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# Clinical Phenotypic Data is a Key Factor Necessary to Improve Interpretation of *de novo* Alterations in Neurodevelopmental Genetic Testing

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## 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. Accurate classification of *de novo* variants in individuals with comprehensive and specific phenotyping can improve diagnostic outcomes and guide treatment decisions.

Table 1. Modified from SVI recommendation for confirmed *De Novo* ACMG/AMP criteria per proband

| Phenotypic Consistency | Evidence Strength |
|---|---|
| Highly specific for gene | Strong |
| Consistent with gene but not specific | Moderate |
| Consistent with gene but not specific & high genetic heterogeneity | Supporting |
| Not consistent with gene | None |

## METHODS

- Cases with a missense *de novo* finding detected in our laboratory from Neurology multi-gene panel testing (MGPT) were reviewed for phenotype and gene-disease association.
- *De novo* evidence strength was assigned and comprehensive variant analysis was performed using multiple lines of evidence to determine final variant classification.

## REFERENCES

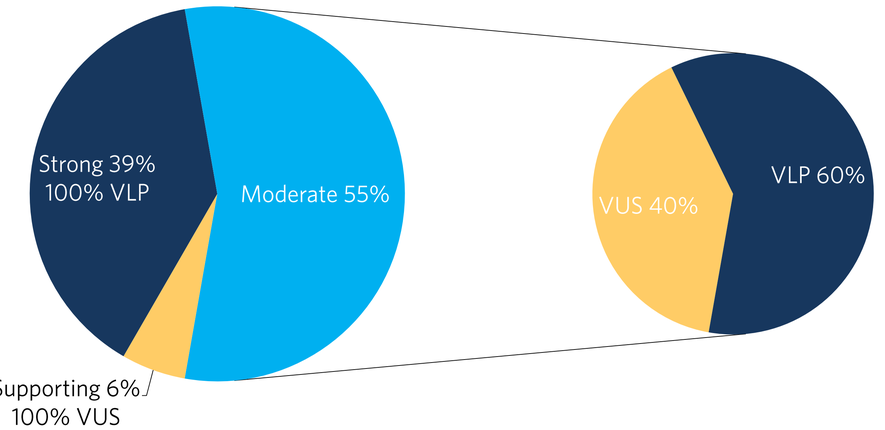
1. Ambry Genetics Scheme for Autosomal Dominant and X-Linked Mendelian Diseases (V2-20-17). www.ambrygen.com
2. PS2/PM6: Recommendation for *de novo* PS2 and PM6 ACMG/AMP criteria (Version 1.0). www.clinicalgenome.org
3. Smith ED et al. *Hum. Mutat.*, 2017 May;38:600-608

Table 2. *De Novo* Missense Variants in Single Proband

| Gene | c. | p. | Strength | Classification |
|---|---|---|---|---|
| *ANKRD11* | c.295G>A | p.G99S | Moderate | VUS |
| *ARID1B* | c.2605G>A | p.G869S | Moderate | VUS |
| *ATP1A2* | c.2810G>A | p.R937H | Moderate | VLP |
| *CHD2* | c.3221G>A | p.R1074Q | Strong | VLP |
| *CREBBP* | c.4493G>A | p.R1498Q | Moderate | VLP |
| *DDX3X* | c.1538T>C | p.V513A | Moderate | VLP |
| *DYNC1H1* | c.10051A>T | p.I3351F | Moderate | VLP |
| *DYNC1H1* | c.568G>A | p.E190K | Moderate | VUS |
| *DYRK1A* | c.848T>G | p.I283S | Strong | VLP |
| *EEF1A2* | c.1084G>T | p.D362Y | Moderate | VLP |
| *EHMT1* | c.2426C>G | p.P809R | Strong | VLP |
| *GNAO1* | c.520G>A | p.D174N | Strong | VLP |
| *GRIN2A* | c.1925T>G | p.L642R | Moderate | VLP |
| *HCN1* | c.459G>T | p.M153I | Moderate | VLP |
| *KCNQ2* | c.839A>G | p.Y280C | Strong | VLP |
| *KCNQ2* | c.1627G>A | p.V543M | Strong | VLP |
| *KCNQ2* | c.704C>T | p.A235V | Moderate | VUS |
| *KCNQ2* | c.994A>G | p.R332G | Strong | VLP |
| *KCNT1* | c.1429G>A | p.A477T | Moderate | VLP |
| *KCNT1* | c.3092C>T | p.S1031F | Moderate | VUS |
| *KCNT1* | c.1421G>T | p.R474L | Strong | VLP |
| *KDM5C* | c.1499C>T | p.P500L | Strong | VLP |
| *NLGN4X* | c.560G>A | p.G187D | Moderate | VUS |
| *PCDH19* | c.593G>C | p.R198P | Moderate | VLP |
| *PCDH19* | c.1697C>A | p.P566Q | Moderate | VLP |
| *PHF8* | c.2405A>C | p.Q802P | Supporting | VUS |
| *PRRT2* | c.640G>C | p.A214P | Supporting | VUS |
| *SCN1A* | c.4154T>G | p.F1385C | Strong | VLP |
| *SCN1A* | c.4327G>C | p.D1443H | Strong | VLP |
| *SCN2A* | c.2636G>C | p.G879A | Strong | VLP |
| *SCN8A* | c.5279T>C | p.M1760T | Moderate | VLP |
| *SCN8A* | c.3967G>A | p.A1323T | Moderate | VLP |
| *SIK1* | c.1063C>T | p.R355C | Moderate | VUS |
| *SMARCA4* | c.2441C>T | p.T814M | Strong | VLP |
| *SMC3* | c.1655T>A | p.V552D | Strong | VLP |
| *SYNGAP1* | c.3009C>G | p.S1003R | Moderate | VUS |

## RESULTS

Figure 1. Evidence strength assigned by phenotypic consistency and final classification in *de novo* missense variants detected in Neurology MGPT




| Table. 3 Main factors resulting in a Moderate/Supporting *de novo* evidence | M/S Variants |
|---|---|
| Specific disease phenotype for gene not well-characterized due to rarity | 30% |
| Insufficient patient phenotypic details provided to laboratory from Clinician | 27% |
| Patient presents with consistent but atypical phenotype in well-characterized gene with specific disease phenotype | 23% |
| Conflicting evidence reducing strength level (ie. partially symptomatic parent) | 14% |

## TAKE-HOME POINTS

- Accurate classification of *de novo* variants is dependent on clinical phenotypic data.
- Deep phenotyping of patients and data sharing can improve diagnostic yield.
- Increased gene-disease association and comprehensive expanded disease phenotype can make a significant impact on variant classification.