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.5763-1050A>G

Version: 1.0

CA115927

3021 (ClinVar)

Gene: ATM (HGNC:472)
Condition: ATM-related cancer predisposition (MONDO:0700270)
Inheritance Mode: Autosomal dominant inheritance
UUID: b257c0e3-7ed5-432e-b2bc-7441d8c0b1dc
Approved on: 2024-11-26
Published on: 2025-01-13

HGVS expressions

NM_000051.4:c.5763-1050A>G
NM_000051.4(ATM):c.5763-1050A>G
NC_000011.10:g.108309110A>G
CM000673.2:g.108309110A>G
NC_000011.9:g.108179837A>G
CM000673.1:g.108179837A>G
NC_000011.8:g.107685047A>G
NG_009830.1:g.91279A>G
NG_054724.1:g.165723T>C
ENST00000452508.7:c.5763-1050A>G
ENST00000713593.1:c.*5234-1050A>G
ENST00000278616.9:c.5763-1050A>G
ENST00000525056.2:n.182-1050A>G
ENST00000682286.1:n.520-1050A>G
ENST00000682302.1:n.181-1050A>G
ENST00000683174.1:n.7247-1050A>G
ENST00000683524.1:n.987-1050A>G
ENST00000684152.1:n.1477-1050A>G
ENST00000527805.6:c.*827-1050A>G
ENST00000675595.1:c.*827-1050A>G
ENST00000675843.1:c.5763-1050A>G
ENST00000278616.8:c.5763-1050A>G
ENST00000452508.6:c.5763-1050A>G
ENST00000524792.5:n.1978-1050A>G
ENST00000525729.5:c.641-39T>C
ENST00000529588.5:c.187-1050A>G
ENST00000532765.1:n.79+1040A>G
ENST00000533690.5:n.1167-1050A>G
NM_000051.3:c.5763-1050A>G
NM_001330368.1:c.641-39T>C
NM_001351110.1:c.*39-39T>C
NM_001351834.1:c.5763-1050A>G
NM_001330368.2:c.641-39T>C
NM_001351110.2:c.*39-39T>C
NM_001351834.2:c.5763-1050A>G

Pathogenic

Met criteria codes 3

PM3_Very Strong | PP1_Strong | PVS1_Strong

Not Met criteria codes 2

PP3 | 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.5763-1050A>G variant in ATM is an intronic variant which results in an intronic A>G substitution before coding exon 38 activating a cryptic splice site leading to alternative splicing. The variant has been observed to cause an insertion of 137 nucleotides of intronic sequence at position 5762 and a premature stop codon at position 1930. Some normal splicing has been reported in patients with ATM c.5763-1050A>G, thus, the splice effect is incomplete (PMIDs 8755918, 10330348, 11382771, 15174027, Ambry internal data). This variant has been detected in many individuals with Ataxia-Telangiectasia, some of whom were described as having a mild presentation and/or later age of onset (PMIDs 8755918, 26896183). The variant has also been reported to segregate with Ataxia-Telangiectasia in 6 affected family members from 3 families (PMIDs 8755918, 15174027). The variant has a minor allele frequency in gnomAD v2.1.1 of 0.00003 (PM2_Supporting, BS1, and BA1 are not met). ATM c.5763-1050A>G has been reported as a founder variant in the British Isles (PMID 9463314). 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_Strong (RNA), PM3_Very Strong, PP1_Strong)

Met criteria codes

PM3_Very Strong	✔	Reported in several patients with AT diagnosis (11 points in total from publications below). 2 additional patients reported by Teraoka 1999 (PMID: 10330348) not counted as points already meets PM3_very strong.
PP1_Strong	✔	6 total affected segregations from 2 publications below. Per guidance from hearing loss VCEP (PMID: 30311386, table 4b), 6 affected segregations and 0 unaffected segregations results in a LOD score of 3.61 which is above the threshold of PP1_Strong (LOD 1.5).
PVS1_Strong	✔	Near complete splicing effect, PVS1 strength reduced by one level to PVS1_RNA_strong. Approved by biocurator group based on publications below as well as Ambry internal data: observed r.5762_5763ins5762+985_5763-1055 p.P1922LFS*9 with a PSI generally around 20% (n >50 HET carriers). This splicing event is completely absent from Ambry non-carrier controls (n =373).

Not Met criteria codes

PP3	✖	No data available for splice prediction

PM2	✖	Reported as a founder variant in the British Isles. Highest subpopulation frequency is 0.00008 which is above the threshold of 0.001%.

Curation History

Showing 1 to 1 of 1 rows