

Variant: NM_000546.6(TP53):c.523C>G (p.Arg175Gly)

Version: 1.0

CA16603066 [↗](#)

376649 (ClinVar) [↗](#)

Gene: TP53 ([HGNC:7157](#))

Condition: Li-Fraumeni syndrome ([MONDO:0018875](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: fd72fc13-1dd7-4c83-938d-845d8cfb8668

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HGVS expressions

NM_000546.6(TP53):c.523C>G (p.Arg175Gly)

NM_000546.6:c.523C>G

NC_000017.11:g.7675089G>C

CM000679.2:g.7675089G>C

NC_000017.10:g.7578407G>C

CM000679.1:g.7578407G>C

NC_000017.9:g.7519132G>C

NG_017013.2:g.17462C>G

ENST00000503591.2:c.523C>G

ENST00000508793.6:c.523C>G

ENST00000509690.6:c.127C>G

ENST00000514944.6:c.244C>G

ENST00000604348.6:c.502C>G

ENST00000269305.9:c.523C>G

ENST00000269305.8:c.523C>G

ENST00000359597.8:c.523C>G

ENST00000413465.6:c.523C>G

ENST00000420246.6:c.523C>G

ENST00000445888.6:c.523C>G

ENST00000455263.6:c.523C>G

ENST00000504290.5:c.127C>G

ENST00000504937.5:c.127C>G

ENST00000505014.5:n.779C>G

ENST00000509690.5:c.127C>G

ENST00000510385.5:c.127C>G

ENST00000514944.5:c.244C>G

ENST00000574684.1:n.31C>G

ENST00000610292.4:c.406C>G

ENST00000610538.4:c.406C>G

ENST00000610623.4:c.46C>G

ENST00000615910.4:c.490C>G

ENST00000617185.4:c.523C>G

ENST00000618944.4:c.46C>G

ENST00000619186.4:c.46C>G

ENST00000619485.4:c.406C>G

ENST00000620739.4:c.406C>G

ENST00000622645.4:c.406C>G

	ENST000000635293.1:c.406C>G
	NM_000546.5:c.523C>G
	NM_001126112.2:c.523C>G
	NM_001126113.2:c.523C>G
	NM_001126114.2:c.523C>G
	NM_001126115.1:c.127C>G
	NM_001126116.1:c.127C>G
	NM_001126117.1:c.127C>G
	NM_001126118.1:c.406C>G
	NM_001276695.1:c.406C>G
	NM_001276696.1:c.406C>G
	NM_001276697.1:c.46C>G
	NM_001276698.1:c.46C>G
	NM_001276699.1:c.46C>G
	NM_001276760.1:c.406C>G
	NM_001276761.1:c.406C>G
	NM_001276695.2:c.406C>G
	NM_001276696.2:c.406C>G
	NM_001276697.2:c.46C>G
	NM_001276698.2:c.46C>G
	NM_001276699.2:c.46C>G
	NM_001276760.2:c.406C>G
	NM_001276761.2:c.406C>G
	NM_001126112.3:c.523C>G
	NM_001126113.3:c.523C>G
	NM_001126114.3:c.523C>G
	NM_001126115.2:c.127C>G
	NM_001126116.2:c.127C>G
	NM_001126117.2:c.127C>G
	NM_001126118.2:c.406C>G
	NM_001276695.3:c.406C>G
	NM_001276696.3:c.406C>G
	NM_001276697.3:c.46C>G
	NM_001276698.3:c.46C>G
	NM_001276699.3:c.46C>G
	NM_001276760.3:c.406C>G
	NM_001276761.3:c.406C>G

Pathogenic

Met criteria codes 6

- PS4_Supporting
- PS3
- PM2_Supporting
- PM1
- PM5
- PP3_Moderate

Not Met criteria codes 5

- BA1
- BS2
- BS1
- BP4
- PP4

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](#)

TP53 VCEP

The NM_000546.6: c.523C>G variant in TP53 is a missense variant predicted to cause substitution of arginine by glycine at amino acid 175 (p.Arg175Gly). This variant has been reported in 2 unrelated probands meeting Revised Chompret criteria. Based on this evidence, this variant scores 1 total point meeting the TP53 VCEP phenotype scoring criteria of 1-1.5 points. (PS4_Supporting; PMIDs: 11370630, 25927356). This variant has an allele frequency of 0.000002542 (3/1180042 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). Another missense variant(c.524G>A, p.Arg175His) (ClinVar Variation ID: 12374), in the same codon has been classified as pathogenic for Li-Fraumeni syndrome by the ClinGen TP53 VCEP’s specifications. (PM5). 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). Computational predictor scores (BayesDel = 0.554513; 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 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). 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_Supporting, PM2_Supporting, PM5, PM1, PP3_Moderate, PS3. (Bayesian Points: 12; VCEP specifications version 2.0; 9/6/2024)

Met criteria codes

PS4_Supporting			This variant has been reported in 2 unrelated probands meeting Revised Chompret criteria. Based on this evidence, this variant scores 1 total point meeting the TP53 VCEP phenotype scoring criteria of 1-1.5 points. (PS4_Supporting; PMIDs: 11370630, 25927356).
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 (PS3; PMIDs: 12826609, 30224644, 29979965).
PM2_Supporting			This variant has an allele frequency of 0.000002542 (3/1180042 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).
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).
PM5			Another missense variant(c.524G>A, p.Arg175His) (ClinVar Variation ID: 12374), in the same codon has been classified as pathogenic for Li-Fraumeni syndrome by the ClinGen TP53 VCEP’s specifications. (PM5).
PP3_Moderate			Computational predictor scores (BayesDel = 0.554513; 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).

Not Met criteria codes

BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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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
BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 	
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