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.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
Approved on: 2024/9/6
Published on: 2024/9/6

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

ENST00000635293.1: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
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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

PM1 PM5 PM2_Supporting PP3_Moderate PS4_Supporting PS3

Not Met criteria codes 5

PP4 BA1 BS2 BS1 BP4

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.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

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).
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).
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).
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).

Not Met criteria codes

PP4	✖	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	✖	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

Curation History

Showing 1 to 1 of 1 rows

See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000546.6(TP53):c.523C>G (p.Arg1…	Pathogenic	Li-Fraumeni Syndrome	2024-09-06	1.0	ClinGen TP53 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TP53 Version 2.0.0	TP53

Showing 1 to 1 of 1 rows

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