Variant: NM_000546.5(TP53):c.480G>A (p.Met160Ile)

Version: 2.0

CA002482

230758 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 569b4177-6cd9-4d9e-9c08-6feaf795f9dc
Approved on: 2025-01-16
Published on: 2025-01-16

HGVS expressions

NM_000546.5:c.480G>A
NM_000546.5(TP53):c.480G>A (p.Met160Ile)
NC_000017.11:g.7675132C>T
CM000679.2:g.7675132C>T
NC_000017.10:g.7578450C>T
CM000679.1:g.7578450C>T
NC_000017.9:g.7519175C>T
NG_017013.2:g.17419G>A
ENST00000503591.2:c.480G>A
ENST00000508793.6:c.480G>A
ENST00000509690.6:c.84G>A
ENST00000514944.6:c.201G>A
ENST00000604348.6:c.459G>A
ENST00000269305.9:c.480G>A
ENST00000269305.8:c.480G>A
ENST00000359597.8:c.480G>A
ENST00000413465.6:c.480G>A
ENST00000420246.6:c.480G>A
ENST00000445888.6:c.480G>A
ENST00000455263.6:c.480G>A
ENST00000504290.5:c.84G>A
ENST00000504937.5:c.84G>A
ENST00000505014.5:n.736G>A
ENST00000508793.5:c.480G>A
ENST00000509690.5:c.84G>A
ENST00000510385.5:c.84G>A
ENST00000514944.5:c.201G>A
ENST00000610292.4:c.363G>A
ENST00000610538.4:c.363G>A
ENST00000610623.4:c.3G>A
ENST00000615910.4:c.447G>A
ENST00000617185.4:c.480G>A
ENST00000618944.4:c.3G>A
ENST00000619186.4:c.3G>A
ENST00000619485.4:c.363G>A
ENST00000620739.4:c.363G>A
ENST00000622645.4:c.363G>A

ENST00000635293.1:c.363G>A
NM_001126112.2:c.480G>A
NM_001126113.2:c.480G>A
NM_001126114.2:c.480G>A
NM_001126115.1:c.84G>A
NM_001126116.1:c.84G>A
NM_001126117.1:c.84G>A
NM_001126118.1:c.363G>A
NM_001276695.1:c.363G>A
NM_001276696.1:c.363G>A
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NM_001276698.1:c.3G>A
NM_001276699.1:c.3G>A
NM_001276760.1:c.363G>A
NM_001276761.1:c.363G>A
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NM_001276760.2:c.363G>A
NM_001276761.2:c.363G>A
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NM_001126112.3:c.480G>A
NM_001126113.3:c.480G>A
NM_001126114.3:c.480G>A
NM_001126115.2:c.84G>A
NM_001126116.2:c.84G>A
NM_001126117.2:c.84G>A
NM_001126118.2:c.363G>A
NM_001276695.3:c.363G>A
NM_001276696.3:c.363G>A
NM_001276697.3:c.3G>A
NM_001276698.3:c.3G>A
NM_001276699.3:c.3G>A
NM_001276760.3:c.363G>A
NM_001276761.3:c.363G>A

Likely Benign

Met criteria codes 3

PM2_Supporting BS3_Supporting BS2_Supporting

Not Met criteria codes 16

BP7 BP4 BP2 BS1 BS4 PP1 PP3 PM1 PM5 PM6 PVS1 PS1 PS2 PS3 PS4 BA1

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 2.1.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

TP53 VCEP

The NM_000546.6: c.480G>A variant in TP53 is a missense variant predicted to cause substitution of methionine by isoleucine at amino acid 160 (p.Met160Ile). 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 contributors). 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 (BS3_Supporting; PMIDs: 12826609, 29979965, 30224644). This variant has an allele frequency of 0.000003390 (4/1180050 alleles) in the European (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, BS3_Supporting, PM2_Supporting. (Bayesian Points: -2; VCEP specifications version 2.1; 1/16/2025).

Met criteria codes

PM2_Supporting	✔	This variant has an allele frequency of 0.000003390 (4/1180050 alleles) in the European (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).
BS3_Supporting	✔	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 (BS3_Supporting; PMIDs: 12826609, 29979965, 30224644).
BS2_Supporting	✔	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 contributors).

Not Met criteria codes

BP7	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4	✖	The results from the computational predictors BayesDel and AlignGVGD do not agree, providing no evidence that correlates with a damaging or benign impact on TP53 function via protein change. Additionally, SpliceAI predicts that the variant has no impact on splicing (score threshold ≤ 0.10) (PP3 and BP4 not met). Bayesdel = 0.2, aGVGD=C0; No splice effect by in silico predictors
BP2	✖	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

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
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	✖	2 different missense variants (c.479T>C p.Met160Thr and c.478A>G p.Met160Val) in the same codon have been reported (PMIDs, ClinVar Variation ID: 2915501 and 444396). However, the variants have not yet met the criteria to 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
PVS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4	✖	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

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000546.5(TP53):c.480G>A (p.Met1…	Likely Benign	Li-Fraumeni Syndrome	2025-01-16	2.0	ClinGen TP53 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TP53 Version 2.1.0	TP53
View	NM_000546.5(TP53):c.480G>A (p.Met1…	Likely Benign	Li-Fraumeni Syndrome 1	2021-09-24	1.0	-	TP53

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