CHEK2: CanVIG-UK Gene-Specific Guidance

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CanVIG-UK review of *CHEK2* 10/05/2024: Consensus to use relevant recommendations from the ClinGen ATM VCEP guidance, v1.3.0 (attached and also available at: https://clinicalgenome.org/affiliation/50039/) for *CHEK2* variants reported under indication R208 of the UK Genomic Test Directory. This scope of this test indication currently includes truncating variants (defined as: nonsense, frameshift and canonical splice site (+/- 1/2) variants) and *CHEK2* c.349A>G p.(Arg117Gly)[1]. Additional points of specification are given below.

For use in conjunction with the ClinGen ATM VCEP Guidance. Evidence lines for which there are no gene-specific recommendations should be reviewed in context of the ClinGen ATM VCEP Guidance.

Evidence towards Pathogenicity

Evidence element and evidence strengths allowed		Thresholds/data-sources/applications specifically relevant to CHEK2
PS4: Case-control: The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls	_STR	As per *ATM* VCEP guidance.
PM2: Absent from controls (or at extremely low frequency if recessive) in ESP, 1000GP, or ExAC	_SUP	Correspondence from the Hereditary Breast, Ovarian and Pancreatic Cancer VCEP on 15/12/2023 states that the allele frequency threshold for PM2 in the *ATM* guidelines is based on rarity of the *ATM* variant in gnomAD v2.1.1. Therefore, CanVIG-UK recommend to use total (male and female) population controls from the gnomAD v2.1.1 non-cancer dataset for *CHEK2*.
PVS1: **Predicted null variant** (in a gene where LOF is a known mechanism of disease)	_VSTR _STR _MOD _SUP	Truncating variants prior to c.1493: use PVS1_vstr *(variants up to the last 50bp of the penultimate exon, therefore predicted to undergo nonsense mediated decay)* Truncating variants occurring from c.1494 to c.1566: use PVS1_str *(not predicted to undergo NMD, truncated/altered region includes nuclear localisation signal and therefore critical to protein function)* Truncating variants from c.1567: use PVS1_mod (*not predicted to undergo NMD, role of region unknown, variant removes <10% of protein*)

		Truncating variants within the first 100bp: use PVS1_mod
PS1: Same amino acid change as an established variant	_MOD _SUP	As per *ATM* VCEP guidance.
PM4: Protein-length-changing variant	_MOD	As per *ATM* VCEP guidance.
PM5: Novel missense change at an amino acid residue where a different missense change determined to be pathogenic seen before	_SUP	PM5_sup can be used for truncating variants after the first 100bp and prior to c.1493.
PP3: In silico: Multiple lines of computational evidence support a deleterious effect on the gene or gene product	_SUP	PP3 not to be used in combination with PVS1 so N/A for truncating variants.
PM1, PP2: Enrichment/constraint: **PP2**: Missense variant in a gene that has a low rate of benign missense variation and in which missense variants are a common mechanism of disease **PM1:** Located in a mutational hot spot and/or critical and well-established functional domain (e.g. active site of an enzyme) without benign variation		PM1/PP2 N/A for truncating variants.
PS3: Functional: Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product	_MOD _SUP	No functional assays in *CHEK2* assessed by CanVIG-UK.
PP1: Co-segregation with disease in multiple affected family members in a gene definitively known to cause the disease		N/A as per *ATM* VCEP guidance
PS2/PM6: De novo (maternity and paternity confirmed/unconfirmed) in a patient with the disease and no family history		N/A as per *ATM* VCEP guidance
PM3: in trans with a pathogenic variant (**recessive disorders)**		N/A no recessive phenotype
PP5: Reputable source recently reports variant as pathogenic, but the evidence is not available to the laboratory to perform an independent evaluation		N/A as per *ATM* VCEP guidance
PP4: Phenotypic specificity (Patient's phenotype or family history is highly specific for a disease with a single genetic aetiology)		N/A as per *ATM* VCEP guidance

Evidence towards Benignity

BA1/BS1: Allele frequency is "too high" in ExAC or gnomAD for disorder	_SA _STR	As per *ATM* VCEP guidance

BS2: Observation in controls inconsistent with disease penetrance. Observed in a healthy adult individual for a recessive (homozygous), dominant (heterozygous), or X-linked (hemizygous) disorder, with full penetrance expected at an early age		N/A as per *ATM* VCEP guidance
BP4: In silico: Multiple lines of computational evidence suggest no impact on gene or gene product (conservation, evolutionary, splicing impact, etc.)	_SUP	N/A for truncating variants
BP1: Missense variant in a gene for which primarily truncating variants are known to cause disease		N/A for truncating variants
BP7: Synonymous (silent) variant for which splicing prediction algorithms predict no impact to the splice consensus sequence	_STR _MOD _SUP	As per *ATM* VCEP guidance (BP7_O)
BP3: In-frame deletions/insertions in a repetitive region		N/A as per *ATM* VCEP guidance
BS3: Well-established *in vitro* or *in vivo* functional studies show no damaging effect on protein function or splicing	_MOD _SUP	No functional studies assessed by CanVIG-UK
BS4: Non segregation with disease		N/A as per *ATM* VCEP guidance
BP2: Observed in trans with a pathogenic variant for a fully penetrant dominant gene/disorder or observed in cis	_STR _MOD _SUP	As per *ATM* VCEP guidance
BP6: Reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation		N/A as per *ATM* VCEP guidance
BP5: Alternate molecular basis for disease		N/A as per *ATM* VCEP guidance

Version History/Amendments

Revised version	Date	Section	Update	Amended by	Approved by
1.1	25/05/23	--	Changed opening statement to clarify that these CanVIG guidelines should be used in conjunction with ClinGen VCEP guidelines.	Allen	CStAG
1.2	25/01/2024	Statement	Reference to current VCEP version (v1.3.0) and additional *CHEK2* missense variant reporting per UKCGG statement.	Allen	CStAG
1.2	23/05/2024	PM2	Updated to match statement for CanVIG ATM guidelines (to use gnomAD v2.1.1 per VCEP correspondence)	Allen	CStAG

References:

1. Exceptional variants/gene-specific variant reporting, UKCGG website (available at: https://www.ukcgg.org/information-education/exceptional-variantsgene-specific-variant-reporting/).

Criteria Specification

ClinGen Hereditary Breast, Ovarian and Pancreatic Cancer Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for ATM Version 1.3.0

Affiliation: Hereditary Breast, Ovarian and Pancreatic Cancer VCEP
Description : ACMG-modified rules specifications for ATM (autosomal dominant and autosomal recessive disorders)
Version : 1.3.0
Released : 3/27/2024
Release Notes :
Release notes v1.3
Clarified application of BP4 + BP7_Variant(RNA) verbiage in CSPEC editor and rules document:
BP7 _Variable(RNA): RNA functional studies
Lack of aberrant splice defect: Please see PVS1(RNA) section (above) for guidance on baseline weights and modifications of weight based on quality for RNA assays
NOTE: BP4 splice predictions may not be used in conjunction with BP7_Variable(RNA)

Rules for ATM

General Comments: Release notes v1.3 Clarified application of BP4 + BP7_Variant(RNA) verbiage in CSPEC editor and rules document: BP7 _Variable(RNA): RNA functional studies Lack of aberrant splice defect: Please see PVS1(RNA) section (above) for guidance on baseline weights and modifications of weight based on quality for RNA assays NOTE: BP4 splice predictions may not be used in conjunction with BP7_Variable(RNA)

Gene: ATM (HGNC:795)
Transcripts:
NM_000051.3

HGNC Name: ATM serine/threonine kinase
Disease:
hereditary breast carcinoma (MONDO:0016419) **Mode of Inheritance:** Autosomal dominant inheritance
ataxia telangiectasia (MONDO:0008840) **Mode of Inheritance:** Autosomal recessive inheritance
ataxia - telangiectasia variant (MONDO:0018266) **Mode of Inheritance:** Autosomal recessive inheritance

Criteria & Strength Specifications

PVS1

Original ACMG
Summary

Null variant (nonsense, frameshift, canonical +/−1 or 2 splice sites, initiation codon, single or multi-exon deletion) in a gene where loss of function (LOF) is a known mechanism of disease.
Caveats:
• Beware of genes where LOF is not a known disease mechanism (e.g. GFAP, MYH7).
• Use caution interpreting LOF variants at the extreme 3’ end of a gene.
• Use caution with splice variants that are predicted to lead to exon skipping but leave the remainder of the protein intact.
• Use caution in the presence of multiple transcripts.

Very Strong

Use ATM PVS1 Decision Tree

Modification Type: Gene-specific,Strength

Strong

Use ATM PVS1 Decision Tree.

Modification Type: Gene-specific,Strength

Moderate

Use ATM PVS1 Decision Tree.

Modification Type: Gene-specific,Strength

Supporting

Use ATM PVS1 Decision Tree

Modification Type: Gene-specific,Strength

Instructions: Use ATM PVS1 Decision Tree.

PS1

Original ACMG
Summary

Same amino acid change as a previously established pathogenic variant regardless of nucleotide change.
Example: Val->Leu caused by either G>C or G>T in the same codon.

Caveat: Beware of changes that impact splicing rather than at the amino acid/protein level.

Strong

Use for protein changes as long as splicing is ruled-out for both alterations. Use ATM PS1 Splicing table for splicing variants with similar predictions or observations of splice defect.

Modification Type: General recommendation

Moderate

Use for protein changes as long as splicing is ruled-out for both alterations. Use ATM PS1 Splicing table for splicing variants with similar predictions or observations of splice defect.

Modification Type: General recommendation,Strength

Instructions: Use as ascribed for protein changes as long as a splice defect is ruled out for both variants; Use Use ATM PS1 Splicing table for splicing variants with similar predictions or observations of splice defect. (PMID: 36865205)

PS2

Original ACMG Summary

De novo (both maternity and paternity confirmed) in a patient with the disease and no family history.
Note: Confirmation of paternity only is insufficient. Egg donation, surrogate motherhood, errors in embryo transfer, etc. can contribute to non-maternity.

Not Applicable

PS3

Original ACMG Summary

Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product.
Note: Functional studies that have been validated and shown to be reproducible and robust in a clinical diagnostic laboratory setting are considered the most well-established.

Strong

Do not use as strong.

Modification Type: Gene-specific

Moderate

Use when a variant fails to rescue both an ATM specifc feature (e.g. phosphorylation of ATM-specific targets) AND radiosensitivity.

Modification Type: Gene-specific,Strength

Supporting

Use when a variant fails to rescue an ATM specifc feature, only (e.g. phosphorylation of ATM-specific targets). Do not use for radiosensitivity-only as that is not a feature specific to ATM deficiency

Modification Type: Gene-specific,Strength

Instructions: For protein, see detailed notes on ATM-specific assays; For RNA use code PVS1_Strength(RNA) and modulate strength based on assay quality and quantity (curator discretion).

PS4

Original ACMG Summary

The prevalence of the variant in affected individuals is significantly increased compared to the prevalence in controls.
Note 1: Relative risk (RR) or odds ratio (OR), as obtained from case-control studies, is >5.0 and the confidence interval around the estimate of RR or OR does not include 1.0. See manuscript for detailed guidance.
Note 2: In instances of very rare variants where case-control studies may not reach statistical significance, the prior observation of the variant in multiple unrelated patients with the same phenotype, and its absence in controls, may be used as moderate level of evidence.

Strong

Case-control studies; p-value ≤.05 AND (Odds ratio, hazard ratio, or relative risk ≥2 OR lower 95% CI ≥1.5).

Modification Type: General recommendation

Moderate

Do not use for proband counting.

Modification Type: Disease-specific,Gene-specific

Instructions: Do not use for 'proband counting' method. Case-control studies; p-value ≤.05 AND (Odds ratio, hazard ratio, or relative risk ≥2 OR lower 95% CI ≥1.5).

PM1

Original ACMG Summary

Located in a mutational hot spot and/or critical and well-established functional domain (e.g. active site of an enzyme) without benign variation.

Not Applicable

PM2

Original ACMG Summary

Absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project, 1000 Genomes or Exome Aggregation Consortium.
Caveat: Population data for indels may be poorly called by next generation sequencing.

Supporting

Frequency ≤.001% if n=1 in a single sub population, that is sufficiently rare and PM2_supporting would apply. n>1 in one or multiple subpopulations would not be considered rare and PM2_supporting would not apply

Modification Type: Gene-specific,Strength

Instructions: Frequency ≤.001% if n=1 in a single sub population, that is sufficiently rare and PM2_supporting would apply. n>1 in one or multiple subpopulations would not be considered rare and PM2_supporting would not apply

PM3

Original ACMG Summary

For recessive disorders, detected in trans with a pathogenic variant
Note: This requires testing of parents (or offspring) to determine phase.

Very Strong

Use ATM PM3/BP2 table.

Modification Disease-specific,General recommendation,Gene-specific,Strength

Type:

Strong

Use ATM PM3/BP2 table.

Modification Type: Disease-specific,General recommendation,Gene-specific,Strength

Moderate

Use ATM PM3/BP2 table.

Modification Type: Disease-specific,General recommendation,Gene-specific,Strength

Supporting

Use ATM PM3/BP2 table

Modification Type: Disease-specific,General recommendation,Gene-specific,Strength

Instructions: Use ATM PM3/BP2 table.

PM4

Original ACMG Summary

Protein length changes due to in-frame deletions/insertions in a non-repeat region or stop-loss variants.

Moderate

Use for stop-loss variants.

Modification Type: General recommendation,Gene-specific

Instructions: Do not use for in-frame insertions or deletions less than a single exon; Use for stop-loss variants, only.

PM5

Original ACMG Summary

Novel missense change at an amino acid residue where a different missense change determined to be pathogenic has been seen before.
Example: Arg156His is pathogenic; now you observe Arg156Cys.

Caveat: Beware of changes that impact splicing rather than at the amino acid/protein level.

Supporting

Use for genomic frameshift and truncating variants with PTC upstream of p.R3047. Apply also to splice variants as PM5_supporting for splice variants can only be applied for variants premature termination codons upstream of p.Arg3047 where PVS1_VS(RNA) is applied based on high quality observed splicing impact and must be NMD prone. Do not use for start-loss variants

Modification Type: Gene-specific,Strength

Instructions: Use for genomic frameshift and truncating variants with PTC upstream of p.R3047. Apply also to splice variants as PM5_supporting for splice variants can only be applied for variants premature termination codons upstream of p.Arg3047 where PVS1_VS(RNA) is applied based on high quality observed splicing impact and must be NMD prone. Do not use for start-loss variants

PM6

Original ACMG Summary

Assumed de novo, but without confirmation of paternity and maternity.

Not Applicable

PP1

Original ACMG Summary

Co-segregation with disease in multiple affected family members in a gene definitively known to cause the disease.
Note: May be used as stronger evidence with increasing segregation data.

Not Applicable

Comments: Informative pedigrees for segregation in families with AR Ataxia-Telangiectasia are not available. However, this VCEP would consider rules similar to the Glanzman and Hearing Loss VCEP rules if a pedigree becomes available.

PP2

Original ACMG

Summary

Missense variant in a gene that has a low rate of benign missense variation and where missense variants are a common mechanism of disease.

Not Applicable

Comments: Do not use: ATM does not have a defined low rate of missense benign variation.

PP3

Original ACMG

Summary

Multiple lines of computational evidence support a deleterious effect on the gene or gene product (conservation, evolutionary, splicing impact, etc.).
Caveat: As many in silico algorithms use the same or very similar input for their predictions, each algorithm should not be counted as an independent criterion. PP3 can be used only once in any evaluation of a variant.

Supporting

Protein: REVEL >.7333; RNA: At least one well-established in silico predictor (e.g. SpliceAI) shows impact on splicing

Modification Type: Gene-specific

Instructions: Protein: REVEL >.7333

RNA: At least one well-established in silico predictor (e.g. SpliceAI) shows impact on splicing

- NOTE: Splice analysis needs to be considered for all variant types (including missense, frameshift, nonsense, etc. as any variant has the potential to impact splicing which may preclude any expected protein effects)
- NOTE: PP3 for splice predictions may not be applied in addition to PVS1 or PVS1_Variable(RNA) codes.
- Use caution in applying the wrong type of computational evidence (protein vs. RNA) towards the cumulative body of evidence for the opposite mechanism.

PP4

Original ACMG

Summary

Patient’s phenotype or family history is highly specific for a disease with a single genetic etiology.

Not Applicable

PP5

Original ACMG Summary

Reputable source recently reports variant as pathogenic, but the evidence is not available to the laboratory to perform an independent evaluation.

Not Applicable

This criterion is not for use as recommended by the ClinGen Sequence Variant Interpretation VCEP Review Committee. PubMed : 29543229

BA1

Original ACMG Summary

Allele frequency is above 5% in Exome Sequencing Project, 1000 Genomes or Exome Aggregation Consortium.

Stand Alone

Filtering Allele Frequency >.5%.

Modification Type: Disease-specific

Instructions: Filtering Allele Frequency >.5%.

BS1

Original ACMG Summary

Allele frequency is greater than expected for disorder.

Strong

Filtering Allele Frequency >.05%.

Modification Type: Disease-specific

Instructions: Filtering Allele Frequency >.05%.

BS2

Original ACMG

Summary

Observed in a healthy adult individual for a recessive (homozygous), dominant (heterozygous), or X-linked (hemizygous) disorder, with full penetrance expected at an early age.

Not Applicable

BS3

Original ACMG
Summary

Well-established in vitro or in vivo functional studies show no damaging effect on protein function or splicing.

Moderate

Use when a variant rescues both an ATM specifc feature (e.g. phosphorylation of ATM-specific targets) AND radiosensitivity.

Modification Type: Disease-specific,Gene-specific,Strength

Supporting

Use when a variant rescues EITHER an ATM specifc feature OR rescues radiosensitivity.

Modification Type: Disease-specific,Gene-specific,Strength

Instructions: For protein, see detailed notes on ATM-specific assays; For RNA use code BP7_RNA and modulate strength based on assay quality and quantity (curator discretion).

BS4

Original ACMG
Summary

Lack of segregation in affected members of a family.
Caveat: The presence of phenocopies for common phenotypes (i.e. cancer, epilepsy) can mimic lack of segregation among affected individuals. Also, families may have more than one pathogenic variant contributing to an autosomal dominant disorder, further confounding an apparent lack of segregation.

Not Applicable

Comments: AD Condition: Co-segregation analysis in lowpenetrance genes can lead to false positive results (PMID 32773770) . AR Condition: informative instances of lack of co-segregation in A-T families are too rare to be

considered for weight at this time and can also be considered for BP2 if biallelic unaffected patients are observed in an A-T family.

BP1

Original ACMG Summary

Missense variant in a gene for which primarily truncating variants are known to cause disease.

Not Applicable

BP2

Original ACMG Summary

Observed in trans with a pathogenic variant for a fully penetrant dominant gene/disorder or observed in cis with a pathogenic variant in any inheritance pattern.

Strong

Use ATM PM3/BP2 table.

Modification Type: Disease-specific,General recommendation,Gene-specific,Strength

Moderate

Use ATM PM3/BP2 table.

Modification Type: Disease-specific,General recommendation,Gene-specific,Strength

Supporting

Use ATM PM3/BP2 table

Modification Type: Disease-specific,General recommendation,Gene-specific,Strength

Instructions: Use ATM PM3/BP2 table.

BP3

Original ACMG Summary

In frame-deletions/insertions in a repetitive region without a known function.

Not Applicable

BP4

Original ACMG Summary

Multiple lines of computational evidence suggest no impact on gene or gene product (conservation, evolutionary, splicing impact, etc)
Caveat: As many in silico algorithms use the same or very similar input for their predictions, each algorithm cannot be counted as an independent criterion. BP4 can be used only once in any evaluation of a variant.

Supporting

- **Protein** Analysis: Metapredictor REVEL score ≤.249
- RNA: At least one well-established in silico predictor (e.g. SpliceAI) shows impact on splicing
  - NOTE: Splice analysis needs to be considered for all variant types (including missense, frameshift, nonsense, etc. as any variant has the potential to impact splicing which may preclude any expected protein effects)
  - NOTE: BP4 for splice predictions may not be applied in conjunction with BP7_Variable(RNA) (a lack of observed RNA defect) Use caution in applying the wrong type of computational evidence (protein vs. RNA) towards the cumulative body of evidence for the opposite mechanism.

Modification Type: General recommendation

Instructions: Protein: REVEL <.249; RNA: multiple in silico predictors agree to a lack of splice defect.

BP5

Original ACMG Summary

Variant found in a case with an alternate molecular basis for disease.

Not Applicable

BP6

Original ACMG Summary

Reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation.

Not Applicable

This criterion is not for use as recommended by the ClinGen Sequence Variant

Interpretation VCEP Review Committee. PubMed : 29543229

BP7

Original ACMG Summary

A synonymous variant for which splicing prediction algorithms predict no impact to the splice consensus sequence nor the creation of a new splice site AND the nucleotide is not highly conserved.

Strong

Can be considered for BP7_(RNA) with curator discretion of quality.

Modification Type: General recommendation

Moderate

Can be considered for BP7_(RNA) with curator discretion of quality.

Modification Type: General recommendation

Supporting

Can be considered for BP7_(RNA) with curator discretion of quality; Use for synonymous and deep intronic variants defined as further than (but not including) +7 and further than (but not including) -40 at donor and acceptor sites, respectively

Modification Type: General recommendation

Instructions:

- **BP7: Synonymous and deep intronic**
  - Can be used for deep intronic variants beyond (but not including) +7 (donor) and -40 (acceptor)
  - May also apply BP4 to achieve Likely Benign
  - Is not considered a conflicting piece of evidence against a body of evidence supporting a pathogenic splice defect
- **BP7 _Variable(RNA): RNA functional studies**
  - Lack of aberrant splice defect: Please see PVS1(RNA) section (above) for guidance on baseline weights and modifications of weight based on quality for RNA assays

NOTE: BP4 splice predictions **may not** be used in conjunction with **BP7_Variable(RNA)**

Rules for Combining Criteria

Pathogenic

1 Very Strong *(PVS1, PM3_Very Strong)* **AND ≥ 1 Strong** *(PVS1_Strong, PS1, PS3, PS4, PM3_Strong)*

1 Very Strong *(PVS1, PM3_Very Strong)* **AND ≥ 2 Moderate** *(PVS1_Moderate, PS1_Moderate, PS3_Moderate, PS4_Moderate, PM3, PM4)*

1 Very Strong *(PVS1, PM3_Very Strong)* **AND 1 Moderate** *(PVS1_Moderate, PS1_Moderate, PS3_Moderate, PS4_Moderate, PM3, PM4)* **AND 1 Supporting** *(PVS1_Supporting, PS3_Supporting, PM2_Supporting, PM3_Supporting, PM5_Supporting, PP3)*

1 Very Strong *(PVS1, PM3_Very Strong)* **AND ≥ 2 Supporting** *(PVS1_Supporting, PS3_Supporting, PM2_Supporting, PM3_Supporting, PM5_Supporting, PP3)*

≥ 2 Strong *(PVS1_Strong, PS1, PS3, PS4, PM3_Strong)*

1 Strong *(PVS1_Strong, PS1, PS3, PS4, PM3_Strong)* **AND ≥ 3 Moderate** *(PVS1_Moderate, PS1_Moderate, PS3_Moderate, PS4_Moderate, PM3, PM4)*

1 Strong *(PVS1_Strong, PS1, PS3, PS4, PM3_Strong)* **AND 2 Moderate** *(PVS1_Moderate, PS1_Moderate, PS3_Moderate, PS4_Moderate, PM3, PM4)* **AND ≥ 2 Supporting** *(PVS1_Supporting, PS3_Supporting, PM2_Supporting, PM3_Supporting, PM5_Supporting, PP3)*

1 Strong *(PVS1_Strong, PS1, PS3, PS4, PM3_Strong)* **AND 1 Moderate** *(PVS1_Moderate, PS1_Moderate, PS3_Moderate, PS4_Moderate, PM3, PM4)* **AND ≥ 4 Supporting** *(PVS1_Supporting, PS3_Supporting, PM2_Supporting, PM3_Supporting, PM5_Supporting, PP3)*

Likely Pathogenic

1 Very Strong *(PVS1, PM3_Very Strong)* **AND 1 Moderate** *(PVS1_Moderate, PS1_Moderate, PS3_Moderate, PS4_Moderate, PM3, PM4)*

1 Strong *(PVS1_Strong, PS1, PS3, PS4, PM3_Strong)* **AND 1 Moderate** *(PVS1_Moderate, PS1_Moderate, PS3_Moderate, PS4_Moderate, PM3, PM4)*

1 Strong *(PVS1_Strong, PS1, PS3, PS4, PM3_Strong)* **AND ≥ 2 Supporting** *(PVS1_Supporting, PS3_Supporting, PM2_Supporting, PM3_Supporting, PM5_Supporting, PP3)*

≥ 3 Moderate *(PVS1_Moderate, PS1_Moderate, PS3_Moderate, PS4_Moderate, PM3, PM4)*

2 Moderate *(PVS1_Moderate, PS1_Moderate, PS3_Moderate, PS4_Moderate, PM3, PM4)* **AND ≥ 2 Supporting** *(PVS1_Supporting, PS3_Supporting, PM2_Supporting, PM3_Supporting, PM5_Supporting, PP3)*

1 Moderate *(PVS1_Moderate, PS1_Moderate, PS3_Moderate, PS4_Moderate, PM3, PM4)* **AND ≥ 4 Supporting** *(PVS1_Supporting, PS3_Supporting, PM2_Supporting, PM3_Supporting, PM5_Supporting, PP3)*

1 Strong *(PVS1_Strong, PS1, PS3, PS4, PM3_Strong)* **AND 2 Moderate** *(PVS1_Moderate, PS1_Moderate, PS3_Moderate, PS4_Moderate, PM3, PM4)*

1 Very Strong *(PVS1, PM3_Very Strong)* **AND 1 Supporting** *(PS3_Supporting, PM2_Supporting, PM3_Supporting, PM5_Supporting, PP3)*

Benign

≥ 2 Strong *(BS1, BP2_Strong, BP7_Strong)*

Likely Benign

1 Strong *(BS1, BP2_Strong, BP7_Strong)* **AND 1 Supporting** *(BS3_Supporting, BP2, BP4, BP7)*

≥ 2 Supporting *(BS3_Supporting, BP2, BP4, BP7)*

1 Strong *(BS1, BP2_Strong, BP7_Strong)*

Files & Images

ATM supplementary Tables 1 and 2 :

ClinGen HBOP ACMG Specifications ATM version 1.3: