Variant: NM_000546.6(TP53):c.845G>T (p.Arg282Leu)

Version: 2.0

CA000456

182938 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 8099c951-8c94-4ef5-9f48-ba68e4b64b16
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HGVS expressions

NM_000546.6:c.845G>T
NM_000546.6(TP53):c.845G>T (p.Arg282Leu)
NC_000017.11:g.7673775C>A
CM000679.2:g.7673775C>A
NC_000017.10:g.7577093C>A
CM000679.1:g.7577093C>A
NC_000017.9:g.7517818C>A
NG_017013.2:g.18776G>T
ENST00000503591.2:c.845G>T
ENST00000508793.6:c.845G>T
ENST00000509690.6:c.449G>T
ENST00000514944.6:c.566G>T
ENST00000604348.6:c.824G>T
ENST00000269305.9:c.845G>T
ENST00000269305.8:c.845G>T
ENST00000359597.8:c.845G>T
ENST00000413465.6:c.782+406G>T
ENST00000420246.6:c.845G>T
ENST00000445888.6:c.845G>T
ENST00000455263.6:c.845G>T
ENST00000504290.5:c.449G>T
ENST00000504937.5:c.449G>T
ENST00000509690.5:c.449G>T
ENST00000510385.5:c.449G>T
ENST00000610292.4:c.728G>T
ENST00000610538.4:c.728G>T
ENST00000610623.4:c.368G>T
ENST00000615910.4:c.812G>T
ENST00000617185.4:c.845G>T
ENST00000618944.4:c.368G>T
ENST00000619186.4:c.368G>T
ENST00000619485.4:c.728G>T
ENST00000620739.4:c.728G>T
ENST00000622645.4:c.728G>T
ENST00000635293.1:c.728G>T
NM_000546.5:c.845G>T
NM_001126112.2:c.845G>T

NM_001126113.2:c.845G>T
NM_001126114.2:c.845G>T
NM_001126115.1:c.449G>T
NM_001126116.1:c.449G>T
NM_001126117.1:c.449G>T
NM_001126118.1:c.728G>T
NM_001276695.1:c.728G>T
NM_001276696.1:c.728G>T
NM_001276697.1:c.368G>T
NM_001276698.1:c.368G>T
NM_001276699.1:c.368G>T
NM_001276760.1:c.728G>T
NM_001276761.1:c.728G>T
NM_001276695.2:c.728G>T
NM_001276696.2:c.728G>T
NM_001276697.2:c.368G>T
NM_001276698.2:c.368G>T
NM_001276699.2:c.368G>T
NM_001276760.2:c.728G>T
NM_001276761.2:c.728G>T
NM_001126112.3:c.845G>T
NM_001126113.3:c.845G>T
NM_001126114.3:c.845G>T
NM_001126115.2:c.449G>T
NM_001126116.2:c.449G>T
NM_001126117.2:c.449G>T
NM_001126118.2:c.728G>T
NM_001276695.3:c.728G>T
NM_001276696.3:c.728G>T
NM_001276697.3:c.368G>T
NM_001276698.3:c.368G>T
NM_001276699.3:c.368G>T
NM_001276760.3:c.728G>T
NM_001276761.3:c.728G>T

Uncertain Significance

Met criteria codes 5

PM2_Supporting BS2 BS3 PP3_Moderate PM1

Not Met criteria codes 18

BS1 BS4 BP4 BP3 BP2 PVS1 BP5 BP7 PS2 PS3 PS4 BA1 PP1 PP4 PM6 PM3 PM5 PM4

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 2.3.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

TP53 VCEP

The NM_000546.6: c.845G>T variant in TP53 is a missense variant predicted to cause substitution of arginine by leucine at amino acid 282 (p.Arg282Leu). This variant has an allele frequency of 0.000003098 (5/1613954 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). 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; PMIDs: 28975465, 34906214). This variant has been observed in 4-7 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_Moderate; Internal lab contributor). 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 = 0.3605; Align GVGD = Class 65) are above recommended thresholds (BayesDel > 0.16 and an Align GVGD Class of 65), evidence that correlates with impact to TP53 via protein change (PP3_Moderate). This variant resides within a codon (NM_00546.4: 175, 245, 248, 249, 273, 282) of TP53 that is defined as a mutational hotspot by the ClinGen TP53 VCEP (PM1; PMID: 8023157). In summary this variant meets the criteria to be classified as a variant of unknown significance for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: PM2_Supporting, BS2_Moderate, PP3_Moderate, PM1, BS3. (Bayesian Points: -1; VCEP specifications version 2.3)

Met criteria codes

PM2_Supporting	✔	This variant has an allele frequency of 0.000003098 (5/1613954 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).
BS2	✔	BS2_MODERATE This variant has been observed in 4-7 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_Moderate; Internal lab contributor).
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).
PP3_Moderate	✔	Computational predictor scores (BayesDel = 0.3605; Align GVGD = Class 65) are above recommended thresholds (BayesDel > 0.16 and an Align GVGD Class of 65), evidence that correlates with impact to TP53 via protein change (PP3_Moderate).
PM1	✔	This variant resides within a codon (NM_00546.4: 175, 245, 248, 249, 273, 282) of TP53 that is defined as a mutational hotspot by the ClinGen TP53 VCEP (PM1; PMID: 8023157).

Not Met criteria codes

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

BP4	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
PVS1	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
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
PP1	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
PM6		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	ℹ	✖	4 other variants in ClinVar at this residue. Current variant has higher Grantham score (102) than two variants , NM_000546.6(TP53):c.844C>T (p.Arg282Trp) (101) and NM_000546.6(TP53):c.845G>A (p.Arg282Gln) (43). Pathogenicity not evaluated since would not change classification.

PM4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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