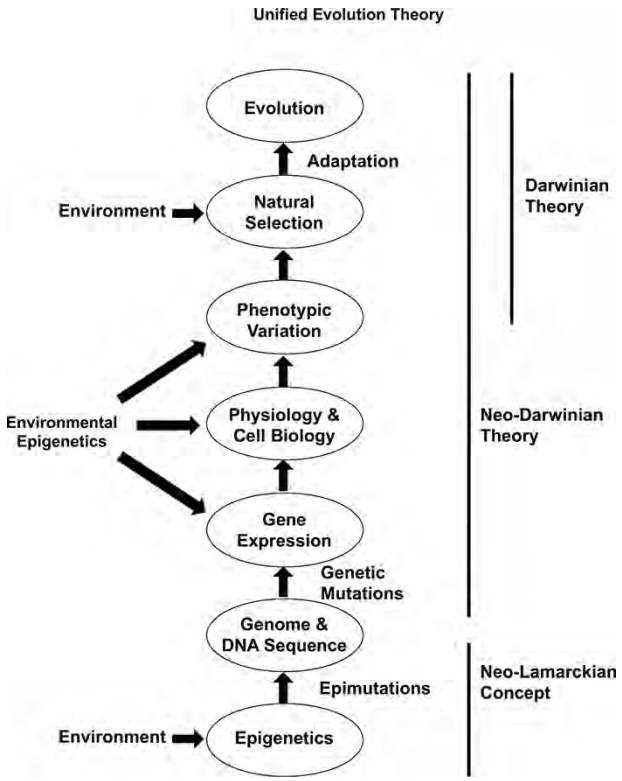

Figure 3: Schematic of the Unified Theory of Evolution. No dominance is suggested by the appearance of specific circles (e.g. epimutations versus genetics) such that all are equally important components. Modified from Skinner [11]

variation being several orders of magnitude higher than genetic variation [73, 105], and being environmentally responsive, the impacts of epigenetic transgenerational inheritance and epigenetic variation on the evolutionary and adaptive trajectory of species are supported [2, 11]. Previous studies have documented epigenetic variation at the level of cellular epigenetics for tissue function and disease [140], and the level of the organism to correlate with phenotypic variation [141]. As with genetics, epigenetics is anticipated to produce adaptive and maladaptive phenotypes and effects. The increased frequency of epigenetic variation is anticipated to provide a spectrum of adaptive and maladaptive phenotypes. An example is the thrifty phenotype induced by caloric restriction during fetal development inducing epigenetic metabolism effects that allow the offspring to survive on fewer calories, but on a normal diet, develop obesity [142]. Therefore, both adaptive and maladaptive phenotypes are expected in an evolutionary setting. The postulates of natural selection are supported by the evidence of epigenetic transgenerational inheritance and phenotypic change. Therefore, the integration of epigenetics and genetics provides a more efficient molecular mechanism and theory than the current Modern Synthesis (i.e. neo-Darwinian) theory alone [11] (Fig. 3). In addition, this is supported by and expands the concepts of the EES [13]. The Unified Theory of environmental epigenetics facilitating (i) the neo-Lamarckian concept of environment directly impacting phenotype that is heritable and (ii) subsequently altering genetic variation and phenotypic variation through the neo-Darwinian theory, (iii) for adaptation and natural selection as per classic Darwinian theory, is proposed as the Unified Theory of Evolution (Fig. 3 and Table 5).

Table 5: Evolution theory components

Neo-Lamarckian Concept:
Environment directly alters phenotype generationally
Darwinian Evolution Theory:
Natural selection acts on phenotypic variation for adaptation
Neo-Darwinian Evolution Theory:
Genetic mutations promote phenotypic variation on which natural selection acts
Environmental Epigenetics:
Environmental epigenetic alterations promote phenotypic variation and facilitate genetic mutations to influence adaptation and natural selection
Unified Evolution Theory:
Environmental epigenetics and genetic mutations both promote heritable phenotypic variation on which natural selection acts

Paradigm Shifts in Science

The vast majority of biological theories today are primarily based on "genetic determinism" in which genetic mutations are the basis for all phenomena from disease etiology to evolution. This genetic determinism paradigm has been in place for the past century and became ingrained in all aspects of the biological sciences. Following the development of modern genomics and sequencing of the human and other species genomes, the past 20 years has demonstrated that most biological phenomena cannot be explained with genetics alone. The crisis developing is that the frequency of genetic mutations is rare, such that correlations with function, pathology, and disease or phenotypes are not common. In the 1970s, Thomas Kuhn described the concept of paradigm shifts in science to help explain the historic development of the sciences and provide insights into the shifts required in rapidly developing science technology and theory [143]. The concept was that when the current paradigm cannot explain phenomena observed, a crisis develops that promotes new science development that allows a new scientific paradigm to develop. Due to the vested interest in the current paradigms, this generally takes a generation of scientists to develop [143]. The developments over the past several decades in the molecular epigenetic area provides a new science that can help explain the deficiencies and problems with genetic determinism. The integration of epigenetics and genetics provides a more complete and efficient molecular explanation of the processes in biology. We now know environmental epigenetics can dramatically influence genetic variation through the promotion of genetic mutations and alterations. Independent of genetics, environmental epigenetics can also promote phenotypic variation, since the epigenetic processes precede and directly regulate the transcriptomes required for the phenotypes observed. The role of epigenetic transgenerational inheritance as a form of non-genetic inheritance allows the transmission of phenotypes for generations. The integration of genetics and epigenetics provides a novel and more efficient molecular model of evolution, not considered within the Modern Synthesis or EES theories (Fig. 3 and Table 4). This does not detract or minimize the essential aspects of Darwinian theory nor advances of the Modern Synthesis, but simply provides new science not previously considered in evolution theory [11]. This Kuhnian paradigm shift in evolutionary biology theory is the integration of the classic established concepts with the new science to create a new paradigm of a more Unified Theory presented (Fig. 3). This is not restricted to evolutionary biology and is now needed in all areas of biology from

disease etiology theory, cell and developmental biology theory, and environmental sciences.

Summary

The support for environmental epigenetics and epigenetic transgenerational inheritance in regulation of phenotypic variation and genetic variation to impact both microevolution and macroevolution is now compelling [6, 8, 34, 79–81, 127, 128] (Tables 2 and 3). This information has been reviewed and the need to integrate epigenetics and genetics in a unified theory of evolution discussed [6, 8, 16, 34, 79–81, 127, 128]. The integration and Unified Evolution Theory proposed (Fig. 3) has a number of parameters to consider: (i) environmental epigenetics provides a molecular mechanism for Lamarck's concept that environment can directly alter phenotype in a heritable manner; (ii) environmental exposures at critical developmental windows promote the epigenetic transgenerational inheritance of germline (e.g. sperm and egg) epimutations that alter phenotypic variation generationally; (iii) direct environmental exposures of developing somatic tissue can alter somatic epigenomes and phenotype in the individual exposed, but this will not be heritable and the phenotypes will often be distinct from transgenerational phenotypes; (iv) phenotypic variation is derived from a combination of integrated genetic and epigenetic processes on which natural selection acts; and (v) environment has a critical role in natural selection, as well as in the induction of heritable adaptive phenotypic variation (i.e. epigenetic transgenerational inheritance). Therefore, the environment has a more direct role, independent of genetics, in driving phenotypic variation, adaptation, and evolutionary biology.

As shown in Fig. 3 and Table 5, the integration of epigenetics and genetics contribute to a Unified Theory of Evolution that explains environmental impacts, phenotypic variation, genetic variation, and adaptation that natural selection acts on. All classic and previously established elements of evolution theory are included, and this unified theory brings in the new advanced science of environmental epigenetics. This shift is a new paradigm in evolution, as defined by classic Kuhn paradigm shifts in science [143]. This does not detract from the critical aspects of Darwinian theory, Modern Synthesis, or EES, but simply integrates the new advanced science of epigenetics and epigenetic transgenerational inheritance. The current review expands this proposed concept [11] and provides a significant amount of supporting literature (Tables 2 and 3) and experimental models to support the role of environmentally induced epigenetic transgenerational inheritance in evolution.

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References

1. Darwin C. *On the Origin of Species*. London: John Murray, 1859, 488.
2. Jablonka E. The evolutionary implications of epigenetic inheritance. *Interface Focus* 2017;**7**:20160135.
3. Huxley J. *Evolution: The Modern Synthesis*. London: George Allen & Unwin Ltd, 1942, 645.
4. Laland K, Uller T, Feldman M *et al*. Does evolutionary theory need a rethink? *Nature* 2014;**514**:161–4.
5. Olson-Manning CF, Wagner MR, Mitchell-Olds T. Adaptive evolution: evaluating empirical support for theoretical predictions. *Nat Rev Genet* 2012;**13**:867–77.
6. Day T, Bonduriansky R. A unified approach to the evolutionary consequences of genetic and nongenetic inheritance. *Am Nat* 2011;**178**:E18–36.
7. Jablonka E, Raz G. Transgenerational epigenetic inheritance: prevalence, mechanisms, and implications for the study of heredity and evolution. *Q Rev Biol* 2009;**84**:131–76.
8. Kuzawa CW, Thayer ZM. Timescales of human adaptation: the role of epigenetic processes. *Epigenomics* 2011;**3**:221–34.
9. Nei M, Nozawa M. Roles of mutation and selection in speciation: from Hugo de Vries to the modern genomic era. *Genome Biol Evol* 2011;**3**:812–29.
10. Burger R, Willensdorfer M, Nowak MA. Why are phenotypic mutation rates much higher than genotypic mutation rates? *Genetics* 2006;**172**:197–206.
11. Skinner MK. Environmental epigenetics and a unified theory of the molecular aspects of evolution: a neo-Lamarckian concept that facilitates neo-Darwinian evolution. *Genome Biol Evol* 2015;**7**:1296–302.
12. Pigliucci M. Do we need an extended evolutionary synthesis? *Evolution* 2007;**61**:2743–9.
13. Laland KN, Uller T, Feldman MW *et al*. The extended evolutionary synthesis: its structure, assumptions and predictions. *Proc Biol Sci Royal Soc* 2015;**282**:20151019.
14. Kratz CP, Edelman DC, Wang Y *et al*. Genetic and epigenetic analysis of monozygotic twins discordant for testicular cancer. *Int J Mol Epidemiol Genet* 2014;**5**:135–9.
15. Zwijnenburg PJ, Meijers-Heijboer H, Boomsma DI. Identical but not the same: the value of discordant monozygotic twins in genetic research. *Am J Med Genet B Neuropsychiatr Genet* 2010;**153B**:1134–49.
16. Skinner MK. Endocrine disruptor induction of epigenetic transgenerational inheritance of disease. *Mol Cell Endocrinol* 2014;**398**:4–12.
17. McClintock B. The significance of responses of the genome to challenge. *Science* 1984;**226**:792–801.
18. Janecka J, Chowdhary B, Murphy W. Exploring the correlations between sequence evolution rate and phenotypic divergence across the Mammalian tree provides insights into adaptive evolution. *J Biosci* 2012;**37**:897–909.
19. Baldwin J. A new factor in evolution. *Am Nat* 1896;**30**:441–51.
20. Calabi L. On Darwin's 'metaphysical notebooks'. I: teleology and the project of a theory. *Riv Biol* 2001;**94**:123–59.
21. Lamarck J. *Recherches sur l'organisation des corps vivans*. Paris: Chez L'auteur, Maillard, 1802.
22. Crispo E. The Baldwin effect and genetic assimilation: revisiting two mechanisms of evolutionary change mediated by phenotypic plasticity. *Evolution* 2007;**61**:2469–79.
23. Vargas AO, Krabichler Q, Guerrero-Bosagna C. An epigenetic perspective on the midwife toad experiments of Paul Kammerer (1880–1926). *J Exp Zool B Mol Dev Evol* 2017;**328**:179–92.

24. Waddington CH. *Organisers and Genes*. Cambridge: Cambridge University Press, 1940.
25. Mayr E. Prologue: some thoughts on the history of the evolutionary synthesis. In: Mayr E, Provine WB (eds.), *The Evolutionary Synthesis: Perspectives on the Unification of Biology*. Cambridge, MA: Harvard University Press, 1980, 1–48.
26. Schork NJ, Murray SS, Frazer KA *et al.* Common vs. rare allele hypotheses for complex diseases. *Curr Opin Genet Dev* 2009;**19**:212–9.
27. Skinner MK, Manikkam M, Guerrero-Bosagna C. Epigenetic transgenerational actions of environmental factors in disease etiology. *Trends Endocrinol Metab* 2010;**21**:214–22.
28. Paenke I, Sendhoff B, Kawecki TJ. Influence of plasticity and learning on evolution under directional selection. *Am Nat* 2007;**170**:E47–58.
29. Husnik F, McCutcheon JP. Functional horizontal gene transfer from bacteria to eukaryotes. *Nat Rev Microbiol* 2018;**16**:67–79.
30. Falconer DS. *Introduction to Quantitative Genetics*. Suffolk, Great Britain: Benjamin-Cummings Publishing Company, 1996, 464.
31. Mousseau TA, Fox CW (eds). *Maternal Effects as Adaptations*. Oxford, United Kingdom: Oxford University Press, 1998, 400.
32. Harvey ZH, Chen Y, Jarosz DF. Protein-based inheritance: epigenetics beyond the chromosome. *Mol Cell* 2018;**69**:195–202.
33. Harvey ZH, Chakravarty AK, Futia RA *et al.* A prion epigenetic switch establishes an active chromatin state. *Cell* 2020;**180**:928–40 e14.
34. Badyaev AV. Epigenetic resolution of the 'curse of complexity' in adaptive evolution of complex traits. *J Physiol* 2014;**592**:2251–60.
35. Van Speybroeck L. From epigenesis to epigenetics: the case of C. H. Waddington. *Ann N Y Acad Sci* 2002;**981**:61–81.
36. Waddington CH. *Principles of Embryology*. London: George Allen & Unwin Ltd., 1956.
37. Waddington CH. The genetic assimilation of the bithorax phenotype. *Evolution* 1956;**10**:1–13.
38. Skinner MK. Environmental epigenetic transgenerational inheritance and somatic epigenetic mitotic stability. *Epigenetics* 2011;**6**:838–42.
39. Holliday R, Pugh JE. DNA modification mechanisms and gene activity during development. *Science* 1975;**187**:226–32.
40. Riggs AD. X inactivation, differentiation, and DNA methylation. *Cytogenet Cell Genet* 1975;**14**:9–25.
41. Dossin F, Heard E. The molecular and nuclear dynamics of X-chromosome inactivation. *Cold Spring Harb Perspect Biol* 2021:a040196.
42. SanMiguel JM, Bartolomei MS. DNA methylation dynamics of genomic imprinting in mouse development. *Biol Reprod* 2018;**99**:252–62.
43. Kan RL, Chen J, Sallam T. Crosstalk between epitranscriptomic and epigenetic mechanisms in gene regulation. *Trends Genet* 2021;**S0168–9525**:00170–0.
44. Yan W. Potential roles of noncoding RNAs in environmental epigenetic transgenerational inheritance. *Mol Cell Endocrinol* 2014;**398**:24–30.
45. Argelaguet R, Clark SJ, Mohammed H *et al.* Multi-omics profiling of mouse gastrulation at single-cell resolution. *Nature* 2019;**576**:487–91.
46. Nilsson E, Sadler-Riggleman I, Skinner MK. Environmentally induced epigenetic transgenerational inheritance of disease. *Environ Epigenet* 2018;**4**:1–13, dvy016.
47. Singer J, Roberts-Ems J, Riggs AD. Methylation of mouse liver DNA studied by means of the restriction enzymes msp I and hpa II. *Science* 1979;**203**:1019–21.
48. Rothbart SB, Strahl BD. Interpreting the language of histone and DNA modifications. *Biochim Biophys Acta* 2014;**1839**:627–43.
49. Bartova E, Krejci J, Harnicarova A *et al.* Histone modifications and nuclear architecture: a review. *J Histochem Cytochem* 2008;**56**:711–21.
50. Taylor BC, Young NL. Combinations of histone post-translational modifications. *Biochem J* 2021;**478**:511–32.
51. Margueron R, Reinberg D. Chromatin structure and the inheritance of epigenetic information. *Nat Rev Genet* 2010;**11**:285–96.
52. Ben Maamar M, Nilsson EE, Skinner MK. Epigenetic transgenerational inheritance, gametogenesis and germline development . *Biol Reprod* 2021;**105**:570–92.
53. Wei JW, Huang K, Yang C *et al.* Non-coding RNAs as regulators in epigenetics. *Oncol Rep* 2017;**37**:3–9.
54. Huang B, Jiang C, Zhang R. Epigenetics: the language of the cell? *Epigenomics* 2014;**6**:73–88.
55. Kornfeld JW, Bruning JC. Regulation of metabolism by long, non-coding RNAs. *Front Genet* 2014;**5**:57.
56. Yue Y, Liu J, He C. RNA N6-methyladenosine methylation in post-transcriptional gene expression regulation. *Genes Dev* 2015;**29**:1343–55.
57. Fu Y, Dominissini D, Rechavi G *et al.* Gene expression regulation mediated through reversible m(6)A RNA methylation. *Nat Rev Genet* 2014;**15**:293–306.
58. Urquiaga MCO, Thiebaut F, Hemerly AS *et al.* From trash to luxury: the potential role of plant LncRNA in DNA methylation during abiotic stress. *Front Plant Sci* 2020;**11**:603246.
59. Lobo J, Henrique R, Jeronimo C. The role of DNA/histone modifying enzymes and chromatin remodeling complexes in testicular germ cell tumors. *Cancers (Basel)* 2018;**11**:6.
60. Beck D, Ben Maamar M, Skinner MK. Integration of sperm ncRNA-directed DNA methylation and DNA methylation-directed histone retention in epigenetic transgenerational inheritance. *Epigenetics Chromatin* 2021;**14**:6.
61. Tan Q, Christiansen L, von Bornemann Hjelmborg J *et al.* Twin methodology in epigenetic studies. *J Exp Biol* 2015;**218**:134–9.
62. Waddington CH. Epigenetics and evolution. *Symp Soc Exp Biol* 1953;**7**:186–99.
63. Jablonka E. Genes as followers in evolution – a post-synthesis synthesis? *Biol Philos* 2006;**21**:143–54.
64. Quina AS, Buschbeck M, Di Croce L. Chromatin structure and epigenetics. *Biochem Pharmacol* 2006;**72**:1563–9.
65. Sibbritt T, Patel HR, Preiss T. Mapping and significance of the mRNA methylome. *Wiley Interdiscip Rev RNA* 2013;**4**:397–422.
66. Sharma A. Transgenerational epigenetics: integrating soma to germline communication with gametic inheritance. *Mech Ageing Dev* 2017;**163**:15–22.
67. Skinner MK, Guerrero-Bosagna C, Haque MM. Environmentally induced epigenetic transgenerational inheritance of sperm epimutations promote genetic mutations. *Epigenetics* 2015;**10**:762–71.
68. West-Eberhard MJ. *Developmental Plasticity and Evolution*. New York: Oxford University Press, 2003, 816.
69. Banta JA, Richards CL. Quantitative epigenetics and evolution. *Heredity* 2018;**121**:210–24.
70. Vogt G. Epigenetic variation in animal populations: sources, extent, phenotypic implications, and ecological and evolutionary relevance. *J Biosci* 2021;**46**:24.
71. McCarrey JR, Lehle JD, Raju SS *et al.* A novel aspect of epigenetic transgenerational inheritance promoting genome instability. *PLoS One* 2016;**11**:1–15, e0168038.

72. Jiang C, Mithani A, Belfield EJ *et al.* Environmentally responsive genome-wide accumulation of de novo Arabidopsis thaliana mutations and epimutations. *Genome Res* 2014;**24**:1821–9.
73. Yao N, Schmitz RJ, Johannes F. Epimutations define a fast-ticking molecular clock in plants. *Trends Genet* 2021;**37**:699–710.
74. Anway MD, Cupp AS, Uzumcu M *et al.* Epigenetic transgenerational actions of endocrine disruptors and male fertility. *Science* 2005;**308**:1466–9.
75. Gapp K, Jawaid A, Sarkies P *et al.* Implication of sperm RNAs in transgenerational inheritance of the effects of early trauma in mice. *Nat Neurosci* 2014;**17**:667–9.
76. Jirtle RL, Skinner MK. Environmental epigenomics and disease susceptibility. *Nat Rev Genet* 2007;**8**:253–62.
77. Cubas P, Vincent C, Coen E. An epigenetic mutation responsible for natural variation in floral symmetry. *Nature* 1999;**401**:157–61.
78. Skinner MK. Environmental stress and epigenetic transgenerational inheritance. *BMC Med* 2014;**12**:153.
79. Flatscher R, Frajman B, Schonswetter P *et al.* Environmental heterogeneity and phenotypic divergence: can heritable epigenetic variation aid speciation? *Genet Res Int* 2012;**2012**:698421.
80. Rebollo R, Horard B, Hubert B *et al.* Jumping genes and epigenetics: towards new species. *Gene* 2010;**454**:1–7.
81. Jablonka E, Lamb MJ. *Evolution in Four Dimensions*, revised edn. Cambridge, MA: MIT Press, 2014.
82. Crews D, Gore AC, Hsu TS *et al.* Transgenerational epigenetic imprints on mate preference. *Proc Natl Acad Sci U S A* 2007;**104**:5942–6.
83. Seisenberger S, Peat JR, Reik W. Conceptual links between DNA methylation reprogramming in the early embryo and primordial germ cells. *Curr Opin Cell Biol* 2013;**25**:281–8.
84. Burdge GC, Hoile SP, Uller T *et al.* Progressive, transgenerational changes in offspring phenotype and epigenotype following nutritional transition. *PLoS One* 2011;**6**:e28282.
85. Pembrey ME, Bygren LO, Kaati G *et al.* Sex-specific, male-line transgenerational responses in humans. *Eur J Hum Genet* 2006;**14**:159–66.
86. Song J, Irwin J, Dean C. Remembering the prolonged cold of winter. *Curr Biol* 2013;**23**:R807–11.
87. Skinner MK. What is an epigenetic transgenerational phenotype? F3 or F2. *Reprod Toxicol* 2008;**25**:2–6.
88. Sarkies P. Molecular mechanisms of epigenetic inheritance: possible evolutionary implications. *Semin Cell Dev Biol* 2020;**97**:106–15.
89. Vogt G. Stochastic developmental variation, an epigenetic source of phenotypic diversity with far-reaching biological consequences. *J Biosci* 2015;**40**:159–204.
90. Angers B, Perez M, Menicucci T *et al.* Sources of epigenetic variation and their applications in natural populations. *Evol Appl* 2020;**13**:1262–78.
91. Herman JJ, Spencer HG, Donohue K *et al.* How stable 'should' epigenetic modifications be? Insights from adaptive plasticity and bet hedging. *Evolution* 2014;**68**:632–43.
92. Hu J, Barrett RDH. Epigenetics in natural animal populations. *J Evol Biol* 2017;**30**:1612–32.
93. Skinner MK, Anway SMI, Gore AC *et al.* Transgenerational epigenetic programming of the brain transcriptome and anxiety behavior. *PLoS One* 2008;**3**:1–11, e3745.
94. Darwin C. *The Varriation of Animals and Plants under Domestication*. London: John Murray, 1868.
95. Jenkins F. The origins of species. *North Br Rev* 1867;**46**:277–318.
96. Guerrero-Bosagna C, Settles M, Lucker B *et al.* Epigenetic transgenerational actions of vinclozolin on promoter regions of the sperm epigenome. *PLoS One* 2010;**5**:1–17, e13100.
97. Hirsch S, Baumberger R, Grossniklaus U. Epigenetic variation, inheritance, and selection in plant populations. *Cold Spring Harb Symp Quant Biol* 2012;**77**:97–104.
98. Bossdorf O, Richards CL, Pigliucci M. Epigenetics for ecologists. *Ecol Lett* 2008;**11**:106–15.
99. Richards CL, Bossdorf O, Verhoeven KJ. Understanding natural epigenetic variation. *New Phytol* 2010;**187**:562–4.
100. Becker C, Weigel D. Epigenetic variation: origin and transgenerational inheritance. *Curr Opin Plant Biol* 2012;**15**:562–7.
101. Aiken CE, Ozanne SE. Transgenerational developmental programming. *Hum Reprod Update* 2014;**20**:63–75.
102. Vogt G. Facilitation of environmental adaptation and evolution by epigenetic phenotype variation: insights from clonal, invasive, polyploid, and domesticated animals. *Environ Epigenet* 2017;**3**:dvx002.
103. Sudan J, Raina M, Singh R. Plant epigenetic mechanisms: role in abiotic stress and their generational heritability. *3 Biotech* 2018;**8**:172.
104. Miryeganeh M, Saze H. Epigenetic inheritance and plant evolution. *Popul Ecol* 2019;**62**:17–27.
105. Quadrana L, Colot V. Plant transgenerational epigenetics. *Annu Rev Genet* 2016;**50**:467–91.
106. Wilschut RA, Oplaat C, Snoek LB *et al.* Natural epigenetic variation contributes to heritable flowering divergence in a widespread asexual dandelion lineage. *Mol Ecol* 2016;**25**:1759–68.
107. Ferreira de Carvalho J, Oplaat C, Pappas N *et al.* Heritable gene expression differences between apomictic clone members in Taraxacum officinale: insights into early stages of evolutionary divergence in asexual plants. *BMC Genomics* 2016;**17**:203.
108. Schmid MW, Heichinger C, Coman Schmid D *et al.* Contribution of epigenetic variation to adaptation in Arabidopsis. *Nat Commun* 2018;**9**:4446.
109. Luo X, Ou Y, Li R *et al.* Maternal transmission of the epigenetic 'memory of winter cold' in Arabidopsis. *Nat Plants* 2020;**6**:1211–8.
110. Rechavi O, Minevich G, Hobert O. Transgenerational inheritance of an acquired small RNA-based antiviral response in C. elegans. *Cell* 2011;**147**:1248–56.
111. Greer EL, Maures TJ, Ucar D *et al.* Transgenerational epigenetic inheritance of longevity in Caenorhabditis elegans. *Nature* 2011;**479**:365–71.
112. Fabrizio P, Garvis S, Palladino F. Histone methylation and memory of environmental stress. *Cells* 2019;**8**:339.
113. Rechavi O, Lev I. Principles of transgenerational small RNA inheritance in Caenorhabditis elegans. *Curr Biol* 2017;**27**:R720–30.
114. Carneiro VC, Lyko F. Rapid epigenetic adaptation in animals and its role in invasiveness. *Integr Comp Biol* 2020;**60**:267–74.
115. Riyahi S, Vilatersana R, Schrey AW *et al.* Natural epigenetic variation within and among six subspecies of the house sparrow, Passer domesticus. *J Exp Biol* 2017;**220**:4016–23.
116. Sheldon EL, Schrey A, Andrew SC *et al.* Epigenetic and genetic variation among three separate introductions of the house sparrow (Passer domesticus) into Australia. *R Soc Open Sci* 2018;**5**:172185.
117. Thorson JLM, Smithson M, Beck D *et al.* Epigenetics and adaptive phenotypic variation between habitats in an asexual snail. *Sci Rep* 2017;**7**:14139.
118. Thorson JLM, Smithson M, Sadler-Riggleman I *et al.* Regional epigenetic variation in asexual snail populations among urban and rural lakes. *Environ Epigenet* 2019;**5**:dvz020.

119. Massicotte R, Angers B. General-purpose genotype or how epigenetics extend the flexibility of a genotype. *Genet Res Int* 2012;**2012**:317175.
120. Leung C, Breton S, Angers B. Facing environmental predictability with different sources of epigenetic variation. *Ecol Evol* 2016;**6**:5234–45.
121. Kelley JL, Tobler M, Beck D *et al.* Epigenetic inheritance of DNA methylation changes in fish living in hydrogen sulfide-rich springs. *Proc Natl Acad Sci U S A* 2021;**118**:e2014929118.
122. Skinner MK, Guerrero-Bosagna C, Haque MM *et al.* Epigenetics and the evolution of Darwin's finches. *Genome Biol Evol* 2014;**6**:1972–89.
123. McNew SM, Beck D, Sadler-Riggleman I *et al.* Epigenetic variation between urban and rural populations of Darwin's finches. *BMC Evol Biol* 2017;**17**:183.
124. Nilsson E, Sadler-Riggleman I, Beck D *et al.* Differential DNA methylation in somatic and sperm cells of hatchery versus wild (natural-origin) steelhead trout populations. *Environ Epigenet* 2021;**7**:1–17, dvab002.
125. Guillette LJ Jr., Parrott BB, Nilsson E *et al.* Epigenetic programming alterations in alligators from environmentally contaminated lakes. *Gen Comp Endocrinol* 2016;**238**:4–12.
126. Legoff L, D'Cruz SC, Tevosian S *et al.* Transgenerational inheritance of environmentally induced epigenetic alterations during mammalian development. *Cells* 2019;**8**:1559.
127. Jaeger J, Monk N. Bioattractors: dynamical systems theory and the evolution of regulatory processes. *J Physiol* 2014;**592**:2267–81.
128. Klironomos FD, Berg J, Collins S. How epigenetic mutations can affect genetic evolution: model and mechanism. *BioEssays* 2013;**35**:571–8.
129. Bonduriansky R, Day T. Nongenetic inheritance and the evolution of costly female preference. *J Evol Biol* 2013;**26**:76–87.
130. Zeh JA, Zeh DW. Maternal inheritance, epigenetics and the evolution of polyandry. *Genetica* 2008;**134**:45–54.
131. Hauser MT, Aufsatz W, Jonak C *et al.* Transgenerational epigenetic inheritance in plants. *Biochim Biophys Acta* 2011; **1809**:459–68.
132. Lamke J, Baurle I. Epigenetic and chromatin-based mechanisms in environmental stress adaptation and stress memory in plants. *Genome Biol* 2017;**18**:124.
133. Chang YN, Zhu C, Jiang J *et al.* Epigenetic regulation in plant abiotic stress responses. *J Integr Plant Biol* 2020;**62**:563–80.
134. Skvortsova K, Iovino N, Bogdanovic O. Functions and mechanisms of epigenetic inheritance in animals. *Nat Rev Mol Cell Biol* 2018;**19**:774–90.
135. van Otterdijk SD, Michels KB. Transgenerational epigenetic inheritance in mammals: how good is the evidence? *FASEB J* 2016;**30**:2457–65.
136. Xu Q, Xie W. Epigenome in early mammalian development: inheritance, reprogramming and establishment. *Trends Cell Biol* 2018;**28**:237–53.
137. Wang Y, Liu H, Sun Z. Lamarck rises from his grave: parental environment-induced epigenetic inheritance in model organisms and humans. *Biol Rev Camb Philos Soc* 2017;**92**: 2084–111.
138. Nilsson EE, Ben Maamar M, Skinner MK. Environmentally induced epigenetic transgenerational inheritance and the Weismann barrier: the dawn of neo-Lamarckian theory. *J Dev Biol* 2020;**8**:28.
139. Bonduriansky R, Crean AJ, Day T. The implications of nongenetic inheritance for evolution in changing environments. *Evol Appl* 2012;**5**:192–201.
140. Chatterjee A, Stockwell PA, Rodger EJ *et al.* Genome-wide DNA methylation map of human neutrophils reveals widespread inter-individual epigenetic variation. *Sci Rep* 2015; **5**:17328.
141. Heyn H, Moran S, Hernando-Herraez I *et al.* DNA methylation contributes to natural human variation. *Genome Res* 2013;**23**:1363–72.
142. Demetriou CA, van Veldhoven K, Relton C *et al.* Biological embedding of early-life exposures and disease risk in humans: a role for DNA methylation. *Eur J Clin Invest* 2015;**45**:303–32.
143. Kuhn TS. *The Structure of Scientific Revolutions*. Chicago, IL, USA: University of Chicago Press, 1962.

"Epigenetics and Systems Biology"

Spring 2025 (Odd Years) – Course Syllabus
Biol 476/576 Undergraduate/Graduate Course (3 Credit)
SLN: (476) – 06655, (576) – 06656
Time - Tuesday and Thursday 10:35 am-11:50 am
Course Lectures recorded on Canvas/Panopto and Discussion Sessions live on WSU Zoom for all campuses (Hybrid Course)
Course Director - Michael Skinner, Abelson Hall 507, 335-1524, skinner@wsu.edu
Co-Instructor – Eric Nilsson, Abelson Hall 507, 225-1835, nilsson@wsu.edu
Learning Objective - The objective of the course is to learn the concept and critical role of systems to understand molecular, cell, development, physiology and evolutionary aspects of biology with a focus on the role of epigenetics in systems biology.
Schedule/Lecture Outline –

Week 1	January 7 & 9	Systems Biology (History/ Definitions/ Theory)
Week 2	January 14 & 16	Systems Biology (Networks & Emergence)
Week 3	January 21 & 23	Systems Biology (Components: DNA to Phenotype)
Week 4	Jan 28 & 30	Systems Biology (Genomics / Technology)
Week 5	February 4 & 6	Epigenetics (History / Molecular Processes)
Week 6	February 11 & 13	Epigenetics (Molecular Processes & Integration)
Week 7	February 18 & 20	Epigenetics (Genomics and Technology)
Week 8	Feb 25 & 27	Cell & Developmental Biology
Week 9	March 4 & 6	Epigenetics of Cell & Developmental Biology (& Midterm Exam)
Week 10	**March 10 – 14**	**Spring Break**
Week 11	March 18 & 20	Environmental Impact on Biology
Week 12	March 25 & 27	Environmental Epigenetics
Week 13	April 1 & 3	Disease Etiology
Week 14	April 8 & 10	Epigenetics & Disease Etiology
Week 15	April 15 & 17	Evolutionary Biology & Genetics
Week 16	April 22 & 24	Epigenetics & Evolutionary Biology
Week 17	Finals Week	Grant Review/ Study Section Meeting (& Final Exam)

Spring 2025 – Epigenetics and Systems Biology
Lecture Outline (Epigenetics and Evolution)
Michael K. Skinner – Biol 476/576
Weeks 15 and 16 (April 15 & 22)

Epigenetics and Evolution

- Darwinian Evolution
- Lamarck's Environment and Evolutionary Biology
- History Environment and Evolutionary Biology
- Waddington Environment and Evolutionary Biology
- Molecular and Genetic Aspects of Evolutionary Biology
- Hopeful Monsters and Evolutionary Biology
- Epigenetics and Evolutionary Biology
- Sociobiology and Evolutionary Biology
- Sexual Selection and Evolutionary Biology
- Epigenetic Transgenerational Inheritance and Evolutionary Biology
- Summary Epigenetics and Evolutionary Biology

Required Reading

Laland, et al. (2014) Does evolutionary theory need a rethink? Nature 54:161-4

Skinner MK (2015) Environmental Epigenetics and a Unified Theory of the Molecular Aspects of Evolution: A Neo-Lamarckian Concept that Facilitates Neo-Darwinian Evolution. Genome Biol Evol. 26;7(5):1296-302

Skinner MK, Nilsson EE. (2021) Role of environmentally induced epigenetic transgenerational inheritance in evolutionary biology: Unified Evolution Theory. Environ Epigenet. 7(1):dvab012.

Books

Jablonka, E. & Lamb, M.J. (2014). Evolution in Four Dimensions: Genetic, Epigenetic, Behavioral and Symbolic Variation in the History of Life. MIT Press, Cambridge.

Spring 2025 – Epigenetics and Systems Biology
Discussion Session (Evolutionary Biology)
Michael K. Skinner – Biol 476/576
Week 15 (April 17)

Epigenetics and Evolutionary Biology

Primary Papers

1. Skinner, et al. (2014) Genome Biology and Evolution 6:1972-1989. (PMID: 25062919)
2. Anastasiadi D, et al. (2021) Trends Ecol Evol. 36(12):1124-1140. (PMID: 34489118)
3. Sadler KC. (2022) Bioessays. 20:e2200036. (PMID: 36403219)

Discussion

Student 37 – Ref #1 above

- What was the model system and experimental design?
- What epigenetic observations were provided and how might environmental epigenetics impact evolution?
- Is this a Lamarckian contribution to evolution?

Student 38 – Ref #2 above

- What was the role of epigenetics in phenotypic variation?
- What epigenetic differences were observed between the species?
- What is the integration of genetics, epigenetics and evolution suggested?

Student 1 – Ref #3 above

- What are the model systems and experimental data considered?
- What phylogeny associations were observed?
- How could epigenetics be involved in the potential adaptive response?

Spring 2025 – Epigenetics and Systems Biology
Discussion Session (Epigenetics and Evolutionary Biology)
Michael K. Skinner – Biol 476/576
Week 16 (April 24)

Epigenetics and Evolutionary Biology

Primary Papers

1. Luo, et al. (2020) Cell Reports 33:108306. (PMID: 33113358)
2. Aagaard, et al. (2020) Mol Ecol. (22):5765-5783. (PMID 36112081)
3. McNew, et al. (2017) BMC Evolution 17(1):183. (PMID: 28835203)

Discussion

Student 3 – Ref #1 above

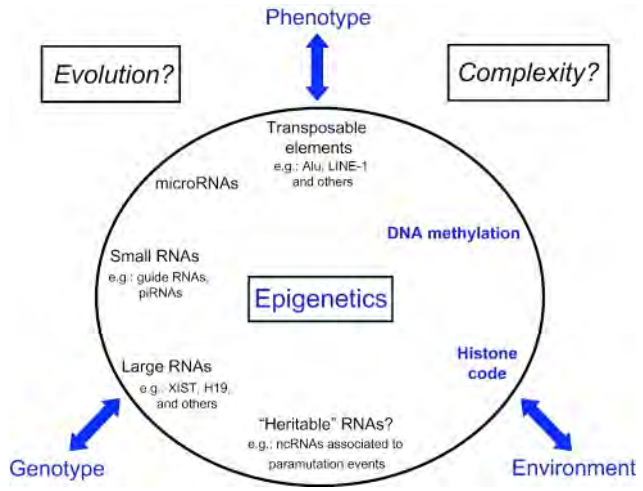
- What was the experimental design and model system?
- What epigenetic process and gene network effects were observed?
- Does this provide evidence for environmental induction of epigenetic alterations in a gene network for evolutionary adaptation?

Student 4 – Ref #2 above

- What is the model system, phenotypic change, and environmental factor?
- What epigenetic change was observed?
- How did the environment, epigenetics and genetics integrate?

Student 5 – Ref #3 above

- What was the experimental design and approach?
- What molecular alterations were observed in what cell types?
- What molecular mechanism can promote rapid evolutionary events?



Darwinian Evolutionary Biology

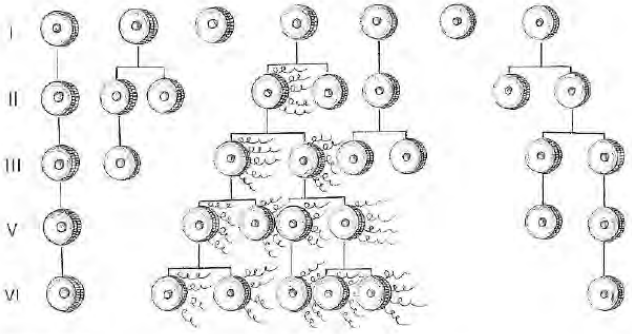
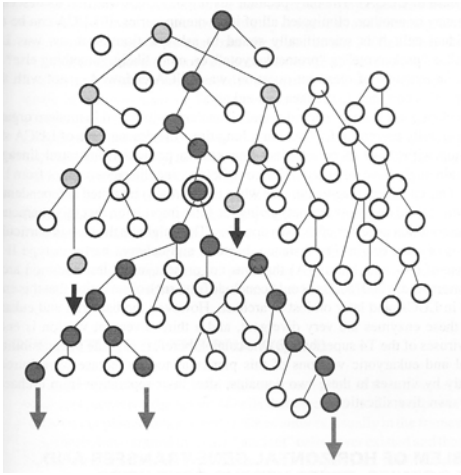


Figure 1.1
Universal Darwinism: the frequency of the hairy entity, which first appears in generation II, increases in subsequent generations because it survives better and multiplies more than its competitors.



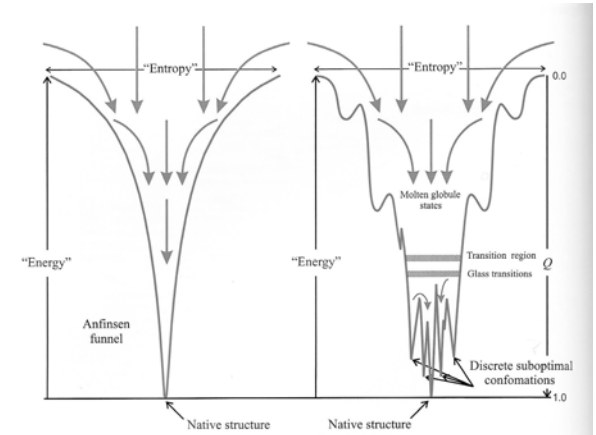
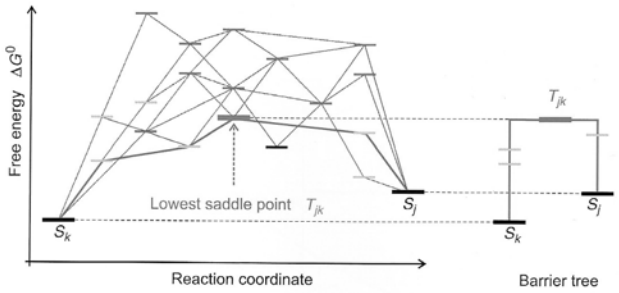


Figure 7.2 (See page 128 for text discussion).



Classical Darwinism: Natural selection

Classical Darwinian emphasis on natural selection can be summarized in a few sentences:

1. There is variation among the individual organisms that make up a population of a species.
2. There is an enormous amount of death, and most individuals will not survive to reproduce.
3. Death is selective. Those individuals that best fit into the environment they encounter are more likely to survive; those that do not fit the environment well are usually eliminated.
4. When those individuals that survive reproduce, their progeny have a high likelihood of inheriting the variations that allowed their parents to survive. If individuals who carry those variations continue to be favored (selected), over time this natural selection will alter the overall characteristics of the population.
5. When populations of a species become reproductively isolated (i.e., separated in such a way that members of one population cannot mate with members of another*), each population can randomly acquire a distinct and separate suite of variations. If the environmental conditions faced by the isolated populations are different, different variations will be selected. Anatomical and physiological

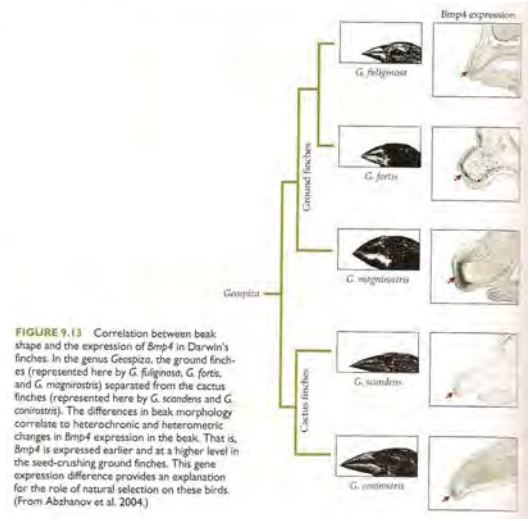


FIGURE 9.13 Correlation between beak shape and the expression of *Bmp4* in Darwin's finches. In the genus *Geospiza*, the ground finches (represented here by *G. fuliginosa*, *G. fortis*, and *G. magnirostris*) separated from the cactus finches (represented here by *G. scandens* and *G. conirostris*). The differences in beak morphology correlate to heterochronic and heteromeric changes in *Bmp4* expression in the beak. That is, *Bmp4* is expressed earlier and at a higher level in the seed-crushing ground finches. This gene expression difference provides an explanation for the role of natural selection on these birds. (From Abzhanov et al. 2004.)

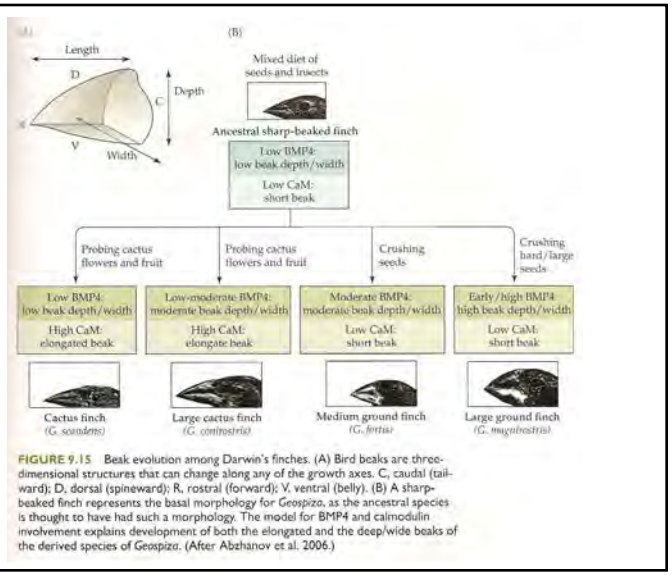


FIGURE 9.15 Beak evolution among Darwin's finches. (A) Bird beaks are three-dimensional structures that can change along any of the growth axes. C, caudal (tail-ward); D, dorsal (spineward); R, rostral (forward); V, ventral (belly). (B) A sharp-beaked finch represents the basal morphology for *Geospiza*, as the ancestral species is thought to have had such a morphology. The model for BMP4 and calmodulin involvement explains development of both the elongated and the deep/wide beaks of the derived species of *Geospiza*. (After Abzhanov et al. 2006.)

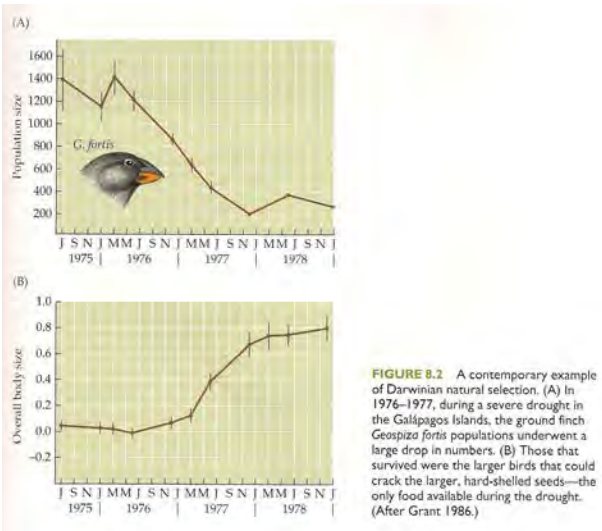


FIGURE 8.2 A contemporary example of Darwinian natural selection. (A) In 1976–1977, during a severe drought in the Galápagos Islands, the ground finch *Geospiza fortis* populations underwent a large drop in numbers. (B) Those that survived were the larger birds that could crack the larger, hard-shelled seeds—the only food available during the drought. (After Grant 1986.)

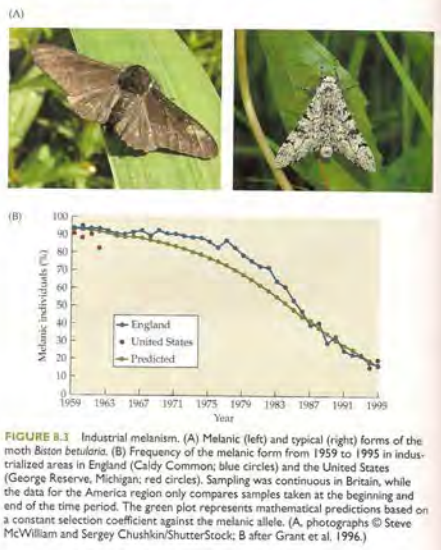
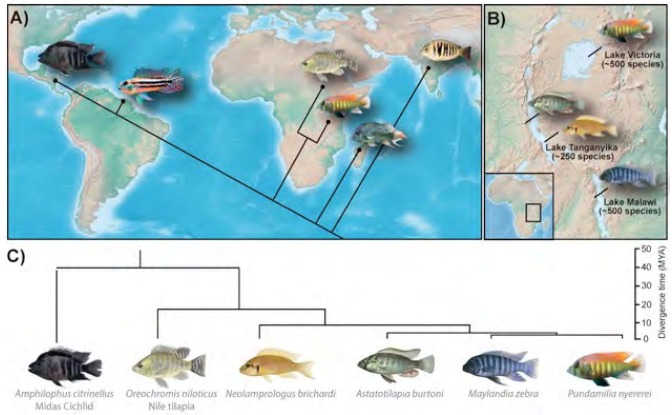


FIGURE 8.3 Industrial melanism. (A) Melanic (left) and typical (right) forms of the moth *Biston betularia*. (B) Frequency of the melanic form from 1959 to 1995 in industrialized areas in England (Caldy Common; blue circles) and the United States (George Reserve, Michigan; red circles). Sampling was continuous in Britain, while the data for the America region only compares samples taken at the beginning and end of the time period. The green plot represents mathematical predictions based on a constant selection coefficient against the melanic allele. (A, photographs © Steve McWilliam and Sergey Chushkin/ShutterStock; B after Grant et al. 1996.)



Overview of cichlid fishes. A: Worldwide geographic distribution of cichlids with representatives from India and Madagascar forming the most basal lineages and the monophyletic African and South and Central American lineages as sister-groups. B: The cichlids' center of biodiversity is East Africa, where more than 1,500 cichlid species are recognized. Estimated species numbers for the big lakes Victoria, Tanganyika and Malawi are given in brackets. C: Phylogenetic tree of the six cichlid species from Central America (A. citrinellus) and Africa with high-quality genome drafts. Divergence times are based on the lower timescale of [51].

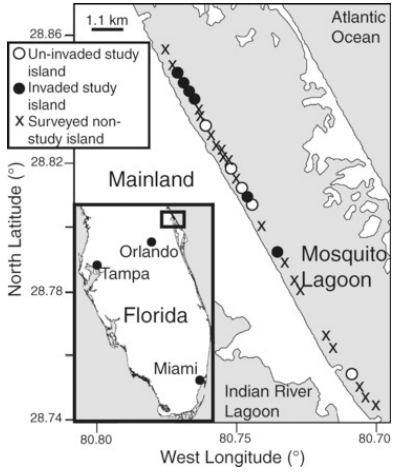
Rapid evolution of a native species following invasion by a congener.

Science. 2014 Oct 24;346(6208):463-6.

Stuart YE, Campbell TS, Hohenlohe PA, Reynolds RG, Revell LJ, Losos JB.

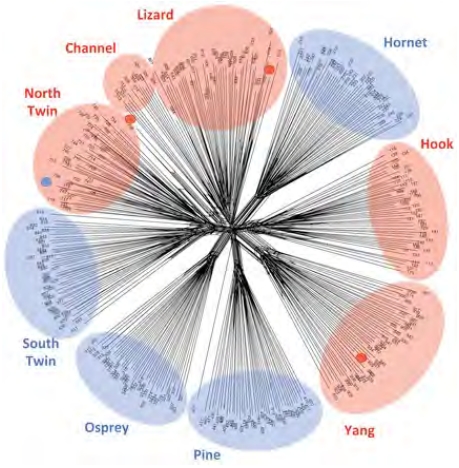
Abstract

In recent years, biologists have increasingly recognized that evolutionary change can occur rapidly when natural selection is strong; thus, real-time studies of evolution can be used to test classic evolutionary hypotheses directly. One such hypothesis is that negative interactions between closely related species can drive phenotypic divergence. Such divergence is thought to be ubiquitous, though well-documented cases are surprisingly rare. On small islands in Florida, we found that the lizard Anolis carolinensis moved to higher perches following invasion by Anolis sagrei and, in response, adaptively evolved larger toepads after only 20 generations. These results illustrate that interspecific interactions between closely related species can drive evolutionary change on observable time scales.



2010 study islands along the Intracoastal Waterway.

Anolis carolinensis inhabits all study islands. Six study islands were invaded by *A. sagrei* sometime between 1995 and 2010 (closed circles), and five study islands remain un-invaded today (open circles). Nineteen additional non–study islands were surveyed ["x"; (12)]; 17 of these contained *A. carolinensis* and were invaded by *A. sagrei*; and two were empty of both species.

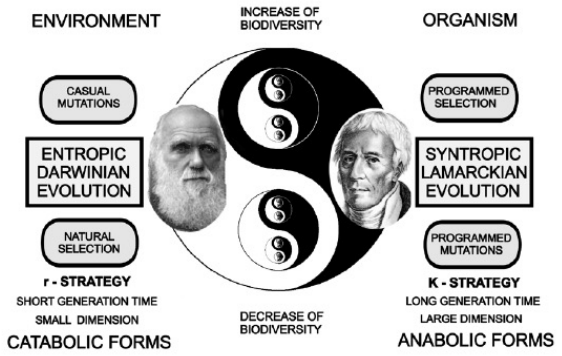


Neighbor-net analysis of genetic distance for *A. carolinensis* individuals from invaded (red) and un-invaded (blue) islands (12).

Small shaded areas enclose individuals that do not cluster with their own island; the color of these areas represents invasion status of their home islands.

Lamarck's

Environment and Evolutionary Biology

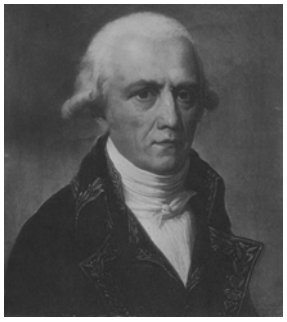


Lamarckian inheritance was based on physiology, behavior, and phenotypic plasticity: if you used your muscles, they grew bigger. Moreover, such muscular changes would be passed on to subsequent generations, so that the offspring of run-

Lamarck concludes:

> Nature has produced all the species of animals in succession, beginning with the most imperfect or simplest, and ending her work with the most perfect, so as to create a gradually increasing complexity in their organisation; these animals have spread at large throughout all the habitable regions of the globe, and every species has derived from its environment the habits that we find in it and the structural modifications which observation shows us.

Lamarck, evolution, and the inheritance of acquired characters.
Genetics. 2013 Aug;194(4):793-805.
Burkhardt RW Jr.



Scientists are not always remembered for the ideas they cherished most. In the case of the French biologist Jean-Baptiste Lamarck, his name since the end of the nineteenth century has been tightly linked to the idea of the inheritance of acquired characters. This was indeed an idea that he endorsed, but he did not claim it as his own nor did he give it much thought. He took pride instead in advancing the ideas that (1) nature produced successively all the different forms of life on earth, and (2) environmentally induced behavioral changes lead the way in species change. This article surveys Lamarck's ideas about organic change, identifies several ironies with respect to how his name is commonly remembered, and suggests that some historical justice might be done by using the adjective "Lamarckian" to denote something more (or other) than a belief in the inheritance of acquired characters.

Is Lamarckian evolution relevant to medicine?

Handel AE, Ramagopalan SV.

BMC Med Genet. 2010 May 13;11:73

Abstract

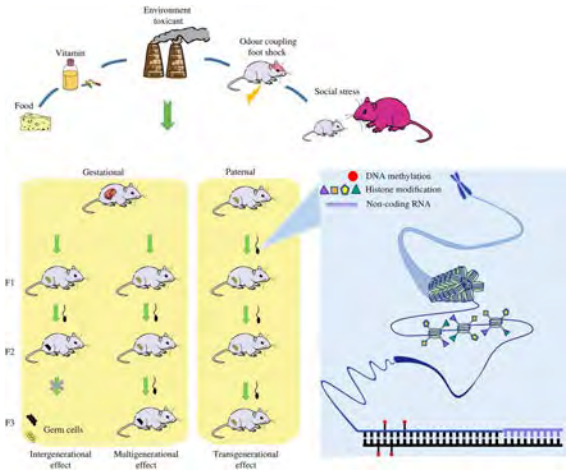
BACKGROUND: 200 years have now passed since Darwin was born and scientists around the world are celebrating this important anniversary of the birth of an evolutionary visionary. However, the theories of his colleague Lamarck are treated with considerably less acclaim. These theories centre on the tendency for complexity to increase in organisms over time and the direct transmission of phenotypic traits from parents to offspring.

DISCUSSION: Lamarckian concepts, long thought of no relevance to modern evolutionary theory, are enjoying a quiet resurgence with the increasing complexity of epigenetic theories of inheritance. There is evidence that epigenetic alterations, including DNA methylation and histone modifications, are transmitted transgenerationally, thus providing a potential mechanism for environmental influences to be passed from parents to offspring: Lamarckian evolution. Furthermore, evidence is accumulating that epigenetics plays an important role in many common medical conditions.

SUMMARY: Epigenetics allows the peaceful co-existence of Darwinian and Lamarckian evolution. Further efforts should be exerted on studying the mechanisms by which this occurs so that public health measures can be undertaken to reverse or prevent epigenetic changes important in disease susceptibility. Perhaps in 2059 we will be celebrating the anniversary of both Darwin and Lamarck.

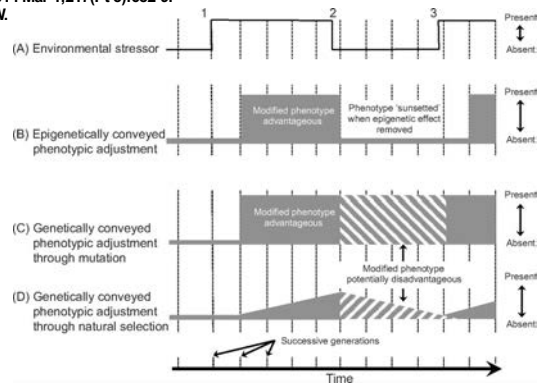
Lamarck rises from his grave: parental environment-induced epigenetic inheritance in model organisms and humans.

Biol Rev Camb Philos Soc. 2017 Nov;92(4):2084-2111.
Wang Y, Liu H, Sun Z



Epigenetics as a source of variation in comparative animal physiology - or - Lamarck is lookin' pretty good these days.

J Exp Biol. 2014 Mar 1;217(Pt 5):682-9.
Burggren WW.



Conceptual diagram of the various time courses for development and/or loss of phenotypic characteristics in response to environmental stressors. (A) In this scheme, which is over-simplified by mainly depicting responses as 'on–off' rather than graded, an environmental stressor intermittently appears in a non-graded fashion over multiple successive generations (indicated by dashed vertical lines). (B) Epigenetically conveyed phenotypic adjustment appears within a generation of the onset of the environmental stressor (at 1), and conveys additional fitness upon the animal. However, when the environmental stressor declines or disappears (2), the epigenetically maintained phenotype (with its associated advantages but also its costs) disappears, to return once again when the environmental stressor returns (3). In contrast, a phenotypic modification arising by mutation (C) or by natural selection (D) persists in the population even with the disappearance of the environmental stressor at 2.

History

Environment and Evolutionary Biology

In the 16th-17th centuries the central question was how a fully integrated multicellular organism develops from a single cell (the fertilized egg). *Preformationism* believed that adult features were present fully formed in the egg and simply unfolded during growth. *Epigenesis* held that traits emerge as a consequence of the progressive interaction of the constituent parts of the zygote.

Environmentally Induced Epigenetic Transgenerational Inheritance and the Weismann Barrier: The Dawn of Neo-Lamarckian Theory

Nilsson EE, Ben Maamar M, Skinner MK.
J Dev Biol. 2020 Dec 4;8(4):28.

Table 1. Weismann's Germ Plasm Theory Components.

(1)	Germ cells are the only cells to transmit molecular heredity information between generations.
(2)	Germ cells are the only cells with a full set of instructions (germ plasm) for development of the next generation. The determinants of germ plasm are divided up among the somatic cells of the embryo. The full set of instructions is kept intact by germ cells from generation to generation by the continuity of the germ line.
(3)	Germ cell molecular determinants are not impacted by changes in somatic cells (germ line—somatic barrier).




Kammerer Weiss von Frisch Steinach

Hans Przibram, Director, Biologische Versuchsanstalt
Institute of Experimental Biology or 'Vivarium'
1903-1938. Spent remainder of life (to 1944) in Theresianstadt.

State-of-the-art research on experimental developmental biology, including first constant temperature rooms. Focus of Institute was to derive the laws (statistical regularities or patterns) governing development of individual organism and its relationship to the environment. Sought to explore a 'third way' between determinism and chance by capturing "the complexity of the interaction between the organism and its environment". In other words, systems biology and the concept of emergence.

Paul Alfred Weiss

Doctoral thesis (1922) under Hans Prizbram on the responses of butterflies to light and gravity. Became Assistant Director of the Vivarium. Studied cell differentiation and the transplanting and reforming of connections in the nerves of limbs; used newts and frogs. Emphasized concept emergence and the idea of "plastic reactions" or the ability to change as a result of experience. Moved to the USA in 1931, published *Principles of Development* in 1939, and in 1954 he became one of the founding professors at the Rockefeller University; awarded the National Medal of Science in 1979.

Table 1.1

Type of theory	Hereditary transmission	Unit of variation	Origin of variation	Target of selection	Unit of evolution
Darwin's Darwinism	Gemmules transferred from the soma to sex cells	Gemmule	Random + induced in the soma	Individual (sometimes also the group)	The population of individuals
Weismann's neo-Darwinism	Transfer of determinants through the germ line	Determinant	Random + induced in the germ line	Individual (mainly) + determinants, cells, organs	The population of individuals, cells, or determinants
Modern Synthesis neo-Darwinism	Transfer of genes in the germ line	Genes in the germ line	Random mutation	Individual	The population of individuals
Molecular neo-Darwinism	DNA replication	DNA sequence	Random DNA changes; rarely also directed changes (see chapter 3)	Mainly the individual (also the gene, the group, lineage, and species)	Mainly the population of individuals
Selfish gene neo-Darwinism	DNA replication	DNA sequence	Random DNA changes	The gene, the individual, the group	The population of alleles of the gene

NEO-DARWINIAN EVOLUTION

Molecular and Genetic Aspects

of Evolutionary Biology

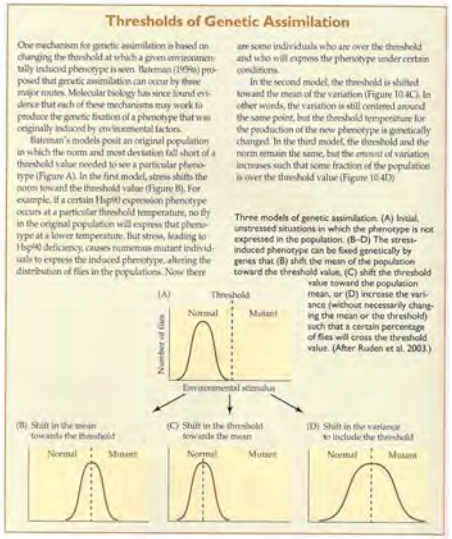
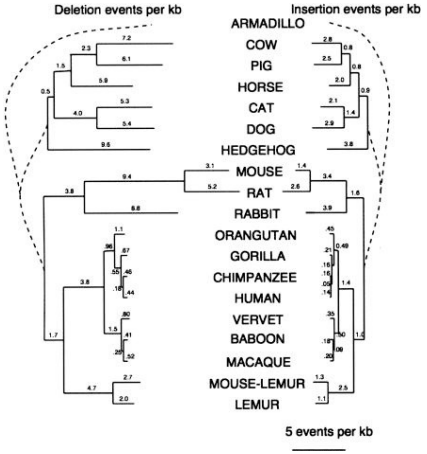


Table 9.1 Example of the Rearrangement Operations That Can Affect (a) the Gene Order or (b) the Gene Content of a Genome

Operation	Original	Target
(a) Operations affecting gene orders		
Reversal	1 2 3 4 5	1 −3 −2 4 5
Translocation	1 2 3 4 5 6 7 8 9	1 2 3 8 9 6 7 4 5
Fusion	1 2 3 4 5 6 7	1 2 3 4 5 6 7
Fission	1 2 3 4 5 6 7	1 2 3 4 5 6 7
Transposition	1 2 3 4 5 6 7 8	1 4 5 6 2 3 7 8
Block interchange (special)	1 2 3 4 5 6 7 8	1 4 5 6 2 3 7 8
Block interchange (general)	1 2 3 4 5 6 7 8	1 6 7 4 5 2 3 8
(b) Operations affecting gene contents		
Duplication	1 2 3 4 5	1 2 3 2′ 3′ 4 5
Insertion	1 2 3 4 5	1 2 3 6 4 5
Deletion	1 2 3 4 5	1 4 5

Blanchette M, Green ED, Miller W, Haussler D. (2004) Reconstructing large regions of an ancestral mammalian genome in silico. Genome Res. 14(12):2412-23.



Frequency of microdeletions (1–10 bp) (left) and microinsertions (right) during eutherian evolution. Indel rates for the branches shown with dashed lines cannot be accurately estimated. Estimates are based on a set of regions totaling about 280 kb, for which sequence data is available for all 19 mammals.

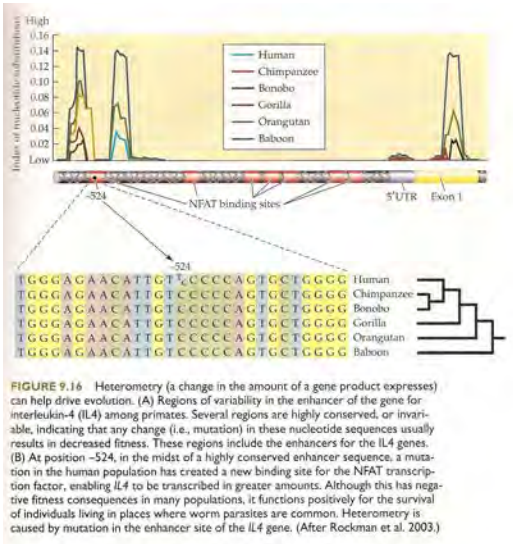


FIGURE 9.16 Heterometry (a change in the amount of a gene product expresses) can help drive evolution. (A) Regions of variability in the enhancer of the gene for interleukin-4 (IL4) among primates. Several regions are highly conserved, or invariable, indicating that any change (i.e., mutation) in these nucleotide sequences usually results in decreased fitness. These regions include the enhancers for the IL4 genes. (B) At position –524, in the midst of a highly conserved enhancer sequence, a mutation in the human population has created a new binding site for the NFAT transcription factor, enabling *IL4* to be transcribed in greater amounts. Although this has negative fitness consequences in many populations, it functions positively for the survival of individuals living in places where worm parasites are common. Heterometry is caused by mutation in the enhancer site of the *IL4* gene. (After Rockman et al. 2003.)

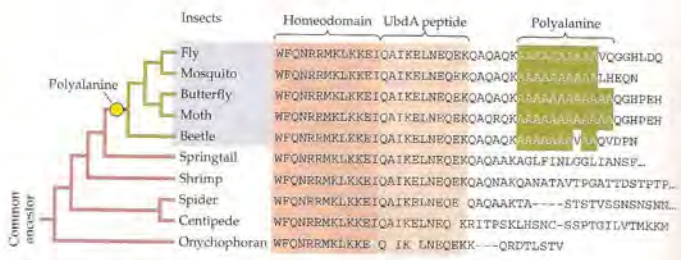


FIGURE 9.17 Changes in Ubx protein associated with the insect clade in the evolution of arthropods. Of all arthropods, only the insects have Ubx protein that is able to repress *Distal-less* gene expression and thereby inhibit abdominal legs. This ability to repress *Distal-less* is due to a mutation wherein a stretch of polyalanine residues is encoded in the carboxyl terminus of the Ubx protein. This mutation is seen only in the insect *Ubx* gene. (After Galant and Carroll 2002 and Ronshaugen et al. 2002).

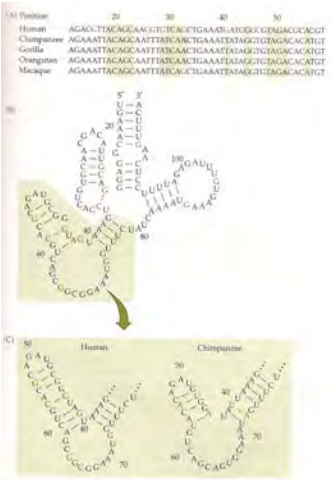


FIGURE 9.18 Molecular evolution among primates. (A) *HAR1* sequence showing sites where humans have accumulated mutations not found in other primates. (B) General secondary structure of the RNA in mammals. (C) How the folding of the chimp HAR1 and human HAR1 would differ. (After Pollard et al. 2006.)

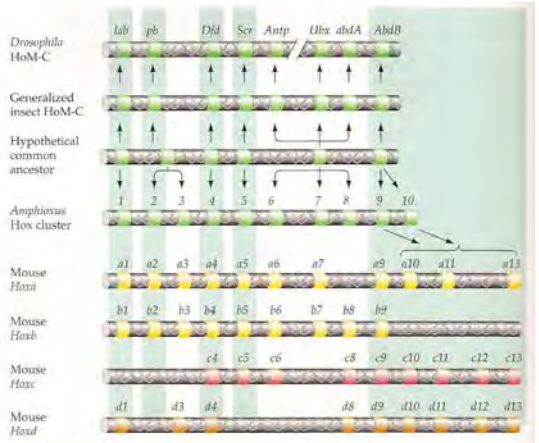


FIGURE 9.2 Postulated ancestry of the Hox genes from a hypothetical ancestor of both protostomes and deuterostomes. The deuterostome, *Amphioxus*, has only one set of Hox genes, just like the protostomes. Vertebrates, derived from an *Amphioxus*-like organism, have four Hox clusters, none of which is complete. (After Holland and Garcia-Fernández 1996.)

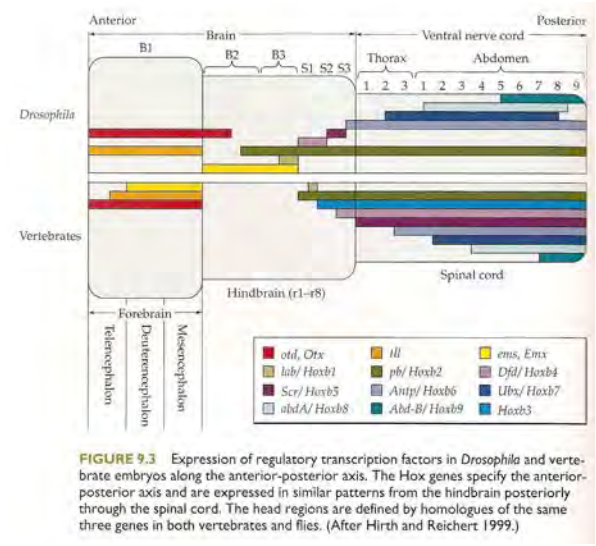


FIGURE 9.3 Expression of regulatory transcription factors in *Drosophila* and vertebrate embryos along the anterior-posterior axis. The Hox genes specify the anterior-posterior axis and are expressed in similar patterns from the hindbrain posteriorly through the spinal cord. The head regions are defined by homologues of the same three genes in both vertebrates and flies. (After Hirth and Reichert 1999.)

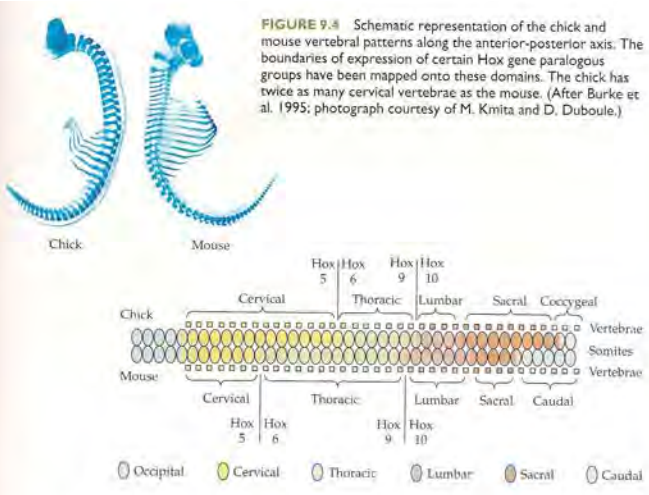


FIGURE 9.4 Schematic representation of the chick and mouse vertebral patterns along the anterior-posterior axis. The boundaries of expression of certain Hox gene paralogous groups have been mapped onto these domains. The chick has twice as many cervical vertebrae as the mouse. (After Burke et al. 1995; photograph courtesy of M. Kmita and D. Duboule.)

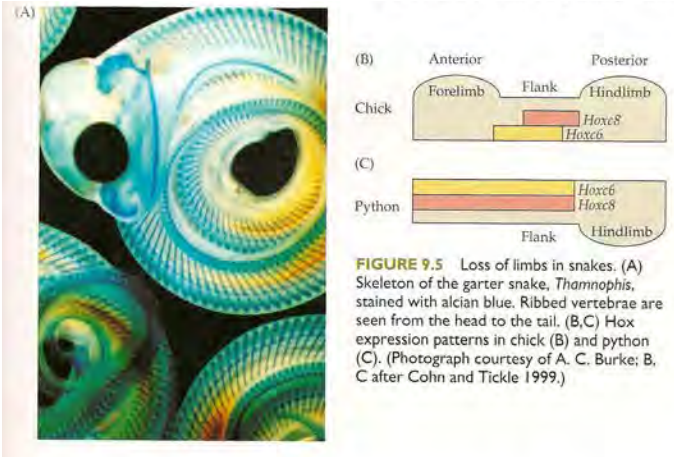


FIGURE 9.5 Loss of limbs in snakes. (A) Skeleton of the garter snake, *Thamnophis*, stained with alcian blue. Ribbed vertebrae are seen from the head to the tail. (B,C) Hox expression patterns in chick (B) and python (C). (Photograph courtesy of A. C. Burke; B, C after Cohn and Tickle 1999.)

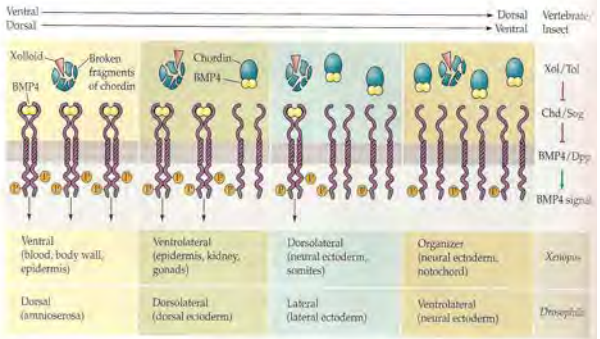
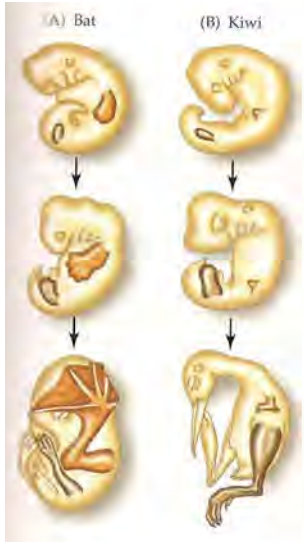


FIGURE 9.6 Homologous pathways specifying the central nervous system and the dorsal-ventral axes of flies and vertebrates. Both pathways involve a source of chordin/Sog protein (the most dorsal region of the vertebrate embryo; the most ventral region of the fly embryo) and a source of BMP4/Dpp (the ventral region of the vertebrate; the dorsal region of the fly). These two regions form antagonistic gradients. Those regions with the most chordin/Sog become central nervous tissue—on the dorsal side of the vertebrate body and on the ventral side of the fly body). The side with the BMP4/Dpp becomes epidermis. In both instances, the gradient is shaped by a constant supply of Xolloid/Tolloid protein, which degrades chordin/Sog. (After Dale and Wardle 1999.)

TABLE 9.1 Developmental regulatory genes conserved between protostomes and deuterostomes

Gene	Function	Distribution
achaete-scute group	Cell fate specification	Cnidarians, *Drosophila*, vertebrates
Bcl2/Dnib-1/ced9	Programmed cell death	*Drosophila*, nematodes, vertebrates
Caudal	Posterior differentiation	*Drosophila*, vertebrates
Delta / Xdelta-1	Primary neurogenesis	*Drosophila*, *Xenopus*
Distal-less / DLX	Appendage formation (proximal-distal axis)	Numerous phyla of protostomes and deuterostomes
Dorsal/NFκB	Immune response	*Drosophila*, vertebrates
forkhead/Fox	Terminal differentiation	*Drosophila*, vertebrates
Fringe/radical fringe	Formation of limb margin (apical ectodermal ridge in vertebrates)	*Drosophila*, chick
Hac-1/Apaf/ced 4	Programmed cell death	*Drosophila*, nematodes, vertebrates
Hox complex	Anterior-posterior patterning	Widespread among metazoans
lin-12/Notch	Cell fate specification	*C. elegans*, *Drosophila*, vertebrates
Otx-1, Otx-2/Otd, Emx-1, Emx-2/ems	Anterior patterning, cephalization	*Drosophila*, vertebrates
Pax6/eyeless; Eyes absent/eya	Anterior CNS/eye regulation	*Drosophila*, vertebrates
Polycomb group	Hox expression/cell differentiation control	*Drosophila*, vertebrates
Netrins, Slit proteins, and their receptors	Axon guidance	*Drosophila*, vertebrates
RAS	Signal transduction	*Drosophila*, vertebrates
sine oculies / Six3	Anterior CNS/eye pattern formation	*Drosophila*, vertebrates
sog / chordin, dpp / BMP4	Dorsal-ventral patterning, neurogenesis	*Drosophila*, *Xenopus*
tinman / Nkx 2-5	Heart/blood vascular system	*Drosophila*, mouse
vnd, msh	Neural tube patterning	*Drosophila*, vertebrates

Source: After Erwin 1999.



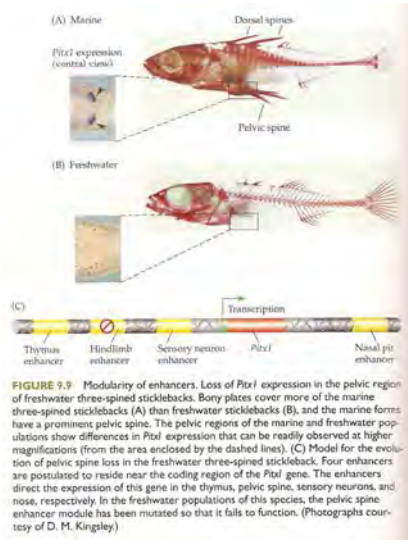


FIGURE 9.9 Modularity of enhancers. Loss of *Pitx1* expression in the pelvic region of freshwater three-spined sticklebacks. Bony plates cover more of the marine three-spined sticklebacks (A) than freshwater sticklebacks (B), and the marine forms have a prominent pelvic spine. The pelvic regions of the marine and freshwater populations show differences in *Pitx1* expression that can be readily observed at higher magnifications (from the area enclosed by the dashed lines). (C) Model for the evolution of pelvic spine loss in the freshwater three-spined stickleback. Four enhancers are postulated to reside near the coding region of the *Pitx1* gene. The enhancers direct the expression of this gene in the thymus, pelvic spine, sensory neurons, and nose, respectively. In the freshwater populations of this species, the pelvic spine enhancer module has been mutated so that it fails to function. (Photographs courtesy of D. M. Kingsley.)

FIGURE 9.10 Heterotopy exemplified by the role of BMPs in the generation of webbed feet in ducks. BMPs cause apoptosis in the interdigital webbing. Autopods of chick feet (upper row) and duck feet (lower row) are shown at similar stages. The in situ hybridizations show that while BMPs are expressed in both the chick and duck hindlimb webbing, the duck limb shows expression of Gremlin protein (arrows) in the webbing as well. Gremlin is an inhibitor of BMPs. The pattern of cell death (shown by neutral red dye accumulation) becomes distinctly different in the two species. (Photographs courtesy of J. Hurle and E. Laufer.)

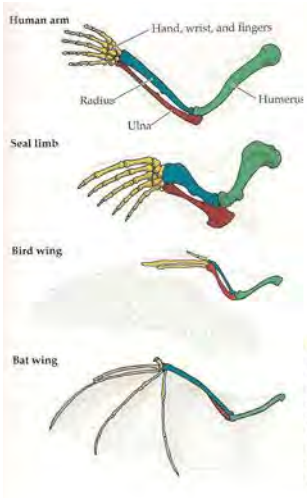
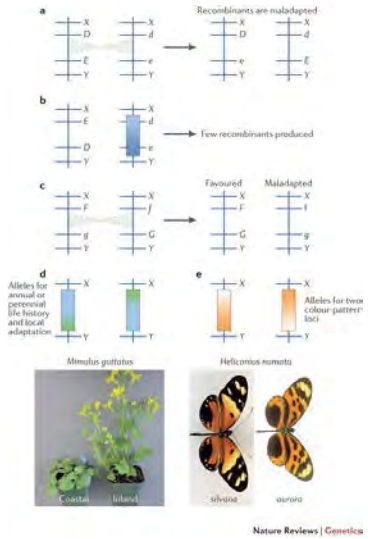
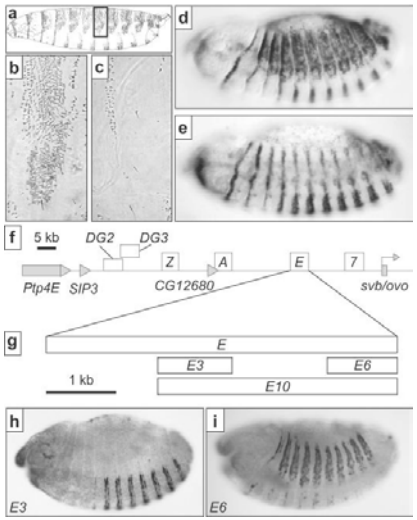


FIGURE 8.1 Homologies of structure among a human arm, a seal forelimb, a bird wing, and a bat wing. (Homologous structures are shown in the same color.) All four are homologous as forelimbs because they derive from a common tetrapod ancestor. The adaptations of bird and bat forelimbs for flight, however, evolved independently of each other, after the two lineages diverged from a common ancestor. Therefore they are homologous as forelimbs but analogous as wings.

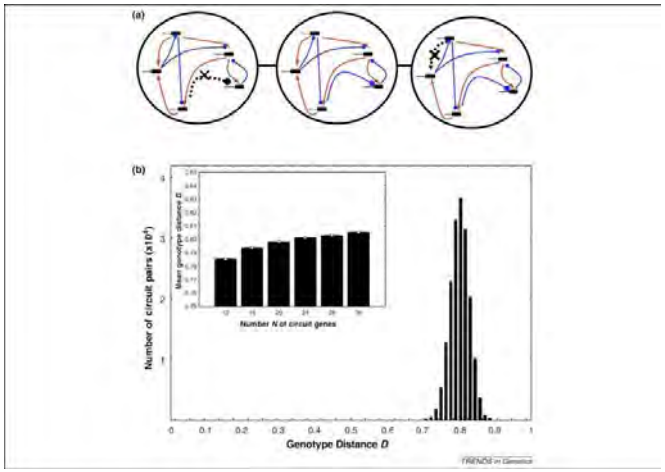


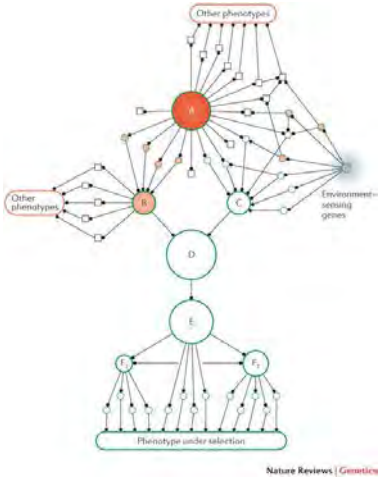
The dual nature of recombination.
a | Consider two ecologically important genes, D and E, segregating for alleles that are adapted to different environments. Alleles D and E are best suited to environment 1, and alleles e and d are best in environment 2. Finally, genes X and Y are neutral loci. Mating between DE and de can produce maladaptive haplotypes De and dE. b | An inversion on the DE haplotype will repress recombination between these loci and increase fitness of these alleles in their favoured environment. c | If alleles f and g are maladapted, then recombination between them will produce the high fitness FG haplotype. In this case, recombination aids in the emergence of adaptive haplotype FG. d | The inland, annual ecotype of Mimulus guttatus occurs in seasonally dry habitats and flowers early in the spring, whereas the sympatric coastal, perennial form is found in wetter areas and is dormant in the early spring and flowers later. Hybridization between these ecotypes would produce offspring that are less fit in either habitat. Traits that confer local adaptation to these distinct environments are located on an inversion (shown as a long rectangle) that preserves these phenotypic combinations81. e | Heliconius butterflies are a classic example of Mullerian mimicry. Many species of the genus Heliconius (for example, Heliconius numata silvana and Heliconius numata aurora) mimic the wing patterns of Melinae spp. to avoid predators. Each of these wing patterns requires a distinct combination of alleles that influence colour and shape, and recombinants between these distinct types are maladapted. The different Heliconius mimics are closely related and occur sympatrically, yet hybrids are rarely found in nature. It has been shown that two phenotypically distinct mimics have an inversion that harbours at least two colour-pattern loci97. Photographic images in panels d and e were provided by David Lowry (University of Texas at Austin, USA) and Mathieu Joron (Muséum National d'Histoire Naturelle, Paris, France), respectively.

Frankel N, Erezyilmaz DF, McGregor AP, Wang S, Payre F, Stern DL. (2011) Morphological evolution caused by many subtle-effect substitutions in regulatory DNA. Nature. 29;474(7353):598-603.



Wagner A. (2011) The molecular origins of evolutionary innovations. Trends Genet. 27(10):397-410.





Importance of network effects for adaptation. A gene's position in a regulatory network influences its effects on a target phenotype and on other traits. Circular node sizes are proportional to the gene's effect on the selected phenotype; the intensity of red colouration is proportional to effects on other traits (where no colour indicates no effect on other traits). Square nodes have no effect on the target phenotype owing to the directionality of the network, but they may influence other phenotypes. Small black circles indicate the directions of the interactions in the network; modes of interaction are not specified. Genes encoding upstream proteins (A) often have large effects because they control many downstream genes influencing a trait, although pleiotropy mediated by other connections may weaken net selection on these 'hub' genes. Compared with protein A, the gene encoding protein B has fewer pleiotropic connections but also less control over the target phenotype. Protein C has lower pleiotropic constraint than protein B and integrates more upstream signals — including environmental inputs — resulting in higher evolvability. Proteins at central or 'bottleneck' positions (D) often have large effects, even if they have few direct connections with other proteins. Proteins with both high centrality and high connectivity (E) may be influenced by large-effect, adaptive alleles. Genes encoding downstream, peripheral proteins (F1 and F2) may have small to moderate effects and are more likely to accumulate neutral or nearly neutral variants than relatively upstream genes of large effect (D and E), which may evolve under positive and then purifying selection.

Box 2 | **Key issues in network evolution**

Integrating targeted genome engineering with laboratory evolution and computational modelling could considerably increase our understanding of the following open issues in network evolution.

Impact of network rewiring on metabolic functioning
What is the adaptive value of introducing new enzymatic reactions or rewiring regulatory links in particular environments? Systematic network modifications by means of genome engineering[90] will allow researchers to map the fitness landscape of metabolic networks and also explore the space of plausible alternative molecular circuits.

Neutral evolution and emergence of key innovations
How does the neutral evolution of metabolic networks influence the emergence of evolutionary innovations[91]? A computational study showed that the presence of alternative metabolic circuits with the same phenotype is a key facilitator of evolutionary novelty (that is, the ability to utilize new nutrients)[92]. In principle, this prediction can be tested experimentally by measuring the fitness of alternative network circuits under various environmental conditions.

Role of promiscuous enzyme activities in network evolution
Promiscuous functions — weak activities for which the enzyme is not directly selected — have been suggested to have important roles as raw materials for future adaptive evolution[93,94]. Generating large pools of mutations in numerous targeted promiscuous enzymes and exposing the mutant strains to repeated rounds of selection will shed light on how novel promiscuous pathways evolve.

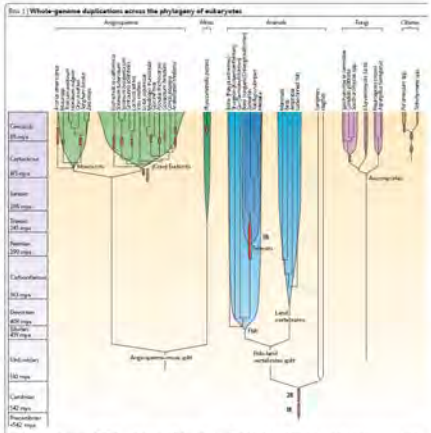
Importance of regulatory versus structural mutations in adaptive evolution
Phenotypic changes could arise through mutations in *cis*-regulatory sequences or coding regions, but their relative importance remains intensely debated[95]. This issue could be addressed by directed evolution *in vitro*[81] by modifying the targets of available genetic variation.

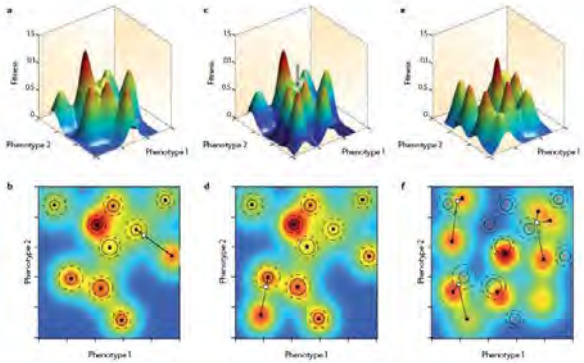
Convergent evolution of network structure and function
How frequent is convergent evolution at the network level[96]? Replaying adaptive network evolution in the laboratory would allow the prevalence of convergence to be estimated and computational predictions on the availability of alternative evolutionary trajectories to be tested.

The evolutionary significance of ancient genome duplications.

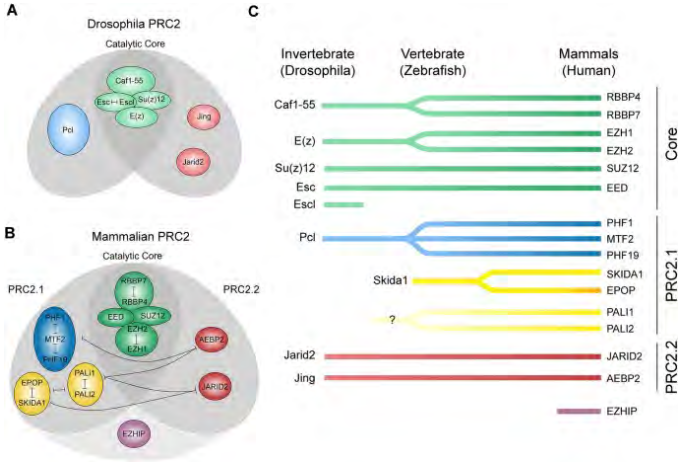
Van de Peer Y, Maere S, Meyer A.

Nat Rev Genet. 2009 Oct;10(10):725-32.



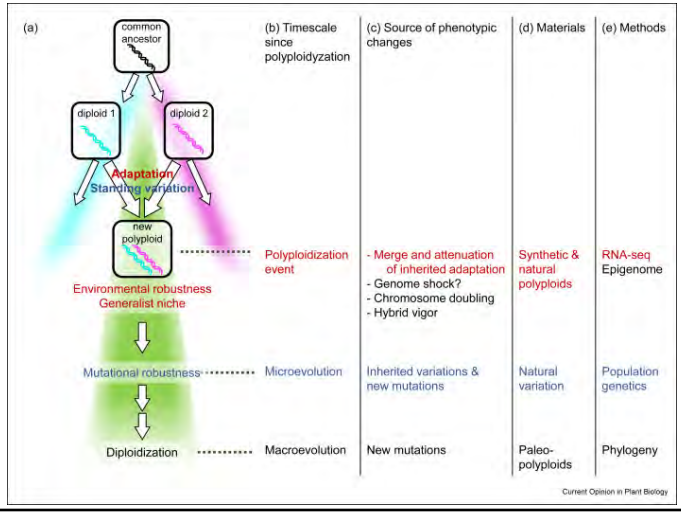


Evolutionary adaptation of the Polycomb repressive complex 2.
Fischer S, Weber LM, Liefke R.
Epigenetics Chromatin. 2022 Feb 22;15(1):7.

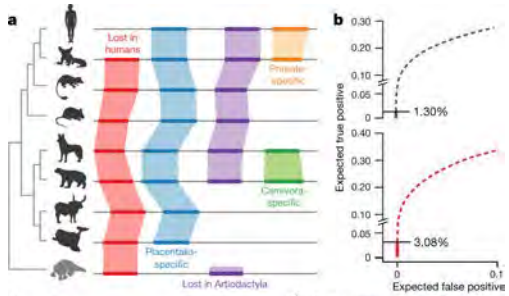


Overview of the main PRC2 members and their competition in Drosophila (**A**) and mammals (**B**), as well as their evolutionary occurrences (**C**).

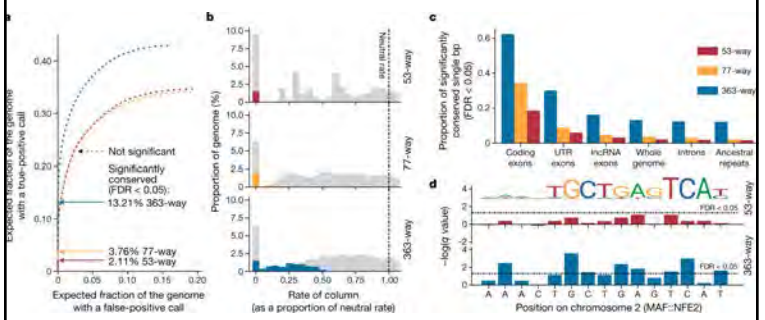
Robustness and the generalist niche of polyploid species: Genome shock or gradual evolution?
Shimizu KK.
Curr Opin Plant Biol. 2022 Oct;69:102292.



A comparative genomics multitool for scientific discovery and conservation.
Zoonomia Consortium.
Nature. 2020 Nov;587(7833):240-245.



Dense sampling of bird diversity increases power of comparative genomics.
Feng S, Stiller J, Deng Y, et al.
Nature. 2020 Nov;587(7833):252-257.



Hopeful Monsters and Evolutionary Biology

The proper place of hopeful monsters in evolutionary biology.

Theissen G.
Theory Biosci. 2006 Mar;124(3-4):349-69.

Abstract

Hopeful monsters are organisms with a profound mutant phenotype that have the potential to establish a new evolutionary lineage. The Synthetic Theory of evolutionary biology has rejected the evolutionary relevance of hopeful monsters, but could not fully explain the mechanism and mode of macroevolution. On the other hand, several lines of evidence suggest that hopeful monsters played an important role during the origin of key innovations and novel body plans by saltational rather than gradual evolution. Homeotic mutants are identified as an especially promising class of hopeful monsters. Examples for animal and plant lineages that may have originated as hopeful monsters are given. Nevertheless, a brief review of the history of the concept of hopeful monsters reveals that it needs refinements and empirical tests if it is to be a useful addition to evolutionary biology. While evolutionary biology is traditionally zoocentric, hopeful monsters might be more relevant for plant than for animal evolution. Even though during recent years developmental genetics has provided detailed knowledge about how hopeful monsters can originate in the first place, we know almost nothing about their performance in natural populations and thus the ultimate difference between hopeful and hopeless. Studying the fitness of candidate hopeful monsters (suitable mutants with profound phenotype) in natural habitats thus remains a considerable challenge for the future.

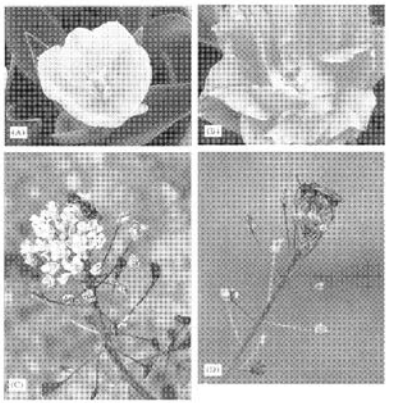


Fig. 1. A putative hopeless (B) and hopeful monster (D). In the upper row, a wild-type flower of tulip (*Tulipa gesneriana*, left) is compared to a "double flower" or "filled flower" mutant (right); while the wild-type flower has male (stamens) and female reproductive organs (carpels) in the centre, the filled flower is sterile, because all reproductive organs are transformed into showy yet sterile perianth organs, thus hampering sexual reproduction and undermining fitness. The lower part shows inflorescences of Shepherd's purse (*Capsella bursa-pastoris*). While wild-type flowers have four different types of floral organs including petals (the white organs in C), all petals are transformed into stamens in the "decandric" variety shown in D, which hence has 10 stamens and 2 carpels in all of its flowers and is fully fertile. Note that while evolutionary biology usually favours animal model systems (an attitude known as zoocentrism), the insects shown here are only decorative elements. (Pictures courtesy of Hannelore Simon (upper row) and Janine Zeemann (lower row)).

Hopeful monsters and morphogens at the beach.

Niswander L, Anderson KV.

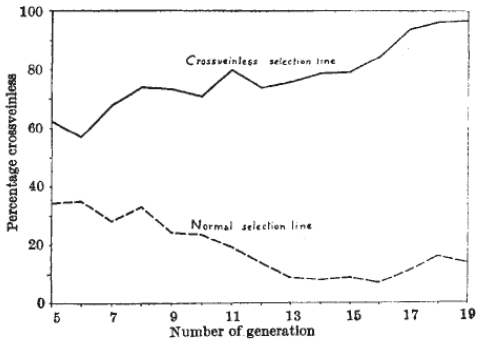
Nat Cell Biol. 2002 Nov;4(11):E259-62.

Crustaceans such as *Artemia* have 11 pairs of legs (left), whereas *Drosophila* has three pairs of legs. A change in a phosphorylation site of *Artemia* Ubx appears to alter the protein such that development is not respressed in the *Artemia* abdominal segements. See text for further details.

"*If it could be demonstrated that any complex organ existed, which could not possibly have been formed by numerous, successive, slight modifications, my theory would absolutely break down.*" (Darwin 1859, p. 189)

Waddington

Environment and Evolutionary Biology



Progress of selection for and against the formation of the cross-veinless phenocopy, from the fifth generation onwards, the temperature shock being applied to pupæ aged 21–23 hr.

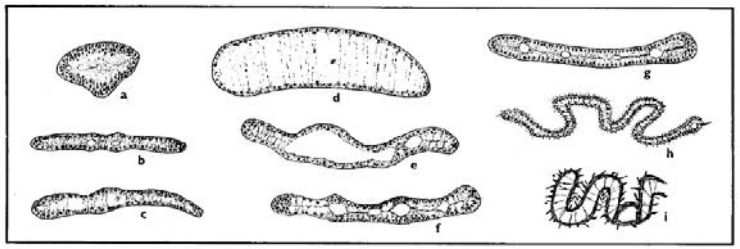


FIGURE 1 – *Diagrammatic drawings of sections of the developing wing in the fruit-fly* Drosophila. *Notice how the wing is at first quite solidly constructed. (Figure* 1 b *is of about the same age as figure* 2 A.) *Then it becomes hollow (figure* 1 d, *which corresponds to figure* 2 B), *contracts again (figures* 1 e, f, g), *and finally becomes folded (figures* 1 h, i).

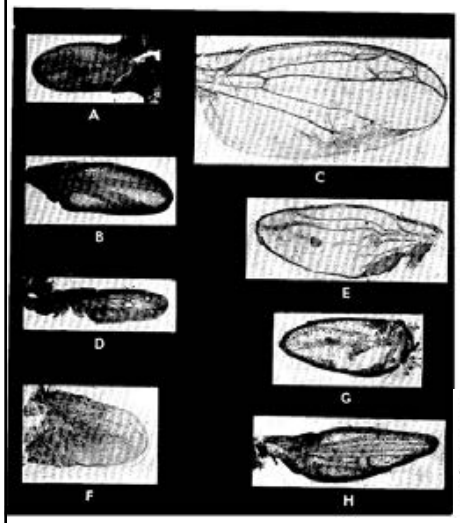


FIGURE 3 – *Some genetically controlled abnormalities in the contraction-phase of wing-development* in Drosophila. *Figures* A, B, *and* C *show wings of the mutant race* net *in which there is a partial failure of contraction, which causes the formation of extra veins in some regions. In figures* D *and* E *the failure of contraction is much more complete, and bubbles of fluid are left between the two wing-surfaces, which remain so far apart that in many areas no veins appear (the mutant* bloated*). In figures* F, G, *and* H *the contraction does not fail, but is abnormal, so that a wing of characteristically elongated form is produced (the mutant* blade *in* D. pseudo-obscura).

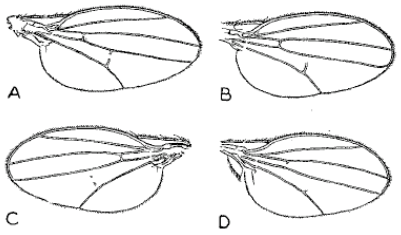


FIG. 1. Four crossveinless wings: *a* grade 4, *b* grade 3, *c* grade 2, *d* grade 1.

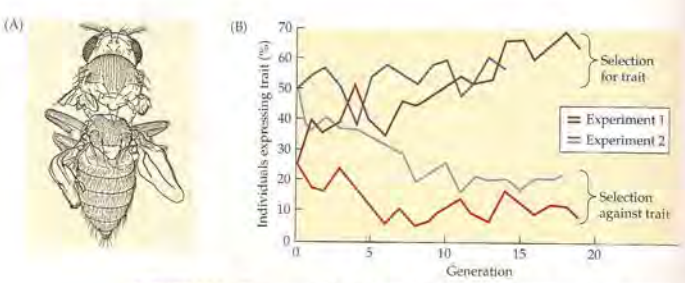


FIGURE 10.3 Phenocopy of the *bithorax* (four-winged) mutation. (A) Waddington's drawing of a *bithorax* mutant phenotype produced after treatment of the fly embryo with ether. The forewings have been removed to show the aberrant metathorax. This particular individual was in fact taken from "assimilated" stock that produced this phenotype without being exposed to ether. (B) Selection experiments for or against *bithorax*-like response to ether treatment. Two experiments are shown (red and blue lines). In each experiment, one group of flies was selected for the trait while the other was selected against the trait. (From Waddington 1956.)

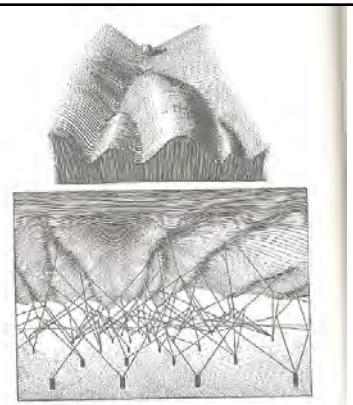
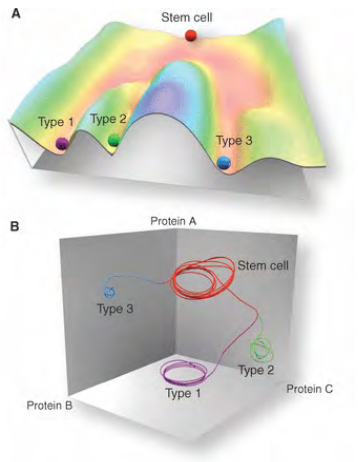
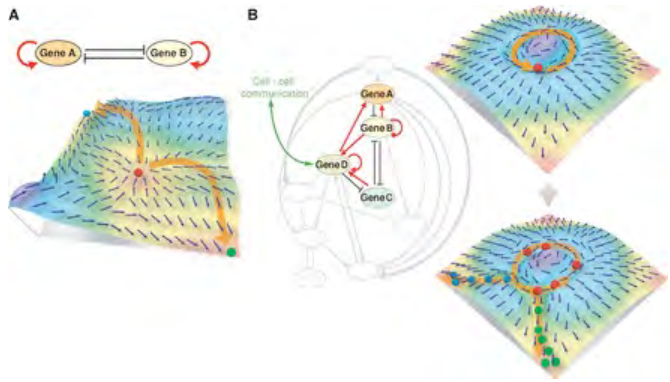


Figure 2.5
Waddington's pictures of epigenetic landscapes. His legend for the upper picture began "Part of an epigenetic landscape. The path followed by the ball as it rolls down towards the spectator, corresponds to the developmental history of a particular part of the egg." The lower picture had the legend "The complex system of interactions underlying the epigenetic landscape. The pegs in the ground represent genes; the sailing boats from them the chemical tendencies which the genes produce. The modelling of the epigenetic landscape, which slopes down from above (one's head towards the ground), is controlled by the pull of these tendencies (ropes which are ultimately anchored to the genes." (Reproduced with permission from C.H. Waddington, *The Strategy of the Genes*. London, Allen and Unwin, 1957, pp. 29, 30.)

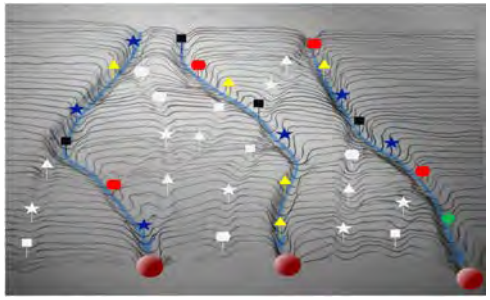


(A) Waddington's epigenetic landscape. The development of a cellular state is represented by a ball rolling down a landscape of bifurcating valleys, each representing different cell types. (B) Dynamical-systems representation of cellular states. Each axis represents the expression of a protein whose time development is depicted as a trajectory in space. Final states are attractors and correspond to distinct cell types.



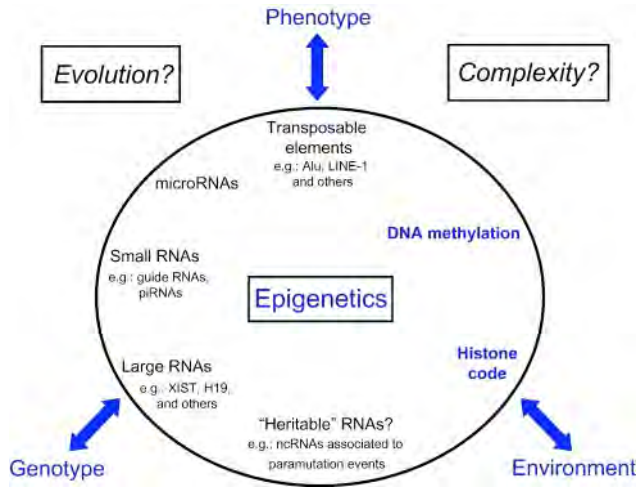
Dynamical-systems view on the differentiation dynamics of a stem cell. (A) By adding self-activation (top, red arrows) to a toggle-switch network, i.e., two mutually repressing genes (9), (bottom) an attractor (red) with balanced expression of the two genes is added between A-activated and B-activated attractors (green and blue, respectively). Differentiation from the balanced expression to either of the biased attractors is triggered by noise. (B) Oscillatory gene expression dynamics (upper right: circulating trajectory shown by an orange arrow) are generated by negative feedback in the regulation network (left, red and black arrows). Cell differentiation is driven by cell-cell communication (green arrow) and fixed through positive feedback in the network (11, 12). An increase in cell number results in some cells leaving the original attractor (stem cell state) to differentiate, whereas those that remain proliferate (lower: orange trajectory bifurcates owing to cell-cell interactions). Orange and blue arrows on the landscape represent the trajectory of cellular state and the gradient of the landscape that affect the movement of the ball, respectively.

The "evolutionary field" hypothesis. Non-Mendelian transgenerational inheritance mediates diversification and evolution.
Prog Biophys Mol Biol. 2018 May;134:27-37.
Spadafora C.



Building of the genome regulatory networks. Colored symbols represent retrotransposal insertions that provide a variety of DNA recognition sites (i.e. transcription- or hormone-binding sequences, promoters, enhancers, splicing sites, insulators etc) required for the assembly of functional regulatory networks and also contribute to expand the copy number of miRNA and trRNA coding sequences. Insertions are represented as specifically targeted within the profile of new canalizations. Non-colored symbols represent the insertions of functionally inactivated branches.

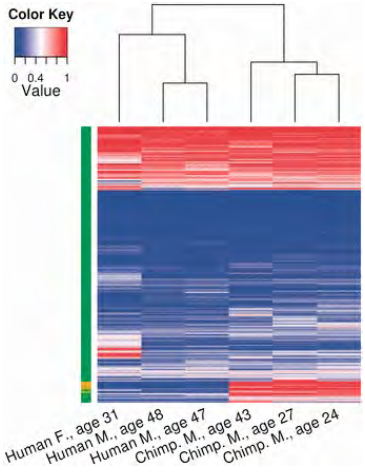
Epigenetics and Evolutionary Biology



Kuzawa CW, Thayer ZM. (2011) Timescales of human adaptation: the role of epigenetic processes. Epigenomics. ;3(2):221-34.

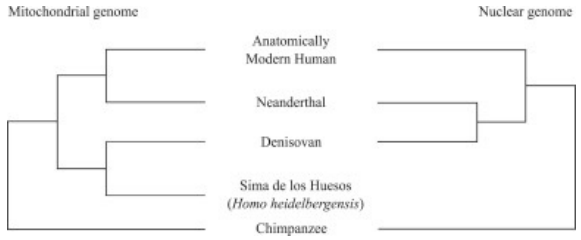
Cycle duration		Adaptation	
Years		Mode	Process
0.00000001	Seconds		
0.0001	Hours	Physiologic	Homeostasis
0.001	Days		
0.1	Months		
1	Years	Developmental	Plasticity
10	Decades	Intergenerational	Inertia
100	Centuries		
1000	Millenia	Genetic	Natural selection
1,000,000	Millions		

Epigenetics and evolution.
Integr Comp Biol. 2014 Jul;54(1):31-42
Mendizabal I, Keller TE, Zeng J, Yi SV.

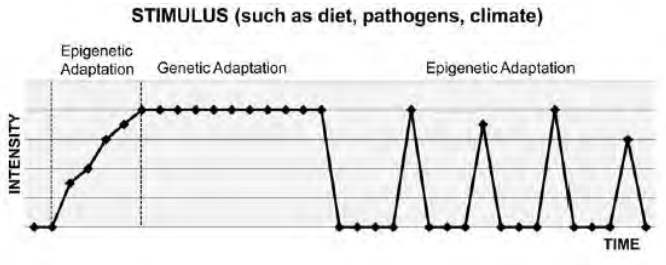


Levels of DNA methylation of 12,063 orthologous promoters in three humans and three chimpanzees analyzed by Zeng et al. (2012). Hierarchical clustering both within and between species was performed using the average methylation of promoters to generate a heatmap. The column to the left of the heatmap designates promoters as similarly methylated (green) or as highly diverged between species (orange).

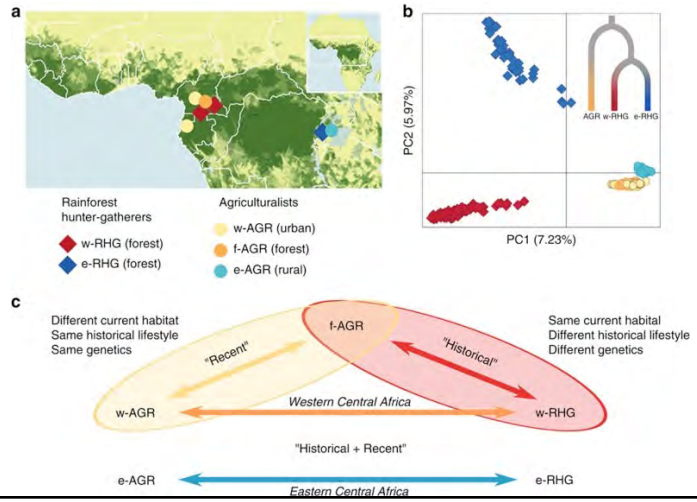
Major transitions in human evolution revisited: a tribute to ancient DNA.
J Hum Evol. 2015 Feb;79:4-20.
Ermini L, Der Sarkissian C, Willerslev E, Orlando L.



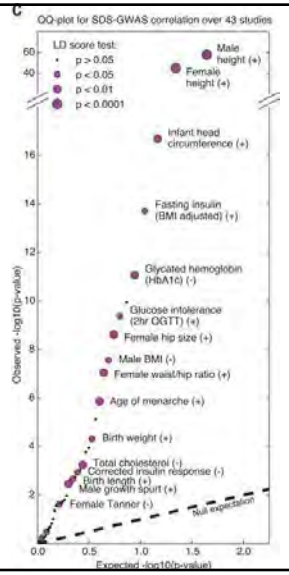
The epigenetic side of human adaptation: hypotheses, evidences and theories.
Ann Hum Biol. 2015 Jan;42(1):1-9.
Giuliani C, Bacalini MG, Sazzini M, Pirazzini C, Franceschi C, Garagnani P, Luiselli D.



The epigenomic landscape of African rainforest hunter-gatherers and farmers.
Fagny M, Patin E, MacIsaac JL, et al.
Nat Commun. 2015 Nov 30;6:10047.



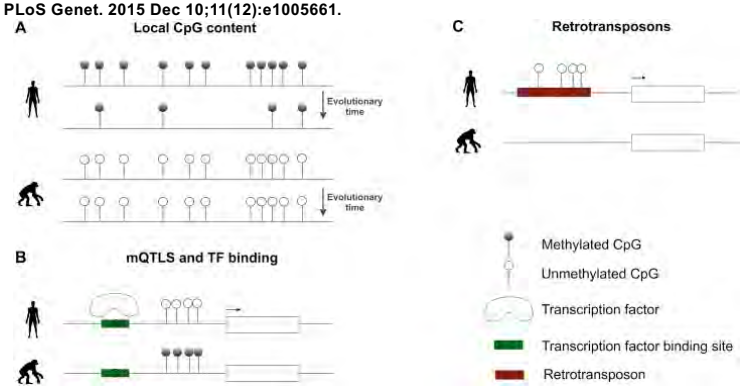
Detection of human adaptation during the past 2000 years.
Field Y, Boyle EA, Telis N, et al.
Science. 2016 Nov 11;354(6313):760-764.



DNA Methylation: Insights into Human Evolution.

Hernando-Herraez I, Garcia-Perez R, Sharp AJ, Marques-Bonet T

PLoS Genet. 2015 Dec 10;11(12):e1005661.



The interplay between the genome and the methylome.

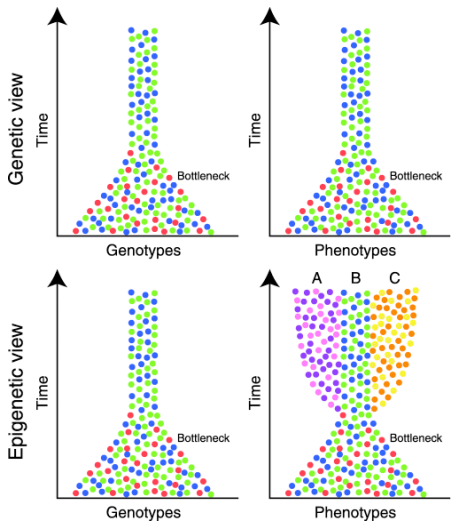
A) Methylated cytosines tend to deaminate over evolutionary time and, thus, the methylation state of cytosines in different species influences the evolution of the underlying genome sequence. B) Species-specific nucleotide changes that disrupt transcription factor (TF) binding sites can alter the methylation state of nearby CpG dinucleotides and, as a consequence, establish species-specific differentially methylated regions (DMRs). C) The insertion of transposable elements in a particular lineage, along with the accumulation of nucleotide changes, can lead to the emergence of novel CpG dinucleotides, creating species-specific regulatory regions.

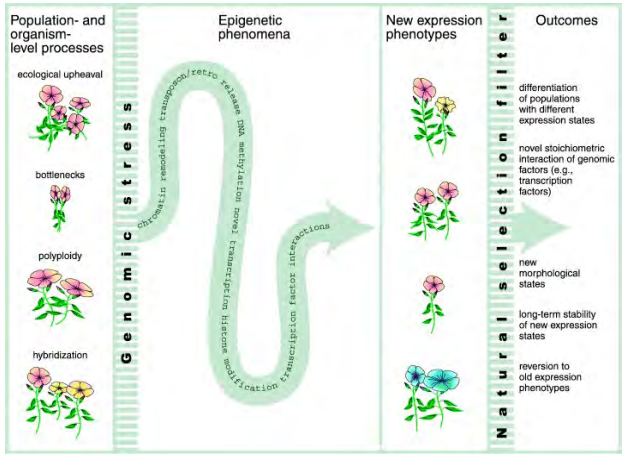
Table 1. Comparative studies of DNA methylation patterns in primates.

Reference	Species	Methodology	Tissue	Highlights
Wang, J. (2012)	Human, Macaque	MeDIP-chip and SEQUENOM MassARRAY	Prefrontal cortex	>100 differentially methylated regions; Validated DMRs associated with genes with neural functions and with schizophrenia and Alzheimer's disease
Pai, A. (2011)	Human, Chimpanzee	Illumina 27K array	Liver, heart, and kidney	14.5% of promoter CpG sites are differentially methylated between tissues; 8.6% of promoter CpG sites are differentially methylated between species; Interspecies differences in promoter methylation underlie 12%–18% of gene expression differences
Molaro, A. (2011)	Human, Chimpanzee	Whole-genome bisulfite sequence	Sperm	70% of genes are hypomethylated in both chimpanzee and human sperm; 6% and 35% of orthologous SVAs had a methylation level below 50% in chimpanzee and human sperm, respectively
Martin, D.I.K. (2011)	Human, Chimpanzee, Orangutan	MethylSeq	Neutrophils	10% of CpG islands-like regions present different methylation states between chimpanzees and humans; Regions with differential methylation might have diverged in gene regulatory function
Fukuda, K. (2013)	Human, Chimpanzee	MeDIP-chip (chromosomes 21 and 22)	Peripheral blood leukocytes	16 sDMRs between chimpanzees and humans in chromosomes 21 and 22; Genetic changes underlying these differences in methylation include gain/loss of CTCF-binding sites and changes in CpG density
Hernando-Herraez, I. (2013)	Human, Chimpanzee, Bonobo, Gorilla, Orangutan	Illumina 450K array	Peripheral blood	~9% of the assayed CpG sites showed significant methylation differences between chimpanzees and humans; 184 genes perfectly conserved at protein level show significant epigenetic differences between chimpanzees and humans
Hernando-Herraez, I. (2015)	Human, Chimpanzee, Gorilla, Orangutan	Whole-genome bisulfite sequence	Peripheral blood	72% of the hypomethylated regions (HMRs) were shared among all four species; 42.6% of HMRs were on human CpG islands; 52.6% of HMRs were on human CpG shores
Gokhman, D. (2014)	Neandertal, Denisovan	Deamination rate as a proxy for DNA methylation	Femur, costae, and tibia bones	>2,000 DMRs between archaic and present-day humans; Substantial changes in methylation in the *HOXD* cluster
Fraser, H. B. (2012)	Human	Illumina 27K array	Lymphoblastoid cell lines	21.4% of CpG sites differed in methylation between populations; 5.4% of these CpG sites were strongly associated with local SNPs
Heyn, H. 2013	Human	Illumina 450K array	Lymphoblastoid cell lines	439 population-specific differentially methylated CpG sites (pop-CpG); Significantly decreased gene expression associated to promoter hypermethylation in 12.9% (13 out of 101) of pop-CpG; Significantly increased gene expression associated to gene body methylation in 23.9% (27 out of 113) of pop-CpG

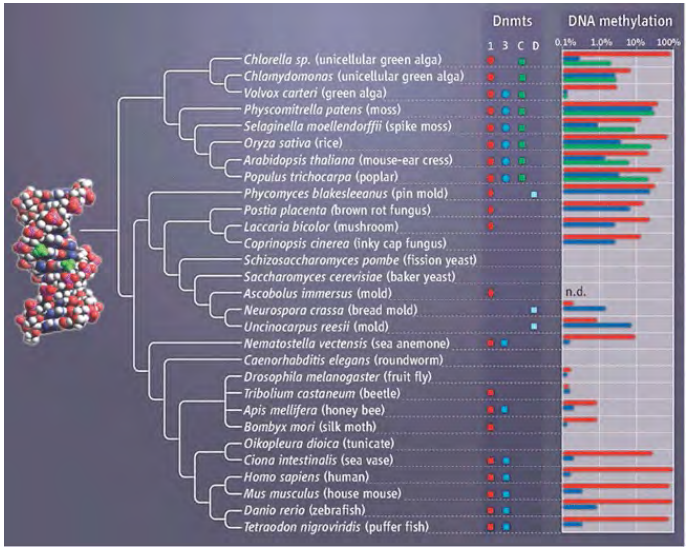
doi:10.1371/journal.pgen.1005661.t001

Rapp RA, Wendel JF. (2005) Epigenetics and plant evolution. New Phytol. 168(1):81-91.





Conceptualization of the interaction between epigenetics and evolutionary change. A number of population-level processes (left) cause genomic stress, leading to the induction of epigenetic phenomena (large arrow, center). These various phenomena operate in an ecological and evolutionary context to produce novel phenotypes (right center), ranging from molecular to morphological. These new phenotypes are subjected to the filter of natural selection – those surviving may then undergo longer-term evolutionary processes such as retention or loss of initially epigenetically fixed states.



Computational approaches for understanding the evolution of DNA methylation in animals.

Yi SV, Goodisman MA.

Epigenetics. 2009 Nov 16;4(8):551-6.

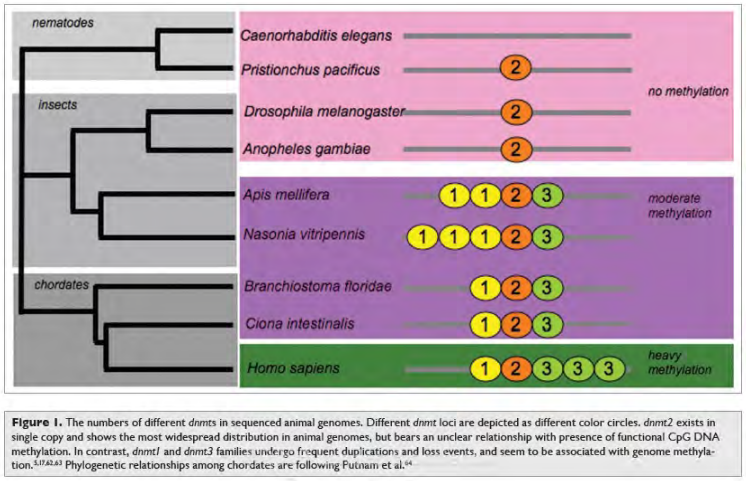
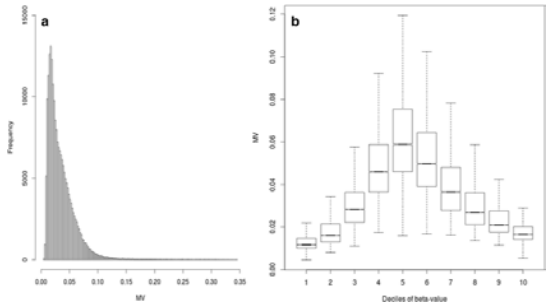
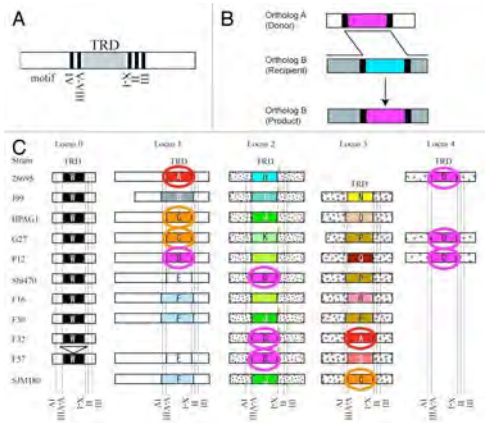


Figure 1. The numbers of different *dnmts* in sequenced animal genomes. Different *dnmt* loci are depicted as different color circles. *dnmt2* exists in single copy and shows the most widespread distribution in animal genomes, but bears an unclear relationship with presence of functional CpG DNA methylation. In contrast, *dnmt1* and *dnmt3* families undergo frequent duplications and loss events, and seem to be associated with genome methylation.[3,17,62,63] Phylogenetic relationships among chordates are following Putnam et al.[64]

DNA Methylation variability among individuals is related to CpGs cluster density and evolutionary signatures.
BMC Genomics. 2018 Apr 2;19(1):229.
Palumbo D, Affinito O, Monticelli A, Cocozza S.

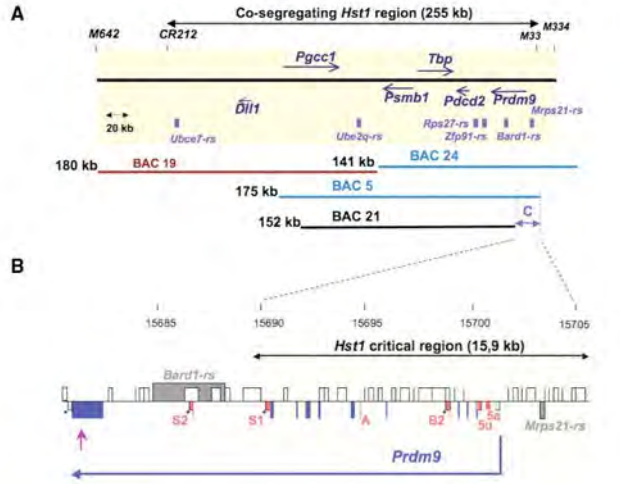


Furuta Y, Kobayashi I. (2012) Mobility of DNA sequence recognition domains in DNA methyltransferases suggests epigenetics-driven adaptive evolution. Mob Genet Elements. 1;2(6):292-296.

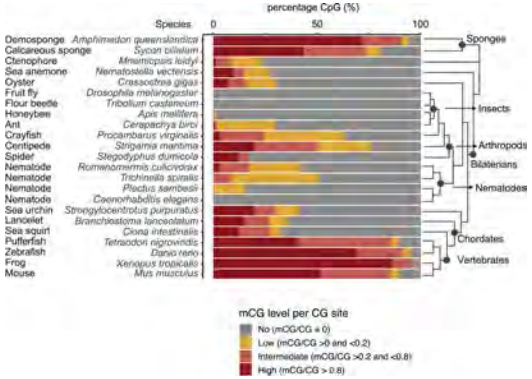


Movement of target DNA recognition domains between non-orthologous genes of Type III mod genes. (A) Gene organization in mod genes. TRD, target recognition domain. Roman numerals, amino-acid sequence motifs conserved among m6A DNA methyltransferases. (B) A likely process of the movement of target recognition domains: DNA recombination at conserved DNA sequences flanking the target recognition domain that encode the conserved amino-acid motifs. (C) Repertoire of orthologs of mod genes in global strains of Helicobacter pylori. Members of the same homology group of target recognition domains are in the same color. Small vertical bars in green and small vertical bars in orange: start codon and stop codon generated by frameshift mutations. Modified from Furuta et al.

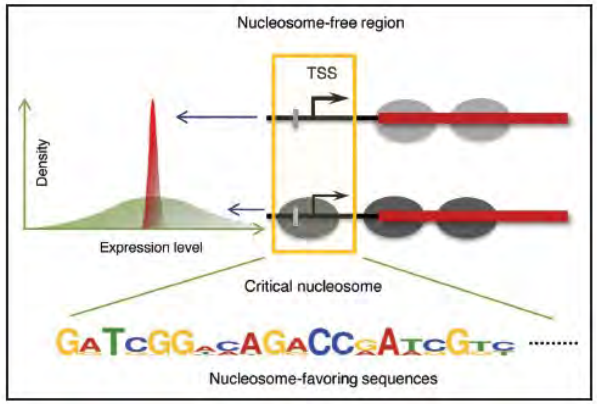
Mihola O, Trachtulec Z, Vlcek C, Schimenti JC, Forejt J. (2009) A mouse speciation gene encodes a meiotic histone H3 methyltransferase. Science. 16;323(5912):373-5.



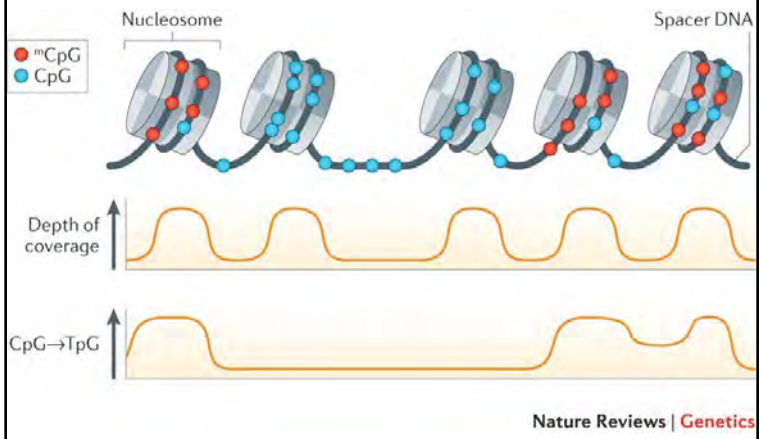
Evolution of DNA Methylome Diversity in Eukaryotes
de Mendoza A, Lister R, Bogdanovic O. J
Mol Biol. 2019 Nov 11:S0022-2836(19)30659-X.



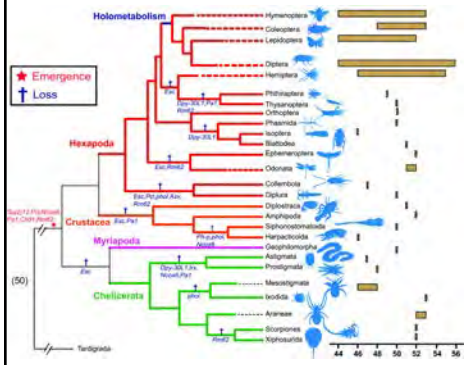
Choi JK, Kim YJ. (2009) Implications of the nucleosome code in regulatory variation, adaptation and evolution. Epigenetics. 1;4(5):291-5.



Reconstructing ancient genomes and epigenomes.
Orlando L, Gilbert MT, Willerslev E.
Nat Rev Genet. 2015 Jul;16(7):395-408

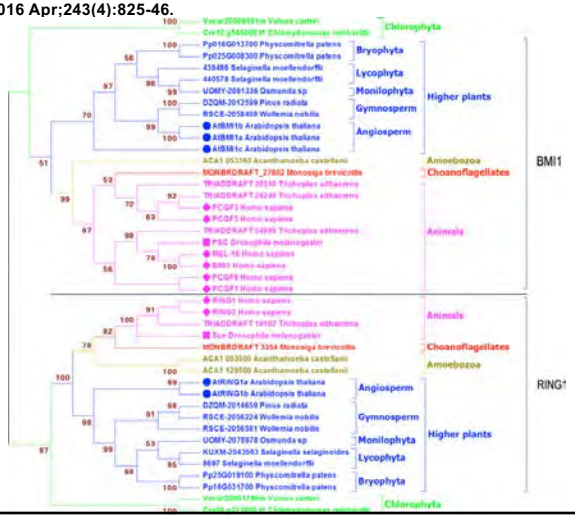


Genomic data reveal high conservation but divergent evolutionary pattern of Polycomb/Trithorax group genes in arthropods.
Insect Sci. 2019 Feb;26(1):20-34.
Jiang F, Liu Q, Liu X, Wang XH, Kang L.

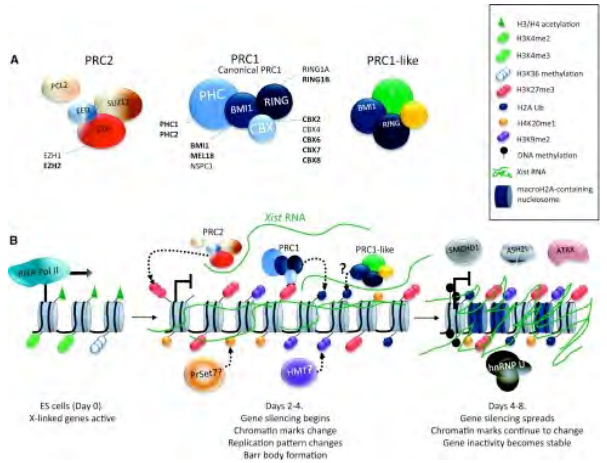


Inference of ancestral state of PcG and TrxG genes along arthropod evolution. The emergence and loss of PcG and TrxG genes are indicated in the internal nodes of the phylogenetic tree. The bars indicate the number ranges of PcG and TrxG genes in each order. The numbers of species in each order are as follows: Amphipoda, 1; Araneae, 2; Astigmata, 1; Blattodea, 1; Coleoptera, 9; Collembola, 1; Diplostraca, 1; Diplura, 1; Diptera, 16; Ephemeroptera, 1; Geophilomorpha, 1; Harpacticoida, 1; Hemiptera, 13; Hymenoptera, 38; Isoptera, 1; Ixodida, 1; Lepidoptera, 9; Mesostigmata, 2; Odonata, 2; Orthoptera, 1; Parachela, 2; Phasmida, 1; Phthiraptera, 1; Prostigmata, 1; Scorpiones, 1; Siphonostomatoida, 1; Thysanoptera, 1; Xiphosurida, 1.

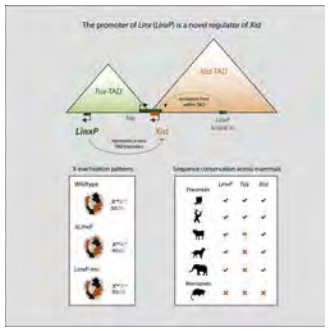
The evolutionary landscape of PRC1 core components in green lineage.
Chen DH, Huang Y, Ruan Y, Shen WH.
Planta. 2016 Apr;243(4):825-46.

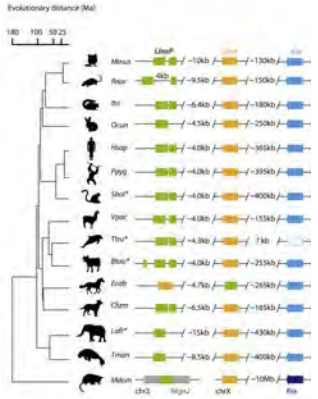


Escamilla-Del-Arenal M, da Rocha ST, Heard E. (2011) Evolutionary diversity and developmental regulation of X-chromosome inactivation. Hum Genet. 130(2):307-27.



A Conserved Noncoding Locus Regulates Random Monoallelic Xist Expression across a Topological Boundary.
Galupa R, Nora EP, Worsley-Hunt R, et al.
Mol Cell. 2020 Jan 16;77(2):352-367.e8.



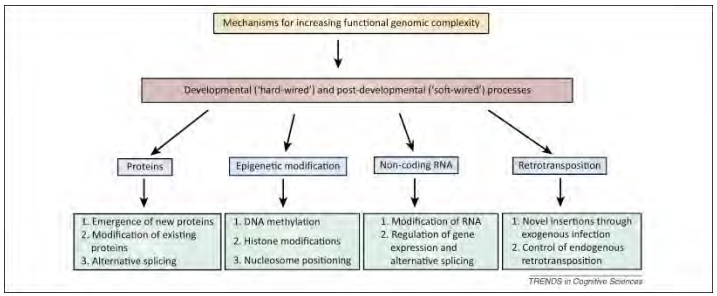


EvoChromo: towards a synthesis of chromatin biology and evolution
Drinnenberg IA, Berger F, Elsässer SJ, et al.
Development . 2019 Sep 26;146(19):dev178962.

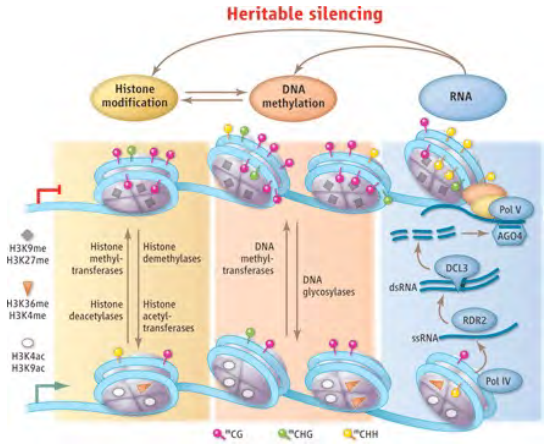
Abstract

Over the past few years, interest in chromatin and its evolution has grown. To further advance these interests, we organized a workshop with the support of The Company of Biologists to debate the current state of knowledge regarding the origin and evolution of chromatin. This workshop led to prospective views on the development of a new field of research that we term 'EvoChromo'. In this short Spotlight article, we define the breadth and expected impact of this new area of scientific inquiry on our understanding of both chromatin and evolution.

Barry G, Mattick JS. (2012) The role of regulatory RNA in cognitive evolution. Trends Cogn Sci. 16(10):497-503.



Potential mechanisms for increasing functional genomic complexity. The human brain may have evolved rapidly through a number of mechanisms, including protein innovations, altered epigenetic programs, expansion of regulatory RNAs that direct chromatin modifications, and retrotransposition. Especially relevant for the evolution of higher-order cognition is the dramatic increase in RNA editing of primate-specific Alu sequences and the human-specific isoforms of APOBEC3 that mediate retrotransposition during post-developmental cellular responses.

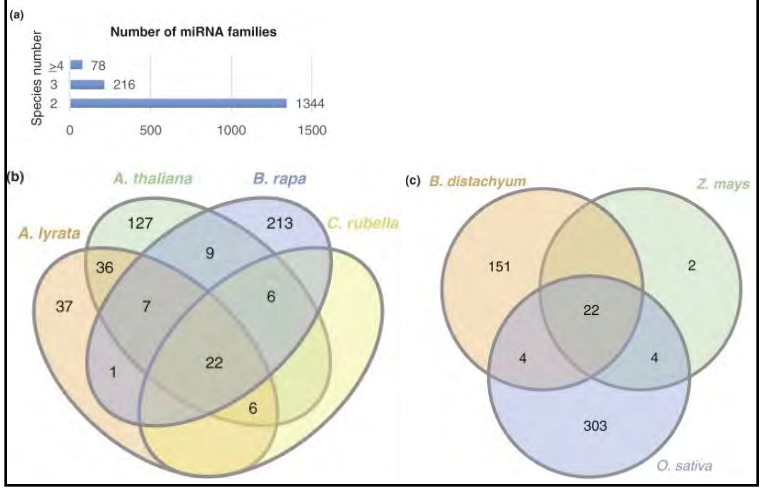


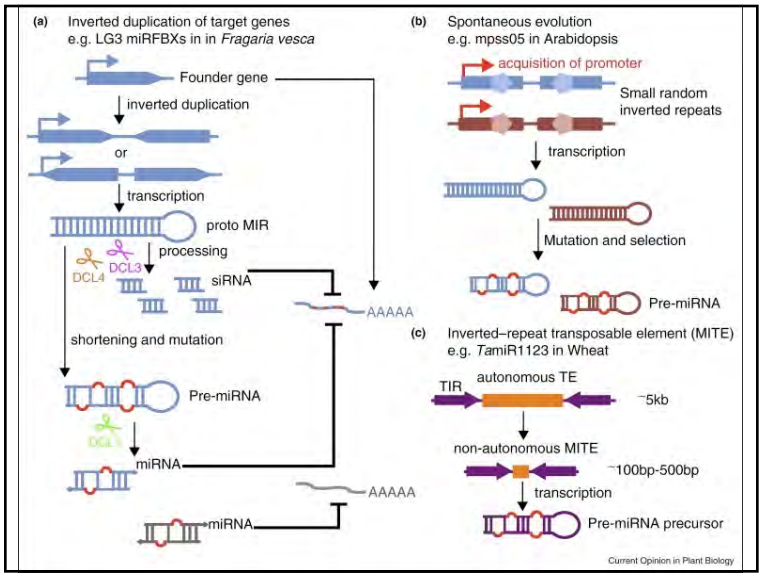
Plant epigenetic mechanisms include DNA methylation, histone modification, and RNA-directed DNA methylation (RdDM). RdDM involves two plant-specific RNA polymerases (Pol IV and Pol V), an RNA-dependent RNA polymerase (RDR2), an enzyme that cleaves double-stranded RNA (DCL3), and an Argonaute-family RNA-binding protein (AGO4). [Adapted with permission from (199)]

The evolution of microRNAs in plants.

Cui J, You C, Chen X.

Curr Opin Plant Biol. 2017 Feb;35:61-67.

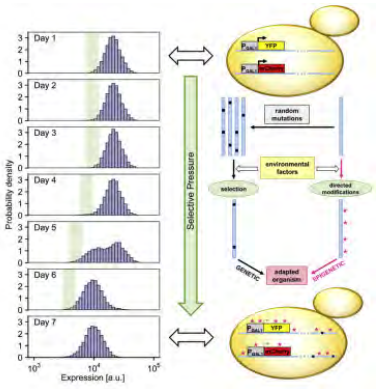




Epigenetic Mechanisms Contribute to Evolutionary Adaptation of Gene Network Activity under Environmental Selection.

Luo X, Song R, Moreno DF, Ryu HY, Hochstrasser M, Acar M.

Cell Rep. 2020 Oct 27;33(4):108306.



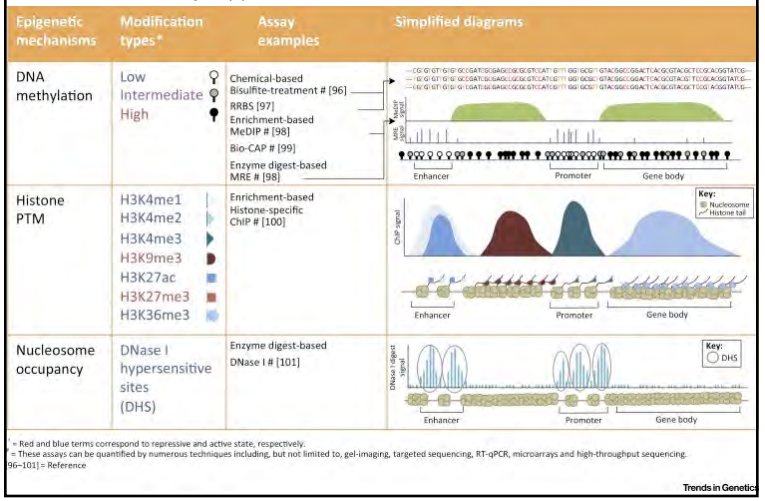
In Brief

Luo et al. demonstrate how epigenetic mechanisms contribute to the evolution of gene network activity. Subjecting yeast cells to repeated environmental selection based on the activity of the galactose network, they observe sustained changes in reporter expression level. They characterize the epigenetic and genetic factors contributing to the observed phenotypes.

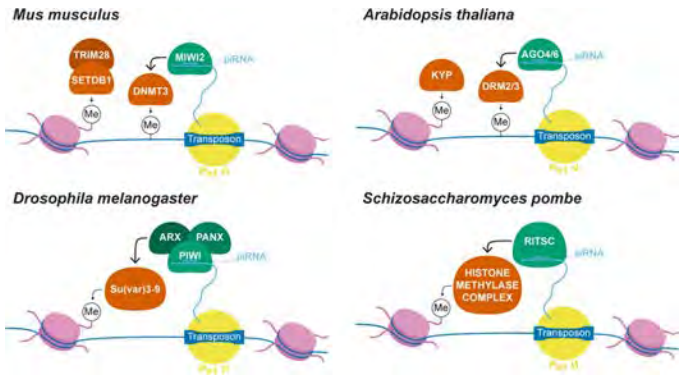
Evolution of Epigenetic Regulation in Vertebrate Genomes.

Lowdon RF, Jang HS, Wang T.

Trends Genet. 2016 May;32(5):269-83.

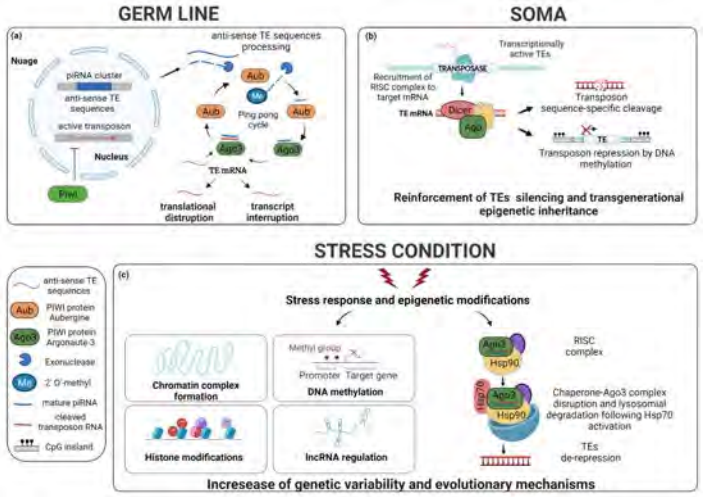


Double-edged sword: The evolutionary consequences of the epigenetic silencing of transposable elements.
Choi JY, Lee YCG.
PLoS Genet. 2020 Jul 16;16(7):e1008872.

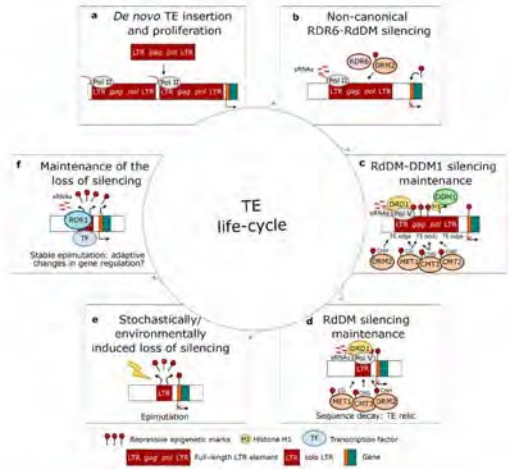


These unique evolutionary consequences indicate that TEs' epigenetic effect is not only a crucial component of TE biology but could also be a significant contributor to genome function and evolution.

Transposable Elements: Major Players in Shaping Genomic and Evolutionary Patterns.
Colonna Romano N, Fanti L.
Cells. 2022 Mar 19;11(6):1048.

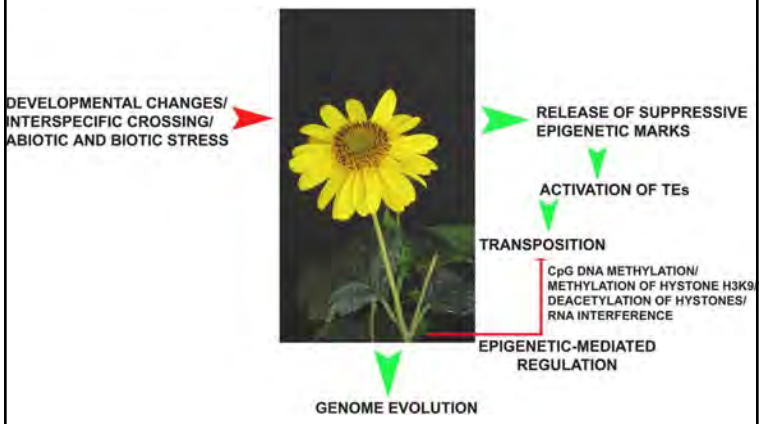


Epigenetic targeting of transposon relics: beating the dead horses of the genome?
Sammarco I, Pieters J, Salony S, Toman I, Zolotarov G, Lafon Placette C.
Epigenetics. 2022 Nov;17(11):1331-1344.



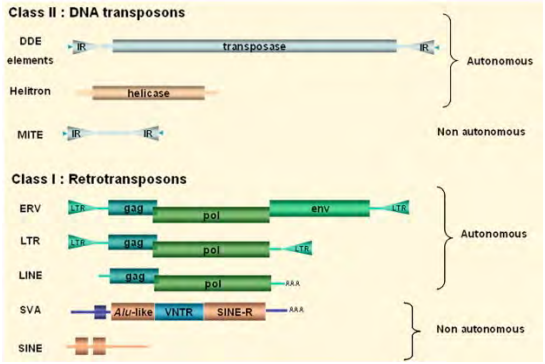
Life-cycle of a transposable element in plants

Impact of transposable elements on the evolution of complex living systems and their epigenetic control.
Viviani A, Ventimiglia M, Fambrini M, Vangelisti A, Mascagni F, Pugliesi C, Usai G.
Biosystems. 2021 Dec;210:104566.



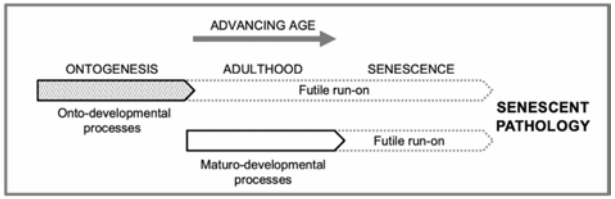
Schematic representation of transposable elements (TEs) activation and mobilization. The combination of TE activity and epigenetic-mediated control impact host evolution.

Rebollo R, Horard B, Hubert B, Vieira C. (2010) Jumping genes and epigenetics: Towards new species. Gene. 1;454(1-2):1-7.

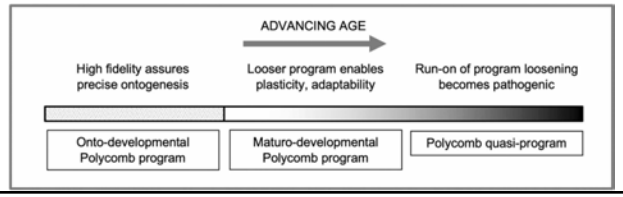


General classification of eukaryote transposable elements. TEs are abundant and ubiquitous mobile sequences capable of jumping inside the genome. TEs are divided into two major classes on the basis of differences in their transposition mechanisms: Class I Retrotransposons "copy and paste" through an RNA intermediate, whereas Class II DNA transposons just "cut and paste" their own molecule. Autonomous retrotransposons harbor long terminal repeats in their ends (LTR) or not (LINE-like), and can be infectious agents (endogenous retroviruses). Non-autonomous retrotransposons, such as SINEs, are dependent on autonomous elements to be "copied and pasted" in trans. The same dependency is observed among DNA transposons, where MITEs need a full-length transposase coded by autonomous DNA transposons to be "cut and pasted" in trans. Full-length helitrons, recently identified Class II DNA transposons, play an important role in exon shuffling thanks to their "rolling circle" replication mechanism. For a recent classification of eukaryote TEs, please refer to Wicker et al., 2007. Boxes represent open reading frames, triangles are either inverted repeats (IR) in blue, or long terminal repeats (LTR) in green, and small blue arrows correspond to duplicated insertion site representations. DDE elements: transposases carrying the aspartate (D), aspartate (D), glutamate and (E) motif. MITE: miniature inverted repeated elements; ERV: endogenous retrovirus; LINE: long interspersed nuclear element; SVA: composite element composed of parts of SINE (short interspersed nuclear element), VNTR (variable number of tandem repeats) and Alu repeats—the first box represents CCCTCT hexamer repeats; SINE red boxes indicate a diagnostic feature; Gag, Pol, Env: retroviral-like proteins coded by TE open reading frames.

Epigenetic clocks and programmatic aging.
Gems D, Virk RS, de Magalhães JP.
Ageing Res Rev. 2024 Nov:101:102546.



Onto-developmental and maturo-developmental process and their run-on in development, maturity and aging. Simplified hypothetical scheme, omitting a number of details, as follows. Some adaptive ontogenetic processes may continue on during early adulthood. Some maturo-developmental processes (wound healing, immunity) will also be operative prior to adulthood, and also in later life in parallel to their futile, quasi-programmed derivatives.



"Epigenetics and Systems Biology"

Spring 2025 (Odd Years) – Course Syllabus
Biol 476/576 Undergraduate/Graduate Course (3 Credit)
SLN: (476) – 06655, (576) – 06656
Time - Tuesday and Thursday 10:35 am-11:50 am
Course Lectures recorded on Canvas/Panopto and Discussion Sessions live on WSU Zoom for all campuses (Hybrid Course)
Course Director - Michael Skinner, Abelson Hall 507, 335-1524, skinner@wsu.edu
Co-Instructor – Eric Nilsson, Abelson Hall 507, 225-1835, nilsson@wsu.edu
Learning Objective - The objective of the course is to learn the concept and critical role of systems to understand molecular, cell, development, physiology and evolutionary aspects of biology with a focus on the role of epigenetics in systems biology.
Schedule/Lecture Outline –

Week 1	January 7 & 9	Systems Biology (History/ Definitions/ Theory)
Week 2	January 14 & 16	Systems Biology (Networks & Emergence)
Week 3	January 21 & 23	Systems Biology (Components: DNA to Phenotype)
Week 4	Jan 28 & 30	Systems Biology (Genomics / Technology)
Week 5	February 4 & 6	Epigenetics (History / Molecular Processes)
Week 6	February 11 & 13	Epigenetics (Molecular Processes & Integration)
Week 7	February 18 & 20	Epigenetics (Genomics and Technology)
Week 8	Feb 25 & 27	Cell & Developmental Biology
Week 9	March 4 & 6	Epigenetics of Cell & Developmental Biology (& Midterm Exam)
Week 10	**March 10 – 14**	**Spring Break**
Week 11	March 18 & 20	Environmental Impact on Biology
Week 12	March 25 & 27	Environmental Epigenetics
Week 13	April 1 & 3	Disease Etiology
Week 14	April 8 & 10	Epigenetics & Disease Etiology
Week 15	April 15 & 17	Evolutionary Biology & Genetics
Week 16	April 22 & 24	Epigenetics & Evolutionary Biology
Week 17	Finals Week	Grant Review/ Study Section Meeting (& Final Exam)

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Spring 2025 – Epigenetics and Systems Biology
Lecture Outline (Epigenetics and Evolution)
Michael K. Skinner – Biol 476/576
Weeks 15 and 16 (April 15 & 22)

Epigenetics and Evolution

- Darwinian Evolution
- Lamarck's Environment and Evolutionary Biology
- History Environment and Evolutionary Biology
- Waddington Environment and Evolutionary Biology
- Molecular and Genetic Aspects of Evolutionary Biology
- Hopeful Monsters and Evolutionary Biology
- Epigenetics and Evolutionary Biology
- Sociobiology and Evolutionary Biology
- Sexual Selection and Evolutionary Biology
- Epigenetic Transgenerational Inheritance and Evolutionary Biology
- Summary Epigenetics and Evolutionary Biology

Required Reading

Laland, et al. (2014) Does evolutionary theory need a rethink? Nature 54:161-4

Skinner MK (2015) Environmental Epigenetics and a Unified Theory of the Molecular Aspects of Evolution: A Neo-Lamarckian Concept that Facilitates Neo-Darwinian Evolution. Genome Biol Evol. 26;7(5):1296-302

Skinner MK, Nilsson EE. (2021) Role of environmentally induced epigenetic transgenerational inheritance in evolutionary biology: Unified Evolution Theory. Environ Epigenet. 7(1):dvab012.

Books

Jablonka, E. & Lamb, M.J. (2014). Evolution in Four Dimensions: Genetic, Epigenetic, Behavioral and Symbolic Variation in the History of Life. MIT Press, Cambridge.

Spring 2025 – Epigenetics and Systems Biology
Discussion Session (Epigenetics and Evolutionary Biology)
Michael K. Skinner – Biol 476/576
Week 16 (April 24)

Epigenetics and Evolutionary Biology

Primary Papers

1. Luo, et al. (2020) Cell Reports 33:108306. (PMID: 33113358)
2. Aagaard, et al. (2020) Mol Ecol. (22):5765-5783. (PMID 36112081)
3. McNew, et al. (2017) BMC Evolution 17(1):183. (PMID: 28835203)

Discussion

Student 3 – Ref #1 above

- What was the experimental design and model system?
- What epigenetic process and gene network effects were observed?
- Does this provide evidence for environmental induction of epigenetic alterations in a gene network for evolutionary adaptation?

Student 4 – Ref #2 above

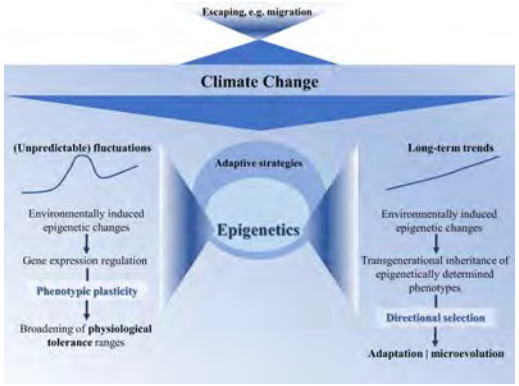
- What is the model system, phenotypic change, and environmental factor?
- What epigenetic change was observed?
- How did the environment, epigenetics and genetics integrate?

Student 5 – Ref #3 above

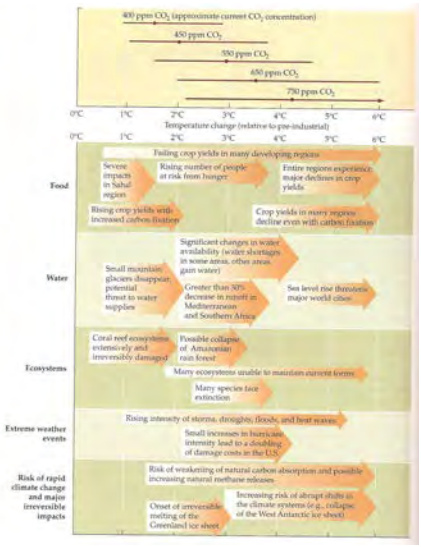
- What was the experimental design and approach?
- What molecular alterations were observed in what cell types?
- What molecular mechanism can promote rapid evolutionary events?

Environment, Epigenetic and Evolution

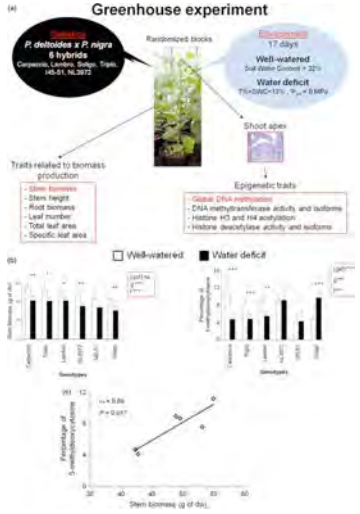
Synthesizing the role of epigenetics in the response and adaptation of species to climate change in freshwater ecosystems.
Mol Ecol. 2018 Jul;27(13):2790-2806.
Jeremias G, Barbosa J, Marques SM, Asselman J, Gonçalves FJM, Pereira JL.



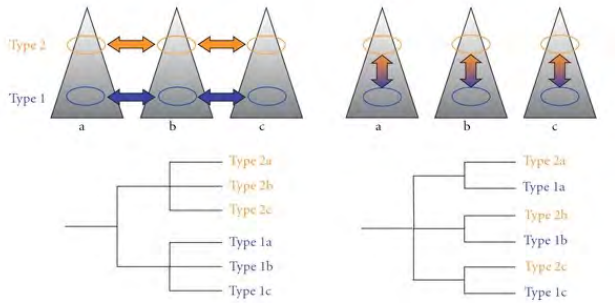
Conceptual diagram representing the role of epigenetics as an adaptive strategy by freshwater organisms while coping to environmental stressors deriving from climate change



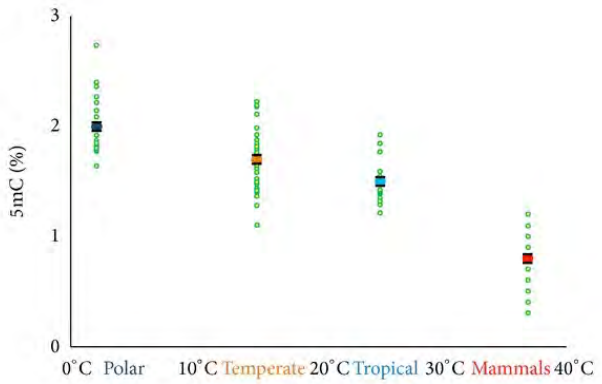
Bräutigam K, et al. (2013) Epigenetic regulation of adaptive responses of forest tree species to the environment. Ecol Evol. 3(2):399-415.



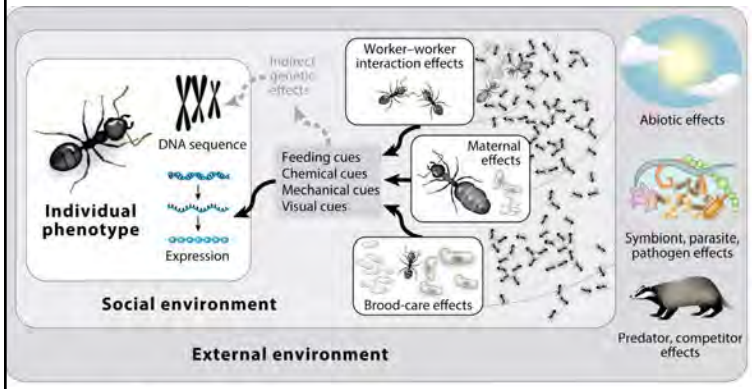
Flatscher R, Frajman B, Schönswetter P, Paun O. (2012) Environmental heterogeneity and phenotypic divergence: can heritable epigenetic variation aid speciation? Genet Res Int. 2012:698421

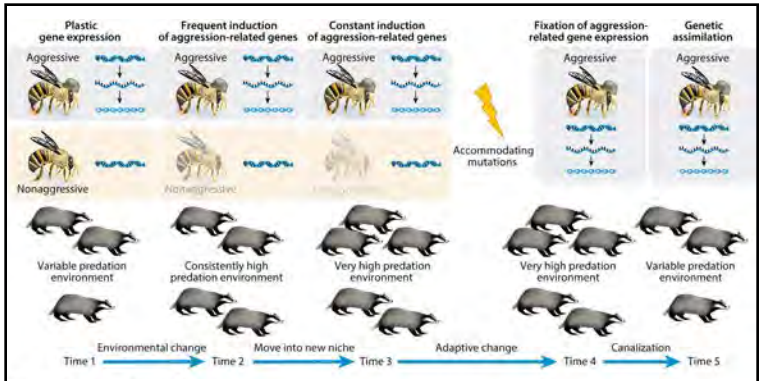


DNA methylation, epigenetics, and evolution in vertebrates: facts and challenges.
Int J Evol Biol. 2014;2014:475981
Varriale A.



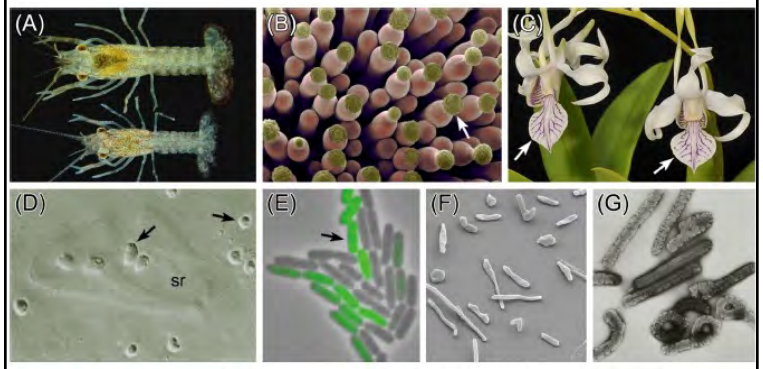
Molecular Evolution of Insect Sociality: An Eco-Evo-Devo Perspective.
Toth AL, Rehan SM.
Annu Rev Entomol. 2017 Jan 31;62:419-442.





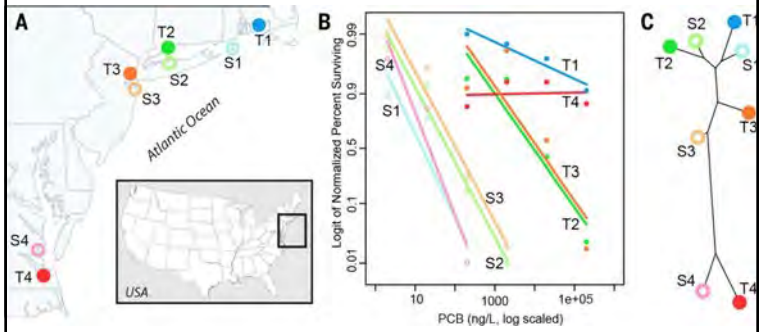
Scenario of genetic assimilation, as applied to the evolution of aggression in honey bees. Initially, individual phenotypic plasticity provides an adaptive response to variable environmental stimuli—for example, aggressive response to predation pressure (time 1). Subsequently, with an environmental change (time 2), such as increased predation pressure, the gene expression pattern inducing the aggressive response is more often exhibited compared to the nonaggressive response. This may allow aggressive colonies to move into previously unoccupied niches in the environment (time 3), such as very high predation environments. Over time, environmentally induced responses in gene expression and aggressive phenotype can become fixed differences as a result of the accumulation of accommodating mutations (time 4). The response then becomes canalized, resulting in a loss of plasticity, and individuals are fixed for the aggressive phenotype, and associated gene expression, even in the absence of the high predation environmental stimulus (time 5).

Stochastic developmental variation, an epigenetic source of phenotypic diversity with far-reaching biological consequences.
Vogt G.
J Biosci. 2015 Mar;40(1):159-204.



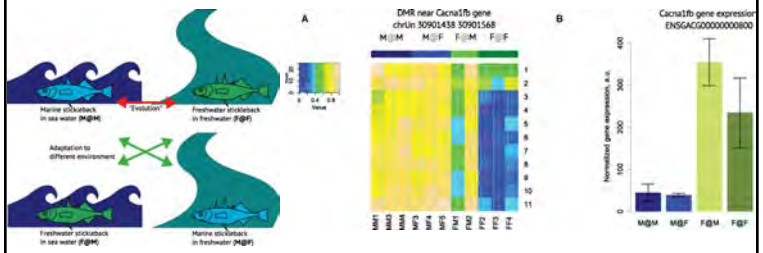
The genomic landscape of rapid repeated evolutionary adaptation to toxic pollution in wild fish.

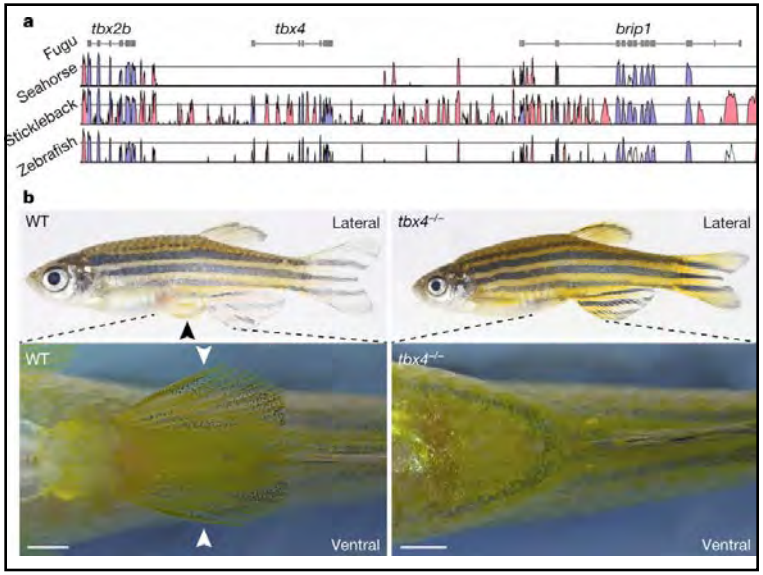
Reid NM, Proestou DA, Clark BW, et al.
Science. 2016 Dec 9;354(6317):1305-1308.



Genome-Wide DNA Methylation Profiling Reveals Epigenetic Adaptation of Stickleback to Marine and Freshwater Conditions.

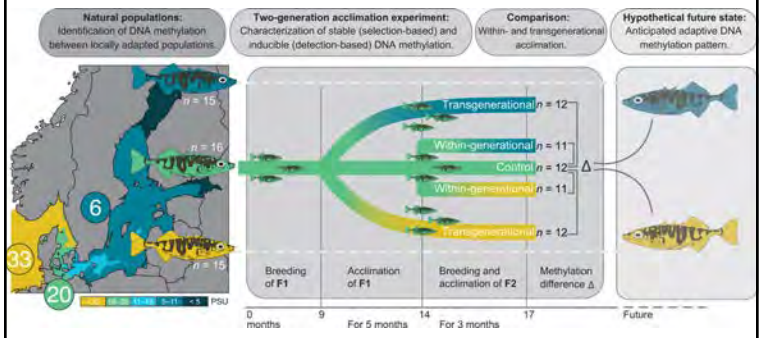
Mol Biol Evol. 2017 Sep 1;34(9):2203-2213.
Artemov AV, Mugue NS, Rastorguev SM, et al.



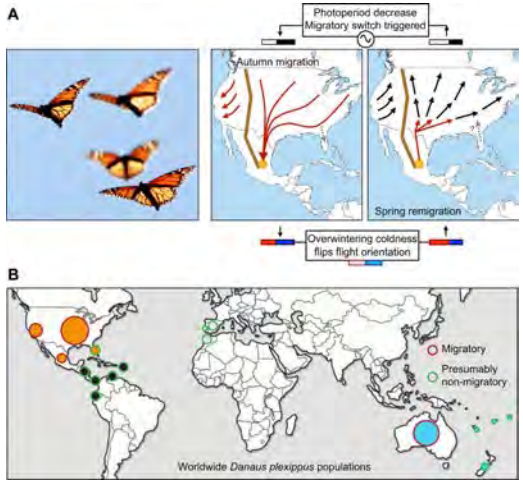


Two different epigenetic information channels in wild three-spined sticklebacks are involved in salinity adaptation

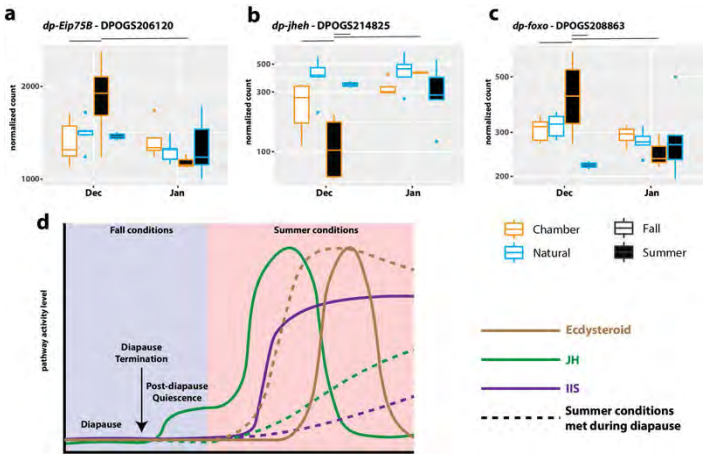
Heckwolf MJ, Meyer BS, Häsler R, Höppner MP, Eizaguirre C, Reusch TBH.
Sci Adv. 2020 Mar 20;6(12):eaaz1138.



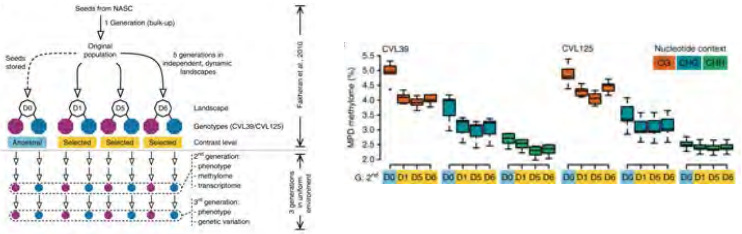
The genetics and epigenetics of animal migration and orientation: birds, butterflies and beyond.
J Exp Biol. 2019 Feb 6;222(Pt Suppl 1).
Merlin C, Liedvogel M.



Monarch butterflies use an environmentally sensitive, internal timer to control overwintering dynamics
Green DA 2nd, Kronforst MR.
Mol Ecol . 2019 Aug;28(16):3642-3655.

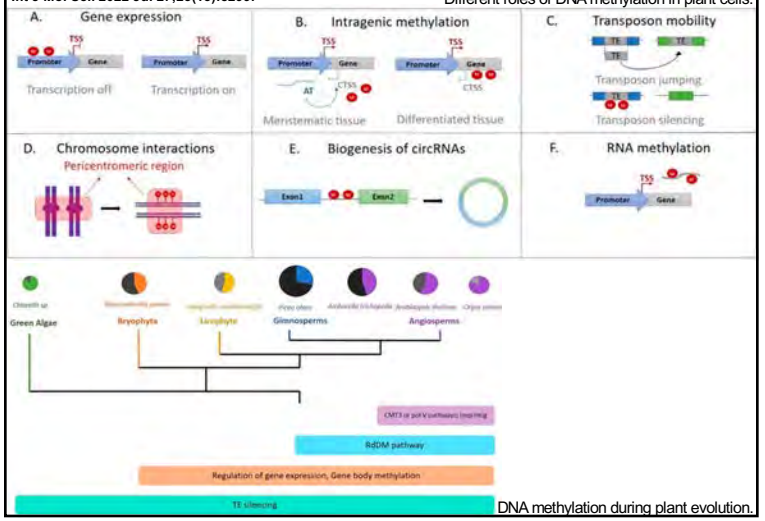


Contribution of epigenetic variation to adaptation in Arabidopsis.
Nat Commun. 2018 Oct 25;9(1):4446.
Schmid MW, Heichinger C, Coman Schmid D, et al.



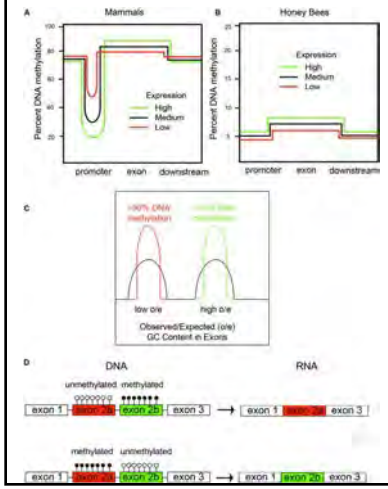
Plant DNA Methylation: An Epigenetic Mark in Development, Environmental Interactions, and Evolution.
Lucibelli F, Valoroso MC, Aceto S.
Int J Mol Sci. 2022 Jul 27;23(15):8299.

Different roles of DNA methylation in plant cells.



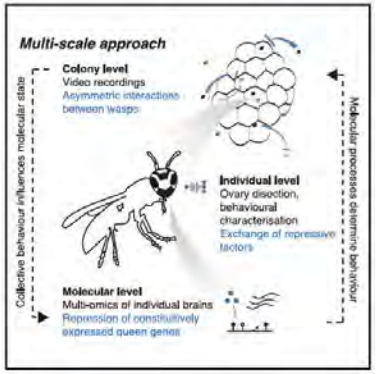
DNA methylation during plant evolution.

Epigenetics as an answer to Darwin's "special difficulty," Part 2: natural selection of metastable epialleles in honeybee castes.
Front Genet. 2015 Feb 24;6:60.
Ruden DM, Cingolani PE, Sen A, Qu W, Wang L, Senut MC, Garfinkel MD, Sollars VE, Lu X.



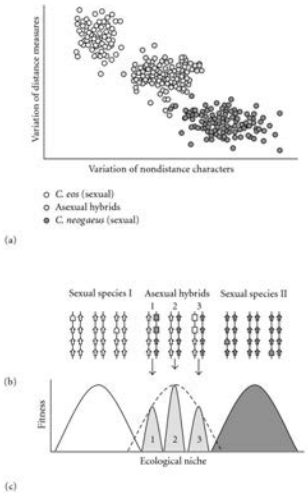
DNA methylation in honeybees correlates with gene expression and alternative splicing. (A) There are two types of DNA methylation in mammals: (1) promoter DNA methylation, which inversely correlates with mRNA expression; and (2) exon DNA methylation, which positively correlates with mRNA expression. (B) Honeybees predominantly have DNA methylation in exons, which, like in mammals, positively correlates with gene expression. (C) There are two types of genes in honeybees: (1) housekeeping genes with low observed/expected (o/e) CG content and high amounts of DNA methylation, and (2) caste-specific and developmental regulatory genes with a high o/e CG content and low amounts of DNA methylation. We have shown that the DNA methylation is at both CpG and CHH sites – CpG methylation primarily in exons and CHH methylation primarily in introns. (D) DNA methylation of cassette exons leads to their exclusion by alternative splicing in honeybees.

Self-organization of plasticity and specialization in a primitively social insect.
Patalano S, Alsina A, Gregorio-Rodríguez C, et al.
Cell Syst. 2022 Sep 21;13(9):768-779.e4.



- Experiments and theory reveal how *Polistes* wasps achieve specialization and plasticity
- Molecular upregulation of queen phenotype is balanced by colony-scale repression
- This allows *Polistes* to distinguish between intrinsic and extrinsic perturbations

The key role of epigenetics in the persistence of asexual lineages.
Genet Res Int. 2012;2012:534289.
Castonguay E, Angers B.



Hypothesis of the epigenetic mechanism underlying the flexibility of a genotype. (a) Phenotypic variation observed in sexual and asexual species. The points represent individual scores of Chrosomus eos, C. neogaeus, and asexual hybrids from two principal component analyses performed on body distance and nondistance measures (modified from [61]). In sexual species, the phenotypic variation among individuals is mostly the result of genetic variation, whereas, in asexual hybrids, it results from differentially expressed alleles of a same genotype. (b) Putative genetic and epigenetic variation at four genes is represented for three individuals per species. Arrows refer to expressed genes, larger arrows to different alleles of an expressed gene (genetic difference), and blocks to silenced genes (epigenetic difference). (c) Under the General Purpose Genotype model, an epigenetically flexible genotype may provide a wide ecological niche for asexual hybrids, where each different epigenetic variant would occupy a narrower niche.

Sociobiology and Evolutionary Biology

Genes, hormones, and circuits: An integrative approach to study the evolution of social behavior.

O'Connell LA, Hofmann HA.
Front Neuroendocrinol. 2010 Dec 14.
[Epub ahead of print]

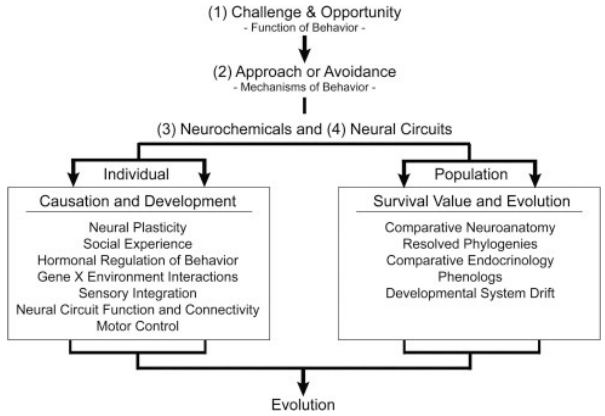
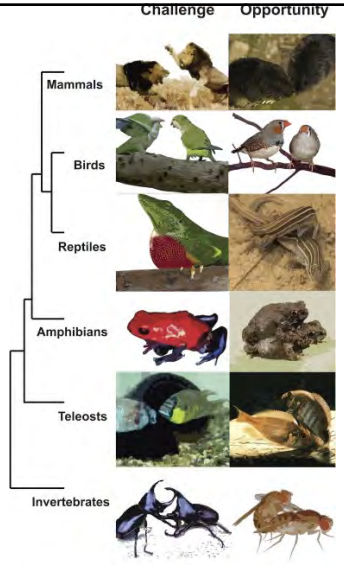


Fig. 1. An integrative framework for the analysis of social behavior and its evolution. Themes for studying both the proximate and ultimate mechanisms of social decision-making are presented on the level of the individual (left panel) and the population (right panel).



Evolution

Fig. 2. Challenge and opportunity: a functional framework. Behavioral responses to challenge and opportunities in the social environment are equivalent across animals, although the specific behavioral response may be divergent across lineages due to life history, ecology, and/or evolutionary history.

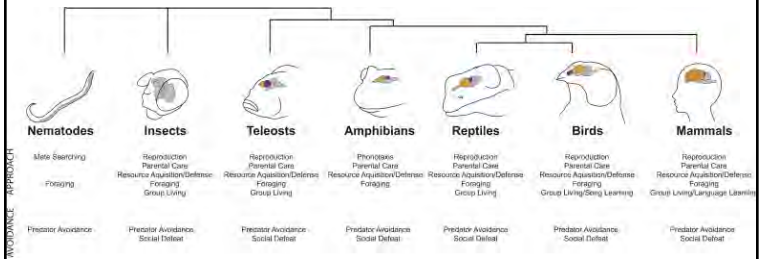


Fig. 3. Approach and avoidance: a mechanistic framework. Quantitative measures of behavioral responses to challenges and opportunities that are tractable in all species provide an important foundation for analyzing the molecular and neural basis of social behavior and its evolution. Brains are shaded differently by forebrain and midbrain.

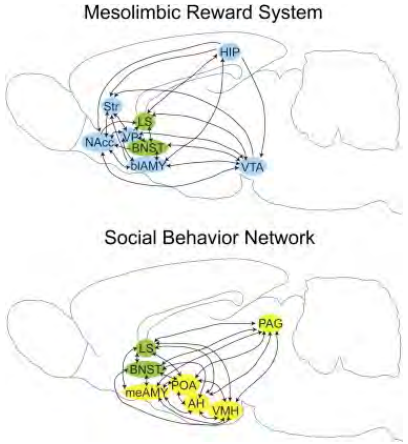


Fig. 4. A neural circuit framework. Schematic representations of a mammalian brain are shown with brain regions of the mesolimbic reward system (blue; top panel) and social behavior network (yellow; bottom panel). Regions shared by both circuits are labeled in green. Adapted from Ref. [199]. Arrows indicated directionality of functional connections between brain regions. Abbreviations: AH: anterior hypothalamus; bIAMY: basolateral amygdala; BNST: bed nucleus of the stria terminalis; HIP: hippocampus; LS: lateral septum; meAMY: medial amygdala; NAcc: nucleus accumbens; PAG/CG: periaquaductal gray/central gray; POA: preoptic area; STR: Striatum; VMH: ventromedial hypothalamus; VP: ventral pallidum; VTA: ventral tegmental area.

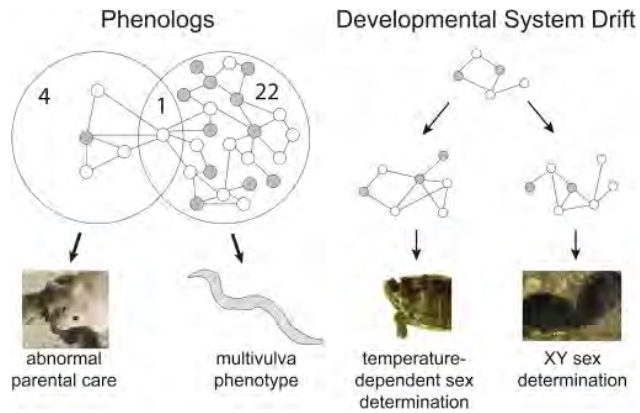


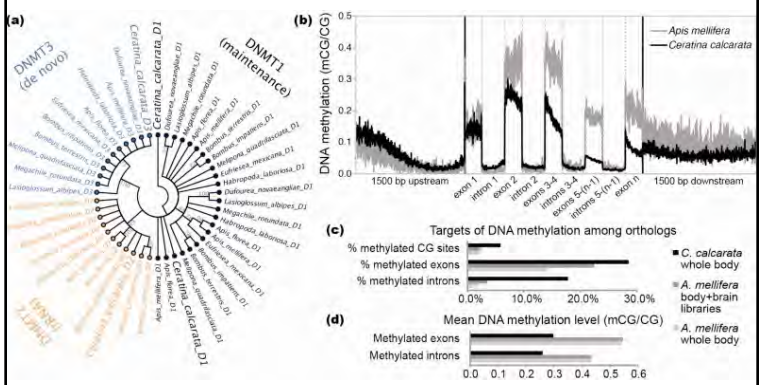
Fig. 5.

Alternative hypotheses for the evolution of neuroethological mechanisms. The phenolog hypothesis predicts that some gene/protein-interaction networks underlying social behavior and other complex phenotypes can be conserved across animals, even if the phenotypes are completely different. The developmental system drift hypothesis states that the molecular mechanisms underlying homologous phenotypes can diverge substantially during the course of evolution. Nodes and edges represent gene networks involved in a phenotype.

The Genome and Methylome of a Subsocial Small Carpenter Bee, Ceratina calcarata.

Rehan SM, Glastad KM, Lawson SP, Hunt BG.

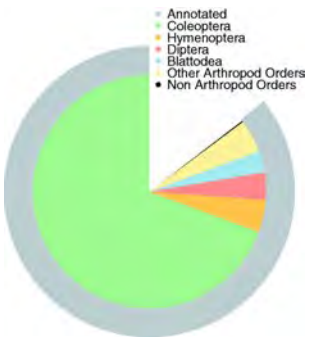
Genome Biol Evol. 2016 May 13;8(5):1401-10.



The Genome and Methylome of a Beetle with Complex Social Behavior, Nicrophorus vespilloides (Coleoptera: Silphidae).

Cunningham CB, Ji L, Wiberg RA, et al.

Genome Biol Evol. 2015 Oct 9;7(12):3383-96.



A two-ring pie chart showing results of annotation with BLAST against the complete UniProtKB database. First outer ring (gray) shows the proportion of gene models that could be annotated. Second ring (multicolored) shows the proportion of best BLAST hits of the annotations by order for all species with five or more best hits (97.8%). The best BLAST hits were overwhelmingly from other beetles and other Arthropods.

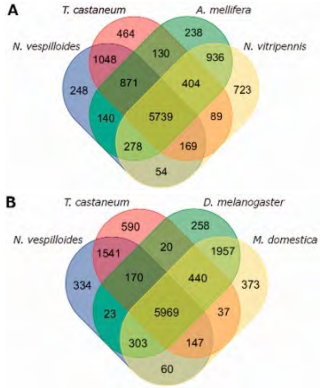
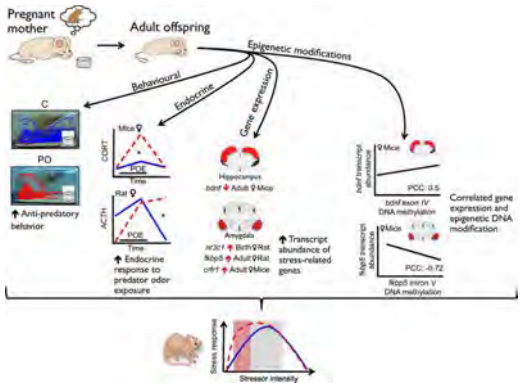


Figure shows the results of the OrthoMCL analysis that clustered the proteomes of *N. vespilloides, T. castaneum, A. mellifera, Na. vitripennis, D. melanogaster,* and *M. domestica* into orthologous groupings. (A) A Venn diagram showing the overlap in the orthologous groupings of the two beetles (*T. castaneum and N. vespilloides*) and the two Hymenoptera (*A. mellifera* and *Na. vitripennis*). (B) A Venn diagram showing the overlap in orthologous groupings of the two beetles (*T. castaneum* and *N. vespilloides*) and the two Diptera (*D. melanogaster* and *M. domestica*).

Adaptation or pathology? The role of prenatal stressor type and intensity in the developmental programing of adult phenotype
Neurotoxicol Teratol. 2018 Mar - Apr;66:113-124.
St-Cyr S, McGowan PO.

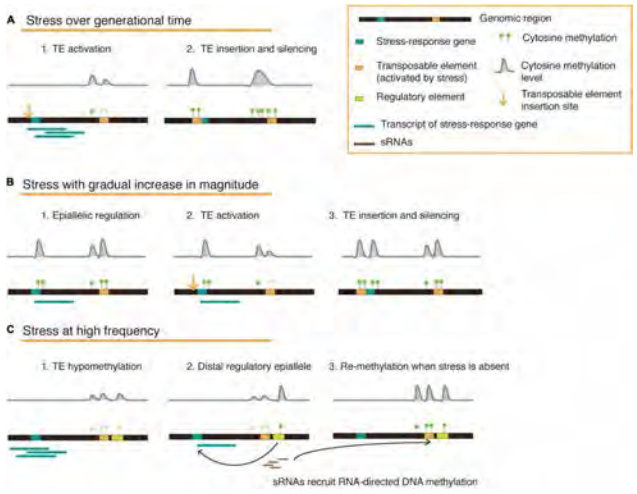


Epigenomics and gene regulation in mammalian social systems
Guerrero TP, Fickel J, Benhaiem S, Weyrich A.
Curr Zool. 2020 Jun;66(3):307-319.

Abstract

Social epigenomics is a new field of research that studies how the social environment shapes the epigenome and how in turn the epigenome modulates behavior. We focus on describing known gene-environment interactions (GEIs) and epigenetic mechanisms in different mammalian social systems. To illustrate how epigenetic mechanisms integrate GEIs, we highlight examples where epigenetic mechanisms are associated with social behaviors and with their maintenance through neuroendocrine, locomotor, and metabolic responses. We discuss future research trajectories and open questions for the emerging field of social epigenomics in nonmodel and naturally occurring social systems. Finally, we outline the technological advances that aid the study of epigenetic mechanisms in the establishment of GEIs and vice versa.

How Stress Facilitates Phenotypic Innovation Through Epigenetic Diversity
Srikant T, Drost H-G.
Front Plant Sci. 2021 Jan 15;11:606800.



Sexual Selection and Evolutionary Biology

On the origin of species by natural and sexual selection.

van Doorn GS, Edelaar P, Weissing FJ.
Science. 2009 Dec 18;326(5960):1704-7.

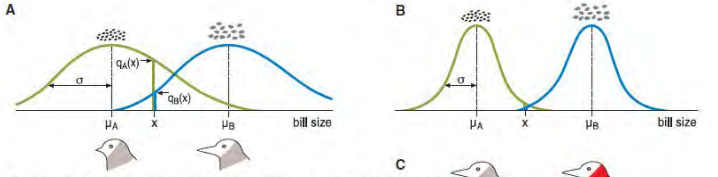


Fig. 1. Illustration of the model structure. Our model considers a patchy environment with differing environmental conditions (small seeds in patch A, large seeds in patch B). Organisms differ in an ecological character (bill size). The green Gaussian curve describes how fitness $q_A(x)$ in patch A varies with bill size x, whereas the blue curve characterizes fitness $q_B(x)$ in patch B. **(A)** In case of a wide fitness curve (large σ), a bird with an intermediate bill size x achieves a higher average fitness across habitats $\frac{1}{2}[q_A(x) + q_B(x)]$ than a small-seed specialist ($x = \mu_A$) or a large-seed specialist ($x = \mu_B$). Hence, selection is stabilizing and favors a generalist food-exploitation strategy (i.e., an intermediate bill size). **(B)** If σ is small, the fitness of the generalist strategy is very low. Selection is disruptive, favoring the two specialist food-exploitation strategies. **(C)** The colored collar represents a sexual ornament that is expressed in a condition-dependent manner. For the same allocation of resources to the ornament, small-billed birds can produce a more attractive (red) ornament in the small-seed patch A (labeled "habitat A" in the figure), whereas large-billed birds can produce a more attractive ornament in the large-seed patch B (labeled "habitat B"). Hence, the ornament functions as an indicator of local adaptation.

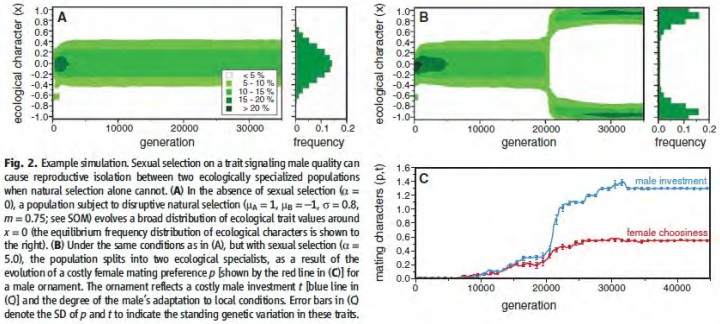


Fig. 2. Example simulation. Sexual selection on a trait signaling male quality can cause reproductive isolation between two ecologically specialized populations when natural selection alone cannot. **(A)** In the absence of sexual selection ($\alpha = 0$), a population subject to disruptive natural selection ($\mu_A = 1$, $\mu_B = -1$, $\sigma = 0.8$, $m = 0.75$; see SOM) evolves a broad distribution of ecological trait values around $x = 0$ (the equilibrium frequency distribution of ecological characters is shown to the right). **(B)** Under the same conditions as in (A), but with sexual selection ($\alpha = 5.0$), the population splits into two ecological specialists, as a result of the evolution of a costly female mating preference p [shown by the red line in (C)] for a male ornament. The ornament reflects a costly male investment t [blue line in (C)] and the degree of the male's adaptation to local conditions. Error bars in (C) denote the SD of p and t to indicate the standing genetic variation in these traits.

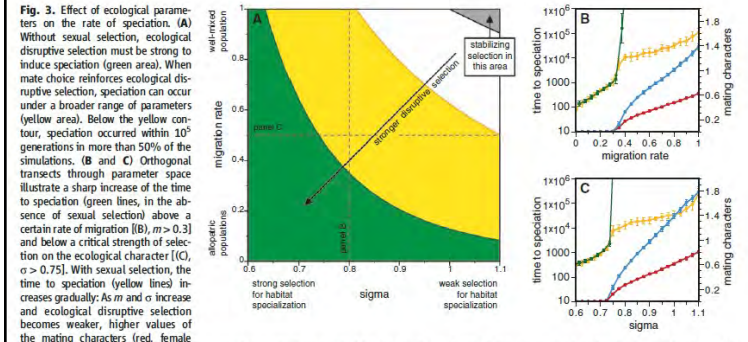
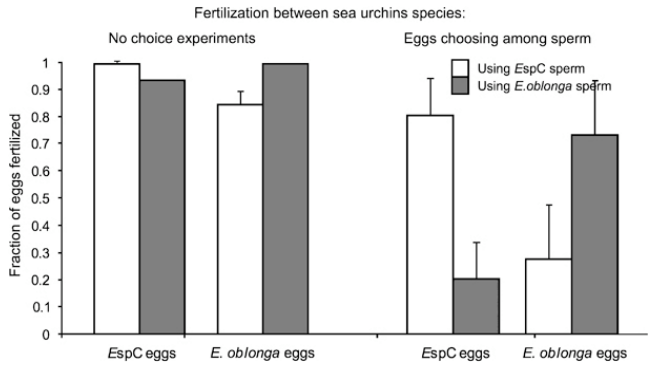


Fig. 3. Effect of ecological parameters on the rate of speciation. **(A)** Without sexual selection, ecological disruptive selection must be strong to induce speciation (green area). When mate choice reinforces ecological disruptive selection, speciation can occur under a broader range of parameters (yellow area). Below the yellow contour, speciation occurred within 10^5 generations in more than 50% of the simulations. **(B** and **C)** Orthogonal transects through parameter space illustrate a sharp increase of the time to speciation (green lines, in the absence of sexual selection) above a certain rate of migration [(B), $m > 0.3$] and below a critical strength of selection on the ecological character [(C), $\sigma > 0.75$]. With sexual selection, the time to speciation (yellow lines) increases gradually: As m and σ increase and ecological disruptive selection becomes weaker, higher values of the mating characters (red, female choosiness; blue, male investment into ornament expression) are required for the population to split. Points are mean ± SD (denoted by error bars) over 20 replicate simulations; other parameters are the same as those in Fig. 2.

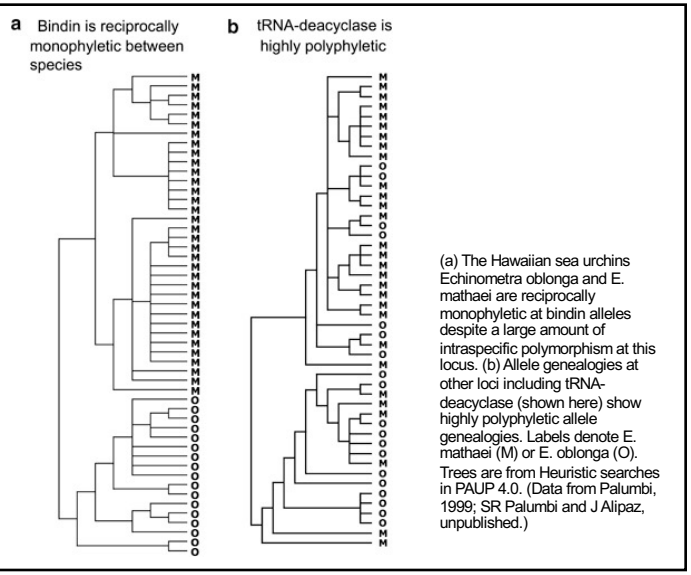
Speciation and the evolution of gamete recognition genes: pattern and process.

Palumbi SR.

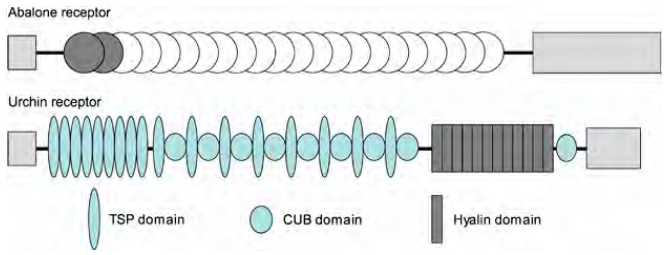
Heredity. 2009 Jan;102(1):66-76.



When eggs of the sea urchins Echinometra oblonga and E. sp. C. are given sperm from either species in no choice experiments, interspecific fertilization rate is high. However, when sperm from the two species are mixed in equal proportions, eggs are 2.5–4 times more likely to be fertilized by conspecific sperm, showing that conspecific sperm precedence is strong in these sympatric species (Geyer and Palumbi, 2005).



(a) The Hawaiian sea urchins Echinometra oblonga and E. mathaei are reciprocally monophyletic at bindin alleles despite a large amount of intraspecific polymorphism at this locus. (b) Allele genealogies at other loci including tRNA-deacyclase (shown here) show highly polyphyletic allele genealogies. Labels denote E. mathaei (M) or E. oblonga (O). Trees are from Heuristic searches in PAUP 4.0. (Data from Palumbi, 1999; SR Palumbi and J Alipaz, unpublished.)

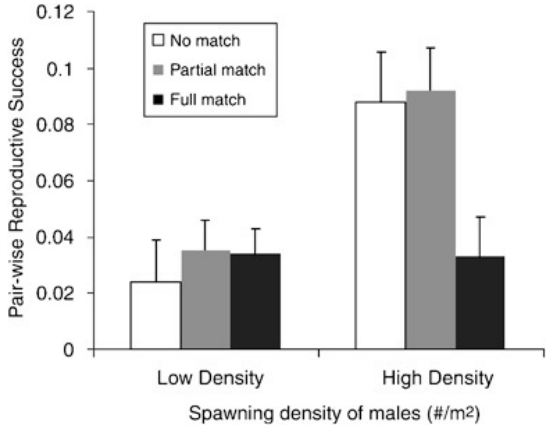


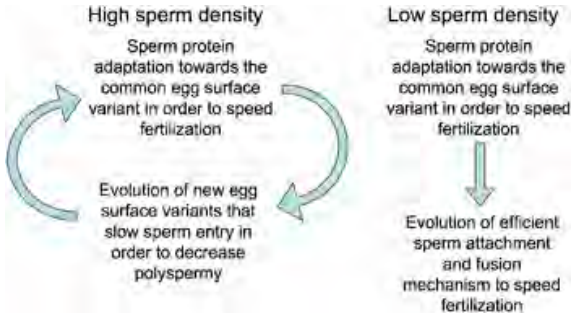
Architecture of sperm receptor proteins in abalone and sea urchins typically includes repeated amino-acid motifs. Motifs that bind sperm proteins are circles in the abalone receptor and rectangles for sea urchins. Motifs under positive selection have dark shading. The sea urchin receptor is modeled after Strongylocentrotus purpuratus. The congener S. franciscanus is reported to have a different arrangement of sperm binding motifs. (Modified from Galindo et al., 2002; Kamei and Glabe, 2003.)

Amino acid sequence of sea urchin sperm binding motif

SpurpEBR1	PVISGCPSDQNVTTDIGNATAVVIWPPTATDNSGSQTLTSTNNPGDDFPIGNNTVTY
SpurpEBR1	.....
SpurpRepeat_1	..F.....N.....
SpurpRepeat_3	..F.....
SpurpRepeat2	.....A..S.....N.....
SpurpRepeat3	..F.....
SpurpRepeat4	.....A.....N.....
SpurpRepeat5	.....
SpurpRepeat6	..F.....
SpurpRepeat7	.....N.....
SpurpRRepeat8	.....A.....T.....VN.....
Em16	..F....VLTFN..P.KV..I.T.I.L.....N...D...HS....H....
Em16	..F.....S.G..S.....T.A.N.....D.....S...Y.....T..N.
Em16	.G.....T.N.FLRKPV.Q.T...N...A.N.....SH.S..T.....T..N.
Em16	..F.....S.N..P...A...T...S.M....T.....N.....
Em16	..F.....S.G.GS.....T.A.N.....D.....S...Y.....T..N.
Eob27	..F.....S.N..P...A...T...S.M....T.....N.....
Eob27	..F.....S.G..S.....A.S...N.....N.I...AS...Y.....
Eob27	..F.....S.N..P.....T...N.....IV.V....S...S.....

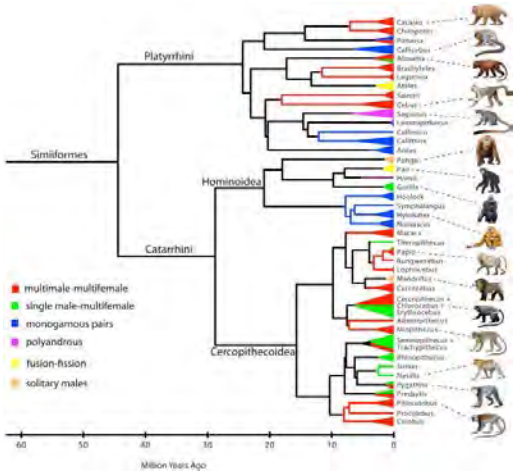
Amino-acid variation in the hyalin-like repeats motifs of the sea urchin sperm receptor within and between species. The top 11 sequences are from different repeats of the EBR1 gene sequenced from Strongylocentrotus purpuratus (Kamei and Glabe, 2003), showing variation at six amino-acid positions. Sequences from one individual Echinometra mathaei (Em16) and one E. oblonga (Eo27) show strong homology to S. purpuratus at about half of the amino-acid positions but are highly variable among repeats. Sequences were obtained by amplifying genomic DNA with primers that recognize intron–exon junctions present in each repeat, cloning PCR products into plasmid vectors and sequencing individual clones. (Data from Kamei and Glabe, 2003; SR Palumbi and J Alipaz, unpublished.)





Cyclic and directional modes of gamete adaptation (left and right, respectively) that derive from ecological conditions favoring high sperm and low sperm densities.

Sexual selection and the evolution of behavior, morphology, neuroanatomy and genes in humans and other primates.
Neurosci Biobehav Rev. 2014 Oct 14;46P4:579-590.
Stanyon R, Bigoni F.



A phylogenetic scheme of Simiiformes at the genus level. The various colors correspond to the predominant social mating system: red = multimale–multifemale (polygynandrous), green = single male–multifemale, blue = monogamous pairs, pink = polyandrous, yellow = fusion–fission, orange = solitary males. Modified from Springer et al. (2012) (http://creativecommons.org/licenses/by/2.5/); data on social structure are from Fleagle (2013). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Unravelling the role of epigenetics in reproductive adaptations to early-life environment.
Bar-Sadeh B, Rudnizky S, Pnueli L, Bentley GR, Stöger R, Kaplan A, Melamed P.
Nat Rev Endocrinol. 2020 Sep;16(9):519-533.

Key points

- Human reproductive function adjusts to changing environmental conditions.
- Key 'windows of susceptibility' during various stages of early development are the most sensitive to events or exposures that can impart long-term reprogramming of adult reproductive function.
- Epigenetic modifications have a role in regulating the central control of reproduction and pubertal onset and likely mediate much of the adaptive response.
- Human cohort data are useful for identifying methylation in proxy tissues that correlates with phenotypic variation, but determining cause and effect is challenging because hormones affect the epigenome and epigenetic ageing.
- Understanding which of the modifications are functional and responsible for the phenotype requires integrating the study of human tissues, animal and cell models and molecular approaches.
- Characterization and elucidation of these adaptive mechanisms are needed to inform the clinician of alternative reproductive strategies, and the implications for fertility treatment and healthy ageing.

Evolutionary history of sexual selection affects microRNA profiles in Drosophila sperm.
Hotzy C, Fowler E, Kiehl B, Francis R, Mason J, Moxon S, Rostant W, Chapman T, Immler S.
Evolution. 2022 Feb;76(2):310-319.

Our findings suggest that long-term adaptation may affect miRNA profiles in sperm and that these may show varied interactions with short-term environmental changes.

Epigenetic Transgenerational Inheritance

and Evolutionary Biology

Epigenetic Inheritance Systems

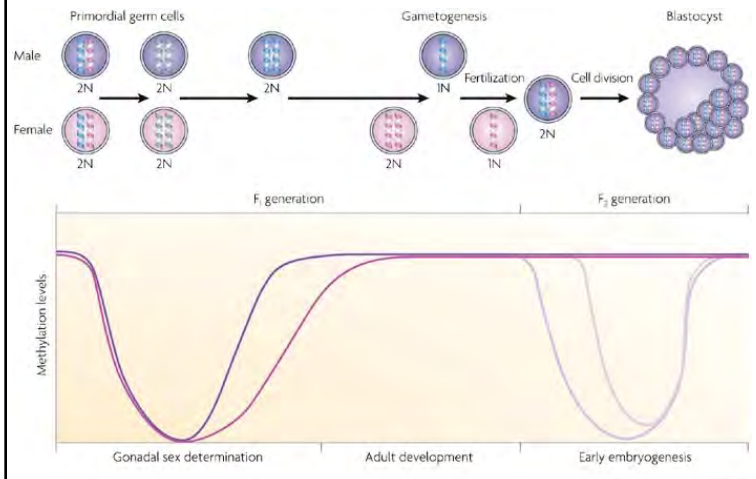
The Inheritance of Environmentally Induced Traits

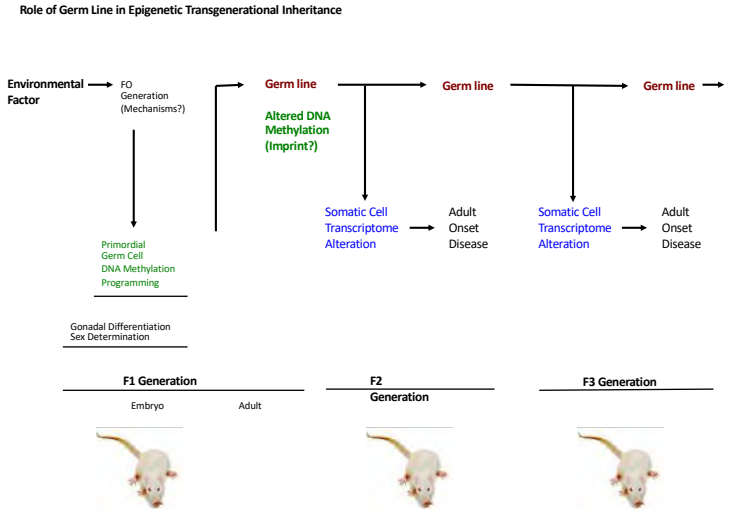
Ecological evolutionary developmental biology, or "eco-evo-devo," has the data to bring two controversial alternative inheritance systems back into the discussion of evolutionary biology. The first idea concerns the inheritance of environmentally acquired traits, an ancient idea usually associated with Jean-Baptiste Lamarck (1744–1829), but which was also used by Charles Darwin and many other Victorian naturalists. The second controversial idea usually goes by the name "genetic assimilation," and it concerns the genetic fixation of an adaptive, plastic response into the genome. In this hypothesis, a response that was once part of a phenotypically plastic repertoire is now part of the normative genetic "program."

The Ghost of Lamarck

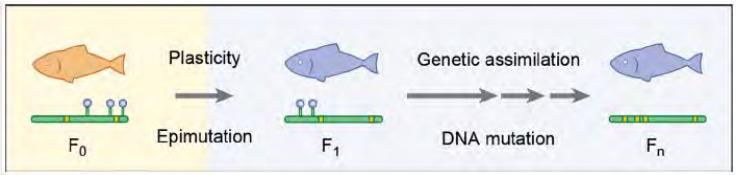
Epigenetic inheritance systems recall the specter of a banished ghost—Lamarckian inheritance. The year 2009 is not only the bicentenary of Darwin's birth and the centenary of the Woltereck and the Johannsen papers described in Chapter 1, it is also the bicentenary of Lamarck's *Philosophie Zoologique*.

Weismann proposed that only the germline counted in heredity, and that the germline was separate from the somatic lineages of cells that formed the body. Therefore, anything that affected the individual could not influence heredity if the germline was not affected. Weismann cut off the tails of mice for nineteen generations and showed that a tailless race did not develop.



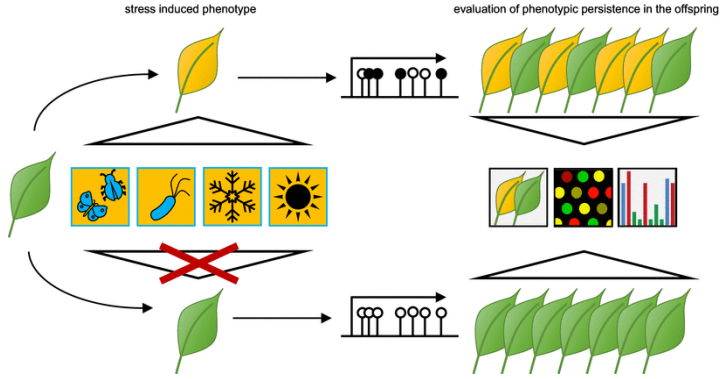


Epigenetic inheritance and reproductive mode in plants and animals.
Anastasiadi D, Venney CJ, Bernatchez L, Wellenreuther M.
Trends Ecol Evol. 2021 Dec;36(12):1124-1140.



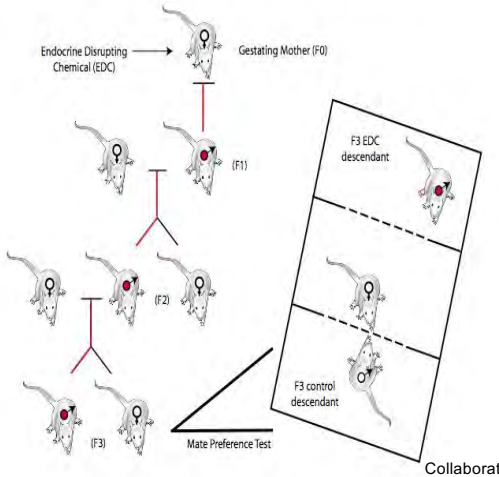
We provide a framework to guide future studies towards understanding the generational persistence and eco-evolutionary significance of epigenomic patterns.

Transgenerational stress-adaption: an opportunity for ecological epigenetics.
Plant Cell Rep. 2018 Jan;37(1):3-9.
Weinhold A.



Experimental setup to investigate the epigenetic origin of transgenerational stress-adaption in plants. A pool of near isogenic plants could be divided into control and stress receiving groups, and treated with either biotic or abiotic stresses. The offspring would be analyzed regarding persistence of a stress-induced phenotype. Candidate genes can be selected based on gene expression differences and analyzed for their epigenetic marks (e.g., cytosine methylation)

Epigenetic Transgenerational Sexual Selection Effect



Collaboration- David Crews UTA

PNAS 2007

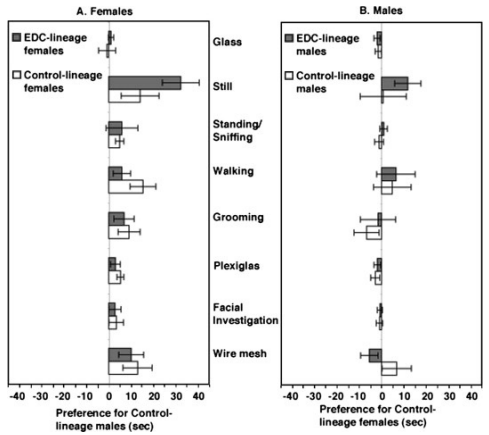
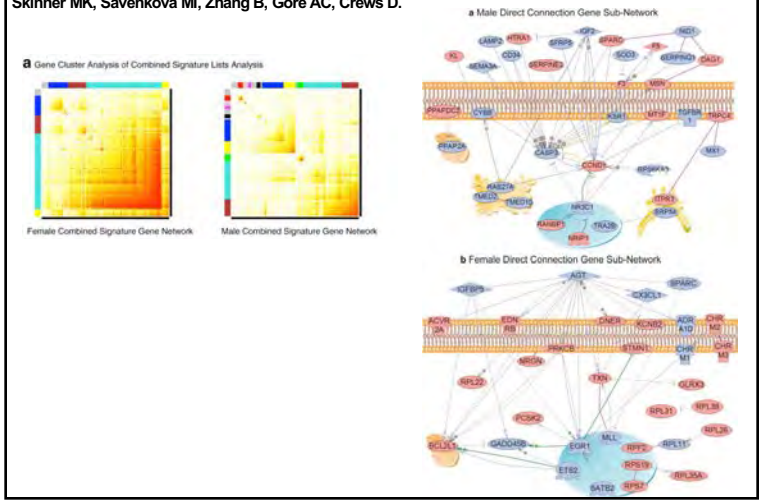
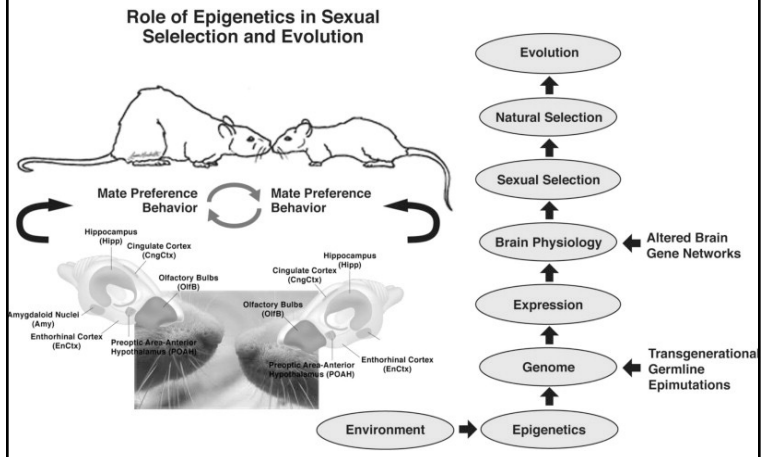
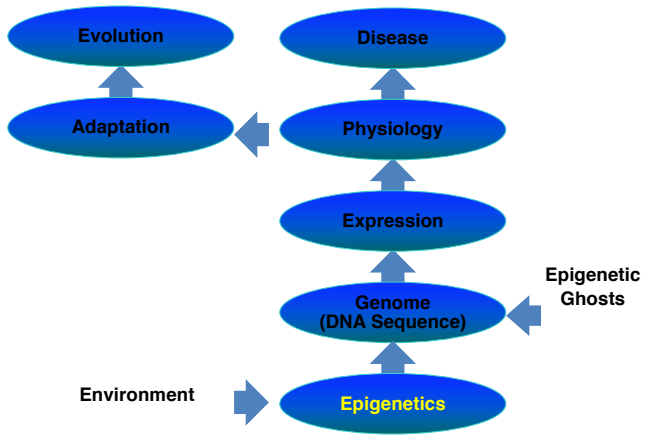


Fig. 7. Third-generation female rats whose progenitors were exposed to vinclozolin, a common-use fungicide with endocrine-disrupting (EDC) properties, and hence epigenetically altered, prefer males from the unexposed Control-lineage. Males do not show this preference. See Fig. 6 for further details. Both females and males from Control- and EDC-lineages were tested with pairs of Control- and EDC-lineage stimulus partners. Presented are the mean (+1 standard error) differences in the time spent in each behavior. Left panel: Behaviors exhibited by females from Control- and EDC-lineages towards males from Control-lineage (positive, right side) and EDC-lineage (negative, left side). Right panel: Behaviors exhibited by males from Control- and EDC-lineages towards females from Control-lineage (positive, right side) and EDC-lineage (negative, left side). The various behavioral measures and test are described in Crews et al. (2007). Reprinted by permission from Crews et al. [24].

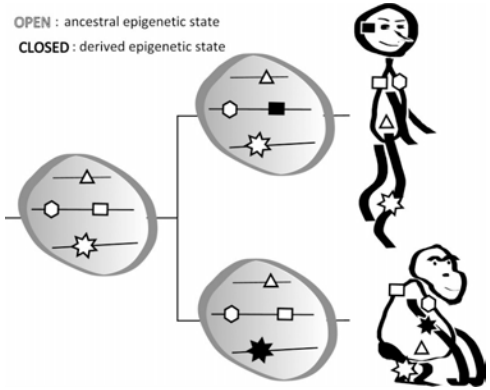
Gene bionetworks involved in the epigenetic transgenerational inheritance of altered mate preference: environmental epigenetics and evolutionary biology.
BMC Genomics. 2014 May 16;15:377.
Skinner MK, Savenkova MI, Zhang B, Gore AC, Crews D.





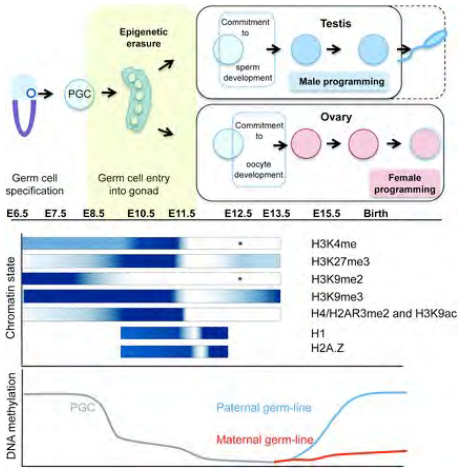


Epigenetic inheritance: a contributor to species differentiation?
DNA Cell Biol. 2012 Oct;31 Suppl 1:S11-6.
Boffelli D, Martin DI.

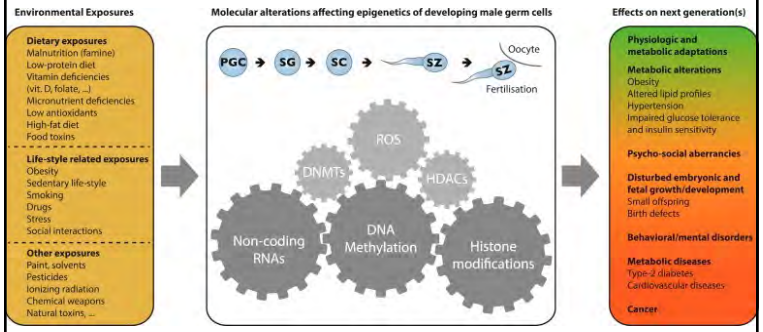


Model for the gain of an active state in somatic tissues following a change of epigenetic state in the germline. We assume that the germline state of certain transcriptional regulatory elements constrains the range of somatic cell types in which those elements will be active (the open elements, representing the ancestral state of an element, are active in a restricted set of cell types). A change in the germline epigenetic state of such an element (e.g., loss of methylation) will result in a broader range of somatic activity, so that the element is now active in cell types where it was silent in the ancestral species (the closed elements are active in more cell types). If germline epigenetic states can be faithfully transmitted between generations, such a change may create a heritable phenotypic difference. This model predicts that CpG islands whose methylation state has been found to deviate from the ancestral state will have activity in a broader range of somatic cell types than in the ancestral state, but this prediction has not yet been tested.

Fine-tuning evolution: germ-line epigenetics and inheritance.
Reproduction. 2013 Jun 14;146(1):R37-48.
Stringer JM, Barrand S, Western P.



Epigenetic inheritance and evolution: A paternal perspective on dietary influences.
Prog Biophys Mol Biol. 2015 Mar 10. pii: S0079-6107(15)00033-4.
Soubry A.



Epigenetic variations in heredity and evolution.
Clin Pharmacol Ther. 2012 Dec;92(6):683-8
Jablonka E.

Table 2 Relations between genetic and epigenetic variations (e.g., marks such as methylation patterns) at a particular locus

	Acquisition (induction) of epigenetic variant		
Inheritance of epigenetic variant	**Obligatory**	**Facilitated**	**Independent of DNA sequence variation**
Obligatory	The variant and its inheritance are fully determined by the specific DNA sequence	The DNA sequence affects the likelihood of acquiring particular variants; their inheritance is dependent on the DNA sequence	The DNA sequence does not determine which variant is acquired, but its inheritance is dependent on the DNA sequence
Facilitated	The variant is determined by the DNA sequence; some variants are more likely to be inherited than others	The DNA sequence affects both the likelihood of acquiring particular variants and the likelihood of their inheritance	The DNA sequence does not determine which variant is acquired but does affect the likelihood of it being inherited
Independent of DNA variation	The variant is determined by the DNA sequence, but the likelihood of it being inherited is not	The DNA sequence affects the likelihood of acquiring particular variants but not the likelihood of their being inherited	The DNA sequence determines neither which variant is acquired nor the likelihood of it being inherited

Obligatory acquisition: the specific DNA sequence determines which of several theoretically possible marks can be acquired; *obligatory inheritance*: the DNA sequence determines whether or not the mark is inherited. Changes in the environment do not change the mark, the likelihood of its inheritance, or the fidelity with which it is inherited. *Facilitated acquisition*: the likelihood of acquiring a particular mark is affected by the DNA sequence, but is not fully determined by it; *facilitated inheritance*: the DNA sequence affects, but does not fully determine, the mark's transmission to the next generation. Environmental conditions affect the likelihood of acquiring particular marks, the likelihood that they are inherited, and the fidelity with which they are inherited. *Independent acquisition and transmission*: total independence of DNA variation is, of course, impossible; "independent" acquisition means that for a given genotype, the same DNA sequence can acquire many different marks; "independent" inheritance means that all these different marks can be inherited. The marks acquired and fidelity of transmission are dependent on environmental conditions in ancestral generations.

Short-term heritable variation overwhelms 200 generations of mutational variance for metabolic traits in Caenorhabditis elegans
Johnson LM, Smith OJ, Hahn DA. Baer CF.
Evolution. 2020 Nov;74(11):2451-2464.

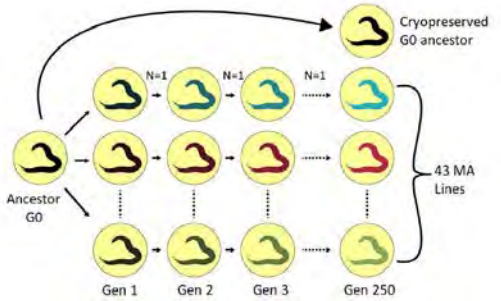
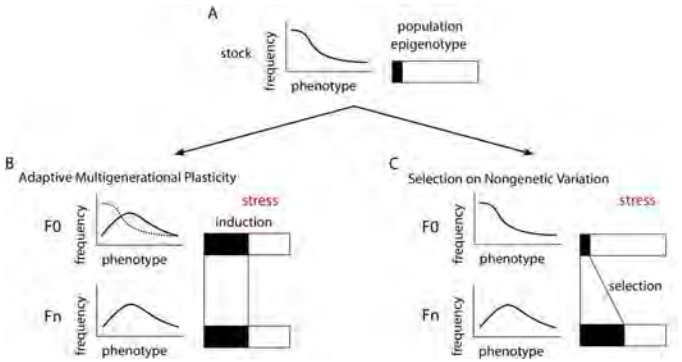
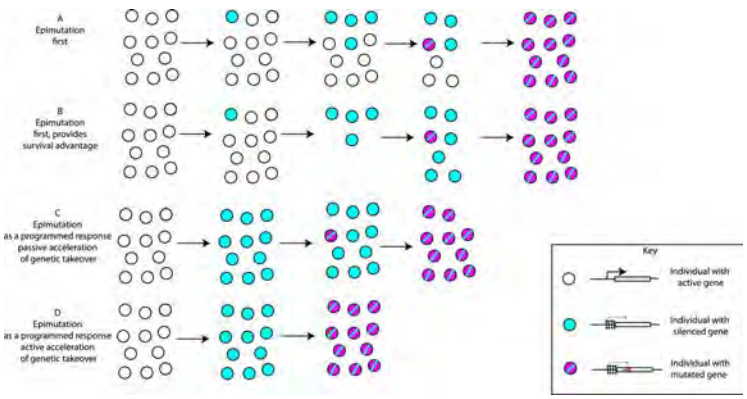


Figure 2. Propagation of mutation accumulation (MA) lines. The G0 ancestor was thawed from a cryopreserved sample and a single hermaphrodite picked onto each of 100 agar plates. MA lines were propagated via single worm descent for ~250 generations. Forty-three MA lines and the G0 ancestor were included in this experiment.

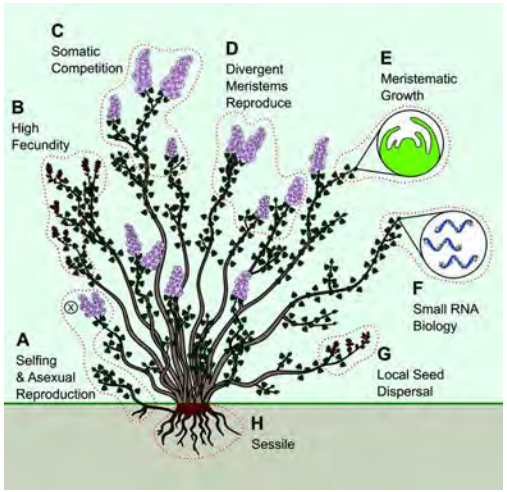
Nongenetic inheritance and multigenerational plasticity in the nematode C. elegans.
Baugh LR, Day T.
Elife. 2020 Aug 25;9:e58498.



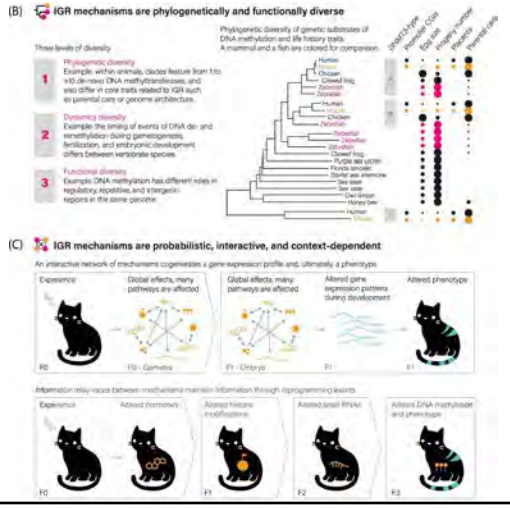
Molecular mechanisms of epigenetic inheritance: Possible evolutionary implications.
Sarkies P.
Semin Cell Dev Biol. 2020 Jan;97:106-115.



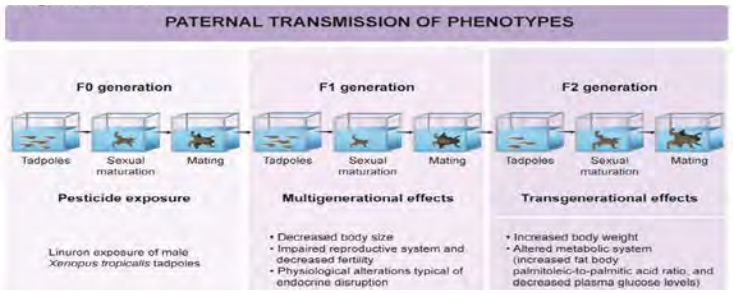
Does variable epigenetic inheritance fuel plant evolution?
Minow MAA, Colasanti J.
Genome. 2020 May;63(5):253-262.



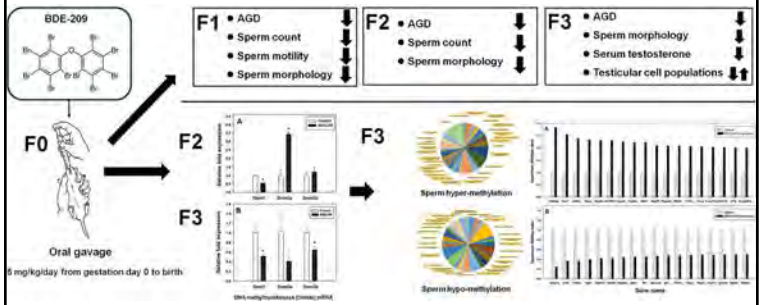
Understanding 'Non-genetic' Inheritance: Insights from Molecular-Evolutionary Crosstalk.
Adrian-Kalchhauser I, Sultan SE, Shama LNS, Spence-Jones H, Tiso S, Keller Valsecchi CI, Weissing FJ.
Trends Ecol Evol. 2020 Dec;35(12):1078-1089.



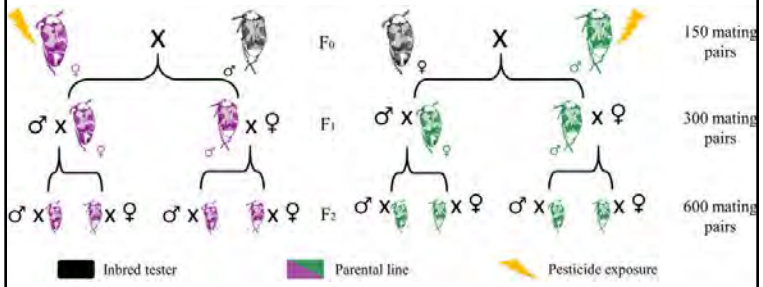
Pesticide induced multigenerational effects on amphibian reproduction and metabolism
Karlsson O, Svanholm S, Eriksson A, Chidiac J, Eriksson J, Jerneren F, Berg C.
Science of the Total Environment. DOI: https://doi.org/10.1016/j.scitotenv.2021.145771



Transgenerational effects of BDE-209 on male reproduction in F3 offspring rats
Hsua P-C, Li Z-K, Lai C-S, Tseng H-L, Lee C-W, Cheng F-J, Chang C-Y, Chena J-R.
Chemosphere. DOI: https://doi.org/10.1016/j.chemosphere.2021.129829

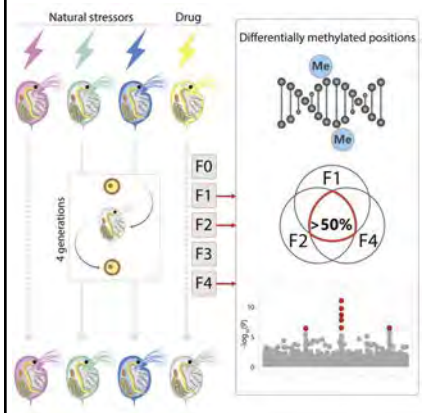


Evolutionary consequences of pesticide exposure include transgenerational plasticity and potential terminal investment transgenerational effects
Veronica Castano-Sanz, Ivan Gomez-Mestre, Francisco Garcia-Gonzalez
Evolution 76(11) 2649-2668



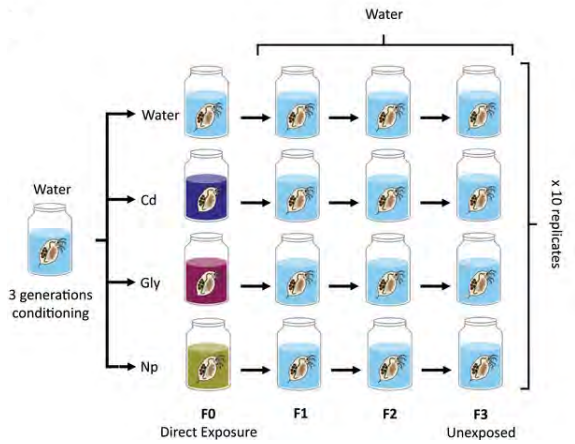
Our results indicate that pesticide exposure leads to unanticipated effects on population dynamics and have far-reaching ecological and evolutionary implications.

Environmentally induced DNA methylation is inherited across generations in an aquatic keystone species.
Feiner N, Radersma R, Vasquez L, Ringnér M, Nystedt B, Raine A, Tobi EW, Heijmans BT, Uller T.
iScience. 2022 Apr 25;25(5):104303.



- Naturally induced DNA-methylation persists until generation F4 in *Daphnia*
- Drug-induced de-methylation is reset after one generation
- Methylation is enriched in exons suggesting a gene regulatory function
- Epigenetic inheritance may influence eco-evolutionary dynamics

Pollution induces epigenetic effects that are stably transmitted across multiple generations.
Harney E, Paterson S, Collin H, Chan BHK, Bennett D, Plaistow SJ.
Evol Lett. 2022 Feb 3;6(2):118-135.



Persistent effects are likely to influence phenotypic development, which could contribute to the rapid adaptation, or extinction, of populations confronted by anthropogenic stressors.

Role of environmentally induced epigenetic transgenerational inheritance in evolutionary biology: Unified Evolution Theory.
Skinner MK, Nilsson EE.
Environ Epigenet. 2021 Oct 30;7(1):dvab012.

Table 1: History of epigenetics

1940s	Conrad Waddington defined epigenetics as environment–gene interactions that induce developmental phenotypes
1975	Holliday and Pugh, and Riggs identify DNA methylation
1988	X-chromosome inactivation and DNA methylation
1990s	Imprinted genes, allelic expression, and DNA methylation
1995	Histone modifications and chromatin structure
2000s	Non-coding RNAs
2005	Epigenome mapping
2005	Epigenetic transgenerational inheritance

Table 4: Examples of epigenetic transgenerational inheritance impacts on evolution

Organism		Reference
Plant	(*Taraxacum officinale*, Arabidopsis)	[77, 97–100, 103–109]
Worm	(*Caenorhabditis elegans*)	[110–113]
Bird	(House sparrow, *Passer domesticus*)	[102, 114–116]
Asexual snail	(*Potamopyrgus antipodarum*)	[117, 118]
Hybrid clonal fish	(*Chrosomus eos-neogaeus*)	[119, 120]
Fish	(*Poecilia mexicana*)	[121]
Bird	(Darwin finch, *Geospiza fortis*)	[122, 123]
Fish	(Steelhead trout, *Oncorhynchus mykiss*)	[124]
Alligator	(*Alligator mississippiensis*)	[125]
Mouse	(*Mus musculus*)	[46, 75]
Rat	(*Rattus norvegicus*)	[46, 74, 82, 93]

Inbreeding, Epigenetics and Evolutionary Biology

FUNDAMENTAL CONCEPTS IN GENETICS

The genetics of inbreeding depression

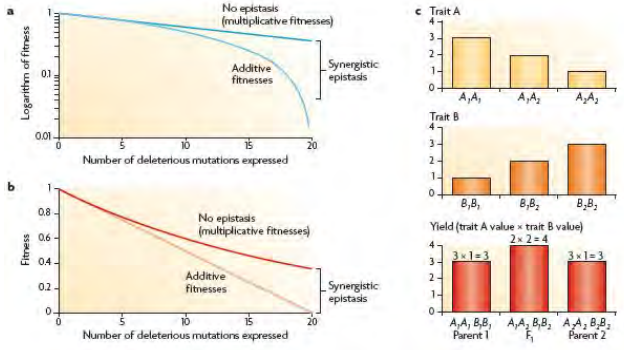
Deborah Charlesworth and John H. Willis‡*

Abstract | Inbreeding depression — the reduced survival and fertility of offspring of related individuals — occurs in wild animal and plant populations as well as in humans, indicating that genetic variation in fitness traits exists in natural populations. Inbreeding depression is important in the evolution of outcrossing mating systems and, because intercrossing inbred strains improves yield (heterosis), which is important in crop breeding, the genetic basis of these effects has been debated since the early twentieth century. Classical genetic studies and modern molecular evolutionary approaches now suggest that inbreeding depression and heterosis are predominantly caused by the presence of recessive deleterious mutations in populations.

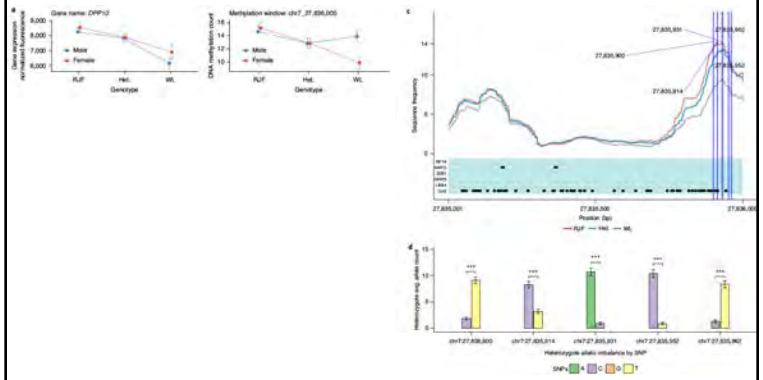
Inversion
Rearrangement in which part of a chromosome is inverted in order with respect to a homologous chromosome in the same species or in a different species.

Meiotic drive regions
Regions containing genes that have non-Mendelian segregation in heterozygotes because one allelic version of the region is rendered non-functional during meiosis.

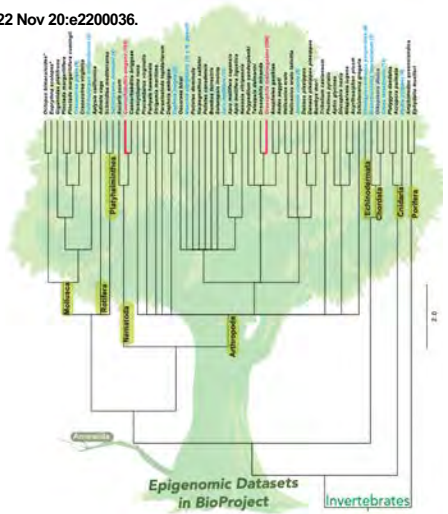
Complementation
Restoration of function in heterozygotes for two genes with recessive loss-of-function mutations (unless both mutations are in the *trans* configuration in the same gene, so that neither allele is functional).



The methylation landscape and its role in domestication and gene regulation in the chicken.
Höglund A, Henriksen R, Fogelholm J, Churcher AM, Guerrero-Bosagna CM, Martinez-Barrio A, Johnsson M, Jensen P, Wright D.
Nat Ecol Evol. 2020 Dec;4(12):1713-1724.



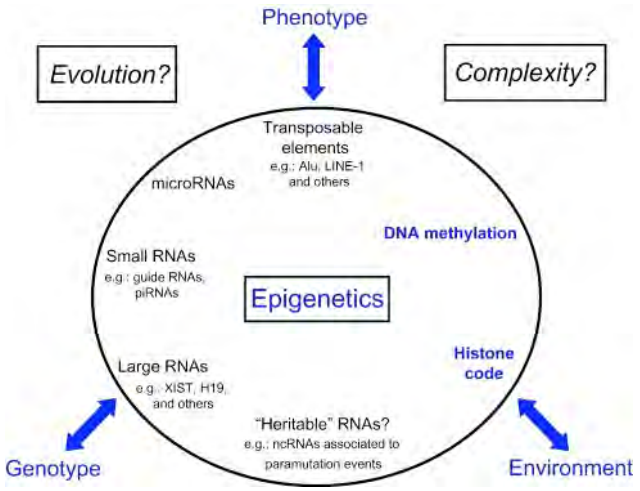
Epigenetics across the evolutionary tree: New paradigms from non-model animals.
Sadler KC.
Bioessays. 2022 Nov 20:e2200036.



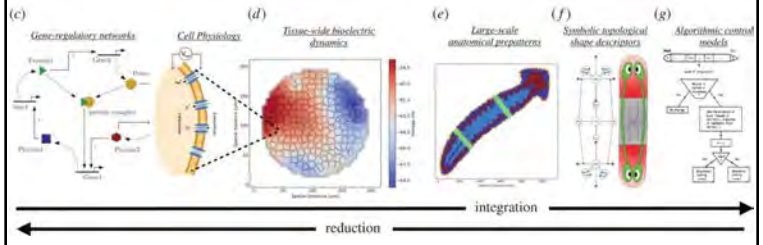
The biodiversity of epigenomic datasets for invertebrate animals cataloged in BioProject (NCBI).

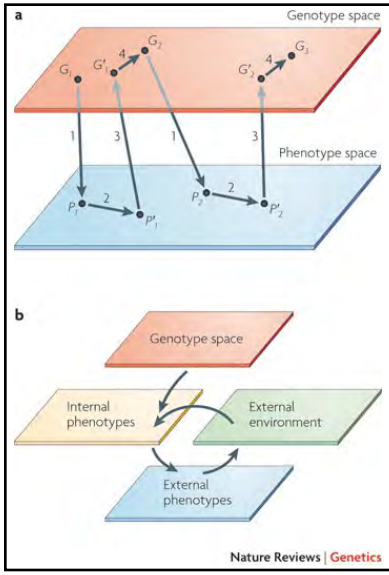
This review puts recent discoveries in the epigenetics of non-model invertebrates in historical context, and describes new insight into the patterning and functions of DNA methylation and other highly conserved epigenetic modifications.

Summary Epigenetics and Evolutionary Biology



Top-down models in biology: explanation and control of complex living systems above the molecular level.
J R Soc Interface. 2016 Nov;13(124).
Pezzulo G, Levin M.





The concept of a genotype–phenotype (G–P) map is a widely used metaphor for the multiple ways in which genotypic information influences the phenotype of an organism. The term dates at least to 1970 when Jim Burns proposed linking population genetic and biochemical variation116, but the importance of the relationship between genotype and phenotype has long been apparent. Two early versions of the G–P map concept are the epigenetic landscape of Conrad Hal Waddington117 and Richard Lewontin's concept of evolution as taking place in the space of all possible genotypes (G space) and the space of all possible phenotypes (P space)118.

This relationship is shown in part **a** of the figure, which indicates the mean position of a population in G and P spaces over two generations. There are four key parts to the evolutionary process, shown as numbered arrows: (1) the epigenetic process creates the phenotype using genotypic information; (2) natural selection acts in P space to change the average phenotype of parents away from the average phenotype of all individuals; (3) the identity of successful parents determines which genotypes are preserved; and (4) genetic processes such as mutation and recombination alter position in G space.An alternative concept of the G–P map at the level of the individual is shown in part **b** of the figure. An individual can be conceptualized as occupying a single point in G space, and this position plus the environment (including other individuals, such as parents) combine to create the internal phenotypic state of the organism throughout its life. These internal phenotypes include cellular, tissue level and physiological properties. These internal phenotypes in turn shape external phenotypes such as morphology and behaviour. Phenotypes can in turn shape the environment that an individual occupies, creating complex feedback relationships between genes, environments and phenotypes. The importance of the environment suggests that we should explicitly broaden the G–P map to the genotype–environment–phenotype (G–E–P) map.

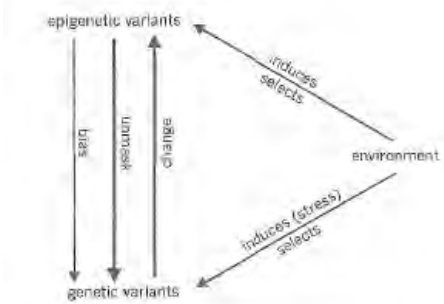


Figure 7.6
The interactions of the genetic and epigenetic systems.

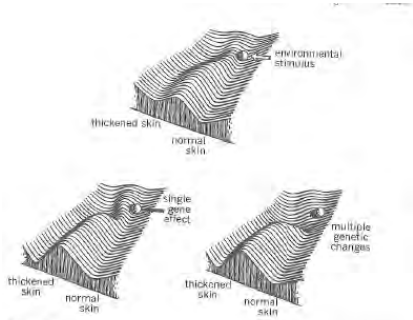
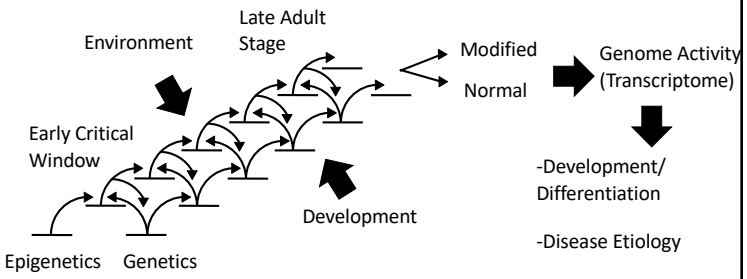


Figure 7.4
Genetic assimilation. At the top, the original epigenetic landscape, in which the main valley leads to normal skin, and a side branch leads to thickened skin. Thick skin is formed only if an environmental stimulus (open arrow) pushes development into the left-hand pathway. Below are two epigenetic landscapes after natural selection has led to genetic assimilation. In both, through selection, the valley leading to thick skin has been furred and deepened, so that it is an easier path to follow. On the left, a major gene effect (solid arrow) pushes development into this pathway, whereas on the right the selection of variations in many genes has so remodeled the landscape that no stimulus is needed. (Adapted with permission from C. H. Waddington, *The Strategy of the Genes*, Allen and Unwin, London, 1957, p. 167.)



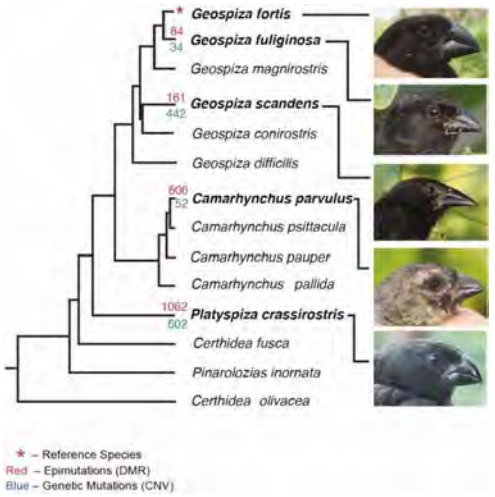
Targeting, constructing, and planning transmitted variation

Inheritance system	Variation is targeted (biased generation)?	Variation subject to developmental filtering and modification?	Variation constructed through direct planning?	Variations can change the selective environment?
Genetic	Generally not, except for the directed changes that are part of development and the various types of interpretive mutation	Usually not, although expressed genetic changes may have to survive selection between cells prior to sexual or asexual reproduction	No	Only insofar as genes can affect all aspects of epigenetics, behavior, and culture
Epigenetic	Yes, a lot of epigenetic variations are produced as specific responses to inducing signals	Yes, selection can occur between cells prior to reproduction; epigenetic states can be modified or reversed during meiosis and early embryogenesis	No	Yes, because the products of cellular activities can affect the environment in which a cell, its neighbors, and its descendants live
Behavioral	Yes, because of emotional, cognitive, and perceptual biases	Yes, behavior is selected and modified during the animal's lifetime	No	Yes, new social behavior and traditions alter the social and sometimes also the physical conditions in which an animal lives
Symbolic	Yes, because of emotional, cognitive, and perceptual biases	Yes, at many levels, in many ways	Yes, at many levels, in many ways	Yes, very extensively, by affecting many aspects of the social and physical conditions of life

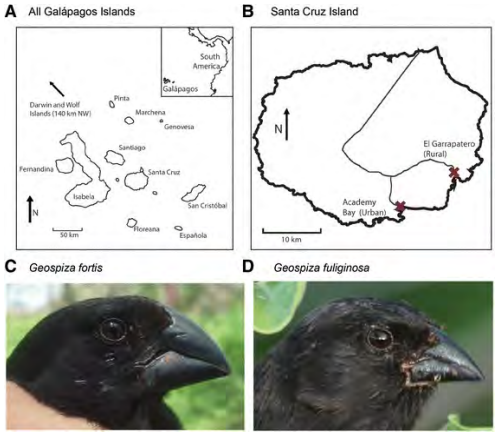
The reproduction of information

Inheritance system	Organization of information	Dedicated copying system?	Transmits latent (nonexpressed) information?	Direction of transmission	Range of variation
Genetic	Modular	Yes	Yes	Mostly vertical	Unlimited
Epigenetic					
Self-sustaining loops	Holistic	No	No	Mostly vertical	Limited at the loop level, unlimited at the cell level
Structural templating	Holistic	No	No	Mostly vertical	Limited at the structure level, unlimited at the cell level
RNA silencing	Holistic	Yes	Sometimes	Vertical and sometimes horizontal	Limited at the single transcript level, unlimited at the cell level
Chromatin marks	Modular and holistic	Yes (for methylation)	Sometimes	Vertical	Unlimited
Organism-level developmental legacies	Holistic	No	No	Mostly vertical	Limited
Behavioral					
Behavior-affecting substances	Holistic	No	No	Both vertical and horizontal	Limited at the single behavior level, unlimited for lifestyles
Nonimitative social learning	Holistic	No	No	Both vertical and horizontal	Limited at the single behavior level, unlimited for lifestyles
Imitation	Modular	Probably	No	Both vertical and horizontal	Unlimited
Symbolic	Modular and holistic	Yes, several	Yes	Both vertical and horizontal	Unlimited

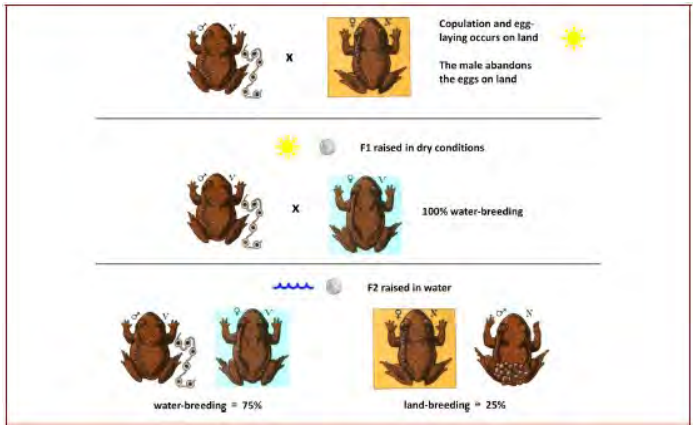
Epigenetics and the evolution of Darwin's Finches.
Genome Biol Evol. 2014 Jul 24;6(8):1972-89.
Skinner MK, Gurerrero-Bosagna C, Haque MM, Nilsson EE, Koop JA, Knutie SA, Clayton DH.



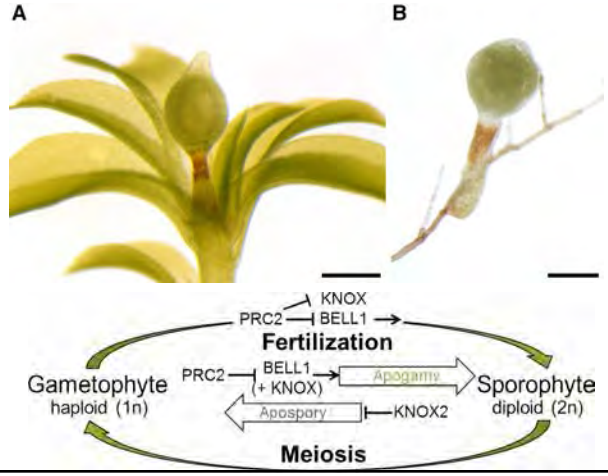
Epigenetic variation between urban and rural populations of Darwin's finches.
BMC Evol Biol. 2017 Aug 24;17(1):183.
McNew SM, Beck D, Sadler-Riggleman I, Knutie SA, Koop JAH, Clayton DH, Skinner MK.



An Epigenetic Perspective on the Midwife Toad Experiments of Paul Kammerer (1880-1926).
Vargas AO, Krabichler Q, Guerrero-Bosagna C.
J Exp Zool B Mol Dev Evol. 2017 Jan;328(1-2):179-192.



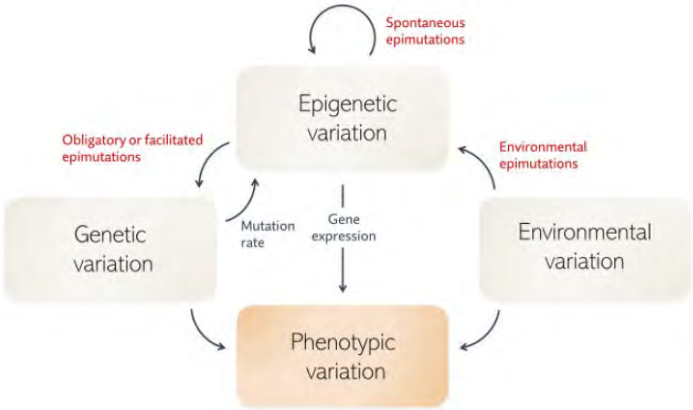
Alternation of generations - unravelling the underlying molecular mechanism of a 165-year-old botanical observation.
Horst NA, Reski R.
Plant Biol (Stuttg). 2016 Jul;18(4):549-51.



Leapfrog to speciation boosted by mother's influence.
Verzijden M.
Nature. 2019 Oct;574(7776):38-39.

It has now been found that mothers of a species of frog affect the behaviour of their offspring — influencing female mating preferences and aggression between males. Such behaviours might lead to the formation of new species.

The Role of Stochasticity in the Origin of Epigenetic Variation in Animal Populations.
Biwer C, Kawam B, Chapelle V, Silvestre F.
Integr Comp Biol. 2020 Dec 16;60(6):1544-1557.



Epigenetic Alterations Promote Genetic Instability

Genetic Mutation	Epigenetic Alteration	DNA Sequence Alteration
Point Mutation (SNP)	DNA Methylation (CpG)	Susceptibility C ➔ T Conversion
Copy Number Variation (CNV)	Hypomethylation (Repeats)	Susceptibility Repeat Element Alteration (CNV)
Transposon Migration	Hypomethylation DNA	Susceptibility Transposon Migration
Translocation	DNA Methylation and Histone Alterations	Susceptibility Translocation at Break Point
Telomere Length	DNA Methylation Alteration	Alteration in Telomere Length

Environmentally Induced Epigenetic Transgenerational Inheritance of Sperm Epimutations Promote Genetic Mutations

Skinner MK, Guerrero-Bosagna C, Haque M.
Epigenetics 2015; 10:8, 762-771

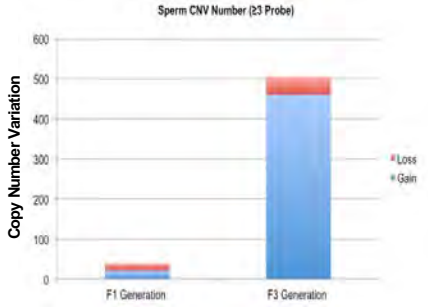
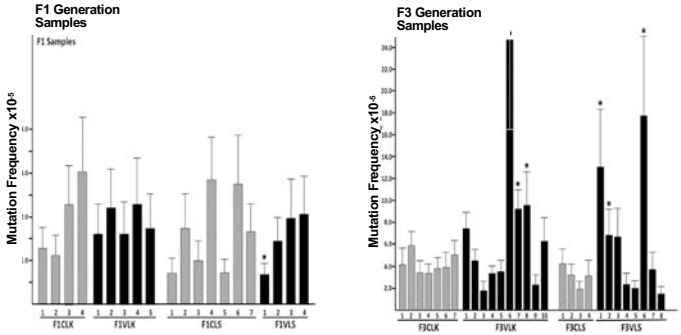


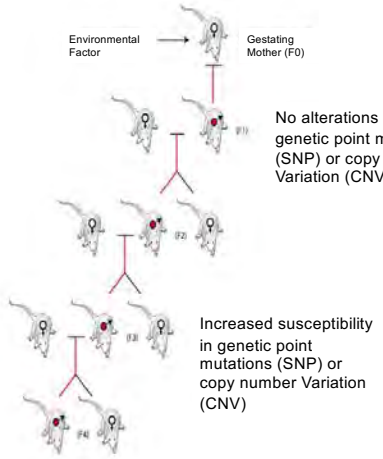
Table 1. (A) Vinclozolin F3 Generation Sperm Genome-wide CNV and Epimutations

Parameters	F1 Generation Sperm CNV	F3 Generation Sperm CNV	F3 Generation Epimutation Sperm
Number (Single Probe)	540(294 Gain / 246 Loss)	4912(4648 Gain / 264 Loss)	9932
Number (≥3 Probe)	39(21 Gain / 18 Loss)	506(461 Gain / 45 Loss)	191
Mean Size (base)	11,633	12,637	2,131
Mean CpG Density (CpG/100 bp)	1.1	1.0	0.9

Epigenetic Transgenerational Inheritance of Sperm Epimutations Promotes Genome Instability and Genetic Point Mutations
McCarrey JR, Lehle JD, Raju SS, Wang Y, Nilsson EE, Skinner MK
(2016) Plos One



Sperm Epimutations Promotes Epigenetic Transgenerational Inheritance of Genetic Mutations



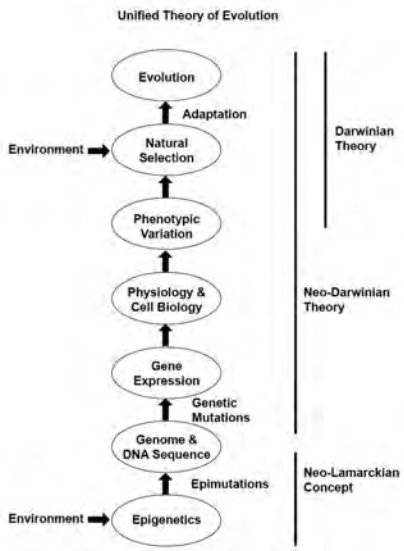
No alterations in genetic point mutations (SNP) or copy number Variation (CNV)

Increased susceptibility in genetic point mutations (SNP) or copy number Variation (CNV)

Environmental Epigenetics and a Unified Theory of the Molecular Aspects of Evolution: A Neo-Lamarckian Concept that Facilitates Neo-Darwinian Evolution.
Skinner MK.
Genome Biol Evol. 2015 Apr 26;7(5):1296-302.

Evolution Theory Components

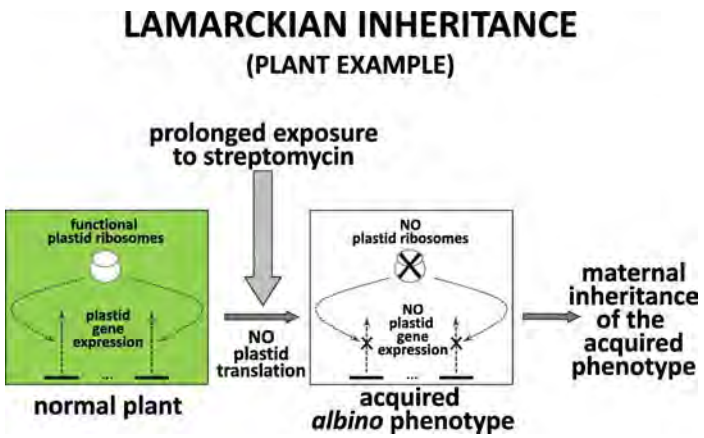
- Neo-Lamarckian concept
  - Environment directly alters phenotype generationally
- Darwinian evolution theory
  - Natural selection acts on phenotypic variation
- Neo-Darwinian evolution theory
  - Genetic mutations promote phenotypic variation on which natural selection acts
- Unified evolution theory
  - Environmental epigenetic alterations promote genetic mutations to alter genotypic variation Environmental epigenetics and genetic mutations both promote phenotypic variation on which natural selection acts



Epigenetics, Darwin, and Lamarck.
Genome Biol Evol. 2015 May 29;7(6):1758-60.
Penny D.

It is not really helpful to consider modern environmental epigenetics as neo-Lamarckian; and there is no evidence that Lamarck considered the idea original to himself. We must all keep learning about inheritance, but attributing modern ideas to early researchers is not helpful, and can be misleading.

Heredity determined by the environment: Lamarckian ideas in modern molecular biology.
Tikhodeyev ON.
Sci Total Environ. 2020 Mar 25;710:135521.



Lamarck and Panspermia - On the Efficient Spread of Living Systems Throughout the Cosmos.
Steele EJ, Gorczynski RM, Lindley RA, Liu Y, Temple R, Tokoro G, Wickramasinghe DT, Wickramasinghe NC.
Prog Biophys Mol Biol. 2019 Dec;149:10-32.

Table 1
Evidence consistent with Lamarckian evolutionary processes.

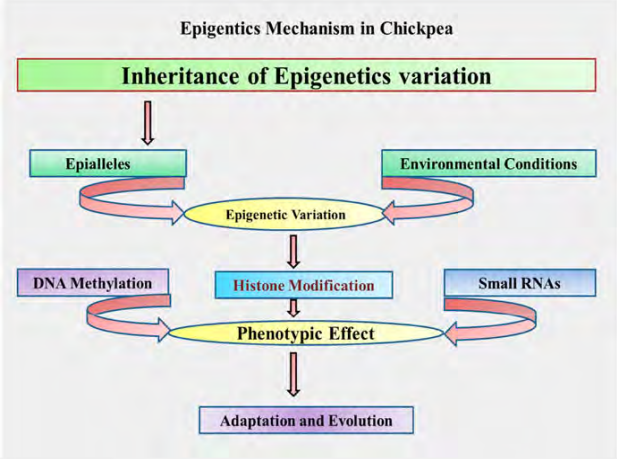
1	Environmental Stimulation as the Directional Mutational Driver
2	Role of Epigenetic Gene Targeting
3	Rapid Genetic Adaptation
4	Penetration of the *Weismann Barrier*
5	Horizontal Gene Transfer (HGT)
6	Central Role of Reverse Transcription

The summaries of evidence for Horizontal Gene Transfer phenomena are well covered at the Wikipedia site https://en.wikipedia.org/wiki/Horizontal_gene_transfer.

Table 2
Cosmic distribution and numbers of living systems.

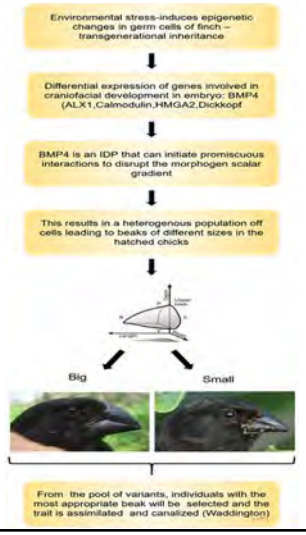
• Viruses – terrestrial number 10^{31}	10^{53}
• Bacteria/Archaea - terrestrial number $\geq 10^{30}$	10^{52}
• Single cell eukaryotes - terrestrial number 10^{20}-10^{30}	10^{32}–10^{52}
• Complex Metazoans - terrestrial number $\geq 10^{20}$	10^{42}
• Higher plants, terrestrial number $\geq 10^{7}$ species	10^{29}
• Higher animals, terrestrial number $\geq 10^{7}$ species	10^{29}

Epigenomics as Potential Tools for Enhancing Magnitude of Breeding Approaches for Developing Climate Resilient Chickpea.
Chandana BS, Mahto RK, Singh RK, Ford R, Vaghefi N, Gupta SK, Yadav HK, Manohar M, Kumar R.
Front Genet. 2022 Jul 22:13:900253.



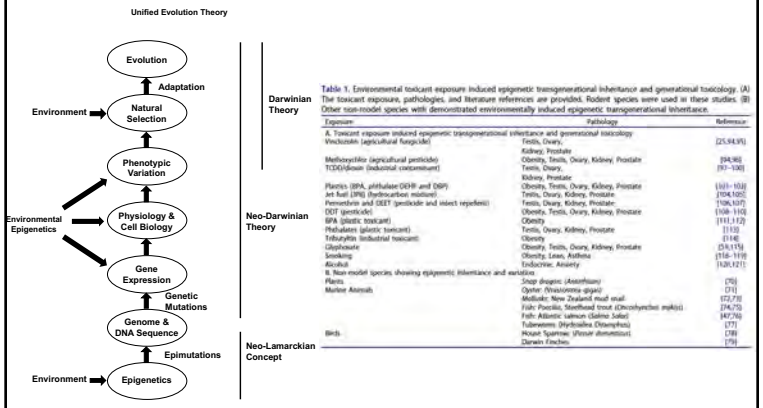
Proposed schematic mechanism/process of epigenetics in chickpea.

Intrinsically disordered BMP4 morphogen and the beak of the finch: Co-option of an ancient axial patterning system.
Kulkarni P, Mohanty A, Salgia R, Uversky VN.
Int J Biol Macromol. 2022 Oct 31;219:366-373.



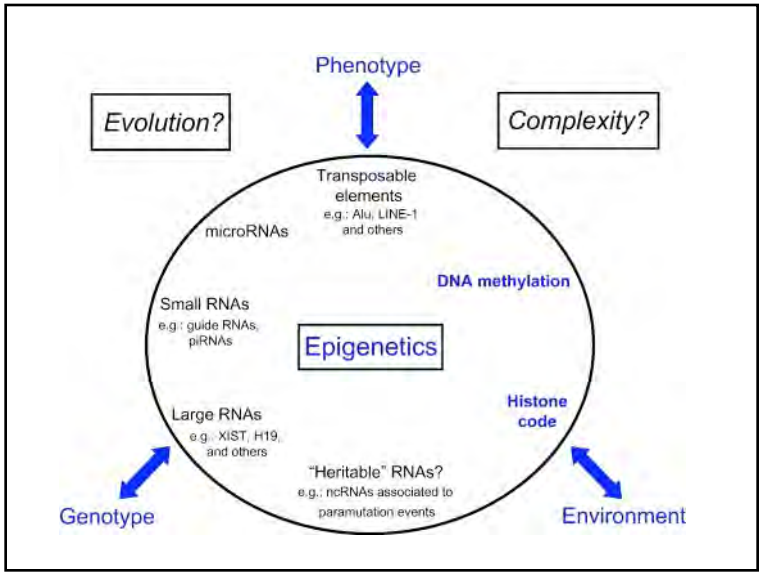
A schematic showing the proposed causal link between epigenetic changes, BMP4 dysregulation and the evolution of the beak of the finch by natural selection.

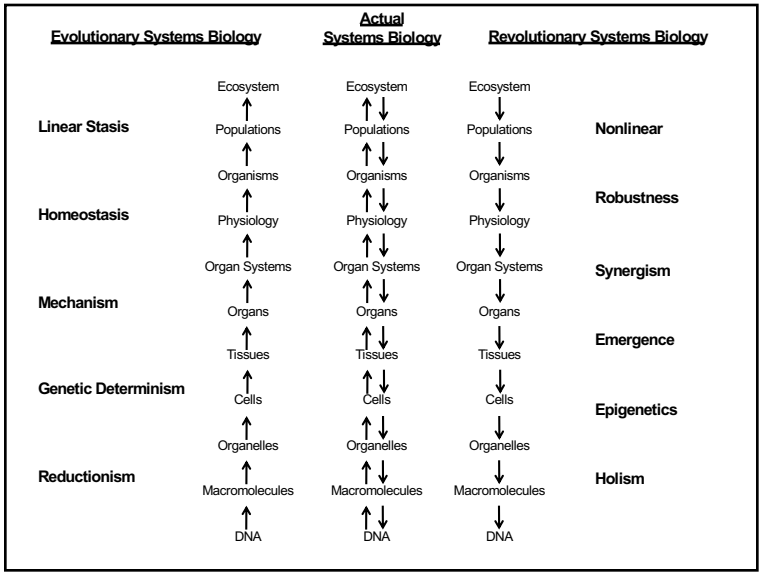
Generational stability of epigenetic transgenerational inheritance facilitates adaptation and evolution.
Korolenko A, Skinner MK.
Epigenetics. 2024 Dec;19(1):2380929.



Epigenetics Research in Evolutionary Biology: Perspectives on Timescales and Mechanisms.
Yi SV.
Mol Biol Evol. 2024 Sep 3;41(9):msae170.

While epigenetic marks can be inherited independently of genetic sequences in some species, there is little evidence that such "transgenerational inheritance" is a general phenomenon. Rather, molecular mechanisms of epigenetic inheritance are highly variable between species.





"Epigenetics and Systems Biology"

Spring 2025 (Odd Years) – Course Syllabus
Biol 476/576 Undergraduate/Graduate Course (3 Credit)
SLN: (476) – 06655, (576) – 06656
Time - Tuesday and Thursday 10:35 am-11:50 am
Course Lectures recorded on Canvas/Panopto and Discussion Sessions live on WSU Zoom for all campuses (Hybrid Course)
Course Director - Michael Skinner, Abelson Hall 507, 335-1524, skinner@wsu.edu
Co-Instructor – Eric Nilsson, Abelson Hall 507, 225-1835, nilsson@wsu.edu
Learning Objective - The objective of the course is to learn the concept and critical role of systems to understand molecular, cell, development, physiology and evolutionary aspects of biology with a focus on the role of epigenetics in systems biology.
Schedule/Lecture Outline –

Week 1	January 7 & 9	Systems Biology (History/ Definitions/ Theory)
Week 2	January 14 & 16	Systems Biology (Networks & Emergence)
Week 3	January 21 & 23	Systems Biology (Components: DNA to Phenotype)
Week 4	Jan 28 & 30	Systems Biology (Genomics / Technology)
Week 5	February 4 & 6	Epigenetics (History / Molecular Processes)
Week 6	February 11 & 13	Epigenetics (Molecular Processes & Integration)
Week 7	February 18 & 20	Epigenetics (Genomics and Technology)
Week 8	Feb 25 & 27	Cell & Developmental Biology
Week 9	March 4 & 6	Epigenetics of Cell & Developmental Biology (& Midterm Exam)
Week 10	**March 10 – 14**	**Spring Break**
Week 11	March 18 & 20	Environmental Impact on Biology
Week 12	March 25 & 27	Environmental Epigenetics
Week 13	April 1 & 3	Disease Etiology
Week 14	April 8 & 10	Epigenetics & Disease Etiology
Week 15	April 15 & 17	Evolutionary Biology & Genetics
Week 16	April 22 & 24	Epigenetics & Evolutionary Biology
Week 17	Finals Week	Grant Review/ Study Section Meeting (& Final Exam)