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Variant: NM_000546.6(TP53):c.379T>A (p.Ser127Thr)

Version: 1.0

CA397843929

824232 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 0edde57d-6d76-4c13-9c87-b8d41d53c381
Approved on: 2026/2/5
Published on: 2026/2/10

HGVS expressions

NM_000546.6(TP53):c.379T>A (p.Ser127Thr)
NM_000546.6:c.379T>A
NC_000017.11:g.7675233A>T
CM000679.2:g.7675233A>T
NC_000017.10:g.7578551A>T
CM000679.1:g.7578551A>T
NC_000017.9:g.7519276A>T
NG_017013.2:g.17318T>A
ENST00000503591.2:c.379T>A
ENST00000508793.6:c.379T>A
ENST00000509690.6:c.-18T>A
ENST00000514944.6:c.100T>A
ENST00000604348.6:c.376-18T>A
ENST00000269305.9:c.379T>A
ENST00000269305.8:c.379T>A
ENST00000359597.8:c.379T>A
ENST00000413465.6:c.379T>A
ENST00000420246.6:c.379T>A
ENST00000445888.6:c.379T>A
ENST00000455263.6:c.379T>A
ENST00000503591.1:c.379T>A
ENST00000504290.5:c.-18T>A
ENST00000504937.5:c.-18T>A
ENST00000505014.5:n.635T>A
ENST00000508793.5:c.379T>A
ENST00000509690.5:c.-18T>A
ENST00000510385.5:c.-18T>A
ENST00000514944.5:c.100T>A
ENST00000604348.5:c.376-18T>A
ENST00000610292.4:c.262T>A
ENST00000610538.4:c.262T>A
ENST00000610623.4:c.-99T>A
ENST00000615910.4:c.346T>A
ENST00000617185.4:c.379T>A
ENST00000618944.4:c.-99T>A
ENST00000619186.4:c.-99T>A
ENST00000619485.4:c.262T>A

ENST00000620739.4:c.262T>A
ENST00000622645.4:c.262T>A
ENST00000635293.1:c.262T>A
NM_000546.5:c.379T>A
NM_001126112.2:c.379T>A
NM_001126113.2:c.379T>A
NM_001126114.2:c.379T>A
NM_001126115.1:c.-18T>A
NM_001126116.1:c.-18T>A
NM_001126117.1:c.-18T>A
NM_001126118.1:c.262T>A
NM_001276695.1:c.262T>A
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NM_001276697.1:c.-99T>A
NM_001276698.1:c.-99T>A
NM_001276699.1:c.-99T>A
NM_001276760.1:c.262T>A
NM_001276761.1:c.262T>A
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NM_001126112.3:c.379T>A
NM_001126113.3:c.379T>A
NM_001126114.3:c.379T>A
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NM_001126116.2:c.-18T>A
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NM_001276698.3:c.-99T>A
NM_001276699.3:c.-99T>A
NM_001276760.3:c.262T>A
NM_001276761.3:c.262T>A

Likely Pathogenic

Met criteria codes 4

PP4_Moderate PP3 PS3 PM2_Supporting

Not Met criteria codes 7

BP4 BS1 BS3 PS4 BA1 PM1 PM5

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(TP53):c.379T>A variant in TP53 is a missense variant predicted to cause substitution of serine by threonine at amino acid 127 (p.Ser127Thr). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). This variant received a total of 0.5 points across 1 proband (PS4 not met; Internal lab contributors). 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, Internal lab contributor). 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 = 0.428891; Align GVGD = Class C55) 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 Likely Pathogenic for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: PP4_Moderate PM2_supporting, PS3, PP3. (Bayesian Points: 8; VCEP specifications version 2.4).

Met criteria codes

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, Internal lab contributor).
PP3	✔	Computational predictor scores (BayesDel = 0.428891; Align GVGD = Class C55) 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).
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).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

Not Met criteria codes

BP4	✖	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
PS4	✖	This variant received a total of 0.5 points across 1 proband. However, PS4 cannot be applied because it does not meet the minimum requirements (PS4 not met; Internal lab contributors).
BA1	✖	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		✖	4 different missense variants (p.Ser127Tyr, p.Ser127Cys, p.Ser127Phe, p.Ser127Pro) in the same codon have been reported (ClinVar Variation IDs: 656751, 219532, 182928, 934410). However, these variants do not meet criteria for PM5 code application as all variant have higher Grantham scores (PM5 not met).

Curation History

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