Variant: NM_000546.5(TP53):c.743G>T (p.Arg248Leu)

Version: 1.1

CA10580924

230253 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 291eceb4-ecb0-489a-b637-b9ff4f5f34d5
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HGVS expressions

NM_000546.5:c.743G>T
NM_000546.5(TP53):c.743G>T (p.Arg248Leu)
NC_000017.11:g.7674220C>A
CM000679.2:g.7674220C>A
NC_000017.10:g.7577538C>A
CM000679.1:g.7577538C>A
NC_000017.9:g.7518263C>A
NG_017013.2:g.18331G>T
ENST00000503591.2:c.743G>T
ENST00000508793.6:c.743G>T
ENST00000509690.6:c.347G>T
ENST00000514944.6:c.464G>T
ENST00000604348.6:c.722G>T
ENST00000269305.9:c.743G>T
ENST00000269305.8:c.743G>T
ENST00000359597.8:c.743G>T
ENST00000413465.6:c.743G>T
ENST00000420246.6:c.743G>T
ENST00000445888.6:c.743G>T
ENST00000455263.6:c.743G>T
ENST00000504290.5:c.347G>T
ENST00000504937.5:c.347G>T
ENST00000509690.5:c.347G>T
ENST00000510385.5:c.347G>T
ENST00000514944.5:c.464G>T
ENST00000610292.4:c.626G>T
ENST00000610538.4:c.626G>T
ENST00000610623.4:c.266G>T
ENST00000615910.4:c.710G>T
ENST00000617185.4:c.743G>T
ENST00000618944.4:c.266G>T
ENST00000619186.4:c.266G>T
ENST00000619485.4:c.626G>T
ENST00000620739.4:c.626G>T
ENST00000622645.4:c.626G>T
ENST00000635293.1:c.626G>T
NM_001126112.2:c.743G>T

NM_001126113.2:c.743G>T
NM_001126114.2:c.743G>T
NM_001126115.1:c.347G>T
NM_001126116.1:c.347G>T
NM_001126117.1:c.347G>T
NM_001126118.1:c.626G>T
NM_001276695.1:c.626G>T
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NM_001276698.1:c.266G>T
NM_001276699.1:c.266G>T
NM_001276760.1:c.626G>T
NM_001276761.1:c.626G>T
NM_001276695.2:c.626G>T
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NM_001276697.2:c.266G>T
NM_001276698.2:c.266G>T
NM_001276699.2:c.266G>T
NM_001276760.2:c.626G>T
NM_001276761.2:c.626G>T
NM_000546.6:c.743G>T
NM_001126112.3:c.743G>T
NM_001126113.3:c.743G>T
NM_001126114.3:c.743G>T
NM_001126115.2:c.347G>T
NM_001126116.2:c.347G>T
NM_001126117.2:c.347G>T
NM_001126118.2:c.626G>T
NM_001276695.3:c.626G>T
NM_001276696.3:c.626G>T
NM_001276697.3:c.266G>T
NM_001276698.3:c.266G>T
NM_001276699.3:c.266G>T
NM_001276760.3:c.626G>T
NM_001276761.3:c.626G>T

Pathogenic

Met criteria codes 9

PS3 PS4_Supporting PP3_Moderate PP1 PS2_Supporting PP4_Moderate PM1 PM2_Supporting PM5_Strong

Not Met criteria codes 7

PS1 BP4 BA1 BS2 BS1 BS4 BS3

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.743G>T variant in TP53 is a missense variant predicted to cause substitution of arginine by leucine at amino acid 248 (p.Arg248Leu). This variant has been reported in 3 unrelated probands meeting Revised Chompret criteria. Based on this evidence, this variant scores 1.5 total points meeting the TP53 VCEP phenotype scoring criteria of of 1-1.5 points. (PS4_Supporting; PMIDs 1359493, 25584008, ClinVar SCV SCV000273723.7, Internal lab contributor). This variant has been identified as a de novo occurrence with unconfirmed parental relationships in an individual with a moderately LFS-associated cancer totaling 1 phenotype point (PS2_Supporting; Internal lab contributors: SCV000273723.7). The variant has been reported to segregate with LFS-associated cancers in 3-4 meioses in 1 family (PP1; PMID: 1359493). 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, Internal lab contributors: SCV000273723.7). In vitro assays performed in yeast and human cell lines showed non-functional transactivation and loss of growth suppression activity indicating that this variant impacts protein function (PMIDs: 12826609, 30224644, 29979965) (PS3). Two different missense variants, c.743G>A; p.Arg248Gln and c.742C>T; p.Arg248Trp, ClinVar IDs 12347 and 12356, in the same codon have been classified as pathogenic for Li-Fraumeni syndrome by the ClinGen TP53 VCEP's specifications. (PM5_Strong). 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). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). Computational predictor scores (BayesDel = 0.570318; Align GVGD = Class C65) 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). In summary, TP53 c.743G>T; p.Arg248Leu meets criteria to be classified as Pathogenic for Li-Fraumeni syndrome. ACMG/AMP criteria applied, as specified by the TP53 Variant Curation Expert Panel: PS4_Supporting, PS2_Supporting, PP1, PP4_Moderate, PS3, PM5_Strong, PM1, PM2_Supporting, PP3_Moderate. (Bayesian Points: 18; VCEP specifications version 2.0; 7/24/2024)

Met criteria codes

PS3	✔	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 (PMIDs: 12826609, 30224644, 29979965) (PS3).
PS4_Supporting	✔	This variant has been reported in 3 unrelated probands meeting Revised Chompret criteria, respectively. Based on this evidence, this variant scores 1.5 total points meeting the TP53 VCEP phenotype scoring criteria of of 1-1.5 points. (PS4_Supporting; PMIDs 1359493, 25584008, ClinVar SCV SCV000273723.7, Internal lab contributor).
PP3_Moderate	✔	Computational predictor scores (BayesDel = 0.570318; Align GVGD = Class C65) 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).
PP1	✔	The variant has been reported to segregate with LFS-associated cancers in 3-4 meioses in 1 family (PP1; PMID: 1359493).
PS2_Supporting	✔	This variant has been identified as a de novo occurrence with unconfirmed parental relationships in an individual with a moderately LFS-associated cancer totaling 1 phenotype point (PS2_Supporting; Internal lab contributors: SCV000273723.7).
PP4_Moderate	✔	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, Internal lab contributors: SCV000273723.7).
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 (PMID: 8023157) (PM1).

PM2_Supporting		✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PM5_Strong		✔	Two different missense variants, c.743G>A; p.Arg248Gln and c.742C>T; p.Arg248Trp, ClinVar IDs 12347 and 12356, in the same codon have been classified as pathogenic for Li-Fraumeni syndrome by the ClinGen TP53 VCEP's specifications. (PM5_Strong).

Not Met criteria codes

PS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4		✖	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
BS2		✖	Absent in FLOSSIES.
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		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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