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Variant: NM_000546.6(TP53):c.473G>C (p.Arg158Pro)

Version: 1.0

CA10584592

246118 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 78d703d3-a05a-4c47-a421-b858b045c2d3
Approved on: 2025/12/5
Published on: 2025/12/5

HGVS expressions

NM_000546.6(TP53):c.473G>C (p.Arg158Pro)
NM_000546.6:c.473G>C
NC_000017.11:g.7675139C>G
CM000679.2:g.7675139C>G
NC_000017.10:g.7578457C>G
CM000679.1:g.7578457C>G
NC_000017.9:g.7519182C>G
NG_017013.2:g.17412G>C
ENST00000503591.2:c.473G>C
ENST00000508793.6:c.473G>C
ENST00000509690.6:c.77G>C
ENST00000514944.6:c.194G>C
ENST00000604348.6:c.452G>C
ENST00000269305.9:c.473G>C
ENST00000269305.8:c.473G>C
ENST00000359597.8:c.473G>C
ENST00000413465.6:c.473G>C
ENST00000420246.6:c.473G>C
ENST00000445888.6:c.473G>C
ENST00000455263.6:c.473G>C
ENST00000504290.5:c.77G>C
ENST00000504937.5:c.77G>C
ENST00000505014.5:n.729G>C
ENST00000508793.5:c.473G>C
ENST00000509690.5:c.77G>C
ENST00000510385.5:c.77G>C
ENST00000514944.5:c.194G>C
ENST00000610292.4:c.356G>C
ENST00000610538.4:c.356G>C
ENST00000610623.4:c.-5G>C
ENST00000615910.4:c.440G>C
ENST00000617185.4:c.473G>C
ENST00000618944.4:c.-5G>C
ENST00000619186.4:c.-5G>C
ENST00000619485.4:c.356G>C
ENST00000620739.4:c.356G>C
ENST00000622645.4:c.356G>C

ENST00000635293.1:c.356G>C
NM_000546.5:c.473G>C
NM_001126112.2:c.473G>C
NM_001126113.2:c.473G>C
NM_001126114.2:c.473G>C
NM_001126115.1:c.77G>C
NM_001126116.1:c.77G>C
NM_001126117.1:c.77G>C
NM_001126118.1:c.356G>C
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NM_001276698.1:c.-5G>C
NM_001276699.1:c.-5G>C
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NM_001276761.1:c.356G>C
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NM_001276761.2:c.356G>C
NM_001126112.3:c.473G>C
NM_001126113.3:c.473G>C
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NM_001126118.2:c.356G>C
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NM_001276698.3:c.-5G>C
NM_001276699.3:c.-5G>C
NM_001276760.3:c.356G>C
NM_001276761.3:c.356G>C

Pathogenic

Met criteria codes 5

PP3_Moderate PM1 PM5 PM2_Supporting PS3

Not Met criteria codes 8

PP4 BA1 BS2 BS1 BS3 BP4 PS1 PS2

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 2.3.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

TP53 VCEP

The NM_000546.6: c.473G>C variant in TP53 is a missense variant predicted to cause substitution of arginine by proline at amino acid 158 (p.Arg158Pro). This variant received a total of 0.5 points in 1 proband on literature search only (internal data not obtained). (PS4 not met; PMID: 35974385). This variant is absent from gnomAD v4.1.0 (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 (PS3; PMIDs: 12826609, 30224644, 29979965). Another missense variant (c.473G>T, p.Arg158Leu) (ClinVar ID: 528248), in the same codon has been classified as pathogenic for Li-Fraumeni syndrome by the ClinGen TP53 VCEP's specifications. (PM5). This variant has 11 somatic occurrences for the same amino acid change in cancerhotspots.org (v2) sufficient to be defined as a mutational hotspot by the Clingen TP53 VCEP (≥ 10 somatic occurrences, PMID: 30311369) (PM1). Computational predictor scores (BayesDel = 0.575563; 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: PS3, PP3_moderate, PM1, PM5, PM2_Supporting. (Bayesian Points: 11; VCEP specifications version 2.3)

Met criteria codes

PP3_Moderate	✔	Computational predictor scores (BayesDel = 0.575563; 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).
PM1	✔	This variant has 11 somatic occurrences for the same amino acid change in cancerhotspots.org (v2) sufficient to be defined as a mutational hotspot by the Clingen TP53 VCEP (≥ 10 somatic occurrences, PMID: 30311369) (PM1).
PM5	✔	Another missense variant (c.473G>T, p.Arg158Leu) (ClinVar ID: 528248), 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 is absent from gnomAD v4.1.0 (PM2_Supporting).
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
BS3	✖	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
PS2	✖	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_000546.6(TP53):c.473G>C (p.Arg1…	Pathogenic	Li-Fraumeni Syndrome	2025-12-05	1.0	ClinGen TP53 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TP53 Version 2.3.0	TP53

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