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Developmental nicotine exposure elicits multigenerational epigenetic anomalies in the frontal cortices, striata, and hippocampi of adolescent mice which co-occur with neurodevelopmental disorder-like phenotypes

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Maternal smoking of traditional or electronic cigarettes during pregnancy constitutes developmental nicotine exposure (DNE), which confers liability to neurodevelopmental disorders such as ADHD, autism, and schizophrenia in children and grandchildren. Modeling the intergenerationally transmissible impacts of smoking during pregnancy in the offspring and grandoffspring of nicotine-exposed female mice, we previously reported that DNE elicits multigenerational nicotine preference, hyperactivity and risk-taking behaviors, aberrant circadian rhythmicity of activity, nicotinic acetylcholine receptor and dopamine transporter dysfunction, impaired proteolytic processing of proBDNF to BDNF, and glucocorticoid receptor hypoactivity in the frontal cortices and striata accompanied by hypocorticosteronemia. This phenotypic ensemble recapitulates behavioral, neuropharmacological, neurotrophic, and neuroendocrine anomalies characteristic of multiple neurodevelopmental disorders including ADHD, autism, and schizophrenia. Given the diverse multigenerational behavioral, neuropharmacological, and neuroendocrinological impacts of DNE, it is probable that epigenetic alterations are centrally involved therein. Examining this possibility, the current study probed for alterations in the DNA methylome as well as the expression and phosphorylation of cardinal epigenetic factors. Results reveal multigenerational global DNA hypomethylation, downregulation of DNA methyltransferase 3A (DNMT3A) and methyl-CpG-binding protein 2 (MeCP2), and downregulation as well as aberrant phosphorylation of histone deacetylase 2 (HDAC2) in the frontal cortices, striata, and/or hippocampi of both first- and second-generation adolescent DNE progeny. Considering the extensive regulatory roles of DNA methylation, MeCP2, DNMT3A, and HDAC2, these findings suggest that epigenetic perturbations may constitute a mechanistic hub for the intergenerational transmission of DNE-induced neurodevelopmental disorder-like phenotypes. Future research is warranted to elucidate the gene- and cell type-specificity of DNE-evoked multigenerational epigenetic anomalies.