Variant: NM_000546.5(TP53):c.818G>A (p.Arg273His)

Version: 1.1

CA000434

12366 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 8d32df42-16ac-41f2-9bf1-e2b9ce206190
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HGVS expressions

NM_000546.5:c.818G>A
NM_000546.5(TP53):c.818G>A (p.Arg273His)
NC_000017.11:g.7673802C>T
CM000679.2:g.7673802C>T
NC_000017.10:g.7577120C>T
CM000679.1:g.7577120C>T
NC_000017.9:g.7517845C>T
NG_017013.2:g.18749G>A
ENST00000503591.2:c.818G>A
ENST00000508793.6:c.818G>A
ENST00000509690.6:c.422G>A
ENST00000514944.6:c.539G>A
ENST00000604348.6:c.797G>A
ENST00000269305.9:c.818G>A
ENST00000269305.8:c.818G>A
ENST00000359597.8:c.818G>A
ENST00000413465.6:c.782+379G>A
ENST00000420246.6:c.818G>A
ENST00000445888.6:c.818G>A
ENST00000455263.6:c.818G>A
ENST00000504290.5:c.422G>A
ENST00000504937.5:c.422G>A
ENST00000509690.5:c.422G>A
ENST00000510385.5:c.422G>A
ENST00000610292.4:c.701G>A
ENST00000610538.4:c.701G>A
ENST00000610623.4:c.341G>A
ENST00000615910.4:c.785G>A
ENST00000617185.4:c.818G>A
ENST00000618944.4:c.341G>A
ENST00000619186.4:c.341G>A
ENST00000619485.4:c.701G>A
ENST00000620739.4:c.701G>A
ENST00000622645.4:c.701G>A
ENST00000635293.1:c.701G>A
NM_001126112.2:c.818G>A
NM_001126113.2:c.818G>A

NM_001126114.2:c.818G>A
NM_001126115.1:c.422G>A
NM_001126116.1:c.422G>A
NM_001126117.1:c.422G>A
NM_001126118.1:c.701G>A
NM_001276695.1:c.701G>A
NM_001276696.1:c.701G>A
NM_001276697.1:c.341G>A
NM_001276698.1:c.341G>A
NM_001276699.1:c.341G>A
NM_001276760.1:c.701G>A
NM_001276761.1:c.701G>A
NM_001276695.2:c.701G>A
NM_001276696.2:c.701G>A
NM_001276697.2:c.341G>A
NM_001276698.2:c.341G>A
NM_001276699.2:c.341G>A
NM_001276760.2:c.701G>A
NM_001276761.2:c.701G>A
NM_000546.6:c.818G>A
NM_001126112.3:c.818G>A
NM_001126113.3:c.818G>A
NM_001126114.3:c.818G>A
NM_001126115.2:c.422G>A
NM_001126116.2:c.422G>A
NM_001126117.2:c.422G>A
NM_001126118.2:c.701G>A
NM_001276695.3:c.701G>A
NM_001276696.3:c.701G>A
NM_001276697.3:c.341G>A
NM_001276698.3:c.341G>A
NM_001276699.3:c.341G>A
NM_001276760.3:c.701G>A
NM_001276761.3:c.701G>A

Pathogenic

Met criteria codes 7

PP4_Moderate **PM2_Supporting** **PS2** **PS3** **PS4** **PP3** **PM1**

Not Met criteria codes 7

BS1 **BS3** **BS2** **BP4** **PS1** **BA1** **PM5**

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.818G>A variant in TP53 is a missense variant predicted to cause substitution of arginine by histidine at amino acid 273 (p.R273H). This variant has been reported in numerous unrelated probands meeting Classic LFS and Revised Chompret criteria. Based on this evidence, this variant scores 8 total points meeting the TP53 VCEP phenotype scoring criteria of ≥ 8 points. (PS4_Very Strong; PMIDs, 16401470, 15390294, 9242456, 10864200, 1565144, 7732013; SCV000186052.8). This variant has been identified as a de novo occurrence with confirmed parental relationships in 1 individual with an LFS-associated cancer totaling 4 phenotype points (PS2; PMID: 1267231). At least two individuals with this variant were found to have a variant allele fraction of 5-25%, which is a significant predictor of variant pathogenicity (PP4_Moderate, PMID: 34906512, SCV000186052.8). This variant has an allele frequency of 0.00001186 (14/1179946 alleles) in the European (non-Finnish) 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 non-functional transactivation and loss of growth suppression activity indicating that this variant impacts protein function (PS3; PMIDs: 12826609, 30224644, 29979965). This variant resides within a codon (NM_00546.4: 273) of TP53 that is defined as a mutational hotspot by the ClinGen TP53 VCEP (PM1; PMID: 8023157). Computational predictor scores (BayesDel = 0.52; Align GVGD = Class 25) are above recommended thresholds (BayesDel > 0.16 and an Align GVGD Class of > 15), evidence that correlates with impact to TP53 via protein change (PP3). In summary, this variant meets the criteria to be classified as pathogenic for Li Fraumeni Syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: PS4_Very Strong, PS2, PM2_Supporting, PS3, PP4_Moderate, PM1, PP3. (Bayesian Points: 22; VCEP specifications version 2.0; 7/24/2024).

Met criteria codes

PP4_Moderate	ℹ	✓	At least two individuals with this variant were found to have a variant allele fraction of 5-25%, which is a significant predictor of variant pathogenicity (PP4_Moderate, PMID: 34906512, SCV000186052.8).
PM2_Supporting	ℹ	✓	This variant has an allele frequency of 0.00001186 (14/1179946 alleles) in the European (non-Finnish) 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).
PS2	ℹ	✓	This variant has been identified as a de novo occurrence with confirmed parental relationships in 1 individual with an LFS-associated cancer totaling 4 phenotype points (PS2; PMID: 1267231).
PS3	ℹ	✓	In vitro assays performed in yeast and/or human cell lines showed non-functional transactivation and loss of growth suppression activity indicating that this variant impacts protein function (PS3; PMIDs: 12826609, 30224644, 29979965).
PS4	ℹ	✓	PS4_VERY STRONG APPLIED This variant has been reported in numerous unrelated probands meeting Classic LFS and Revised Chompret criteria. Based on this evidence, this variant scores 8 total points meeting the TP53 VCEP phenotype scoring criteria of ≥ 8 points. (PS4_Very Strong; PMIDs, 16401470, 15390294, 9242456, 10864200, 1565144, 7732013; SCV000186052.8)
PP3	ℹ	✓	Computational predictor scores (BayesDel = 0.52; Align GVGD = Class 25) are above recommended thresholds (BayesDel > 0.16 and an Align GVGD Class of > 15), evidence that correlates with impact to TP53 via protein change (PP3).
PM1	ℹ	✓	This variant resides within a codon (NM_00546.4: 273) of TP53 that is defined as a mutational hotspot by the ClinGen TP53 VCEP (PM1; PMID: 8023157)

Not Met criteria codes

BS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4	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
BA1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	ℹ	✖	5 different missense variants (p.Arg273Leu; p.Arg273Pro; p.Arg273Gly; p.Arg273Ser; p.Arg273Cys) in the same codon have been reported (ClinVar Variation IDs: 376655, 231060, 634682, 376656, 43594). 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).

Curation History

Showing 1 to 2 of 2 rows

See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000546.5(TP53):c.818G>A (p.Arg2…	Pathogenic	Li-Fraumeni Syndrome	2024-08-05	1.1	ClinGen TP53 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TP53 Version 2.0.0	TP53
View	NM_000546.5(TP53):c.818G>A (p.Arg2…	Pathogenic	Li-Fraumeni Syndrome	2020-01-24	1.0	-	TP53

Showing 1 to 2 of 2 rows