

ClinGen InSiGHT Hereditary Colorectal Cancer/Polyposis Variant Curation Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1

This version specified for the following gene: *APC*

Expert Panel Page: <https://www.clinicalgenome.org/affiliation/50099>

Table 1. Point system for phenotypic description relevant to criteria PS2, PS4, PM6, PP1 and BS4 (max. 1 point per proband)

Phenotypic consistency	Phenotype highly specific for <i>APC</i>	Phenotype consistent with <i>APC</i> but not highly specific
Phenotype point per proband	1	0.5
Polyposis	Typical colorectal phenotype: 20-99 colorectal adenomas ^a and ≤ 20 yr OR ≥ 100 colorectal adenomas ^a and ≤ 30 yr OR ≥ 1000 colorectal adenomas ^a at any age OR other accepted descriptor ^b of colorectal adenomas ^a at any age	Other colorectal phenotype: ≥ 20 colorectal adenomas ^a at 20 to 70 yr OR a documented diagnosis of FAP / AFAP OR ≥ 100 / any accepted descriptor ^b of colorectal polyps without histological confirmation
Desmoid(s)	without somatic <i>CTNNB1</i> variant	Unknown <i>CTNNB1</i> status
Medulloblastoma	WNT subtype without somatic <i>CTNNB1</i> variant	Unknown subtype and/or <i>CTNNB1</i> status
Hepatoblastoma	without somatic <i>CTNNB1</i> variant	Unknown <i>CTNNB1</i> status
CHRPE		Multifocal/bilateral
Multiple gastric adenomas		Presence (≥ 2 gastric adenomas)
Multiple duodenal adenomas		Presence (≥ 2 duodenal adenomas)
Osteoma(s)		Presence
Family history		Typical FAP family history (dominant pedigree pattern) ^c

^a histologically confirmed adenomas, description of colorectal polyps without confirmation of histology is not acceptable.

^b other accepted descriptors include uncountable, innumerable, countless, and carpeting, which refers to the coverage of the entire colon with distinct polyps. A single laterally spreading lesion covering a local area is not acceptable.

^c excluded from scoring for PS2 / PM6 and not applicable if PP1 is already used; can only be used if at least one variant carrier from the family and one additional relative each fulfill at least 0.5 point

Abbreviations: AFAP - Attenuated familial adenomatous polyposis, CHRPE - Congenital hypertrophy of the retinal pigment epithelium, FAP - Familial adenomatous polyposis

Table 2. Curation of *de novo* score for PS2 / PM6 based on the phenotype point system*

Phenotype point per proband	<i>De novo</i> score per proband	
	<i>De novo</i> with confirmed parental relationships	<i>De novo</i> with unconfirmed parental relationships
≥ 1	2	1
0.5	1	0.5

*Note that the *de novo* score is distinct from phenotype points and are not equivalent to the points used to classify a variant according to Tavgigian et al. 2020 (PMID: 32720330).

The parents are considered unaffected if they either

- have less than five colorectal adenomas in a colonoscopy and no other phenotypic conspicuities from Table 1 OR
- are older than 60 years of age, have no signs of a gastrointestinal tumor (e. g. rectal bleeding), no phenotypic conspicuities from Table 1 and the family history is unremarkable.

Related publication(s): PMIDs 30192042, 33348689, 4843792

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5

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