HOW MANY DISEASES CAN ONE GENE CAUSE?

WHY MECHANISM MATTERS FOR GENE CURATION, VARIANT CLASSIFICATION, AND PATIENT COUNSELING

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OBJECTIVES

To assess the number and define the types of multiple disease relationships among genes with at least one characterized neurodevelopmental disorder (NDD) association.

- How many genes have multiple disease associations?
- What factors influence curation of genes with multiple disease associations?
- What is the impact of multiple disease associations on clinical reporting?
- How can we create language to discuss the various types of multiple disease associations?

METHODS

- Reviewed 1502 NDD genes with gene-disease validity (GDV) scored for all gene-disease relationships (GDR).
- Excluded GDRs with:
  - No differences in MoI or MoD; Limited GDV
- Genes with >1 characterized GDR were grouped into four main categories.
  - MoI, MoD, and clinical presentation were tabulated for all characterized GDRs

RESULTS

- 1678 disorders associated with 1502 NDD genes [range:1-4 GDR/gene]
- 10.2% (153/1502) of genes with >1 GDR
  - Associated with 329/1678 (19.6%) total characterized GDR **[Fig. 2]**

Figure 1: Categories of genes with multiple disease relationships

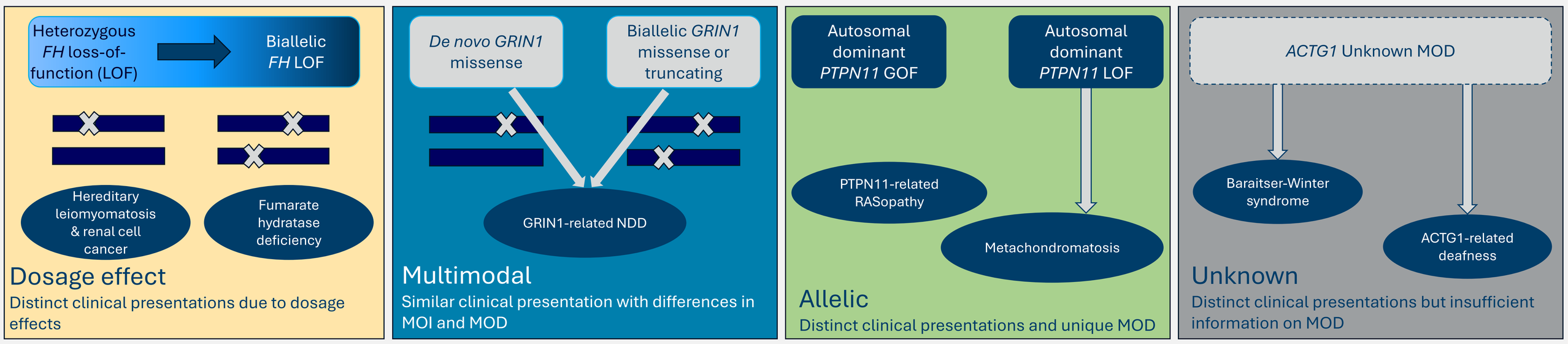


Figure 2: Genes with multiple disease associations

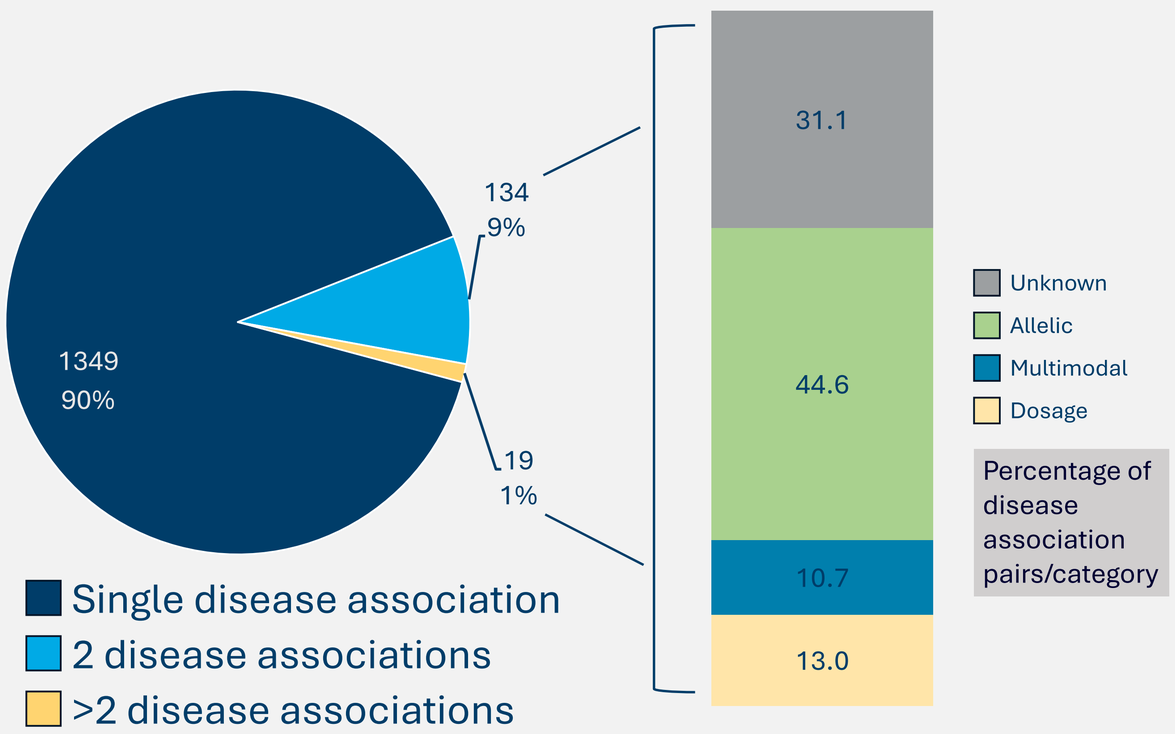
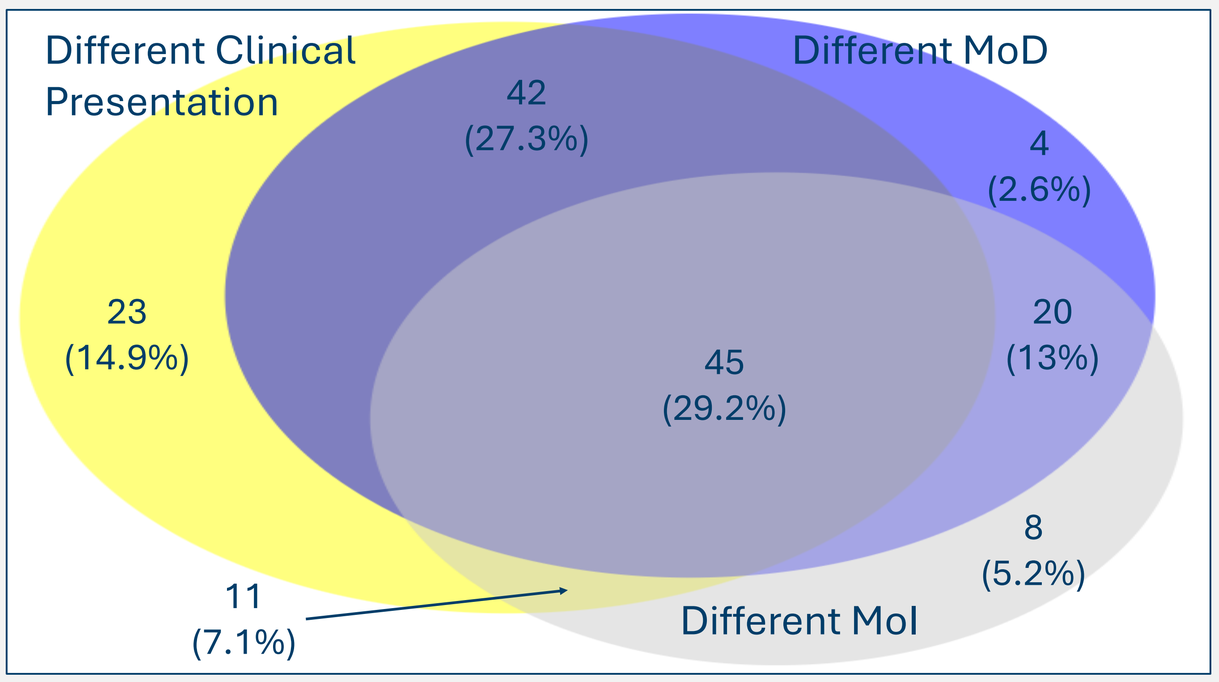
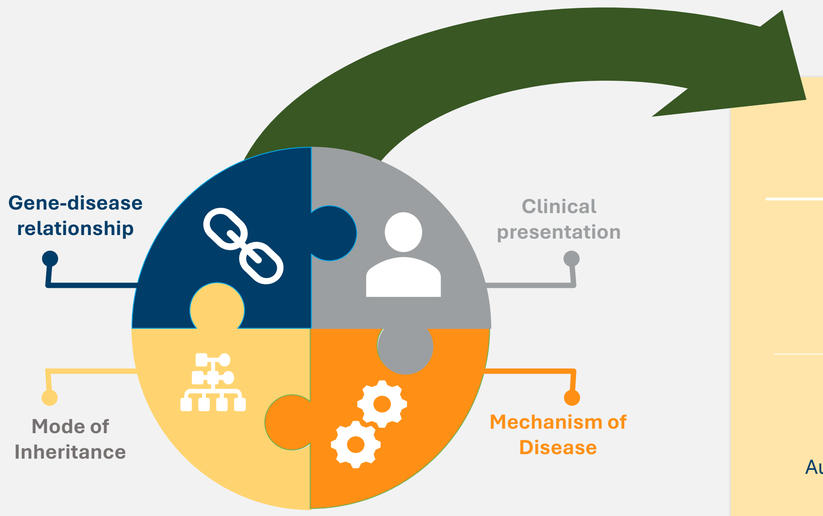


Figure 3: Differentiating factors of disorders associated with the same gene



Case Example: Impact of accurate gene-disease relationship curation on variant classification



PTPN11
c.236A>G (p.Q79R)

PTPN11-related RASopathy
Gain of function
Autosomal dominant
GDV score = Definitive
Pathogenic

Metachondromatosis
Loss of function
Autosomal dominant, reduced penetrance
GDV score = Strong
VUS

TAKE HOME POINTS

- >10% of assessed NDD genes are associated with >1 GDR. Genes had up to four GDRs.
- Clinical presentation, MoI, and MoD all impact curation of multiple GDR.
- Thorough curation of GDR is essential to accurately classify variants and provide informative clinical reports
- We propose several categories to describe multiple disease associations.

Functional confirmation of MoD is necessary for accurately defining genetic disorders.

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