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ClinGen Sequence Variant Interpretation Work Group recommendations for ACMG/AMP guideline criteria code modifications nomenclature

In 2015, the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) published a guideline for variant interpretation that provides a framework to classify variants (Richards et al., 2015, PMID:25741868). The guideline defines 28 criteria, each with an assigned code, that address types of variant evidence. Each criterion code is assigned a direction, benign (B) or pathogenic (P), and a level of strength: stand-alone (A), very strong (VS), strong (S), moderate (M), or supporting (P). The ClinGen Sequence Variant Interpretation (SVI) Working Group aims to standardize application of the ACMG/AMP guidelines by providing recommendations and harmonizing approaches to adapting the guidelines.

The ACMG/AMP guideline states that criteria listed as one weight can be moved to another weight using professional judgment; however, no guidance was provided on how to code or describe such designations. For strength-modified evidence, SVI recommends using the original criteria code followed by an underscore and new level of strength. This shifting of criteria weight is especially important for quantitative evidence types. For example, co-segregation with disease in affected family members defaults to supporting strength level (PP1) but can increase in strength with increasing segregation data. We suggest that segregation data that are modified in strength to moderate and strong be described as PP1_Moderate or PP1_Strong, respectively. The same process can be used for decreasing strength. For instance, a well-established functional study supportive of a damaging role is a criterion for pathogenicity at a strong strength level (PS3); however, this evidence could be downgraded to the moderate strength level with code PS3_Moderate and supporting strength level with code PS3_Supporting.