

ATM: CanVIG-UK Gene-Specific Guidance

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CanVIG-UK review of ATM May 2024. Consensus to use ClinGen ATM VCEP guidance, v1.3.0 (attached and also available at: <https://clinicalgenome.org/affiliation/50039/>) for ATM variants reported under indication R208 of the UK Genomic Test Directory. Additional points of specification are given below. This scope of this test indication currently includes truncating variants (defined as nonsense, frameshift and canonical splice site (+/- 1/2) variants) and ATM c.7271T>G Val2424Gly.

Evidence towards Pathogenicity

Evidence element and evidence strengths allowed		Thresholds/data-sources/applications specifically relevant to ATM
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 ATM.
PVS1: Predicted null variant (in a gene where LOF is a known mechanism of disease)	_VSTR _STR _MOD _SUP	As per ATM VCEP guidance
PS1: Same amino acid change as an established variant	_STR _MOD	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	As per ATM VCEP guidance
PP3: In silico: Multiple lines of computational evidence support a deleterious effect on the gene or gene product	_SUP	As per ATM VCEP guidance

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		N/A as per <i>ATM</i> VCEP guidance
PS3: Functional: Well-established <i>in vitro</i> or <i>in vivo</i> functional studies supportive of a damaging effect on the gene or gene product	_MOD _SUP	As per <i>ATM</i> VCEP guidance. No <i>ATM</i> functional studies have been 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 <i>ATM</i> 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 <i>ATM</i> VCEP guidance
PM3: in trans with a pathogenic variant (recessive disorders)	_VSTR _STR _MOD _SUP	As per <i>ATM</i> VCEP guidance
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 <i>ATM</i> 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 <i>ATM</i> VCEP guidance

Evidence towards Benignity

BA1/BS1: Allele frequency is "too high" in ExAC or gnomAD for disorder	_SA _STR	As per <i>ATM</i> 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 <i>ATM</i> VCEP guidance
BP4: In silico: Multiple lines of computational evidence suggest no impact on gene or gene product (conservation, evolutionary, splicing impact, etc.)	_SUP	As per <i>ATM</i> VCEP guidance
BP1: Missense variant in a gene for which primarily truncating variants are known to cause disease		N/A as per <i>ATM</i> VCEP guidance
BP7: Synonymous (silent) variant for which splicing prediction algorithms predict no impact to the splice consensus sequence	_STR _MOD _SUP	As per <i>ATM</i> VCEP guidance
BP3: In-frame deletions/insertions in a repetitive region		N/A as per <i>ATM</i> VCEP guidance
BS3: Well-established <i>in vitro</i> or <i>in vivo</i> functional studies show no damaging effect on protein function or splicing	_MOD _SUP	As per <i>ATM</i> VCEP guidance
BS4: Non segregation with disease		N/A as per <i>ATM</i> VCEP guidance

BP2: Observed in trans with a pathogenic variant for a fully penetrant dominant gene/disorder or observed in cis	_STR	As per <i>ATM</i> VCEP guidance
	_MOD	
	_SUP	
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 <i>ATM</i> VCEP guidance
BP5: Alternate molecular basis for disease		N/A as per <i>ATM</i> VCEP guidance

Revisions

Revised version	Date	Section	Update	Amended by	Approved by
1.1	30/06/2023	--	Clarification to use <i>ATM</i> VCEP guidance (not CanVIG-UK consensus) where no specific guidance given.	Allen	CStAG
1.2	29/01/2024	PM2	Specified to use controls from gnomAD v2.1.1 non-cancer.	Allen	CStAG
1.2	25/01/2024	PS4	Removed additional guidance as this addition is now incorporated in the VCEP guidance.	Allen	CStAG
1.2	30/04/2024	Statement	Update to statement to reference current VCEP version (v1.3.0)	Allen	CStAG

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 \pm 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 Gene-specific,Strength

Type:

Strong

Use ATM PVS1 Decision Tree.

Modification Gene-specific,Strength

Type:

Moderate

Use ATM PVS1 Decision Tree.

Modification Gene-specific,Strength

Type:

Supporting

Use ATM PVS1 Decision Tree

Modification Gene-specific,Strength

Type:

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 General recommendation

Type:

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 General recommendation,Strength

Type:

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 Gene-specific

Type:

Moderate

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

Modification Gene-specific,Strength

Type:

Supporting

Use when a variant fails to rescue an ATM specific 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 Gene-specific,Strength

Type:

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; $p\text{-value} \leq .05$ AND (Odds ratio, hazard ratio, or relative risk ≥ 2 OR lower 95% CI ≥ 1.5).

Modification General recommendation

Type:

Moderate

Do not use for proband counting.

Modification Disease-specific, Gene-specific

Type:

Instructions: Do not use for 'proband counting' method. Case-control studies; p-value $\leq .05$ 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 $\leq .001\%$ 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 Gene-specific, Strength
Type:

Instructions: Frequency $\leq .001\%$ 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 Disease-specific,General recommendation,Gene-specific,Strength

Type:

Moderate

Use ATM PM3/BP2 table.

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

Type:

Supporting

Use ATM PM3/BP2 table

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

Type:

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 General recommendation,Gene-specific

Type:

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 Gene-specific, Strength

Type:

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 Gene-specific

Type:

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 Disease-specific
Type:

Instructions: Filtering Allele Frequency >.5%.

BS1

Original ACMG Summary

Allele frequency is greater than expected for disorder.

Strong

Filtering Allele Frequency >.05%.

Modification Disease-specific
Type:

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 specific feature (e.g. phosphorylation of ATM-specific targets) AND radiosensitivity.

Modification Disease-specific, Gene-specific, Strength

Type:

Supporting

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

Modification Disease-specific, Gene-specific, Strength

Type:

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 $\leq .249$
- 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 General recommendation

Type:

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

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 General recommendation

Type:

Moderate

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

Modification General recommendation

Type:

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 General recommendation

Type:

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_Visible(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_Visible(RNA)**

Pathogenic

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

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

\geq **2 Strong** (*PVS1_Strong, PS1, PS3, PS4, PM3_Strong*)

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

\geq **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** \geq **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** \geq **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

\geq **2 Strong** (*BS1, BP2_Strong, BP7_Strong*)

Likely Benign

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

\geq **2 Supporting** (*BS3_Supporting, BP2, BP4, BP7*)

1 Strong (*BS1, BP2_Strong, BP7_Strong*)

Files & Images

ATM supplementary Tables 1 and 2 : [↓](#)

