Current work of the *APC* subcommittee of the InSiGHT - ClinGen Hereditary CRC / Polyposis Variant Curation Expert Panel: Interpretation of selected *APC* variants based on the *APC*-specific ACMG/AMP variant classification criteria

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Background and Aim: The Hereditary CRC/Polyposis Variant Curation Expert Panel was recently established by InSiGHT and ClinGen. As part of the ClinGen process, the *APC* subcommittee (*APC* VCEP) developed gene-specific ACMG/AMP variant classification criteria (Spier & Yin et al. 2023; https://cspec.genome.network/cspec/ui/svi/doc/GN089). After approval of the *APC* VCEP in December 2022, the ongoing variant assessment and curation was implemented to continue long-term variant evaluation by use of the specified criteria.

Method: As part of the validation process, the gene-specific criteria had been applied to 58 *APC* variants covering a wide range of scenarios (pilot variants). In addition, 20 variants with borderline evidence levels between uncertain significance (VUS) and (Likely) Pathogenic (LP/P) were selected by the *APC* VCEP for intensive re-evaluation (promising variants). These variants were the subject of further in-depth data mining including a survey of clinical and RNA data among *APC* VCEP members. All variants were first evaluated by a group of 11 biocurators, afterwards reviewed and discussed by expert members in virtual VCEP meetings, and finally made publicly available via ClinVar and the ClinGen Evidence Repository.

Results: Of 78 evaluated variants, 87% with a previous established classification in ClinVar were confirmed (14/15 (Likely) Benign [LB/B], 27/32 (Likely) Pathogenic [LP/P]). About half of the 31 previous VUS in ClinVar were reclassified: 10 as LB/B (32%) and 6 as LP/P (19%). Out of the 20 promising variants, 13 (65%) were evaluated as LP/P and 7 (35%) as VUS. The classification for 5 of the promising variants changed compared to the previous evaluations in ClinVar based on additional RNA analysis and clinical data (2 VUS were upgraded to LP and 3 LP/P variants were downgraded to VUS). The most challenging/interesting variants will be discussed in detail.

Conclusions: So far, 78 variants have been approved by the *APC* VCEP. The application of the *APC* specifications has led to the reclassification of ~50% of VUS into a clinically relevant pathogenicity class, which is a particular encouraging result given the large number of *APC* VUS listed in ClinVar awaiting reclassification. For selected promising variants a more comprehensive and valid evaluation could be achieved particularly with RNA and clinical data. The *APC* VCEP will continue to interpret prioritised lists of conflicting variants / VUS to improve clinical utility.