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Variant: NM_000051.4(ATM):c.4394T>C (p.Leu1465Pro)

Version: 2.0

CA298357

181996 (ClinVar)

Gene: ATM (HGNC:472)
Condition: ATM-related cancer predisposition (MONDO:0700270)
Inheritance Mode: Autosomal dominant inheritance
UUID: afccc577-2d42-4940-8bb7-bbf0b5ea06e3
Approved on: 2024/1/25
Published on: 2025/9/15

HGVS expressions

NM_000051.4:c.4394T>C
NM_000051.4(ATM):c.4394T>C (p.Leu1465Pro)
NC_000011.10:g.108289759T>C
CM000673.2:g.108289759T>C
NC_000011.9:g.108160486T>C
CM000673.1:g.108160486T>C
NC_000011.8:g.107665696T>C
NG_009830.1:g.71928T>C
ENST00000452508.7:c.4394T>C
ENST00000713593.1:c.*3865T>C
ENST00000278616.9:c.4394T>C
ENST00000533733.6:n.1657T>C
ENST00000683174.1:n.4544T>C
ENST00000527805.6:c.4394T>C
ENST00000675595.1:c.4229T>C
ENST00000675843.1:c.4394T>C
ENST00000278616.8:c.4394T>C
ENST00000452508.6:c.4394T>C
ENST00000524792.5:n.609T>C
ENST00000531525.2:c.401T>C
ENST00000533733.5:n.823T>C
NM_000051.3:c.4394T>C
NM_001351834.1:c.4394T>C
NM_001351834.2:c.4394T>C

Likely Pathogenic

Met criteria codes 3

PM3_Strong PM2_Supporting PP3

Not Met criteria codes 1

PS3

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 1.2.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Hereditary Breast, Ovarian and Pancreatic Cancer VCEP

The c.4394T>C variant in ATM is a missense variant predicted to cause substitution of leucine by proline at amino acid 1465 (p.Leu1465Pro). The highest population minor allele frequency in gnomAD v2.1.1 is 0.001% in European (non-Finnish) population, which is lower than the ClinGen HBOP threshold (</=0.001%) for PM2_Supporting, meeting this criterion. This variant has been detected in at least one individual with Ataxia-Telangiectasia (PMID 9463314, 10234507, 26896183). The computational predictor, Revel (Score: 0.802), predicts a damaging effect on ATM function. In summary, this variant meets criteria to be classified as likely pathogenic for autosomal dominant hereditary breast cancer and autosomal recessive Ataxia-Telangiectasia based on the ACMG/AMP criteria applied, as specified by the HBOP VCEP (PM2_supporting, PM3_strong, PP3).

Met criteria codes

PM3_Strong	✔	This variant has been detected in an individual with Ataxia-Telangiectasia in the compound heterozygous state with a pathogenic variant (c.1355del) confirmed in trans by parental testing (4 points: PMID 9463314, 10234507, 26896183).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.001% in European (non-Finnish) population, which is lower than the ClinGen HBOP threshold (</=0.001%) for PM2_Supporting, meeting this criterion.
PP3	✔	The computational predictor REVEL gives a score of 0.802, which is above the threshold of ≥.733, evidence that correlates with impact to ATM function. No splicing impact per Splice AI

Not Met criteria codes

PS3	✖	No rescue studies, therefore, PS3 is not met according to HBOP VCEP rules.

Curation History

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