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.946C>A (p.Pro316Thr)

Version: 2.0

CA001212

230382 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: f2e706ef-eea4-48c8-917b-970c7c07543c
Approved on: 2025-03-04
Published on: 2025-06-23

HGVS expressions

NM_000546.6:c.946C>A
NM_000546.6(TP53):c.946C>A (p.Pro316Thr)
NC_000017.11:g.7673582G>T
CM000679.2:g.7673582G>T
NC_000017.10:g.7576900G>T
CM000679.1:g.7576900G>T
NC_000017.9:g.7517625G>T
NG_017013.2:g.18969C>A
ENST00000503591.2:c.946C>A
ENST00000508793.6:c.946C>A
ENST00000509690.6:c.550C>A
ENST00000514944.6:c.667C>A
ENST00000604348.6:c.925C>A
ENST00000269305.9:c.946C>A
ENST00000269305.8:c.946C>A
ENST00000359597.8:c.946C>A
ENST00000413465.6:c.782+599C>A
ENST00000420246.6:c.946C>A
ENST00000445888.6:c.946C>A
ENST00000455263.6:c.946C>A
ENST00000504290.5:c.550C>A
ENST00000504937.5:c.550C>A
ENST00000509690.5:c.550C>A
ENST00000510385.5:c.550C>A
ENST00000576024.1:c.6C>A
ENST00000610292.4:c.829C>A
ENST00000610538.4:c.829C>A
ENST00000610623.4:c.469C>A
ENST00000615910.4:c.913C>A
ENST00000617185.4:c.946C>A
ENST00000618944.4:c.469C>A
ENST00000619186.4:c.469C>A
ENST00000619485.4:c.829C>A
ENST00000620739.4:c.829C>A
ENST00000622645.4:c.829C>A
ENST00000635293.1:c.829C>A
NM_000546.5:c.946C>A

NM_001126112.2:c.946C>A
NM_001126113.2:c.946C>A
NM_001126114.2:c.946C>A
NM_001126115.1:c.550C>A
NM_001126116.1:c.550C>A
NM_001126117.1:c.550C>A
NM_001126118.1:c.829C>A
NM_001276695.1:c.829C>A
NM_001276696.1:c.829C>A
NM_001276697.1:c.469C>A
NM_001276698.1:c.469C>A
NM_001276699.1:c.469C>A
NM_001276760.1:c.829C>A
NM_001276761.1:c.829C>A
NM_001276695.2:c.829C>A
NM_001276696.2:c.829C>A
NM_001276697.2:c.469C>A
NM_001276698.2:c.469C>A
NM_001276699.2:c.469C>A
NM_001276760.2:c.829C>A
NM_001276761.2:c.829C>A
NM_001126112.3:c.946C>A
NM_001126113.3:c.946C>A
NM_001126114.3:c.946C>A
NM_001126115.2:c.550C>A
NM_001126116.2:c.550C>A
NM_001126117.2:c.550C>A
NM_001126118.2:c.829C>A
NM_001276695.3:c.829C>A
NM_001276696.3:c.829C>A
NM_001276697.3:c.469C>A
NM_001276698.3:c.469C>A
NM_001276699.3:c.469C>A
NM_001276760.3:c.829C>A
NM_001276761.3:c.829C>A

Likely Benign

Met criteria codes 3

BS2_Supporting BP4 PM2_Supporting

Not Met criteria codes 13

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

Evidence Links 2

Expert Panel

TP53 VCEP

Criteria Specification Information

Criteria Specification: *ClinGen TP53 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TP53 Version 2.3.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

TP53 VCEP

The NM_000546.6:c.946C>A variant in TP53 is a missense variant predicted to cause substitution of proline by threonine at amino acid 316 (p.Pro316Thr). Although this variant has been observed in germline cases, to our knowledge, this variant has not been reported in individuals meeting classical LFS or Chompret criteria (PS4 not met; Internal lab contributors). This variant has been observed in 2-3 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_Supporting; Internal lab contributor). This variant has an allele frequency of 0.000003098 (5/1614040 alleles) across gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00003) for PM2_Supporting and has a subpopulation allele frequency of <0.00004 in all non-bottleneck populations with 2 or more alleles present (PM2_Supporting). In vitro assays performed in yeast and/or human cell lines showed conflicting results with respect to transactivation, growth suppression activity, and/or tetramer formation (PS3/BS3 not met; PMIDs: 12826609, 16007150, 29979965, 30224644). Computational predictor scores (BayesDel = -0.0226052; 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: BS2_Supporting, PM2_Supporting, BP4_Moderate. (Bayesian Points: -2; VCEP specifications version 2.3)

Met criteria codes

BS2_Supporting	✔	This variant has been observed in 2-3 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_Supporting; Internal lab contributor).
BP4	✔	BP4_MODERATE Computational predictor scores (BayesDel = -0.0226052; 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 0.000003098 (5/1614040 alleles) across gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00003) for PM2_Supporting and has a subpopulation allele frequency of <0.00004 in all non-bottleneck populations with 2 or more alleles present (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	✖	2 different missense variants (p.Pro316Leu, p.Pro316Ser) in the same codon have been reported (ClinVar Variation IDs:528273, 823268). However, these variants have a higher Grantham score than p.Pro316Thr and do not meet criteria for PM5 code application (PM5 not met).
PM6	✖	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	✖	In vitro assays performed in yeast and/or human cell lines showed conflicting results with respect to transactivation, growth suppression activity, and/or tetramer formation (PS3/BS3 not met; PMIDs: 12826609, 30224644) No LOF, 0.5457 PubMed:30224644 Non-functional 12.9% PubMed:12826609
PS4	✖	Although this variant has been observed in germline cases, to our knowledge, this variant has not been reported in individuals meeting classical LFS or Chompret criteria (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
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 conflicting results with respect to transactivation, growth suppression activity, and/or tetramer formation (PS3/BS3 not met; PMIDs: 12826609, 16007150, 29979965, 30224644) No LOF, 0.5457 PubMed:30224644 Non-functional 12.9% PubMed:12826609

Curation History

Showing 1 to 2 of 2 rows

See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000546.6(TP53):c.946C>A (p.Pro3...	Likely Benign	Li-Fraumeni Syndrome	2025-06-23	2.0	ClinGen TP53 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TP53 Version 2.3.0	TP53
View	NM_000546.5(TP53):c.946C>A (p.Pro3...	Uncertain Significance	Li-Fraumeni Syndrome 1	2021-09-24	1.0	-	TP53

Showing 1 to 2 of 2 rows