ClinGen InSiGHT Hereditary Colorectal Cancer/Polyposis Variant Curation Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 2
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 *APC*	Phenotype consistent with *APC* 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 *CTNNB1* variant	Unknown *CTNNB1* status
Medulloblastoma	WNT subtype without somatic *CTNNB1* variant	Unknown subtype and/or *CTNNB1* status
Hepatoblastoma	without somatic *CTNNB1* variant	Unknown *CTNNB1* status
CHRPE	[redacted]	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	*De novo* score per proband	
	De novo with confirmed parental relationships	*De novo* 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 Tavtigian 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