HAPLOINSUFFICIENCY AND DOMINANCE

Haploinsufficiency is a mechanism where the loss of one functional allele results in insufficient protein levels to maintain normal function, leading to a dominant phenotype. The inroductory section of the paper by Veitia (1), summarizes various ways haploinsufficiency can arise.

Dominant diseases are caused by single-allele mutations such as nonsense, frameshift, missense mutations, trinucleotide expansions, regulatory region mutations, or gain-of-function mutations. Juvik et al. (2) examine how mutants causing mRNA decay trigger transcriptional adaptation, where the decay products upregulate “adaptive genes” which compensate for the loss of function. However, in some cases, these genes exacerbate the pathological phenotype via gain-of-function effects. The mutation itself is not inherently deleterious but becomes harmful because it triggers mRNA decay, which can have deleterious effects through adaptive genes.

1. https://www.cell.com/trends/genetics/abstract/S0168-9525(24)00235-X?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS016895252400235X%3Fshowall%3Dtrue
2. https://www.cell.com/trends/genetics/fulltext/S0168-9525(24)00291-9?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS016895252400291 9%3Fshowall%3Dtrue