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Variant: NM_000546.5(TP53):c.742C>T (p.Arg248Trp)

Version: 1.1

CA000382

12347 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 55c3283e-f0f6-4e18-b837-99a275ea7d90
Approved on: 2024/8/5
Published on: 2024/8/5

HGVS expressions

NM_000546.5:c.742C>T
NM_000546.5(TP53):c.742C>T (p.Arg248Trp)
NC_000017.11:g.7674221G>A
CM000679.2:g.7674221G>A
NC_000017.10:g.7577539G>A
CM000679.1:g.7577539G>A
NC_000017.9:g.7518264G>A
NG_017013.2:g.18330C>T
ENST00000503591.2:c.742C>T
ENST00000508793.6:c.742C>T
ENST00000509690.6:c.346C>T
ENST00000514944.6:c.463C>T
ENST00000604348.6:c.721C>T
ENST00000269305.9:c.742C>T
ENST00000269305.8:c.742C>T
ENST00000359597.8:c.742C>T
ENST00000413465.6:c.742C>T
ENST00000420246.6:c.742C>T
ENST00000445888.6:c.742C>T
ENST00000455263.6:c.742C>T
ENST00000504290.5:c.346C>T
ENST00000504937.5:c.346C>T
ENST00000509690.5:c.346C>T
ENST00000510385.5:c.346C>T
ENST00000514944.5:c.463C>T
ENST00000610292.4:c.625C>T
ENST00000610538.4:c.625C>T
ENST00000610623.4:c.265C>T
ENST00000615910.4:c.709C>T
ENST00000617185.4:c.742C>T
ENST00000618944.4:c.265C>T
ENST00000619186.4:c.265C>T
ENST00000619485.4:c.625C>T
ENST00000620739.4:c.625C>T
ENST00000622645.4:c.625C>T
ENST00000635293.1:c.625C>T
NM_001126112.2:c.742C>T

NM_001126113.2:c.742C>T
NM_001126114.2:c.742C>T
NM_001126115.1:c.346C>T
NM_001126116.1:c.346C>T
NM_001126117.1:c.346C>T
NM_001126118.1:c.625C>T
NM_001276695.1:c.625C>T
NM_001276696.1:c.625C>T
NM_001276697.1:c.265C>T
NM_001276698.1:c.265C>T
NM_001276699.1:c.265C>T
NM_001276760.1:c.625C>T
NM_001276761.1:c.625C>T
NM_001276695.2:c.625C>T
NM_001276696.2:c.625C>T
NM_001276697.2:c.265C>T
NM_001276698.2:c.265C>T
NM_001276699.2:c.265C>T
NM_001276760.2:c.625C>T
NM_001276761.2:c.625C>T
NM_000546.6:c.742C>T
NM_001126112.3:c.742C>T
NM_001126113.3:c.742C>T
NM_001126114.3:c.742C>T
NM_001126115.2:c.346C>T
NM_001126116.2:c.346C>T
NM_001126117.2:c.346C>T
NM_001126118.2:c.625C>T
NM_001276695.3:c.625C>T
NM_001276696.3:c.625C>T
NM_001276697.3:c.265C>T
NM_001276698.3:c.265C>T
NM_001276699.3:c.265C>T
NM_001276760.3:c.625C>T
NM_001276761.3:c.625C>T

Pathogenic

Met criteria codes 9

PM1 PM5 PP1_Strong PM2_Supporting PP3_Moderate PP4_Moderate PS2 PS3 PS4

Not Met criteria codes 9

BA1 BS2 PVS1 BS1 BS4 BS3 BP5 BP4 PS1

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.742C>T variant in TP53 is a missense variant predicted to cause substitution of arginine by tryptophan at amino acid 248 (p.Arg248Trp). This variant has been identified as a de novo occurrence with confirmed parental relationships in one individual with an LFS-associated cancer totaling four phenotype points (PS2; PMID: 10089074). This variant has been reported in >10 unrelated probands meeting Classic and Revised Chompret criteria. Based on this evidence, this variant scores 13.5 total points meeting the TP53 VCEP phenotype scoring criteria of ≥ 8 points. (PS4_Very Strong; PMIDs: 8527048, 9242456, 20522432, 8425176, 32658383, 9825943, 1978757. Internal lab contributors: SCV000212766.7, SCV000218912.13). The variant has been reported to segregate with LFS-associated cancers in ≥ 7 meioses in six families (PP1_Strong; PMID: 8527048, 9825943, 8527048, 1978757, 9825943, 9242456). 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: SCV000212766.7). This variant has an allele frequency of 0.000005933 (7/1179814 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 (PMIDs: 12826609, 30224644, 29979965) (PS3). 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). Another missense variant c.743G>A; p.Arg248Gln (ClinVar Variation ID 12356), in the same codon have been classified as pathogenic for Li-Fraumeni syndrome by the ClinGen TP53 VCEP's specifications. (PM5). Computational predictor scores (BayesDel = 0.5336; 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, 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: PS2, PS4_Very Strong, PP1_Strong, PP4_Moderate, PM2_Supporting, PS3, PM1, PM5, PP3_Moderate. (Bayesian Points: 29; VCEP specifications version 2.0; 7/24/2024)

Met criteria codes

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).
PM5	✔	Another missense variant c.743G>A; p.Arg248Gln (ClinVar Variation ID 12356), in the same codon have been classified as pathogenic for Li-Fraumeni syndrome by the ClinGen TP53 VCEP's specifications.(PM5).
PP1_Strong	✔	The variant has been reported to segregate with LFS-associated cancers in ≥ 7 meioses in six families (PP1_Strong; PMID: 8527048, 9825943, 8527048, 1978757, 9825943, 9242456).
PM2_Supporting	✔	This variant has an allele frequency of 0.000005933 (7/1179814 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).
PP3_Moderate	✔	Computational predictor scores (BayesDel = 0.5336; 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).
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: SCV000212766.7).
PS2	✔	This variant has been identified as a de novo occurrence with confirmed parental relationships in one individual with an LFS-associated cancer totaling four phenotype points (PS2; PMID: 10089074).

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		✔	PS4_VERY STRONG MET This variant has been reported in >10 unrelated probands meeting Classic and Revised Chompret criteria. Based on this evidence, this variant scores 13.5 total points meeting the TP53 VCEP phenotype scoring criteria of ≥ 8 points. (PS4_Very Strong; PMIDs: 8527048, 9242456, 20522432, 8425176, 32658383, 9825943, 1978757. Internal lab contributors: SCV000212766.7, SCV000218912.13).

Not Met criteria codes

BA1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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
BP5		✖	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
PS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000546.5(TP53):c.742C>T (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.742C>T (p.Arg2…	Pathogenic	Li-Fraumeni Syndrome	2020-01-24	1.0	-	TP53

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