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Variant: NM_000546.6(TP53):c.380C>G (p.Ser127Cys)

Version: 1.0

CA349567

219532 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 43b0cc2c-d3f6-44c3-a913-cd16520ea78b
Approved on: 2026/3/4
Published on: 2026/4/22

HGVS expressions

NM_000546.6(TP53):c.380C>G (p.Ser127Cys)
NM_000546.6:c.380C>G
NC_000017.11:g.7675232G>C
CM000679.2:g.7675232G>C
NC_000017.10:g.7578550G>C
CM000679.1:g.7578550G>C
NC_000017.9:g.7519275G>C
NG_017013.2:g.17319C>G
ENST00000503591.2:c.380C>G
ENST00000508793.6:c.380C>G
ENST00000509690.6:c.-17C>G
ENST00000514944.6:c.101C>G
ENST00000604348.6:c.376-17C>G
ENST00000269305.9:c.380C>G
ENST00000269305.8:c.380C>G
ENST00000359597.8:c.380C>G
ENST00000413465.6:c.380C>G
ENST00000420246.6:c.380C>G
ENST00000445888.6:c.380C>G
ENST00000455263.6:c.380C>G
ENST00000503591.1:c.380C>G
ENST00000504290.5:c.-17C>G
ENST00000504937.5:c.-17C>G
ENST00000505014.5:n.636C>G
ENST00000508793.5:c.380C>G
ENST00000509690.5:c.-17C>G
ENST00000510385.5:c.-17C>G
ENST00000514944.5:c.101C>G
ENST00000604348.5:c.376-17C>G
ENST00000610292.4:c.263C>G
ENST00000610538.4:c.263C>G
ENST00000610623.4:c.-98C>G
ENST00000615910.4:c.347C>G
ENST00000617185.4:c.380C>G
ENST00000618944.4:c.-98C>G
ENST00000619186.4:c.-98C>G
ENST00000619485.4:c.263C>G

ENST00000620739.4:c.263C>G
ENST00000622645.4:c.263C>G
ENST00000635293.1:c.263C>G
NM_000546.5:c.380C>G
NM_001126112.2:c.380C>G
NM_001126113.2:c.380C>G
NM_001126114.2:c.380C>G
NM_001126115.1:c.-17C>G
NM_001126116.1:c.-17C>G
NM_001126117.1:c.-17C>G
NM_001126118.1:c.263C>G
NM_001276695.1:c.263C>G
NM_001276696.1:c.263C>G
NM_001276697.1:c.-98C>G
NM_001276698.1:c.-98C>G
NM_001276699.1:c.-98C>G
NM_001276760.1:c.263C>G
NM_001276761.1:c.263C>G
NM_001276695.2:c.263C>G
NM_001276696.2:c.263C>G
NM_001276697.2:c.-98C>G
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NM_001276760.2:c.263C>G
NM_001276761.2:c.263C>G
NM_001126112.3:c.380C>G
NM_001126113.3:c.380C>G
NM_001126114.3:c.380C>G
NM_001126115.2:c.-17C>G
NM_001126116.2:c.-17C>G
NM_001126117.2:c.-17C>G
NM_001126118.2:c.263C>G
NM_001276695.3:c.263C>G
NM_001276696.3:c.263C>G
NM_001276697.3:c.-98C>G
NM_001276698.3:c.-98C>G
NM_001276699.3:c.-98C>G
NM_001276760.3:c.263C>G
NM_001276761.3:c.263C>G

Likely Pathogenic

Met criteria codes 4

PS3 PP4 PM2_Supporting PP3_Moderate

Not Met criteria codes 12

PS1 PS2 PS4 PP1 PM1 PM5 BA1 BS1 BS4 BS3 BS2 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 2.4.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

TP53 VCEP

The NM_000546.6:c.380C>G variant in TP53 is a missense variant predicted to cause the substitution of serine by cysteine at amino acid position 127 (p.Ser127Cys). Although this variant has been observed in germline cases, to our knowledge, this variant has not been reported in individuals meeting classical LFS or Chompret criteria (PS4 not met; https://doi.org/10.37349/emed.2024.00246, Internal lab contributor). At least one individual with this variant was found to have a variant allele fraction of 5-35%, which is a significant predictor of variant pathogenicity (PP4, PMID: 34906512, Internal lab contributor).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 by the majority of available assays indicating that this variant impacts protein function (PS3; PMIDs: 12826609, 30224644, 29979965, 39774325). Computational predictor scores (BayesDel = 0.556749; 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 Likely Pathogenic for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: PP4, PM2_supporting, PS3, PP3_moderate. (Bayesian Points: 8; VCEP specifications version 2.4)

Met criteria codes

PS3	✔	In vitro assays performed in yeast and/or human cell lines showed non-functional transactivation and loss of growth suppression activity by the majority of available assays indicating that this variant impacts protein function (PS3; PMIDs: 12826609, 30224644, 29979965, 39774325).
PP4	✔	At least one individual with this variant was found to have a variant allele fraction of 5-35%, which is a significant predictor of variant pathogenicity (PP4, PMID: 34906512, Internal lab contributor).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PP3_Moderate	✔	Computational predictor scores (BayesDel = 0.556749; 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

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
PS4	✖	Although this variant has been observed in germline cases, to our knowledge, this variant has not been reported in individuals meeting classical LFS or Chompret criteria (PS4 not met; https://doi.org/10.37349/emed.2024.00246, Internal lab contributor).
PP1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PM1		✖	This variant does not reside within a region of TP53 that is defined as a mutational hotspot by the ClinGen TP53 VCEP (PM1 not met).
PM5		✖	Two other missense variants (p.Ser127Pro and p.Ser127Thr) (ClinVar Variation IDs: 934410, 824232), with Grantham scores equal to or less than the current variant in the same codon has been classified as likely pathogenic for Li-Fraumeni syndrome by the ClinGen TP53 VCEP's specifications. However, these variants do not meet criteria for PM5 code application (PM5 not met) as they do not have clinical data demonstrating pathogenicity.
BA1		✖	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
BS2		✖	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

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000546.6(TP53):c.380C>G (p.Ser1...	Likely Pathogenic	Li-Fraumeni Syndrome	2026-04-22	1.0	ClinGen TP53 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TP53 Version 2.4.0	TP53

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