ClinGen Sequence Variant Interpretation Recommendation for de novo Criteria (PS2/PM6) - Version 1.0
Working Group Page: https://clinicalgenome.org/working-groups/sequence-variant-interpretation/
Date Approved: March 18, 2018

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## SVI Recommendation for *De Novo* Criteria (PS2 & PM6) - Version 1.0

The Sequence Variant Interpretation (SVI) Working Group proposes a point-based system to determine the strength of *de novo* evidence (ACMG/AMP criteria codes PS2 and PM6) based upon three parameters:

- confirmed versus assumed status
- phenotypic consistency
- number of *de novo* observations

To determine the appropriate strength level to apply for *de novo* occurrence(s), each proband with a *de novo* variant is awarded a point value based upon phenotypic consistency and confirmed or assumed *de novo* status (Table 1). The combined point value of all *de novo* occurrences is then compared to Table 2 to determine the applicable evidence strength level. For example, if a *NIPBL* variant occurred confirmed *de novo* in one patient with Cornelia de Lange syndrome (2 points; Table 1) and assumed *de novo* in two additional unrelated patients with Cornelia de Lange syndrome (1 + 1 points; Table 1), then VeryStrong evidence level is applied (PS2_VeryStrong) based on combined point value of 4 (Table 2).

### Table 1. Points awarded per de novo occurrence

| Phenotypic consistency | Points per Proband | |
|---|---|---|
| | Confirmed de novo | Assumed de novo |
| Phenotype highly specific for gene | 2 | 1 |
| Phenotype consistent with gene but not highly specific | 1 | 0.5 |
| Phenotype consistent with gene but not highly specific and high genetic heterogeneity* | 0.5 | 0.25 |
| Phenotype not consistent with gene | 0 | 0 |

*Maximum allowable value of 1 may contribute to overall score

### Table 2. Recommendation for determining the appropriate ACMG/AMP evidence strength level for de novo occurrence(s)

| **Supporting** (PS2_Supporting or PM6_Supporting) | **Moderate** (PS2_Moderate or PM6) | **Strong** (PS2 or PM6_Strong) | **Very Strong** (PS2_VeryStrong or PM6_VeryStrong) |
|---|---|---|---|
| 0.5 | 1 | 2 | 4 |

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For all uses of *de novo* criteria, the phenotype in the patient must be consistent with the gene/disease association as recommended in the ACMG/AMP guidelines. When the patient's phenotype is consistent with the gene/disease association but not highly specific, we recommend decreasing the points awarded. For example:

- A patient with early infantile epileptic encephalopathy and a confirmed *de novo SIK1* variant is awarded 1 point (as the patient's phenotype is consistent with the gene but not highly specific and the variant is confirmed *de novo*). If this patient is the only *de novo* occurrence for the variant, then a Moderate strength level (PS2_Moderate) is applied.
    - If two additional unrelated patients with early infantile epileptic encephalopathy and a confirmed *de novo SIK1* variant are identified, then the combined point value is 3 (as each patient is awarded 1 point). For these combined occurrences, a Strong strength level (PS2) is applied as the points reach the Strong threshold (2 points) but not the VeryStrong threshold (4 points).

- A patient with nonsyndromic intellectual disability and a confirmed *de novo ASH1L* variant is awarded 0.5 points (as the variant is confirmed *de novo* and patient's phenotype is consistent with the gene but not highly specific and there is significant evidence of genetic heterogeneity). If this patient is the only *de novo* occurrence for the variant, then a Supporting strength level (PS2_Supporting) is applied.
    - If a second patient with nonsyndromic intellectual disability and a confirmed *de novo ASH1L* variant is identified, then the combined point value is 1 (as each patient is awarded 0.5 points). For these combined occurrences, a Moderate strength level (PS2_Moderate) is applied.

- A patient with developmental delay but no other features of Cornelia de Lange syndrome and an assumed *de novo* NIPBL variant is awarded zero points as this phenotype is not consistent with the gene/disease association. If this patient was the only *de novo* occurrence for the variant, then no *de novo* criteria are applied.

Additional considerations for applying *de novo* criteria based on inheritance:

- X-linked conditions: if an X-linked variant occurs *de novo* in an unaffected carrier mother, and family history is consistent - i.e. she has no affected brothers/other male relatives apart from her affected son(s) – *de novo* criteria may be applied despite the fact that she is unaffected.

- Autosomal recessive conditions: for a *de novo* occurrence in a gene associated with an autosomal recessive condition without an additional pathogenic/likely pathogenic variant identified, the strength of evidence should be decreased by one level.

- Mosaicism: for cases with apparent germline mosaicism (multiple affected siblings with both parents negative for the variant), paternity/maternity must be confirmed in order for *de novo* criteria to apply.