GENOTYPE–PHENOTYPE CORRELATION IN HAPLOINSUFFICIENT GENES

Large-scale genomic screenings have revealed that individuals in the general population can carry pathogenic, even “fully penetrant”, Mendelian mutations without developing the expected disease (see 1). This prompted a fundamental shift in the understanding of genotype–phenotype relationships. Crucially, these observations are possible only when surveying ostensibly healthy individuals, rather than focusing exclusively on patients

Within this conceptual framework, the study by Blair and Risch (2), leveraging the scale of the UK Biobank, investigates why certain variants predicted to cause severe haploinsufficiency do not generate the anticipated clinical phenotype. By integrating population-level variant annotation with functional assays, the authors show that many alleles currently classified as loss-of-function are not truly null, but instead retain residual allelic activity sufficient to buffer the organism against disease. Rather than a binary ON/OFF model, the data reveal a continuum of allelic function, where even modest residual activity can significantly mitigate pathogenicity.

Taken together, these findings highlight how incomplete penetrance may stem either from resilience within the variant itself, or from resilience provided by the broader genome. Both levels challenge classical deterministic models and emphasize how dynamic, multilayered, and context-dependent genotype–phenotype relationships truly are.

1. https://pubmed.ncbi.nlm.nih.gov/27065010/
2. https://www.cell.com/ajhg/abstract/S0002-9297(25)00427-6