Summary of updates to the ClinGen Gene Clinical Validity Curation SOP

Updates from Version 5 to Version 6 (08/2018):

- **Required components (p3):** Additional links and information have been added, including a link to guidance from the ClinGen Lumping and Splitting working group on how to determine a disease entity for curation, and updated details on the information to provide when requesting access to the Gene Curation Interface (GCI).
- **Assignment of clinical validity classification using gene curation matrix (p 4):** The following sentence has been added - "While all evidence will be reviewed by disease experts, curators should flag any evidence that requires further discussion with an expert in the disease area."
- **Deciding on the disease entity (p8):** A paragraph has been added to introduce the guidelines of the ClinGen Lumping and Splitting working group. These guidelines were developed to help curators decided upon a disease entity for curation. These guidelines are particularly useful when a gene has been implicated in multiple disease entities, and when a known disease entity may be split into two or more conditions.
- **Literature search, section 3 (p 8)**: Examples have been added to facilitate conducting PubMed searches for specific types of evidence.
- **Case level data (p 10)**: Included a statement to indicate the sufficient evidence must be available in the publication to support the diagnosis, and guidance is given on collection of clinical information by HPO codes and/or free text.
- **Genetic evidence summary, Figure 3 (p 11):** Minor updates to description of variant evidence types.
- **Variant evidence (pp13-15):** The order in which the variant types (*de novo*, predicted or proven null, other) is described has been reversed to match the order in Figure 3 (Genetic Evidence Summary table). Details have been added, including testing paternity in patients with *de novo* variants in X-linked genes, and counting mosaicism as a "*de novo*" variant. In "Predicted or proven null variants", added, "other variants types, such as missense, may be included in this category if there is sufficient evidence for complete loss of function." In "other variant with gene impact" added, "….in addition to variants of any type that result in gain of function or have a dominant-negative impact."
- **Counting segregations in monozygotic and dizygotic twins (p17):** Details have been provided.
- **Counting Segregations and Calculating Simplified LOD Scores; autosomal recessive conditions (p18):** Revised to include "The eLOD scores provided in Figure 5 refer only to the classic AR disease model. If a pedigree differs from this situation, please adjust the base numbers in the equation above to reflect the risk of inheritance, and use the equation to estimate the LOD score. For example, if one parent is affected with an autosomal recessive condition and the other is a carrier, replace "0.25" and "0.75" with 0.5."
- **New formula and logic for calculating scoring for segregation (pp 21-22):** Added a description of the formula, logic, and examples.
- **Functional alteration (p 28):** Changed description to "Evidence showing that cultured cells, in which the function of the gene has been disrupted, have a phenotype that is consistent with the human disease process. Examples include experiments involving expression of a genetic variant, gene knock-down, overexpression, etc"
- **Rescue (p 28):** Added details on rescue of gain of function variants.

- **Appendices:** Appendix A (useful websites for curators) and Appendix B (experimental evidence examples) were previously separate documents. The details remain the same, but these appendices have now been added to the end of the SOP.

Updates from Version 4 to Version 5 (11/2017):

- **gnomAD and Variant Minor Allele Frequencies (p 12):** Further guidance is given on how to evaluate the pathogenicity of a variant before scoring it, including looking up minor allele frequencies in control databases, such as gnomAD.
- **Upgrading and Downgrading Variant Evidence Scores (p 13):** The genetic evidence matrix provides a score range for variant evidence. In this section, guidance is given on when to score above and below the default suggested points per case for each variant type.
- **Segregation Scoring (p 15):** In this segregation scoring update, the maximum segregation points are decreased from 7 to 3. Although the simplified LOD score calculation is the same, the required size to score autosomal recessive pedigrees has changed from two affecteds to three. Awarding points to LOD scores has also changed and we have added guidance for awarding different amounts of segregation points depending on the methods used to investigate the linkage interval. This section now provides a) instructions how to count segregations and calculate a simplified LOD score and b) how to evaluate the sequencing methods for the linkage interval and award points accordingly.
- **Experimental Evidence Matrix Wording (p 24)**: Although experimental evidence scoring has not changed, some clarifying wording changes were made to the experimental evidence summary matrix. More specifically, "Animal model" was changed to "Non-human model organism" to accommodate disease areas with non-animal model organisms (such as yeast), "Rescue" was extended to patient cells and humans to encompass studies such as enzyme replacement therapies, and "Rescue in an engineered equivalent" was changed to "Rescue in a cell culture model" for clarification.
- **Scoring Variant vs Experimental Evidence (p 27)** Not all evidence supports the role of the gene in the disease. Therefore, the curator must carefully consider whether to count functional evidence in the experimental evidence section or in the case-level data section. Experimental evidence that does not directly support the role of the gene in the disease but indicates that the variant is damaging to the gene function can, instead, be used to increase points in the case-level data section. Further guidance on how to score some common general pieces of evidence is provided in this section.
- **Websites for curators (Appendix A, separate document on this page):** A list of websites that may be useful for ClinGen gene curators.
- **Extended Experimental Evidence Examples (Appendix B, separate document on this page):** The experimental evidence section in the SOP has been trimmed and extensive examples of each category of experimental evidence are available in the new Appendix B.