Title: How many diseases can one gene cause? Why mechanism matters for gene curation, variant classification, and patient counseling.

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Objective: The “one gene-one disease” paradigm has evolved through recognition that genes may cause multiple disorders. The multiple disease model requires variant interpretation for all associated disorders, which can result in divergent classifications for different disorders. We aim to assess and define the scope of this phenomenon and its impact on variant curation and clinical reporting.

Methods: We reviewed a large set of neurodevelopmental disorder (NDD) genes and all associated monogenic gene-disease relationships (GDR), curating them by mode of inheritance (MoI), mechanism of disease (MoD), and/or clinical presentation. Genes associated with multiple disorders were grouped into four categories based on these attributes.

Results: We curated 1679 distinct disorders associated with 1502 genes (range: 1-4 disorders/gene). 10.1% (153/1502) of genes are associated with >1 genetic disorder, totaling 19.7% (330/1679) of all the disorders reviewed. Approximately 53% (81/153) of these genes are associated with disorders with different MoI, 70% (108/153) with different MoD, and in 41% (63/153) both MoI and MoD were different. Genes associated with >1 genetic disorder were categorized as: 1) Dosage Effect (13%; 21/153): distinct presentations with different MoI; 2) Multimodal (12%; 18/153): similar presentation despite differences in MoI/MoD; 3) Allelic (56%; 86/153): distinct presentations with different MoD; and 4) Unknown (31%; 48/153): unique presentations with insufficient MoD information.

Conclusions: A significant number of NDD genes are associated with >1 distinct genetic disorder. Dosage Effect, Multimodal, Allelic, and Unknown are four proposed GDR categories that can optimize variant curation, clinical reporting, and patient counseling for variants in genes associated with multiple disorders.