

Variant: NM_000546.6(TP53):c.857A>T (p.Glu286Val)

Version: 1.0

CA16603014 [↗](#)

376592 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 8d37f3ab-2635-42d8-a422-ed44f21e256d

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HGVS expressions

NM_000546.6:c.857A>T

NM_000546.6(TP53):c.857A>T (p.Glu286Val)

NC_000017.11:g.7673763T>A

CM000679.2:g.7673763T>A

NC_000017.10:g.7577081T>A

CM000679.1:g.7577081T>A

NC_000017.9:g.7517806T>A

NG_017013.2:g.18788A>T

ENST00000503591.2:c.857A>T

ENST00000508793.6:c.857A>T

ENST00000509690.6:c.461A>T

ENST00000514944.6:c.578A>T

ENST00000604348.6:c.836A>T

ENST00000269305.9:c.857A>T

ENST00000269305.8:c.857A>T

ENST00000359597.8:c.857A>T

ENST00000413465.6:c.782+418A>T

ENST00000420246.6:c.857A>T

ENST00000445888.6:c.857A>T

ENST00000455263.6:c.857A>T

ENST00000504290.5:c.461A>T

ENST00000504937.5:c.461A>T

ENST00000509690.5:c.461A>T

ENST00000510385.5:c.461A>T

ENST00000610292.4:c.740A>T

ENST00000610538.4:c.740A>T

ENST00000610623.4:c.380A>T

ENST00000615910.4:c.824A>T

ENST00000617185.4:c.857A>T

ENST00000618944.4:c.380A>T

ENST00000619186.4:c.380A>T

ENST00000619485.4:c.740A>T

ENST00000620739.4:c.740A>T

ENST00000622645.4:c.740A>T

ENST00000635293.1:c.740A>T

NM_000546.5:c.857A>T

NM_001126112.2:c.857A>T

	NM_001126113.2:c.857A>T
	NM_001126114.2:c.857A>T
	NM_001126115.1:c.461A>T
	NM_001126116.1:c.461A>T
	NM_001126117.1:c.461A>T
	NM_001126118.1:c.740A>T
	NM_001276695.1:c.740A>T
	NM_001276696.1:c.740A>T
	NM_001276697.1:c.380A>T
	NM_001276698.1:c.380A>T
	NM_001276699.1:c.380A>T
	NM_001276760.1:c.740A>T
	NM_001276761.1:c.740A>T
	NM_001276695.2:c.740A>T
	NM_001276696.2:c.740A>T
	NM_001276697.2:c.380A>T
	NM_001276698.2:c.380A>T
	NM_001276699.2:c.380A>T
	NM_001276760.2:c.740A>T
	NM_001276761.2:c.740A>T
	NM_001126112.3:c.857A>T
	NM_001126113.3:c.857A>T
	NM_001126114.3:c.857A>T
	NM_001126115.2:c.461A>T
	NM_001126116.2:c.461A>T
	NM_001126117.2:c.461A>T
	NM_001126118.2:c.740A>T
	NM_001276695.3:c.740A>T
	NM_001276696.3:c.740A>T
	NM_001276697.3:c.380A>T
	NM_001276698.3:c.380A>T
	NM_001276699.3:c.380A>T
	NM_001276760.3:c.740A>T
	NM_001276761.3:c.740A>T

Pathogenic

Met criteria codes 6

- PS3PM1_SupportingPP4PM5
- PP3_ModeratePM2_Supporting

Not Met criteria codes 20

- PS1PS2PS4BP4BP3BP1
- BP2BP5BP7PP1PP2
- PVS1PM6PM3PM4BA1
- BS2BS1BS4BS3

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

[Criteria Specification Approval History](#)

[Criteria Specifications for this VCEP](#)

Evidence submitted by expert panel

TP53 VCEP

The NM_000546.6: c.857A>T variant in TP53 is a missense variant predicted to cause substitution of glutamic acid by valine at amino acid 286 (p.Glu286Val). 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 contributors). In addition, this variant received a total of 0.5 points across 1 proband (PS4 not met; Internal lab contributors). 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). Another missense variant(c.857A>G, p.Glu286Gly) (ClinVar Variation ID: 376590), with Grantham score equal to or less than the current variant in the same codon has been classified as pathogenic for Li-Fraumeni syndrome by the ClinGen TP53 VCEP’s specifications. (PM5). Computational predictor scores (BayesDel = 0.4044; Align GVG D = Class C65) are above recommended thresholds (BayesDel > 0.16 and an Align GVG D Class of 65), evidence that correlates with impact to TP53 via protein change (PP3_Moderate). This variant has 3 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 (2-9 somatic occurrences, PMID: 30311369) (PM1_Supporting). 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, PM5, PP3_Moderate, PM1_Supporting, PM2_Supporting, PP4. (Bayesian Points: 11; 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).
PM1_Supporting			This variant has 3 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 (2-9 somatic occurrences, PMID: 30311369) (PM1_Supporting).
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 contributors).
PM5			Another missense variant(c.857A>G, p.Glu286Gly) (ClinVar Variation ID: 376590), with Grantham score equal to or less than the current variant 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 = 0.4044; Align GVG D = Class C65) are above recommended thresholds (BayesDel > 0.16 and an Align GVG D Class of 65), evidence that correlates with impact to TP53 via protein change (PP3_Moderate).
PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

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			This variant received a total of 0.5 points across 1 proband (PS4 not met; Internal lab contributors).
BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4			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
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

Curation History 		
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