ATM: CanVIG-UK Gene-Specific Guidance

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CanVIG-UK review of *ATM* April 2022. Consensus to use ClinGen *ATM* VCEP guidance (attached and also available at: https://clinicalgenome.org/affiliation/50039/) for *ATM* 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 *ATM* c.7271T>G Val2424Gly. Any points of specification in addition to the *ATM* VCEP guidance are given below.

For use in conjunction with CanVIG-UK Consensus Specification for Cancer susceptibility Genes of ACGS Best Practice Guidelines for Variant Classification. Evidence lines for which there are no gene-specific recommendations should be reviewed in context of CanVIG-UK Consensus Specification for Cancer Susceptibility Genes.

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	p-value ≤.05 AND (Odds Ratio ≥2 OR lower 95% CI of Odds Ratio ≥1.5)
PM2: Absent from controls (or at extremely low frequency if recessive) in ESP, 1000GP, or ExAC	_SUP	
PVS1: **Predicted null variant** (in a gene where LOF is a known mechanism of disease)	_VSTR _STR _MOD _SUP	
PS1: Same amino acid change as an established variant	_STR	
PM4: Protein-length-changing variant	_MOD _MOD	
PM5: Novel missense change at an amino acid residue where a different missense change determined to be pathogenic seen before	_SUP	
PP3: In silico: Multiple lines of computational evidence support a deleterious effect on the gene or gene product	_SUP	

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		
PS3: Functional: Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product	_VSTR _STR _MOD _SUP	
PP1: Co-segregation with disease in multiple affected family members in a gene definitively known to cause the disease		
PS2/PM6: De novo (maternity and paternity confirmed/unconfirmed) in a patient with the disease and no family history		
PM3: in trans with a pathogenic variant (**recessive disorders)**	_STR _MOD _SUP	
PP5: Reputable source recently reports variant as pathogenic, but the evidence is not available to the laboratory to perform an independent evaluation		
PP4: Phenotypic specificity (Patient's phenotype or family history is highly specific for a disease with a single genetic aetiology)		

Evidence towards Benignity

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

BP2: Observed in trans with a pathogenic variant for a fully penetrant dominant gene/disorder or observed in cis	_SUP	
BP6: Reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation		
BP5: Alternate molecular basis for disease		

Revised version	Date	Section	Update	Amended by	Approved by