

Variant: *NM_000051.4(ATM):c.1844T>C (p.Leu615Pro)*

Version: 1.0

CA197807 [↗](#)

187501 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 818bf464-ba1b-47c5-946b-f1ab49ee4823

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HGVS expressions

NM_000051.4:c.1844T>C

NM_000051.4(ATM):c.1844T>C (p.Leu615Pro)

NC_000011.10:g.108252858T>C

CM000673.2:g.108252858T>C

NC_000011.9:g.108123585T>C

CM000673.1:g.108123585T>C

NC_000011.8:g.107628795T>C

NG_009830.1:g.35027T>C

ENST00000452508.7:c.1844T>C

ENST00000713593.1:c.*1315T>C

ENST00000278616.9:c.1844T>C

ENST00000682516.1:n.1978T>C

ENST00000683174.1:n.1994T>C

ENST00000683605.1:n.1339T>C

ENST00000684037.1:c.*779T>C

ENST00000684061.1:n.1978T>C

ENST00000527805.6:c.1844T>C

ENST00000675595.1:c.1679T>C

ENST00000675843.1:c.1844T>C

ENST00000278616.8:c.1844T>C

ENST00000452508.6:c.1844T>C

ENST00000525012.5:n.38T>C

ENST00000527805.5:c.1844T>C

ENST00000533526.1:n.38T>C

NM_000051.3:c.1844T>C

NM_001351834.1:c.1844T>C

NM_001351834.2:c.1844T>C

Likely Pathogenic

Met criteria codes 3

PM2_Supporting PP3 PM3_Strong

Not Met criteria codes 23

PVS1 BS2 BS1 BS4 BS3
BP4 BP3 BP1 BP2 BP5 BP7
PS1 PS2 PS3 PS4 BA1 PP1

Expert Panel

Hereditary Breast, Ovarian and Pancreatic Cancer VCEP [↗](#)

Criteria Specification Information

[↗](#) **Criteria Specification:** ClinGen Hereditary Breast, Ovarian and Pancreatic Cancer Expert Panel Specifications

Evidence submitted by expert panel

Hereditary Breast, Ovarian and Pancreatic Cancer VCEP

The c.1844T>C variant in ATM is a missense variant predicted to cause substitution of leucine by proline at amino acid 615 (p.Leu615Pro). This variant has been detected in at least three unrelated individuals with Ataxia-Telangiectasia (PMID: 30549301, 32901917, external communication with Labcorp Genetics (formerly Invitae)). The highest population minor allele frequency in gnomAD v4.1.0 is 0.000003392 in the European (non-Finnish) population, which is lower than the HBOP VCEP threshold (≤ 0.00001) for PM2_Supporting, and therefore meets this criterion. The computational predictor REVEL gives a score of 0.792, 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 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, PP3)

Met criteria codes

PM2_Supporting			The highest population minor allele frequency in gnomAD v4.1.0 is 0.000003392 (4/1179414 alleles) in European (non-Finnish) population, which is lower than the ClinGen HBOP threshold (< 0.00001) for PM2_Supporting, meeting this criterion (PM2_Supporting).
PP3			The computational predictor REVEL gives a score of 0.792, which is above the threshold of 0.7333, evidence that correlates with impact to ATM function (PP3).
PM3_Strong			This variant has been detected in at least 3 individuals with Ataxia Telangiectasia. Of these individuals, two are compound heterozygous with P/LP variants, with one confirmed to be in trans (PMID: 30549301, Invitae patient). (6 points). The third individual is a compound heterozygote with the second variant, c.8687A>C, confirmed to be in trans but classified as a VUS (PMID: 32901917) (0.5 points). Total 6.5 points - (PM3_strong)

Not Met criteria codes

PVS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2			not applicable
BS1			Present at a low frequency in gnomADv4 which is below the threshold of 0.05%.
BS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3			No functional studies available

BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1			not applicable
BP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5			not applicable
BP7			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2			not applicable
PS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1			Present at a low frequency in gnomADv4
PP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2			not applicable
PP4			Ataxia patients counted under PM3
PM1			not applicable
PM5			4 different missense variants, (c.1843C>T, p.Leu615Phe,c.1843C>G, c.1843C>G, p.Leu615Val, c.1844T>G p.Leu615Arg, c.1844T>A, p.Leu615His), in the same codon have been reported in patients with breast cancer or ataxia telangiectasia. However, these variants have not yet met the criteria to be classified as pathogenic or likely pathogenic by the ClinGen HBOP.

PM4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6			not applicable

Curation History 

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