20 Generation Study
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Korolenko AA, Nilsson EE, Beck D, and Skinner MK (2026) Stability of Environmentally Induced Epigenetic Transgenerational Inheritance of Adult-Onset Disease and Parturition Abnormalities. PNAS 123(8):e2523071123. PMID: 41701841

Summary

Previous research on the generational stability of epigenetic transgenerational inheritance was conducted through a ten-generation study of all transgenerational generations in mammals. This study demonstrated both the stability of epigenetic inheritance across generations and demonstrated a generational increase incidence of disease pathology. Building on this research, the present study follows the same lineage of rats with ancestral vinclozolin exposure through twenty generations. The findings offer important insights into long-term mammalian models of epigenetic transgenerational inheritance. Observations demonstrate an increase in differential DNA methylated regions (DMRs) across multiple generations. This indicates a persistent and stable transmission of epigenetic alterations. Additionally, deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) apoptosis assays revealed elevated levels of germline apoptosis in the male rats of the maternal and paternal lineages. This suggests a potential consequence of epigenetic dysregulation in spermatogenesis. Ancestrally exposed rats to vinclozolin showed significant parturition abnormalities in both the maternal and paternal lineages after 16 generations. This included maternal deaths during labor and stillbirths. Pathological assessments revealed abnormalities across multiple tissue types and an increased incidence of disease. This suggests the physiological consequences of the generational stability of epigenetic inheritance. Observations establish the generational stability of epigenetic inheritance over twenty generations in a mammalian model system, however, new pathology in later generations involving parturition abnormalities were also observed. The generational stability of transgenerational effects observed in this study has implications for human health, particularly regarding environmental toxicant exposures, reproductive health disorders, and disease susceptibility.