Variant: NM_000546.5(TP53):c.935C>G (p.Thr312Ser)

Version: 1.1

CA000505

141102 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: c3655e4d-7f5e-4830-b702-3893ec9be6ac
Approved on: 2024-08-05
Published on: 2024-08-05

HGVS expressions

NM_000546.5:c.935C>G
NM_000546.5(TP53):c.935C>G (p.Thr312Ser)
NC_000017.11:g.7673593G>C
CM000679.2:g.7673593G>C
NC_000017.10:g.7576911G>C
CM000679.1:g.7576911G>C
NC_000017.9:g.7517636G>C
NG_017013.2:g.18958C>G
ENST00000503591.2:c.935C>G
ENST00000508793.6:c.935C>G
ENST00000509690.6:c.539C>G
ENST00000514944.6:c.656C>G
ENST00000604348.6:c.914C>G
ENST00000269305.9:c.935C>G
ENST00000269305.8:c.935C>G
ENST00000359597.8:c.935C>G
ENST00000413465.6:c.782+588C>G
ENST00000420246.6:c.935C>G
ENST00000445888.6:c.935C>G
ENST00000455263.6:c.935C>G
ENST00000504290.5:c.539C>G
ENST00000504937.5:c.539C>G
ENST00000509690.5:c.539C>G
ENST00000510385.5:c.539C>G
ENST00000610292.4:c.818C>G
ENST00000610538.4:c.818C>G
ENST00000610623.4:c.458C>G
ENST00000615910.4:c.902C>G
ENST00000617185.4:c.935C>G
ENST00000618944.4:c.458C>G
ENST00000619186.4:c.458C>G
ENST00000619485.4:c.818C>G
ENST00000620739.4:c.818C>G
ENST00000622645.4:c.818C>G
ENST00000635293.1:c.818C>G
NM_001126112.2:c.935C>G
NM_001126113.2:c.935C>G

NM_001126114.2:c.935C>G
NM_001126115.1:c.539C>G
NM_001126116.1:c.539C>G
NM_001126117.1:c.539C>G
NM_001126118.1:c.818C>G
NM_001276695.1:c.818C>G
NM_001276696.1:c.818C>G
NM_001276697.1:c.458C>G
NM_001276698.1:c.458C>G
NM_001276699.1:c.458C>G
NM_001276760.1:c.818C>G
NM_001276761.1:c.818C>G
NM_001276695.2:c.818C>G
NM_001276696.2:c.818C>G
NM_001276697.2:c.458C>G
NM_001276698.2:c.458C>G
NM_001276699.2:c.458C>G
NM_001276760.2:c.818C>G
NM_001276761.2:c.818C>G
NM_000546.6:c.935C>G
NM_001126112.3:c.935C>G
NM_001126113.3:c.935C>G
NM_001126114.3:c.935C>G
NM_001126115.2:c.539C>G
NM_001126116.2:c.539C>G
NM_001126117.2:c.539C>G
NM_001126118.2:c.818C>G
NM_001276695.3:c.818C>G
NM_001276696.3:c.818C>G
NM_001276697.3:c.458C>G
NM_001276698.3:c.458C>G
NM_001276699.3:c.458C>G
NM_001276760.3:c.818C>G
NM_001276761.3:c.818C>G

Benign

Met criteria codes 4

BP4 BS1 BS3 BS2

Not Met criteria codes 16

BP7 BP3 PVS1 BS4 PP1 PP3 PP4 PS1 PS2 PS3 PS4 BA1 PM1 PM5 PM4 PM2

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.935C>G variant in TP53 is a missense variant predicted to cause substitution of threonine by serine at amino acid 312 (p.Thr312Ser). This variant has been observed in at least 8 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; SCV000261663, SCV000184232). The filtering allele frequency is 0.0003446 in the African/African American population in gnomAD v4.1.0, which is higher than the ClinGen TP53 VCEP threshold (≥0.0003 but <0.001) for BS1, and therefore meets this criterion (BS1). 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 = -0.0123; 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 Benign for Li Fraumeni Syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: BS2, BS1, BS3, BP4_moderate. (Bayesian Points: -14; VCEP specifications version 2.0; 7/24/2024)

Met criteria codes

BP4	ℹ	✓	BP4_MODERATE Computational predictor scores (BayesDel = -0.0123; 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).
BS1	ℹ	✓	The filtering allele frequency is 0.0003446 in the African/African American population in gnomAD v4.1.0, which is higher than the ClinGen TP53 VCEP threshold (≥0.0003 but <0.001) for BS1, and therefore meets this criterion (BS1).
BS3	ℹ	✓	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).
BS2	ℹ	✓	This variant has been observed in at least 8 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; SCV000261663, SCV000184232).

Not Met criteria codes

BP7	ℹ	✗	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3		✗	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1	ℹ	✗	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4	ℹ	✗	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1	ℹ	✗	

			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	ℹ	✖	2 different missense variants (c.935C>A, p.Thr312Asn and c.935C>T, p.Thr312Ile) in the same codon have been reported (ClinVar Variation IDs: , 1766672, 1697592). 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).
PM4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

Showing 1 to 2 of 2 rows