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_001126112.2(TP53):c.1150A>G (p.Met384Val)

Version: 2.0

CA000046

182939 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: dd48c400-334d-4397-a13e-9b192453e234
Approved on: 2025-01-16
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HGVS expressions

NM_001126112.2:c.1150A>G
NM_001126112.2(TP53):c.1150A>G (p.Met384Val)
NC_000017.11:g.7669641T>C
CM000679.2:g.7669641T>C
NC_000017.10:g.7572959T>C
CM000679.1:g.7572959T>C
NC_000017.9:g.7513684T>C
NG_017013.2:g.22910A>G
ENST00000503591.2:c.1150A>G
ENST00000508793.6:c.1150A>G
ENST00000509690.6:c.754A>G
ENST00000514944.6:c.871A>G
ENST00000604348.6:c.1129A>G
ENST00000269305.9:c.1150A>G
ENST00000269305.8:c.1150A>G
ENST00000359597.8:c.994-3397A>G
ENST00000413465.6:c.782+4540A>G
ENST00000420246.6:c.*257A>G
ENST00000445888.6:c.1150A>G
ENST00000455263.6:c.*169A>G
ENST00000504290.5:c.*169A>G
ENST00000504937.5:c.754A>G
ENST00000510385.5:c.*257A>G
ENST00000576024.1:c.103A>G
ENST00000610292.4:c.1033A>G
ENST00000610538.4:c.*169A>G
ENST00000610623.4:c.*169A>G
ENST00000615910.4:c.1117A>G
ENST00000617185.4:c.*257A>G
ENST00000618944.4:c.*257A>G
ENST00000619186.4:c.673A>G
ENST00000619485.4:c.1033A>G
ENST00000620739.4:c.1033A>G
ENST00000622645.4:c.*257A>G
ENST00000635293.1:c.983+968A>G
NM_000546.5:c.1150A>G
NM_001126113.2:c.*169A>G

NM_001126114.2:c.*257A>G
NM_001126115.1:c.754A>G
NM_001126116.1:c.*257A>G
NM_001126117.1:c.*169A>G
NM_001126118.1:c.1033A>G
NM_001276695.1:c.*169A>G
NM_001276696.1:c.*257A>G
NM_001276697.1:c.673A>G
NM_001276698.1:c.*257A>G
NM_001276699.1:c.*169A>G
NM_001276760.1:c.1033A>G
NM_001276761.1:c.1033A>G
NM_001276695.2:c.*169A>G
NM_001276696.2:c.*257A>G
NM_001276697.2:c.673A>G
NM_001276698.2:c.*257A>G
NM_001276699.2:c.*169A>G
NM_001276760.2:c.1033A>G
NM_001276761.2:c.1033A>G
NM_000546.6:c.1150A>G
NM_001126112.3:c.1150A>G
NM_001126113.3:c.*169A>G
NM_001126114.3:c.*257A>G
NM_001126115.2:c.754A>G
NM_001126116.2:c.*257A>G
NM_001126117.2:c.*169A>G
NM_001126118.2:c.1033A>G
NM_001276695.3:c.*169A>G
NM_001276696.3:c.*257A>G
NM_001276697.3:c.673A>G
NM_001276698.3:c.*257A>G
NM_001276699.3:c.*169A>G
NM_001276760.3:c.1033A>G
NM_001276761.3:c.1033A>G

Likely Benign

Met criteria codes 3

PM2_Supporting BS2 BP4

Not Met criteria codes 14

BA1 BS1 BS4 BS3 PS1 PS2 PS3 PS4 PP1 PP3 PP4 PM1 PM5 PM6

Evidence Links 0

Expert Panel

TP53 VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen TP53 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TP53 Version 2.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

TP53 VCEP

The NM_000546.6: c.1150A>G variant in TP53 is a missense variant predicted to cause substitution of methionine by valine at amino acid 384 (p.Met384Val). This variant has been observed in 4-7 heterozygous unrelated females from the same data source with no personal history of cancer prior to age 60 years and no personal history of sarcoma at any age (BS2_Moderate; Internal lab contributor: Invitae). Computational predictor scores (BayesDel = -0.073; Align GVGD Class C0) are below the recommended thresholds (BayesDel ≤ -0.008 and an Align GVGD Class ≤ 55), evidence that does not predict a damaging effect on TP53 via protein change. SpliceAI predicts that the variant has no impact on splicing. (BP4_Moderate). This variant has an allele frequency of 0.00001780 (21/1179926 alleles) in the Europen (non-Finnish) population in gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00004) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting). In summary, this variant meets the criteria to be classified as Likely Benign for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: BS2_Moderate, BP4_Moderate, PM2_Supporting. (Bayesian Points: -3; VCEP specifications version 2.0; 1/16/2025).

Met criteria codes

PM2_Supporting	✔	This variant has an allele frequency of 0.00001780 (21/1179926 alleles) in the Europen (non-Finnish) population in gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00004) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting).
BS2	✔	BS2_MODERATE This variant has been observed in 4-7 heterozygous unrelated females from the same data source with no personal history of cancer prior to age 60 years and no personal history of sarcoma at any age (BS2_Moderate; Internal lab contributor: Invitae).
BP4	✔	BP4_MODERATE Computational predictor scores (BayesDel = -0.073; Align GVGD Class C0) are below the recommended thresholds (BayesDel ≤ -0.008 and an Align GVGD Class ≤ 55), evidence that does not predict a damaging effect on TP53 via protein change. SpliceAI predicts that the variant has no impact on splicing. (BP4_Moderate).

Not Met criteria codes

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
BS4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	✖	In vitro assays performed in yeast and/or human cell lines showed partially functional transactivation and retained growth suppression activity indicating that this variant does not impact protein function; however a third assay corroborating these findings was not available (BS3 not met; PMIDs: 12826609, 30224644).
PS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PS3	✖	In vitro assays performed in yeast and/or human cell lines showed partially functional transactivation and retained growth suppression activity indicating that this variant does not impact protein function; however a third assay corroborating these findings was not available (BS3 not met; PMIDs: 12826609, 30224644).
PS4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1	✖	This variant does not reside within a region of TP53 that is defined as a mutational hotspot by the ClinGen TP53 VCEP (PM1 not met).
PM5	✖	Missense variant c.1151T>C, p.Met384Thr has been determined by the TP53 VCEP to be a likely benign variant. 3 different missense variants (p.Met384Ile, p.Met384Arg, p.Met384Leu) in the same codon have been reported (ClinVar Variation IDs: 639734, 458521, 1493091). However, the variants have not yet been curated to determine if they would be classified as pathogenic or likely pathogenic by the ClinGen TP53 VCEP's specifications (PM5 not evaluated).
PM6	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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