

Variant: NM_000051.4(ATM):c.7355T>C (p.Leu2452Pro)

Version: 1.0

CA382559953 [↗](#)

481101 (ClinVar) [↗](#)

Gene: ATM ([HGNC:472](#))

Condition: ATM-related cancer predisposition ([MONDO:0700270](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: 0d34d5a3-4333-4679-b03f-0ee4e7269d8b

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HGVS expressions

NM_000051.4(ATM):c.7355T>C (p.Leu2452Pro)

NM_000051.4:c.7355T>C

NC_000011.10:g.108330261T>C

CM000673.2:g.108330261T>C

NC_000011.9:g.108200988T>C

CM000673.1:g.108200988T>C

NC_000011.8:g.107706198T>C

NG_009830.1:g.112430T>C

NG_054724.1:g.144572A>G

ENST00000452508.7:c.7355T>C

ENST00000713593.1:c.*6826T>C

ENST00000278616.9:c.7355T>C

ENST00000525056.2:n.1774T>C

ENST00000525537.3:n.312T>C

ENST00000638786.2:n.192T>C

ENST00000682286.1:n.2112T>C

ENST00000682302.1:n.1773T>C

ENST00000683174.1:n.8839T>C

ENST00000683524.1:n.2579T>C

ENST00000684152.1:n.3069T>C

ENST00000684447.1:n.1818T>C

ENST00000527805.6:c.*2419T>C

ENST00000675595.1:c.*2490T>C

ENST00000675843.1:c.7355T>C

ENST00000278616.8:c.7355T>C

ENST00000452508.6:c.7355T>C

ENST00000524792.5:n.3570T>C

ENST00000525729.5:c.641-21190A>G

ENST00000533690.5:n.2759T>C

NM_000051.3:c.7355T>C

NM_001330368.1:c.641-21190A>G

NM_001351110.1:c.*38+4959A>G

NM_001351834.1:c.7355T>C

NM_001330368.2:c.641-21190A>G

NM_001351110.2:c.*38+4959A>G

NM_001351834.2:c.7355T>C

Likely Pathogenic

Met criteria codes 4

PS3_SupportingPM3_StrongPP3PM2_Supporting

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.7355T>C variant in ATM is a missense variant predicted to cause substitution of leucine by proline at amino acid 2452 (p.Leu2452Pro). This variant has been detected in at least two individuals with Ataxia-Telangiectasia (PMIDs: 19431188, 26896183). The highest population minor allele frequency in gnomAD v4.1.0 is 0.000001695 in the European (non-Finnish) population, which is lower than the HBOP threshold (≤ 0.00001) for PM2_Supporting, meeting this criterion. Western blotting in ATM null cells transfected with cDNA carrying this variant showed inactive 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 0.914, which is above the threshold of 0.733, evidence that correlates with impact to ATM function. In summary, this variant meets the criteria to be classified as likely 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_Strong, PM2_Supporting, PS3_Supporting, PP3)

Met criteria codes

PS3_Supporting	i ✓	Experimental studies showed that this variant has no ATM kinase activity compared to wild type in an expression system.
PM3_Strong	i ✓	This Variant has been detected in atleast 2 individuals with Ataxia-Telangiectasia(PMID:19431188,: 26896183)
PP3	i ✓	The computational predictor REVEL gives a score of 0.914,which is above the threshold of $\geq .733$, evidence that correlates with impact to ATM function
PM2_Supporting	i ✓	This variant is absent in gnomAD v2.1.1

Curation History

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