Variant: NM_000051.4(ATM):c.5228C>T (p.Thr1743Ile)

Version: 1.0

CA286882

127403 (ClinVar)

Gene: ATM (HGNC:472)
Condition: ATM-related cancer predisposition (MONDO:0700270)
Inheritance Mode: Autosomal dominant inheritance
UUID: 6ecae11f-0052-46e5-8b68-b07412d09b04
Approved on: 2025-06-11
Published on: 2025-07-10

HGVS expressions

NM_000051.4:c.5228C>T
NM_000051.4(ATM):c.5228C>T (p.Thr1743Ile)
NC_000011.10:g.108301698C>T
CM000673.2:g.108301698C>T
NC_000011.9:g.108172425C>T
CM000673.1:g.108172425C>T
NC_000011.8:g.107677635C>T
NG_009830.1:g.83867C>T
ENST00000452508.7:c.5228C>T
ENST00000713593.1:c.*4699C>T
ENST00000278616.9:c.5228C>T
ENST00000683174.1:n.6712C>T
ENST00000683524.1:n.452C>T
ENST00000684152.1:n.942C>T
ENST00000527805.6:c.*292C>T
ENST00000675595.1:c.*292C>T
ENST00000675843.1:c.5228C>T
ENST00000278616.8:c.5228C>T
ENST00000452508.6:c.5228C>T
ENST00000524792.5:n.1443C>T
ENST00000533690.5:n.632C>T
ENST00000534625.1:n.457C>T
NM_000051.3:c.5228C>T
NM_001351834.1:c.5228C>T
NM_001351834.2:c.5228C>T

Pathogenic

Met criteria codes 3

PS3_Supporting PP3 PM3_Very Strong

Not Met criteria codes 4

BP4 BS1 BA1 PM2

Evidence Links 0

Expert Panel

Hereditary Breast, Ovarian and Pancreatic Cancer VCEP

Criteria Specification Information

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*

Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Hereditary Breast, Ovarian and Pancreatic Cancer VCEP

The c.5228C>T variant in ATM is a missense variant predicted to cause substitution of threonine by isoleucine at amino acid 1743 (p.Thr1743Ile). This variant has been detected in numerous unrelated individuals with Ataxia-Telangiectasia (PMIDs: 19147735, 21792198, 26896183, 31921190). The highest population minor allele frequency in gnomAD v4.1.0 is 0.00008476 in the European (non-Finnish) population (PM2_Supporting, BS1, and BA1 are not met). Western blotting in ATM null cells transfected with cDNA carrying this variant showed a reduction in phosphorylation of ATM downstream targets as compared to wild-type controls, indicating that this variant impacts protein function (PMID: 19431188). The computational predictor REVEL gives a score of 0.835 which is above the threshold of 0.7333, evidence that correlates with impact to ATM function. In summary, this variant meets the criteria to be classified as pathogenic for autosomal dominant ATM-related cancer predisposition and autosomal recessive Ataxia-Telangiectasia based on the ACMG/AMP criteria applied as specified by the HBOP VCEP. (PM3_VeryStrong, PS3_Supporting, PP3).

Met criteria codes

PS3_Supporting	✔	Western blotting in ATM null cells transfected with cDNA carrying this variant showed a reduction in phosphorylation of ATM downstream targets as compared to wild-type controls, indicating that this variant impacts protein function (PMID: 19431188).
PP3	✔	The computational predictor REVEL gives a score of 0.835 which is above the threshold of 0.7333, evidence that correlates with impact to ATM function (PP3).
PM3_Very Strong	✔	This variant has been detected in numerous individuals with Ataxia-Telangiectasia (PMIDs: 31921190, 26896183, 21792198, 19147735)

Not Met criteria codes

BP4	✖	SpliceAI 0.03 AL, not significant.
BS1	✖	The filtering allele frequency (the lower threshold of the 95% CI of 2/113458) is 0.00001123 for European (non-Finnish) chromosomes by gnomAD v2.1.1, which is lower than the ClinGen HBOP VCEP threshold (>0.0005) for BS1, and therefore does not meet this criterion (BS1 not met).
BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM2	✖	The highest population minor allele frequency in gnomAD v2.1.1 is 0.00004005 (1/24970) which exceeds the PM2 threshold of 0.00001 (PM2_Supporting not met).

Curation History

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