

# Transgenerational effects of ancestral prenatal stress on the gut-brain axis

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## Abstract

The effects of ancestral prenatal stress can propagate across generations to alter the well-being of directly and indirectly exposed descendants via epigenetic mechanisms. Prenatal stress has been shown to alter the function of the gut-brain axis, a bi-directional signaling pathway between the gut microbiome and the enteric and central nervous systems. There has been no study investigating the impact of remote prenatal stress in ancestors on the gut-microbiome connection. Here we investigated if exposure to transgenerational ancestral stress affects the gut-brain axis through changes in the microbiome and microbiota. A multigenerational rat cohort consisting of a F0, F1, F2, and F3 generation was utilized in this study. Pregnant dams in the F0 generation were exposed to repeated restraint stress and overnight social isolation from gestational days 12-18. Breeding of three successive generations occurred in the absence of gestational stress along with a lineage of yoked controls. Fecal collection occurred for males and female in each generation at the age of 30 days, 90 days, and 115 days. Fecal samples were analyzed using <sup>1</sup>H-NMR spectroscopy to examine the metabolome. The data are being analysed using supervised and unsupervised machine learning approaches. The data are expected to reveal that the fecal metabolome is characteristically altered by ancestral prenatal stress in each generation, resulting in a biomarker signature that is linked to the behavioural phenotype. We predict changes in the gut metabolome and microbiome to be most significant in the F3 generation. These findings could lead to further understanding of intestinal dysbiosis and its impact on the brain, and sex-specific metabolic biomarkers that are predictive of stress-associated adverse health outcomes.

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**Cite as:** Mulik C., Scott, H., Inglis, D., Montana, T., Metz, G.A.S. 2019. Transgenerational effects of ancestral prenatal stress on the gut-brain axis. Alberta Academic Review, Vol 2 (3) 18, CASCH Special Issue (not peer-reviewed), DOI: 10.29173/aar109.

