ATM: CanVIG-UK Gene-Specific Guidance

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A Garrett[1], L Loong[1], S Allen[1], M Durkie[2], J. Drummond[3], G.J. Burghel[4], R. Robinson[5], A Callaway[6,7], I. Berry[5], A. Wallace[4], H. Hanson[1,8], C. Turnbull[1,9]

1) Division of Genetics and Epidemiology, The Institute of Cancer Research, London, UK.
2) Sheffield Diagnostic Genetics Service, Sheffield Children's NHS Foundation Trust
3) East Anglian Medical Genetics Service, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
4) Manchester Centre for Genomic Medicine and NW Laboratory Genetics Hub, Manchester University Hospitals NHS Foundation Trust, Manchester, UK
5) Yorkshire Regional Genetics Service, Leeds Teaching Hospitals NHS Trust, Leeds, UK
6) Wessex Regional Genetics Laboratory, Salisbury NHS Foundation Trust, Salisbury, UK
7) Human Genetics and Genomic Medicine, Faculty of Medicine, University of Southampton, Southampton, UK
8) St George's University Hospitals NHS Foundation Trust, Tooting, London, UK
9) The Royal Marsden NHS Foundation Trust, Fulham Road, London

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 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 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	As per *ATM* VCEP guidance
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		N/A as per *ATM* VCEP guidance

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	_MOD _SUP	As per *ATM* VCEP guidance. No *ATM* 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 *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)**	_VSTR _STR _MOD _SUP	As per *ATM* 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 *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	As per *ATM* VCEP guidance
BP1: Missense variant in a gene for which primarily truncating variants are known to cause disease		N/A as per *ATM* VCEP guidance
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
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	As per *ATM* VCEP guidance
BS4: Non segregation with disease		N/A as per *ATM* VCEP guidance
	_STR	

BP2: Observed in trans with a pathogenic variant for a fully penetrant dominant gene/disorder or observed in cis	_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

Revisions

Revised version	Date	Section	Update	Amended by	Approved by
1.1	30/06/2023	--	Clarification to use ATM VCEP guidance (not CanVIG-UK consensus) where no specific guidance given.	Allen	