Clinical utility of Multiplexed Assays of Variant Effects (MAVEs) in a pediatric cohort

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ABSTRACT

Advances in genome sequencing have outpaced our ability to interpret the functional consequence of many DNA variants identified during clinical genomic testing. Consequently, a majority of variants catalogued in ClinVar, a database of DNA variants and their association with disease, are classified as Variants of Uncertain Significance (VUS), limiting their clinical utility. Multiplexed Assays of Variant Effects (MAVEs), which are high-throughput functional assays that characterize libraries of variants, are revolutionizing our capacity to study variant impact in disease genes. When properly calibrated, data generated from these assays can now be directly translated into standardized evidence strengths (very strong, strong, moderate, or supporting) for benign or pathogenic classification, enabling integration into clinical evaluation and classification.

We evaluated the utility of MAVEs datasets for 12 disease-associated genes to reclassify VUSs identified in a pediatric cohort who underwent clinical genomic testing at the Children's Hospital of Philadelphia. MAVEs data was obtained from published sources and calibrated to derive evidence weights. Across the genes, 787 variants were detected of which 276 had available MAVEs data. Among these, 145 previously classified as benign, likely benign, likely pathogenic, or pathogenic were used to validate the predictive power of MAVEs data. The remaining 131 variants were classified as VUS. Preliminary analysis demonstrated that 105 (78.9%) of these VUS had MAVEs data consistent with normal function, while 16 (12%) demonstrated abnormal function. This data may be useful in reclassification of these variants. Applying calibrated MAVEs functional evidence to these variants has the power to drive systemic reclassification, improving genomic diagnostics and advancing precision medicine.