Clinical translation of a MUTYH MAVE into a diagnostic laboratory workflow enables large-scale VUS resolution

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Abstract

Variant-to-function maps (or MAVEs) offer opportunities for resolving variants of uncertain significance (VUS). However, VUS resolution in medically relevant genes requires calibration and translation into diagnostic workflows to generate clinically actionable results. The recent publication of a MUTYH MAVE offered opportunity for large-scale VUS resolution, which constitute ~90% of missense variants in ClinVar. Biallelic, loss of function variants cause MUTYH-associated polyposis (MAP), an autosomal recessive (AR) condition predisposing to colorectal polyps and cancer. Population-based estimates from repositories like UK Biobank serve as resources for associating clinical risk with functional categorization. However, for AR conditions like MAP, these repositories may yield insufficient data due to rarity of biallelic pathogenic (LP/P) genotypes and/or phasing requirements. To circumvent this, records were obtained from a diagnostic laboratory. The burden of MAP-associated phenotype for >200 individuals with an assumed or confirmed pathogenic genotype was compared to 155 individuals with one MUTYH pathogenic variant and one functionally abnormal or neutral VUS, revealing that functionally abnormal missense VUS confer similar risk to MAP as pathogenic genotypes and its contrapositive. Given this association, the OddsPath was calculated, resulting in strong odds of pathogenicity for abnormal (>18.7) and neutral (<0.053) variants. Application of this evidence within a diagnostic laboratory, using an ACMG/AMP framework, resulted in reclassification of 80 VUS to LP/P and 451 VUS to LB/B (~69% of missense VUS), impacting 4,664 individuals. In summary, this study provides insight into the implementation of MAVE data into a diagnostic workflow, leading to large-scale VUS resolution and more accurate clinical care.