MISSING HERITABILITY

In studies based solely on affected individuals, the link between a variant and a clinical phenotype seemed straightforward and deterministic. With the advent of large-scale population sequencing, however, it has become clear that many people carry variants previously linked to severe disorders yet display no signs of disease. This shows that a mutation associated with a phenotype does not necessarily cause disease, and that penetrance must be reconsidered in the context of genome-wide variation.

The study by Wainschtein et al. (1) leverages whole-genome sequencing from 347,630 UK Biobank participants to investigate this discrepancy. By analysing over 40 million variants, the authors quantify how much heritable phenotypic variation is attributable to rare versus common variants. They find that rare variants account for roughly 20% of total heritability, with important contributions emerging not only from coding sequences but also from non-coding regions, which explain the majority of rare-variant heritability. The analysis identifies hundreds of rare-variant associations and shows that, for several traits—especially metabolic traits such as lipid levels—a significant proportion of the rare-variant contribution can already be assigned to specific loci.

Together, these results explain why some carriers of mutations historically labelled as pathogenic remain unaffected: clinical outcomes depend on the combined effect of the entire genomic background, rather than on a single mutation considered in isolation. The work provides a more nuanced framework for interpreting penetrance and variant pathogenicity in the era of population-scale genomics. In summary, the work demonstrates that the "missing" heritability is largely hiding in rare variants and can be successfully mapped using large-scale whole-genome sequencing.

1. https://www.nature.com/articles/s41586-025-09720-6