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_000546.6(TP53):c.743G>A (p.Arg248Gln)

Version: 1.1

CA000387

12356 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: cf887752-8539-4177-a74d-dc5c8f8a36ed
Approved on: 2024-08-05
Published on: 2024-08-05

HGVS expressions

NM_000546.6:c.743G>A
NM_000546.6(TP53):c.743G>A (p.Arg248Gln)
NC_000017.11:g.7674220C>T
CM000679.2:g.7674220C>T
NC_000017.10:g.7577538C>T
CM000679.1:g.7577538C>T
NC_000017.9:g.7518263C>T
NG_017013.2:g.18331G>A
ENST00000503591.2:c.743G>A
ENST00000508793.6:c.743G>A
ENST00000509690.6:c.347G>A
ENST00000514944.6:c.464G>A
ENST00000604348.6:c.722G>A
ENST00000269305.9:c.743G>A
ENST00000269305.8:c.743G>A
ENST00000359597.8:c.743G>A
ENST00000413465.6:c.743G>A
ENST00000420246.6:c.743G>A
ENST00000445888.6:c.743G>A
ENST00000455263.6:c.743G>A
ENST00000504290.5:c.347G>A
ENST00000504937.5:c.347G>A
ENST00000509690.5:c.347G>A
ENST00000510385.5:c.347G>A
ENST00000514944.5:c.464G>A
ENST00000610292.4:c.626G>A
ENST00000610538.4:c.626G>A
ENST00000610623.4:c.266G>A
ENST00000615910.4:c.710G>A
ENST00000617185.4:c.743G>A
ENST00000618944.4:c.266G>A
ENST00000619186.4:c.266G>A
ENST00000619485.4:c.626G>A
ENST00000620739.4:c.626G>A
ENST00000622645.4:c.626G>A
ENST00000635293.1:c.626G>A
NM_000546.5:c.743G>A

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

Pathogenic

Met criteria codes 8

PS2 PS3 PS4 PP1_Moderate PP3 PP4_Moderate PM1 PM2_Supporting

Not Met criteria codes 8

PS1 BP4 BA1 PM5 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>A variant in TP53 is a missense variant predicted to cause substitution of arginine by glutamine at amino acid 248 (p.Arg248Gln). This variant has been identified as a de novo occurrence with confirmed parental relationships in 1 individual and as a de novo occurrence with unconfirmed parental relationships in 1 individual with a strongly LFS-associated cancer, and in 1 individual with a moderately LFS-associated cancer totaling 7 phenotype points (PS2; PMIDs, 15381368; 35974385; 1565143). This variant has been reported in an additional two unrelated probands meeting Classic and seven probands meeting Revised Chompret criteria. Based on this evidence, this variant scores 5.5 total points meeting the TP53 VCEP phenotype scoring criteria of 4-7.5 points. (PS4; PMID: 9242456, 7887414, 36457625, 21601526, ClinVar SCV SCV000185472.8, Internal lab contributor). The variant has been reported to segregate with LFS-associated cancers in 5-6 meioses in four families (PP1_Moderate; PMID: 1565143, 9242456, 7887414, 36457625). 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, ClinVar GTRs, Internal lab contributors). This variant has an allele frequency of 0.000007629 (9/1179752 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). Computational predictor scores (BayesDel = 0.4738; Align GVGD = Class C35) 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: PS2, PS4, PP1_Moderate, PP4_Moderate, PS3, PM1, PM2_Supporting, PP3. (Bayesian Points: 20; VCEP specifications version 2.0; 7/24/2024)

Met criteria codes

PS2	✔	This variant has been identified as a de novo occurrence with confirmed parental relationships in 1 individual and as a de novo occurrence with unconfirmed parental relationships in 1 individual with a strongly LFS-associated cancer, and in 1 individual with a moderately LFS-associated cancer totaling 7 phenotype points (PS2; PMIDs, 15381368; 35974385; 1565143).
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	✔	This variant has been reported in an additional two unrelated probands meeting Classic and seven probands meeting Revised Chompret criteria. Based on this evidence, this variant scores 5.5 total points meeting the TP53 VCEP phenotype scoring criteria of 4-7.5 points. (PS4; PMID: 9242456, 7887414, 36457625, 21601526, ClinVar SCV SCV000185472.8, Internal lab contributor).
PP1_Moderate	✔	The variant has been reported to segregate with LFS-associated cancers in 5-6 meioses in four families (PP1_Moderate; PMID: 1565143, 9242456, 7887414, 36457625).
PP3	✔	Computational predictor scores (BayesDel = 0.4738; Align GVGD = Class C35) 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).
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, ClinVar GTRs, Internal lab contributors).
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 has an allele frequency of 0.000007629 (9/1179752 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).

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
PM5	✖	Two different missense variants (c.743G>C, p.Arg248Pro and c.742C>G, p.Arg248Gly) (ClinVar Variation ID 237954 and 376652) in the same codon have been classified as pathogenic for Li-Fraumeni syndrome by the ClinGen TP53 VCEP's specifications. However, these variants have higher Grantham scores and are therefore more chemically different than the c.743G>A p.Arg248Gln variant, and can not be used for PM5 weight. (PM5 not met).
BS2	✖	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

Curation History

Showing 1 to 2 of 2 rows