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:c.1564_1565del

Version: 1.0

CA273990

127340 (ClinVar)

Gene: ATM (HGNC:472)
Condition: ATM-related cancer predisposition (MONDO:0700270)
Inheritance Mode: Autosomal dominant inheritance
UUID: e53b8866-dc19-40f8-95f7-9fd6d2524f64
Approved on: 2025-06-11
Published on: 2025-07-10

HGVS expressions

NM_000051.4:c.1564_1565del
NC_000011.10:g.108251029_108251030del
CM000673.2:g.108251029_108251030del
NC_000011.9:g.108121756_108121757del
CM000673.1:g.108121756_108121757del
NC_000011.8:g.107626966_107626967del
NG_009830.1:g.33198_33199del
ENST00000452508.7:c.1564_1565del
ENST00000713593.1:c.*1035_*1036del
ENST00000278616.9:c.1564_1565del
ENST00000682516.1:n.1698_1699del
ENST00000682956.1:n.1698_1699del
ENST00000683174.1:n.1714_1715del
ENST00000683605.1:n.1059_1060del
ENST00000684037.1:c.*499_*500del
ENST00000684061.1:n.1698_1699del
ENST00000684179.1:n.1533_1534del
ENST00000527805.6:c.1564_1565del
ENST00000675595.1:c.1399_1400del
ENST00000675843.1:c.1564_1565del
ENST00000278616.8:c.1564_1565del
ENST00000452508.6:c.1564_1565del
ENST00000527805.5:c.1564_1565del
NM_000051.3:c.1564_1565del
NM_001351834.1:c.1564_1565del
NM_001351834.2:c.1564_1565del

Pathogenic

Met criteria codes 3

PVS1 PM3_Very Strong PM5_Supporting

Not Met criteria codes 3

BA1 BS1 PM2

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.1564_1565del (p.Glu522Ilefs*43) variant in ATM is a frameshift variant predicted to cause a premature stop codon in a biologically-relevant-exon leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism. This alteration results in a termination codon upstream of the most C-terminus pathogenic alteration (ATM p.Arg3047*), as classified by the HBOP VCEP, and is expected to be more deleterious. This variant has been detected in numerous unrelated individuals with Ataxia-Telangiectasia (PMIDs: 26896183, 10330348, 9792409, 12497634, 15880721, 31407689, 30549301, 30772474, 9887333, 28126470, 23566627, 22213089, 21792198, 17985259, 8755918, 16266405, 21965147, 10817650, 8789452, 9463314, 19535770). The highest population minor allele frequency in gnomAD v4.1.0 0.00007373 in the European (non-Finnish) population (PM2_Supporting, BS1, and BA1 are not met). In summary, this variant meets criteria to be classified as 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. (PVS1, PM5_Supporting, PM3_VeryStrong)

Met criteria codes

PVS1	✔	The c.1564_1565del (p.Glu522IlefsTer?) variant in ATM is a frameshift variant in a biologically-relevant-exon predicted to cause a premature stop codon leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1).
PM3_Very Strong	✔	This variant has been detected in numerous individuals with Ataxia-Telangiectasia (PMIDs: 10330348, 9792409, 12497634, 15880721, 31407689, 30549301, 30772474, 9887333, 28126470, 23566627, 22213089, 21792198, 17985259, 8755918, 16266405, 21965147, 10817650, 8789452, 9463314, 19535770). Of those individuals, at least four were compound heterozygous for the variant and a pathogenic or likely pathogenic variant (c.6100C>T p.R2034*, c.3382C>T p.Q1128*, c. 7542T>G p.Y2514*, c.5515C>T p.Q1839*, 8.0 points, PMIDs: 10330348, 9792409).
PM5_Supporting	✔	In the absence of potential splicing rescue mechanisms in ATM, all PVS1-eligble truncating variants are expected to be pathogenic based on the existence of known pathogenic C-terminal truncations in the last exon (PM5_Supporting)

Not Met criteria codes

BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	✖	The filtering allele frequency (the lower threshold of the 95% CI of 12/113526) of the c.1564_1565del variant in ATM is 0.00006023 for Non-Finish European chromosomes by gnomAD v2.1.1, which is lower than the ClinGen HBOP threshold (>0.0005) for BS1, and therefore does not meet this criterion (BS1).
PM2	✖	

The highest population minor allele frequency in gnomAD v2.1.1 0.0003280 (2/6098) which exceeds the PM2 threshold of 0.00001 (PM2_Supporting not met).

Curation History

Showing 1 to 1 of 1 rows