Methods for Validation of Curation Framework

Development of the quantitative aspect of this framework was based on the qualitative descriptions outlined in the framework publication (Strande and Riggs, et al., 2017). Both the qualitative classifications and their quantitative counterparts were determined by consensus of the ClinGen Gene Curation Working Group members comprised of a diverse group of genetics experts and professionals with additional input from experts in multiple clinical domains. Throughout development of the framework several gene-disease pairs (see Figure 5 in Strande and Riggs, et al., 2017) were iteratively curated as benchmarks with a known "anticipated classification" to determine appropriate scores and assigned ranges (e.g. *FGFR3*:achondroplasia). Furthermore the framework was designed to intentionally impose constraints on the weight of each type of evidence to ensure that no single factor could unduly influence the classification. For example, these constraints prevent a gene-disease association based on a single study from reaching a "Definitive" classification regardless of the cohort size or how long ago the study was published. Per the definition of a "Strong" or "Definitive" association, substantial replication is required.

We then tested the accuracy and reproducibility of our overall clinical validity framework by dual curation of the thirty-three gene-disease pairs presented in Figure 5. Gene-disease pairs were intentionally chosen to represent a wide spectrum of monogeneic disorders with various inheritance patterns, disease prevalence, and levels of evidence to support a relationship. Each curator independently searched for and evaluated the available literature for each gene-disease pair that he/she was assigned. All major discrepancies between curators were discussed and resolved when possible. When available, the appropriate ClinGen Clinical Domain Working Group (CDWG) was asked to review each gene-disease pair within their clinical domain. For gene-disease pairs without an existing CDWG at the time of review, *ad hoc* disease experts (see acknowledgments) reviewed the classifications. Both CDWG members and *ad hoc* reviewers were given a brief overview of the clinical validity framework prior to reviewing gene-disease curations.