ANOTHER EXAMPLE OF HOW GENOMIC BACKGROUND CAN MODULATE PENETRANCE

Huntington's disease (HD) is caused by an expanded CAG repeat in the HTT gene, a highly penetrant mutation with predictable, devastating consequences. Yet onset can vary by decades among carriers.

A new PNAS study (1) points to LIG1, the gene encoding DNA Ligase 1. A rare missense variant, K845N, substitutes a lysine for an asparagine in the oligonucleotide-binding domain of LIG1 and is associated with a 7–8 year delay in motor onset in HD patients.

The mechanism: K845N increases the enzyme's ability to discriminate against mismatched DNA substrates — particularly promutagenic 8-oxoG:A mispairs — thereby enhancing repair fidelity and slowing the somatic CAG repeat expansion that drives HD progression. Mouse knock-in models confirmed that the orthologous K843N variant significantly suppresses somatic expansion in striatum and liver.

1. 10.1073/pnas.2518854123