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.556G>A (p.Asp186Asn)

Version: 2.0

CA16615707

406601 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 8e43f0c3-2b97-4bca-97a7-e3afcfa1cd50
Approved on: 2025/1/16
Published on: 2025/1/16

HGVS expressions

NM_000546.6:c.556G>A
NM_000546.6(TP53):c.556G>A (p.Asp186Asn)
NC_000017.11:g.7675056C>T
CM000679.2:g.7675056C>T
NC_000017.10:g.7578374C>T
CM000679.1:g.7578374C>T
NC_000017.9:g.7519099C>T
NG_017013.2:g.17495G>A
ENST00000503591.2:c.556G>A
ENST00000508793.6:c.556G>A
ENST00000509690.6:c.160G>A
ENST00000514944.6:c.277G>A
ENST00000604348.6:c.535G>A
ENST00000269305.9:c.556G>A
ENST00000269305.8:c.556G>A
ENST00000359597.8:c.556G>A
ENST00000413465.6:c.556G>A
ENST00000420246.6:c.556G>A
ENST00000445888.6:c.556G>A
ENST00000455263.6:c.556G>A
ENST00000504290.5:c.160G>A
ENST00000504937.5:c.160G>A
ENST00000505014.5:n.812G>A
ENST00000509690.5:c.160G>A
ENST00000510385.5:c.160G>A
ENST00000514944.5:c.277G>A
ENST00000574684.1:n.64G>A
ENST00000610292.4:c.439G>A
ENST00000610538.4:c.439G>A
ENST00000610623.4:c.79G>A
ENST00000615910.4:c.523G>A
ENST00000617185.4:c.556G>A
ENST00000618944.4:c.79G>A
ENST00000619186.4:c.79G>A
ENST00000619485.4:c.439G>A
ENST00000620739.4:c.439G>A
ENST00000622645.4:c.439G>A

ENST00000635293.1:c.439G>A
NM_000546.5:c.556G>A
NM_001126112.2:c.556G>A
NM_001126113.2:c.556G>A
NM_001126114.2:c.556G>A
NM_001126115.1:c.160G>A
NM_001126116.1:c.160G>A
NM_001126117.1:c.160G>A
NM_001126118.1:c.439G>A
NM_001276695.1:c.439G>A
NM_001276696.1:c.439G>A
NM_001276697.1:c.79G>A
NM_001276698.1:c.79G>A
NM_001276699.1:c.79G>A
NM_001276760.1:c.439G>A
NM_001276761.1:c.439G>A
NM_001276695.2:c.439G>A
NM_001276696.2:c.439G>A
NM_001276697.2:c.79G>A
NM_001276698.2:c.79G>A
NM_001276699.2:c.79G>A
NM_001276760.2:c.439G>A
NM_001276761.2:c.439G>A
NM_001126112.3:c.556G>A
NM_001126113.3:c.556G>A
NM_001126114.3:c.556G>A
NM_001126115.2:c.160G>A
NM_001126116.2:c.160G>A
NM_001126117.2:c.160G>A
NM_001126118.2:c.439G>A
NM_001276695.3:c.439G>A
NM_001276696.3:c.439G>A
NM_001276697.3:c.79G>A
NM_001276698.3:c.79G>A
NM_001276699.3:c.79G>A
NM_001276760.3:c.439G>A
NM_001276761.3:c.439G>A

Likely Benign

Met criteria codes 3

BS3 BP4 PM2_Supporting

Not Met criteria codes 15

PM1 PM5 BS2 PVS1 BS1 BS4 BP7 BA1 PS1 PS2 PS3 PS4 PP1 PP3 PP4

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 2.2.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

TP53 VCEP

The NM_000546.6: c.556G>A variant in TP53 is a missense variant predicted to cause substitution of aspartic acid by asparagine at amino acid 186 (p.Asp186Asn). This variant has an allele frequency of 0.00003332 (2/60018 alleles) in the Admixed American 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 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 = -0.0517; 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: PM2_Supporting, BS3, BP4_Moderate. (Bayesian Points: -5; VCEP specifications version 2.1; 1/16/2025).

Met criteria codes

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). Kotler = -1.736005696 PubMed:29979965 Kato transactivation = 92.15 PubMed:12826609 A549_p53WT_Nutlin-3_Z-score (DN=>0.61) = 0.095621624; A549_p53NULL_Etoposide_Z-score (LOF <=-0.21) = 0.307883038 PubMed:30224644
BP4	✔	BP4_MODERATE Computational predictor scores (BayesDel = -0.0517; 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 has an allele frequency of 0.00003332 (2/60018 alleles) in the Admixed American 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).

Not Met criteria codes

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	✖	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

PVS1		✖	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
BP7		✖	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
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		✖	This variant received a total of 0.5 points across 1 proband. However, PS4 cannot be applied (PS4 not met; Internal lab contributors).
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

Curation History

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