GENETIC MUTATIONS: WHEN THE SAME GENE TELLS TWO DIFFERENT STORIES

Genetic mutations can fundamentally alter how a protein behaves: they can lead to a complete loss of function (LOF) or, in rarer cases, to an increased or persistent activity, known as gain of function (GOF). Generally, loss-of-function mutations tend to be recessive, requiring two affected copies of the gene, while gain-of-function mutations often act in a dominant manner.
The phenotypic outcomes of these two mechanisms can be so strikingly different that, without molecular investigation, it would be nearly impossible to guess that the same gene is responsible for both conditions.
A perfect example of this is the recent study by Bertola et al.(1) regarding the ATOH1 gene:
Recessive Loss-of-Function (LOF): When both copies of the ATOH1 gene are "broken," the result is a severe neurodevelopmental disorder. Patients exhibit profound hearing loss and significant brain underdevelopment, specifically severe cerebellar and pontine hypoplasia, leading to major cognitive and motor deficits.
Dominant Gain-of-Function (GOF): In contrast, specific mutations at the end of the gene (C-terminal) create a "hyper-stable" protein that doesn't degrade when it should. This leads to a much milder and distinct phenotype: a recognizable brainstem malformation, mild motor symptoms, and only mild-to-moderate hearing loss.

1. https://www.cell.com/ajhg/abstract/S0002-9297(25)00487-2?dgcid=raven_jbs_aip_email