Systematic application of ClinGen InSiGHT *APC*-specific ACMG/AMP variant classification criteria alleviates the burden of variants of uncertain significance in ClinVar and LOVD databases

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ABSTRACT

Background/Objectives: To resolve the interpretative challenges of variants of uncertain significance (VUS), gene-specific ACMG/AMP variant classification criteria were developed and validated for the *APC* gene by the ClinGen-InSiGHT Hereditary Colorectal Cancer/Polyposis Variant Curation Expert Panel (VCEP) (https://cspec.genome.network/cspec/ui/svi/doc/GN089).

Methods: A streamlined algorithm using the *APC*-specific criteria was developed and applied to reassess all *APC* variants in ClinVar and the reference *APC* gene variant database in the Leiden Open Variation Database (LOVD).

Results: A total of 10,228 unique *APC* variants were analysed. 94% and 96% of the ClinVar and LOVD variants, respectively, with an initial classification of (Likely) Benign or (Likely) Pathogenic remained in their original categories. 41% of ClinVar and 61% of LOVD VUS were reclassified into clinically actionable classes, the vast majority as (Likely) Benign. The total number of VUS was reduced by 37% from 6142 to 3865. For 36 promising *APC* variants that remained VUS despite evidence for pathogenicity, a data mining-driven work-up was undertaken to curate additional evidence which allowed the further reclassification of 18 VUS as (Likely) Pathogenic.

Conclusions: The application of *APC*-specific classification criteria substantially reduced the number of VUS in ClinVar and LOVD. The study also demonstrates the feasibility of a systematic approach to variant classification with large datasets, which serves as a generalisable model for other gene-/disease-specific variant interpretation initiatives. It also allows for the prioritization of VUS that will benefit from in-depth evidence collection. The reclassified promising *APC* variants will be subjected to VCEP approval and made publicly available through ClinVar and LOVD for widespread clinical use.

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