THE DARK GENOME

This is a proof of concept that highly penetrant Mendelian disease can hide in the "dark genome" — noncoding RNA genes that routine exome/genome pipelines tend to filter out or deprioritize. They get overlooked precisely because they are noncoding and hard to interpret.

A new Nature Genetics study led by Quinodoz et al (1) [comment in TIG (2)] identifies a previously unrecognized genetic cause of autosomal dominant retinitis pigmentosa (adRP), a progressive blinding disease. The cause: heterozygous variants in the noncoding genes encoding the U4 and U6 small nuclear RNAs (snRNAs). These are core components of the spliceosome, the molecular machine that removes introns from pre-mRNA.

Starting from one unsolved family, the team found a recurrent insertion in RNU4-2 (the gene for U4). They then screened nearly 4,722 undiagnosed retinitis pigmentosa cases internationally. This turned up the same variant again, plus additional ones — and, critically, similar variants in four paralogs of RNU6 (the gene for U6, which exists in five near-identical copies scattered across the genome). Altogether, these variants explain adRP in 153 people from 67 families. They are estimated to account for ~1.4% of all molecularly undiagnosed RP cases — a meaningful slice of the "missing heritability" that still leaves 30–50% of retinitis pigmentosa patients without a genetic diagnosis.

All the disease variants cluster in one specific spot: the three-way junction where U4 and U6 pair up. This is right where they dock onto splicing factor proteins (PRPF3, PRPF31) that were already independently known to cause the same disease when mutated. Biochemically, these variants don't break splicing wholesale — patients' blood cells showed no major splicing defects. Instead, the mutant snRNAs bind more tightly to early-assembly factors (SART3, PRPF31) and less to later ones (SNRNP200). This suggests a subtle traffic jam in spliceosome assembly rather than a catastrophic failure.

What makes this especially interesting is that RNU4-2 was already known to cause a completely different, much more severe disease when mutated: ReNU syndrome, a common neurodevelopmental disorder. The Trends in Genetics commentary highlights why the same gene produces two distinct phenotypes. ReNU-causing variants sit in a different region (stem III/T-loop, involved in recognizing splice sites) and cause severe, global splicing failure. The RP variants, in contrast, sit in the assembly-interface region and cause only a mild, retina-specific defect. The commentators propose that photoreceptors are simply uniquely vulnerable to even subtle spliceosome slowdowns. Two factors explain why: they have an unusually heavy splicing workload (continuous renewal of outer segments, high rates of alternative splicing), and RNU4-2/RNU6 are more highly expressed in retina than in most other tissues. So, a defect too mild to affect the brain becomes rate-limiting in the eye.

1. https://www.nature.com/articles/s41588-025-02451-4

2. https://www.cell.com/trends/genetics/abstract/S0168-9525(26)00064-8?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0168952526000648%3Fshowall%3Dtrue