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_000546.6(TP53):c.143A>G (p.Asp48Gly)

Version: 1.0

CA397846727

2795844 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: fa959fea-3322-4774-8693-a9eff8f88209
Approved on: 2025/1/16
Published on: 2025/1/16

HGVS expressions

NM_000546.6:c.143A>G
NM_000546.6(TP53):c.143A>G (p.Asp48Gly)
NC_000017.11:g.7676226T>C
CM000679.2:g.7676226T>C
NC_000017.10:g.7579544T>C
CM000679.1:g.7579544T>C
NC_000017.9:g.7520269T>C
NG_017013.2:g.16325A>G
ENST00000503591.2:c.143A>G
ENST00000508793.6:c.143A>G
ENST00000509690.6:c.-21-990A>G
ENST00000514944.6:c.96+156A>G
ENST00000604348.6:c.143A>G
ENST00000269305.9:c.143A>G
ENST00000269305.8:c.143A>G
ENST00000359597.8:c.143A>G
ENST00000413465.6:c.143A>G
ENST00000420246.6:c.143A>G
ENST00000445888.6:c.143A>G
ENST00000455263.6:c.143A>G
ENST00000503591.1:c.143A>G
ENST00000505014.5:n.399A>G
ENST00000508793.5:c.143A>G
ENST00000509690.5:c.-21-990A>G
ENST00000514944.5:c.96+156A>G
ENST00000604348.5:c.143A>G
ENST00000610292.4:c.26A>G
ENST00000610538.4:c.26A>G
ENST00000615910.4:c.143A>G
ENST00000617185.4:c.143A>G
ENST00000619485.4:c.26A>G
ENST00000620739.4:c.26A>G
ENST00000622645.4:c.26A>G
ENST00000635293.1:c.26A>G
NM_000546.5:c.143A>G
NM_001126112.2:c.143A>G
NM_001126113.2:c.143A>G

NM_001126114.2:c.143A>G
NM_001126118.1:c.26A>G
NM_001276695.1:c.26A>G
NM_001276696.1:c.26A>G
NM_001276760.1:c.26A>G
NM_001276761.1:c.26A>G
NM_001276695.2:c.26A>G
NM_001276696.2:c.26A>G
NM_001276760.2:c.26A>G
NM_001276761.2:c.26A>G
NM_001126112.3:c.143A>G
NM_001126113.3:c.143A>G
NM_001126114.3:c.143A>G
NM_001126118.2:c.26A>G
NM_001276695.3:c.26A>G
NM_001276696.3:c.26A>G
NM_001276760.3:c.26A>G
NM_001276761.3:c.26A>G

Likely Benign

Met criteria codes 3

BP4 PM2_Supporting BS3

Not Met criteria codes 13

PS2 PS3 PS4 PM1 PM5 PM6 BA1 BP2 BS2 BS1 BS4 PP1 PP3

Evidence Links 3

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.143A>G variant in TP53 is a missense variant predicted to cause substitution of aspartic acid by glycine at amino acid 48 (p.Asp48Gly). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). In vitro assays performed in yeast and/or human cell lines showed functional transactivation and retained growth suppression activity indicating that this variant does not impact protein function (BS3; PMIDs: 12826609, 29979965, 30224644). Computational predictor scores (BayesDel = -0.086; 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). 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: BS3, BP4_Moderate, PM2_Supporting. (Bayesian Points: -5; VCEP specifications version 2.0; 1/16/2025).

Met criteria codes

BP4	✔		BP4_MODERATE Computational predictor scores (BayesDel = -0.086; 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).

PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
BS3	✔	In vitro assays performed in yeast and/or human cell lines showed functional transactivation and retained growth suppression activity indicating that this variant does not impact protein function (BS3; PMIDs: 12826609, 29979965, 30224644). Non-functional PubMed:12826609 noLOF PubMed:30224644 N/A PubMed:29979965

Not Met criteria codes

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
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	✖	Another missense variant(c.144C>A, p.Asp48Glu) in the same codon has been reported (ClinVar Variation ID 141056). However, this variant has not yet met the criteria to be classified as pathogenic or likely pathogenic by the ClinGen TP53 VCEP's specifications (PM5 not met).
PM6	✖	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
BP2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2	✖	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

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000546.6(TP53):c.143A>G (p.Asp4…	Likely Benign	Li-Fraumeni Syndrome	2025-01-16	1.0	ClinGen TP53 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TP53 Version 2.0.0	TP53

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