

Summary of updates to the ClinGen Gene Clinical Validity Curation SOP

Note: Significant updates were included in version 8, including several new sections and the rearrangement of prior sections. It is highly recommended for all curators (new and existing) to read version 8 in full.

Updates from Version 7 to Version 8 (10/2020):

- **Figure 1: Gene Curation Workflow (p5):** This figure was updated to include programs used for each step of the gene curation process.
- **Establishing the Gene-Disease Mode of Inheritance (p9):** Precurations are recorded in the GeneTracker and if discrepancies occur between the GeneTracker and the GCI, it is now recommended that curators contact their GCEP's coordinators.
- **Evidence Collection (p12):** A curator can use PMIDs from DECIPHER to enter information into the GCI. A reminder to curators to contact their GCEP's chairs and coordinators for a list of trusted public databases for curations was added.
- **Useful Publication Search Engines (p13):** Once the maximum number of points have been reached for a given category, it is now not necessary to document any further evidence.
- **Genetic Evidence Summary Matrix (p15):** The genetic evidence summary matrix figure has been updated to reflect new genetic evidence scoring guidelines.
- **Scoring Genetic Evidence (p16):** New section heading "Case-Level Data" has replaced the previous heading "Default Range Score per Case".
- **Case-Level Data (p16-17):** In this new section, there are multiple updates to guide curators to assess case-level data. Clinical information is now collected using Human Phenotype Ontology (HPO) codes and/or free text. Guidelines have been added to identify variants that are a plausible cause of disease and should be scored. Default scoring for each genetic evidence type have been added to provide initial suggestion for scoring. Default scores can be upgraded or downgraded based on the strength of evidence of each case. Reasons for upgrades or downgrades have been included in this updated version. A range for both the minimum and maximum scores allowed per case with examples have been added.
- **Heterozygous or Hemizygous Variants (p18):** A new example, example 2, has been added for cases where a heterozygous or hemizygous variant causes disease.
- **Biallelic Variants (p19):** A new example, example 2, has been included to provide more instruction for cases in which biallelic variants cause disease.
- **Predicted or Proven Null Variants (p21-22):** More description has been added for scoring individuals with large deletions, duplications and other chromosomal rearrangements. Additionally, more guidance has been provided for entering intragenic deletions and duplications in the GCI.
- **Recurrent Variants (p22):** Curators should now document the contribution of other variants even if they will not be scored.
- **Experimental Evidence (p41):** An example scenario was added for expression evidence.

- **Summary and Final Matrix (p46):** The evidence summary is now required. A link to example evidence summary text is now included in the SOP. Curators should acknowledge secondary contributors on the approving page of the GCI.