Clinical Validity scoring of Gene-Disease Associations in Diagnostic Exome Sequencing: Effects on Reporting and Reanalysis

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Diagnostic Exome Sequencing (DES) requires interpretations on multiple levels to be clinically valuable. Before scoring rare variants detected in patient samples, diagnostic labs must critically assess the level of evidence linking a gene to disease. While frameworks to evaluate the pathogenicity of alterations have been established, there are no officially published guidelines for evaluating gene-Mendelian disease associations. With the massive generation of genomic data in patient cohorts in recent years, many new potential Mendelian loci are reported at a rapid pace. However, many have been erroneously or weakly linked to diseases in publications. Currently, the ClinGen gene curation workgroup is leading the endeavor to develop a tiered system for clinical validity scoring.

In our clinical laboratory, we score gene-disease associations using a points system based on ClinGen Clinical Validity criteria. A majority of the weight is given to previous publications reporting patients with overlapping clinical features and rare alterations in the gene. In addition, we review evidence from non-patient resources including control populations, animal models, functional experiments and gene pathways. A gene-disease association with at least moderate level of supportive evidence in the scoring system is considered a characterized genetic etiology (CGE) that may provide a definitive molecular diagnosis. The internal gene-disease association database is curated daily with new literature, external database updates, and reanalysis requests.

We have utilized the clinical validity scoring system to reanalyze previous cases with no definitive diagnosis as part of the CGE curation efforts. When a new CGE is established, rare alterations detected in the gene in previous patients are reviewed for clinical correlation and reclassification reports are issued with significant findings. A total of 963 sequential patients submitted to Ambry Genetics for testing prior to 2015 were analyzed. Patient overall results were changed in 36 reclassification reports. Of the reclassified cases, 27 patient results (75%) were reclassified to a positive/likely positive CGE.

Overall, Ambry-initiated reclassification reports are predominantly prompted by new findings in the literature and usually cause patient reports to be upgraded in strength. This system both benefits patients and increases diagnostic yield. Here we present our clinical validity scoring criteria and the reclassification outcomes that result from active curation of the gene-disease database.