ONE GENE, MANY FACES

A commentary in Trends in Genetics (1) puts the spotlight on one of the most complex phenomena in human genetics: a single gene that manifests across apparently unrelated disorders.

GRIN2A encodes a subunit of the NMDA receptor, a key player in glutamatergic signaling in the brain. Over the years it has been linked to epilepsy, language impairment, and, more recently, schizophrenia. But how can phenotypes so different all trace back to the same gene?

The answer, at least in part, lies in how patients are studied. Lemke et al. (2) recontacted a cohort of carriers of pathogenic GRIN2A variants, many of whom had originally been recruited for epilepsy and aphasia, and found that roughly one in five also carried psychiatric diagnoses, particularly associated with loss-of-function variants. A finding that had simply been invisible in earlier studies, because the recruitment criteria weren't designed to look for it.

It is a powerful reminder: genotype–phenotype relationships are not fixed properties of genes; they also reflect the methodological choices of those who study them. Broadening the boundaries of observation, both over time and in phenotypic depth, can radically change the picture.

1. https://doi.org/10.1016/j.tig.2026.02.004
2. https://doi.org/10.1038/s41380-025-03279-4