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TITLE: Clinical phenotypic data is a key factor necessary to improve molecular interpretation of *de novo* alterations in neurodevelopmental genetic testing.

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OBJECTIVE: Explore the impact of expanded phenotype on diagnostic yield of individuals with *de novo* alterations detected in neurodevelopmental multi-gene panel testing (MGPT).

BACKGROUND: Neurodevelopmental disorders (NDDs) involve a wide range of symptoms and severity. Individuals may present with multiple indications, including epilepsy, autism, intellectual disability, developmental delay, dysmorphic features, and other congenital anomalies. The broad nature of NDDs can lead to significant diagnostic challenges. *De novo* alterations account for a significant portion of diagnosed NDD patients. Detection of *de novo* variants in individuals with concordant phenotype can improve diagnostic outcomes and guide treatment decisions.

METHODS: All cases with a *de novo* finding detected in our laboratory from neurodevelopmental MGPT were reviewed for phenotype and gene-disease association.

RESULTS: A positive finding of likely pathogenic or pathogenic mutation, was identified in ~75% of individuals with a *de novo* variant detected in neurodevelopmental multi-gene panels. Though a pathogenic classification is dependent on multiple lines of evidence, including population allele frequency, *in vitro* and *in vivo* functional assays, protein structural analysis, and computational *in silico* predictors, the key determining factor is clinical phenotypic data. The clinical presentation of these individuals consistently showed phenotypic overlap with known gene-disease associations. However, in depth phenotyping also provided novel information on comorbidities and expanded phenotypic spectrums. The majority of *de novo* alterations that remained variants of unknown significance (VUS) were due to limited information of the full disease spectrum or lack of phenotype data provided. Only a small minority of alterations, in moderate penetrant genes, had conflicting data resulting in a VUS.

CONCLUSION: Pathogenic *de novo* findings are dependent on clinical phenotype data. In depth patient phenotyping and data sharing can increase knowledge of gene-disease associations and provide the necessary element to improve molecular diagnostic yield.