MATTER ARISING — NATURAL PARAMUTATION IN MAMMALS FINALLY CAUGHT IN THE ACT

Paramutation has long been a curiosity of plant genetics: an allele that, when present alongside its homolog in a heterozygous cell, alters the methylation state of it, and this altered state is then inherited by the next generation, independent of DNA sequence. Maize geneticists have known this since the 1950s. Mammalian biologists have largely treated it as someone else's problem.

A paper just published in Nature Genetics (1) changes that. The key methodological enabler is long-read Oxford Nanopore sequencing, which reads genetic sequence and DNA methylation simultaneously on the same DNA molecule. Because a single long read can span multiple SNPs, each read can be unambiguously assigned to a specific parental haplotype. This makes it possible to determine, for every CpG site in the genome, whether its methylation state is of maternal or paternal origin. Short-read bisulfite sequencing cannot do this: it destroys haplotype information and forces averaging across alleles.

Using Oxford Nanopore sequencing across three generations of mice, the authors mapped epigenetic inheritance genome-wide and confirmed the first naturally occurring intergenerational paramutation in a mammal, at the Capn11 locus, with two additional highly likely cases involving strain-specific transposable elements.

The broader picture is equally striking: roughly 7% of autosomal epigenetic inheritance patterns are non-Mendelian. That is not a rounding error. It has direct implications for incomplete penetrance, transgenerational effects of environmental exposures, and the still-underexplored space between genetics and phenotype.

Mendel's laws remain a good first approximation. But at 7% of autosomal loci, the exceptions are too frequent to ignore.

1. https://www.nature.com/articles/s41588-026-02604-z