The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000051.3(ATM):c.8546G>C (p.Arg2849Pro)

Version: 2.0

CA382518439

490737 (ClinVar)

Gene: ATM (HGNC:472)
Condition: ATM-related cancer predisposition (MONDO:0700270)
Inheritance Mode: Autosomal dominant inheritance
UUID: ac4b4286-3493-4bcb-9cea-f24086ea7f27
Approved on: 2022-03-16
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HGVS expressions

NM_000051.3:c.8546G>C
NM_000051.3(ATM):c.8546G>C (p.Arg2849Pro)
NC_000011.10:g.108345870G>C
CM000673.2:g.108345870G>C
NC_000011.9:g.108216597G>C
CM000673.1:g.108216597G>C
NC_000011.8:g.107721807G>C
NG_009830.1:g.128039G>C
NG_054724.1:g.128963C>G
ENST00000452508.7:c.8546G>C
ENST00000713593.1:c.*8017G>C
ENST00000278616.9:c.8546G>C
ENST00000638786.2:n.1244G>C
ENST00000682286.1:n.3303G>C
ENST00000682302.1:n.2964G>C
ENST00000683174.1:n.10030G>C
ENST00000683524.1:n.3770G>C
ENST00000684152.1:n.3962G>C
ENST00000684180.1:n.1020G>C
ENST00000684447.1:n.5039G>C
ENST00000527805.6:c.*3610G>C
ENST00000675595.1:c.*3681G>C
ENST00000675843.1:c.8546G>C
ENST00000278616.8:c.8546G>C
ENST00000452508.6:c.8546G>C
ENST00000524755.5:c.227-10578C>G
ENST00000524792.5:n.4761G>C
ENST00000525729.5:c.641-36799C>G
ENST00000526725.1:n.272-5506C>G
ENST00000527531.5:c.*1196+9045C>G
ENST00000615746.4:c.*1196+9045C>G
NM_001330368.1:c.641-36799C>G
NM_001351110.1:c.695-10578C>G
NM_001351834.1:c.8546G>C
NR_147053.2:n.2301+9045C>G
NM_001330368.2:c.641-36799C>G
NM_001351110.2:c.695-10578C>G

NM_001351834.2:c.8546G>C
NM_000051.4:c.8546G>C
NR_147053.3:n.2299+9045C>G

Likely Pathogenic

Met criteria codes 4

PP3 PM3 PS3_Moderate PM2_Supporting

Not Met criteria codes 3

BP4 BA1 BS1

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 1.1*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Hereditary Breast, Ovarian and Pancreatic Cancer VCEP

The ATM c.8546G>C (p.Arg2849Pro) variant has been observed in a compound heterozygous state (presumed) in an individual with biallelic disease and in heterozygosity in an individual with biallelic disease with a second variant unidentified (PM3, PMID: 23667852, PMID: 9887333). This variant is non-functional in multiple different protein assays (PS3_Moderate, PMID: 11805335). In silico protein predictors (ALIGN GVGD: Class C65; REVEL: 0.919; SIFT: damaging; PolyPhen2: probably damaging) predict that this alteration is deleterious (PP3). This variant is absent in gnomAD v2.1.1 (PM2_Supporting). In summary, this variant meets criteria to be classified as likely pathogenic based on the ACMG/AMP criteria applied as specified by the HBOP Variant Curation Expert Panel.

Met criteria codes

PP3	✔	In silico protein predictors (ALIGN GVGD: Class C65; REVEL: 0.919; SIFT: damaging; PolyPhen2: probably damaging) predict that this alteration is deleterious (PP3). In silico splicing predictors (SpliceAI: AL 0.00/DL 0.01/AG 0.00/DG 0.00; MaxEntScan: 0.00% (wild type = 3.39, variant = 3.39)) find that this variant is unlikely to affect splicing.
PM3	✔	This variant has been observed in a compound heterozygous state (presumed) in an individual with biallelic disease and in heterozygosity in an individual with biallelic disease with a second variant unidentified (PM3, PMID: 23667852, PMID: 9887333).
PS3_Moderate	✔	This variant is non-functional in multiple different protein assays. Transfection of ATM cDNA carrying this variant into AT1ABR (ATM-null) cells failed to elicit ATM kinase activity (measured by p53 substrate in vitro phosphorylation and p53 Ser-15 in vivo phosphorylation) and failed to correct radiosensitivity (PMID: 11805335) (PS3_Moderate).
PM2_Supporting	✔	This variant is absent in gnomAD v2.1.1 (PM2_Supporting).

Not Met criteria codes

BP4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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