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_000051.4(ATM):c.8480T>G (p.Phe2827Cys)

Version: 1.0

CA115928

3022 (ClinVar)

Gene: ATM (HGNC:472)
Condition: ATM-related cancer predisposition (MONDO:0700270)
Inheritance Mode: Autosomal dominant inheritance
UUID: 3d40ca22-dc53-407e-8b14-a96f224ae3a4
Approved on: 2025/6/19
Published on: 2025/7/10

HGVS expressions

NM_000051.4(ATM):c.8480T>G (p.Phe2827Cys)
NM_000051.4:c.8480T>G
NC_000011.10:g.108345804T>G
CM000673.2:g.108345804T>G
NC_000011.9:g.108216531T>G
CM000673.1:g.108216531T>G
NC_000011.8:g.107721741T>G
NG_009830.1:g.127973T>G
NG_054724.1:g.129029A>C
ENST00000452508.7:c.8480T>G
ENST00000713593.1:c.*7951T>G
ENST00000278616.9:c.8480T>G
ENST00000638786.2:n.1178T>G
ENST00000682286.1:n.3237T>G
ENST00000682302.1:n.2898T>G
ENST00000683174.1:n.9964T>G
ENST00000683524.1:n.3704T>G
ENST00000684152.1:n.3896T>G
ENST00000684180.1:n.954T>G
ENST00000684447.1:n.4973T>G
ENST00000527805.6:c.*3544T>G
ENST00000675595.1:c.*3615T>G
ENST00000675843.1:c.8480T>G
ENST00000278616.8:c.8480T>G
ENST00000452508.6:c.8480T>G
ENST00000524755.5:c.227-10512A>C
ENST00000524792.5:n.4695T>G
ENST00000525729.5:c.641-36733A>C
ENST00000526725.1:n.272-5440A>C
ENST00000527531.5:c.*1196+9111A>C
ENST00000615746.4:c.*1196+9111A>C
NM_000051.3:c.8480T>G
NM_001330368.1:c.641-36733A>C
NM_001351110.1:c.695-10512A>C
NM_001351834.1:c.8480T>G
NR_147053.2:n.2301+9111A>C
NM_001330368.2:c.641-36733A>C

NM_001351110.2:c.695-10512A>C
NM_001351834.2:c.8480T>G
NR_147053.3:n.2299+9111A>C

Likely Pathogenic

Met criteria codes 3

PS3_Supporting PM3_Strong PP3

Not Met criteria codes 23

PVS1 BS1 BS4 BS3 BS2
BP5 BP7 BP4 BP3 BP1 BP2
PS1 PS2 PS4 BA1 PM6
PM2 PM1 PM5 PM4 PP1
PP2 PP4

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.8480T>G variant in ATM is a missense variant predicted to cause the substitution of phenylalanine by cysteine at amino acid 2827 (p.Phe2827Cys). This variant has been detected in at least one individual with Ataxia-Telangiectasia, who was described having a mild presentation (PMIDs: 8755918, 9000145, 9463314, 15928302, 19431188, 25040471, 30549301). The highest population minor allele frequency in gnomAD v4.1 is 0.00002196 in the South Asian population (PM2_Supporting, BS1, and BA1 are not met). Stable transfection of ATM-based cDNA constructs in an ATM-null lymphoblastoid cell line showed slightly decreased levels of kinase activity (caused by protein instability) indicating that this variant impacts protein function (PMID 19431188). The computational predictor, REVEL, gives a score of 0.889, which is above the threshold of 0.7333, evidence that correlates with impact on 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. (PS3_Supporting, PM3_Strong, PP3)

Met criteria codes

PS3_Supporting	✔	Stable transfection of ATM-based cDNA constructs in an ATM-null lymphoblastoid cell line showed slightly decreased levels of kinase activity (caused by protein instability) indicating that this variant impacts protein function (PMID:19431188).
PM3_Strong	✔	This variant has been detected in at least 1 individual with an A-T phenotype (reported to be variant A-T (milder phenotype)). The individual is compound heterozygous for the variant and a pathogenic variant (c.1563_1564delAG) with phase in trans (PMID: 8755918). It is highly likely that the same individual is reported in studies, PMID 30549301, PMID: 25040471, PMID:19431188, PMID:15928302, PMID: 9463314, PMID:8755918, PMID: 9000145.
PP3	✔	The computational predictor, REVEL gives a score of 0.889, which is above the threshold of 0.73, evidence that correlates with impact to ATM function (PP3).

Not Met criteria codes

PVS1	ℹ	✖	This is a missense variant and therefore not applicable
BS1	ℹ	✖	gnomAD v4.1 FAF of 0.00000385 (SAS) is less than BS1 threshold of 0.0005
BS4		✖	Not applicable to ATM
BS3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2		✖	not applicable to ATM
BP5		✖	not applicable to ATM
BP7	ℹ	✖	missense variant therefore does not apply
BP4	ℹ	✖	The computational predictor, REVEL gives a score of 0.889, which is above the threshold of 0.73, evidence that correlates with impact to ATM function (PP3).
BP3		✖	Not applicable to ATM
BP1		✖	Not applicable for ATM according to HBOP_VCEP
BP2	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1	ℹ	✖	no variants resulting in same amino acid change.
PS2		✖	Not applicable to ATM
PS4	ℹ	✖	case-control data not available for this variant
BA1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6		✖	Not applicable to ATM
PM2		✖	The highest population minor allele frequency in gnomAD v4.1 is 0.00002196 in the South Asian population (PM2_Supporting, BS1, and BA1 are not met).
PM1		✖	Not applicable for HBOP_VCEP specifications for ATM
PM5		✖	other variants at this position have conflicting classifications/VUS

PM4		✖	This is missense variant therefore not applicable
PP1		✖	Not applicable to ATM
PP2		✖	Not applicable for ATM according to HBOP_VCEP
PP4		✖	Not applicable to ATM

Curation History

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