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_000546.5(TP53):c.869G>A (p.Arg290His)

Version: 1.1

CA000468

127825 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: de5ede53-7b6d-40ad-8a0e-0b3aa4c7ecd8
Approved on: 2024/8/5
Published on: 2024/8/5

HGVS expressions

NM_000546.5:c.869G>A
NM_000546.5(TP53):c.869G>A (p.Arg290His)
NC_000017.11:g.7673751C>T
CM000679.2:g.7673751C>T
NC_000017.10:g.7577069C>T
CM000679.1:g.7577069C>T
NC_000017.9:g.7517794C>T
NG_017013.2:g.18800G>A
ENST00000503591.2:c.869G>A
ENST00000508793.6:c.869G>A
ENST00000509690.6:c.473G>A
ENST00000514944.6:c.590G>A
ENST00000604348.6:c.848G>A
ENST00000269305.9:c.869G>A
ENST00000269305.8:c.869G>A
ENST00000359597.8:c.869G>A
ENST00000413465.6:c.782+430G>A
ENST00000420246.6:c.869G>A
ENST00000445888.6:c.869G>A
ENST00000455263.6:c.869G>A
ENST00000504290.5:c.473G>A
ENST00000504937.5:c.473G>A
ENST00000509690.5:c.473G>A
ENST00000510385.5:c.473G>A
ENST00000610292.4:c.752G>A
ENST00000610538.4:c.752G>A
ENST00000610623.4:c.392G>A
ENST00000615910.4:c.836G>A
ENST00000617185.4:c.869G>A
ENST00000618944.4:c.392G>A
ENST00000619186.4:c.392G>A
ENST00000619485.4:c.752G>A
ENST00000620739.4:c.752G>A
ENST00000622645.4:c.752G>A
ENST00000635293.1:c.752G>A
NM_001126112.2:c.869G>A
NM_001126113.2:c.869G>A

NM_001126114.2:c.869G>A
NM_001126115.1:c.473G>A
NM_001126116.1:c.473G>A
NM_001126117.1:c.473G>A
NM_001126118.1:c.752G>A
NM_001276695.1:c.752G>A
NM_001276696.1:c.752G>A
NM_001276697.1:c.392G>A
NM_001276698.1:c.392G>A
NM_001276699.1:c.392G>A
NM_001276760.1:c.752G>A
NM_001276761.1:c.752G>A
NM_001276695.2:c.752G>A
NM_001276696.2:c.752G>A
NM_001276697.2:c.392G>A
NM_001276698.2:c.392G>A
NM_001276699.2:c.392G>A
NM_001276760.2:c.752G>A
NM_001276761.2:c.752G>A
NM_000546.6:c.869G>A
NM_001126112.3:c.869G>A
NM_001126113.3:c.869G>A
NM_001126114.3:c.869G>A
NM_001126115.2:c.473G>A
NM_001126116.2:c.473G>A
NM_001126117.2:c.473G>A
NM_001126118.2:c.752G>A
NM_001276695.3:c.752G>A
NM_001276696.3:c.752G>A
NM_001276697.3:c.392G>A
NM_001276698.3:c.392G>A
NM_001276699.3:c.392G>A
NM_001276760.3:c.752G>A
NM_001276761.3:c.752G>A

Benign

Met criteria codes 3

BS3 BS2 BP4

Not Met criteria codes 20

PS1 PS2 PS3 PS4 PP1 PP3 PP4 PM2 PM1 PM3 PM5 PM4 BA1 PVS1 BS1 BS4 BP5 BP7 BP3 BP2

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.869G>A variant in TP53 is a missense variant predicted to cause substitution of arginine by histidine at amino acid 290 (p.Arg290His). 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; SCV000187277.8). 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 = 0.09; Align GVGD Class 0) are below the recommended thresholds (BayesDel < 0.16 and > -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). In summary, this variant meets the criteria to be classified as Benign for Li Fraumeni Syndrome. ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: BS2, BS3, BP4 (Bayesian Points: -9; VCEP specifications version 2.0; 7/24/2024)

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).
BS2	✔	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; SCV000187277.8).
BP4	✔	Computational predictor scores (BayesDel = 0.09; Align GVGD Class 0) are below the recommended thresholds (BayesDel < 0.16 and > -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).

Not Met criteria codes

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	✖	IARC database calls this supertrans & 2 studies show no effect on protein.
PS4	✖	This variant has been observed in 2 unrelated families meeting Revised Chompret criteria. Based on this evidence, this variant scores 1 total points meeting the TP53 VCEP phenotype scoring criteria of 1-1.5 points. (PS4_Supporting; PMIDs: 10435620, 19468865) but this evidence is not applied as PM2_Supporting is not applied.
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

PM2		✖	The highest population minor allele frequency in gnomAD v41.0 is 0.0002602 (307/1180030 alleles) in the European (non-Finnish) population (PM2, BS1, and BA1 are not met).
PM1	ℹ	✖	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).
PM3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	ℹ	✖	4 different missense variants (p.Arg290Leu; p.Arg290Pro; p.Arg290Gly; p.Arg290Cys) in the same codon have been reported (ClinVar Variation IDs: 633445, 458572, 628970, 216472). 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
BA1	ℹ	✖	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
BS1	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
BP5		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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
BP2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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