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.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
Approved on: Thu, 06 Aug 2026 00:00:00 +0000
Published on: Tue, 22 Sep 2026 00:00:00 +0000

HGVS expressions

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

PP4 PP3_Moderate PM1_Supporting PM5 PM2_Supporting PS3

Not Met criteria codes 20

PP1 PP2 PM3 PM4 PM6 BA1 BS2 BS1 BS4 BS3 BP5 BP7 BP4 BP3 BP1 BP2 PVS1 PS1 PS2 PS4

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 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). 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

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).
PP3_Moderate	✔	Computational predictor scores (BayesDel = 0.4044; 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_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).
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).
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 by the majority of available assays indicating that this variant impacts protein function (PS3; PMIDs: 12826609, 30224644, 29979965, 39774325).

Not Met criteria codes

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

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
PM6		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	ℹ	✖	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	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4	ℹ	✖	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
PVS1	ℹ	✖	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
PS4		✖	This variant received a total of 0.5 points across 1 proband (PS4 not met; Internal lab contributors).

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.857A>T (p.Glu2…)	Pathogenic	Li-Fraumeni Syndrome	2026-09-22	1.0	ClinGen TP53 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TP53 Version 2.4	TP53

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