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.840A>T (p.Arg280Ser)

Version: 1.0

CA397836831

988616 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 54ad9d59-0134-41c7-92ef-3b86fb2181d5
Approved on: 2026/4/2
Published on: 2026/4/22

HGVS expressions

NM_000546.6(TP53):c.840A>T (p.Arg280Ser)
NM_000546.6:c.840A>T
NC_000017.11:g.7673780T>A
CM000679.2:g.7673780T>A
NC_000017.10:g.7577098T>A
CM000679.1:g.7577098T>A
NC_000017.9:g.7517823T>A
NG_017013.2:g.18771A>T
ENST00000503591.2:c.840A>T
ENST00000508793.6:c.840A>T
ENST00000509690.6:c.444A>T
ENST00000514944.6:c.561A>T
ENST00000604348.6:c.819A>T
ENST00000269305.9:c.840A>T
ENST00000269305.8:c.840A>T
ENST00000359597.8:c.840A>T
ENST00000413465.6:c.782+401A>T
ENST00000420246.6:c.840A>T
ENST00000445888.6:c.840A>T
ENST00000455263.6:c.840A>T
ENST00000504290.5:c.444A>T
ENST00000504937.5:c.444A>T
ENST00000509690.5:c.444A>T
ENST00000510385.5:c.444A>T
ENST00000610292.4:c.723A>T
ENST00000610538.4:c.723A>T
ENST00000610623.4:c.363A>T
ENST00000615910.4:c.807A>T
ENST00000617185.4:c.840A>T
ENST00000618944.4:c.363A>T
ENST00000619186.4:c.363A>T
ENST00000619485.4:c.723A>T
ENST00000620739.4:c.723A>T
ENST00000622645.4:c.723A>T
ENST00000635293.1:c.723A>T
NM_000546.5:c.840A>T
NM_001126112.2:c.840A>T

NM_001126113.2:c.840A>T
NM_001126114.2:c.840A>T
NM_001126115.1:c.444A>T
NM_001126116.1:c.444A>T
NM_001126117.1:c.444A>T
NM_001126118.1:c.723A>T
NM_001276695.1:c.723A>T
NM_001276696.1:c.723A>T
NM_001276697.1:c.363A>T
NM_001276698.1:c.363A>T
NM_001276699.1:c.363A>T
NM_001276760.1:c.723A>T
NM_001276761.1:c.723A>T
NM_001276695.2:c.723A>T
NM_001276696.2:c.723A>T
NM_001276697.2:c.363A>T
NM_001276698.2:c.363A>T
NM_001276699.2:c.363A>T
NM_001276760.2:c.723A>T
NM_001276761.2:c.723A>T
NM_001126112.3:c.840A>T
NM_001126113.3:c.840A>T
NM_001126114.3:c.840A>T
NM_001126115.2:c.444A>T
NM_001126116.2:c.444A>T
NM_001126117.2:c.444A>T
NM_001126118.2:c.723A>T
NM_001276695.3:c.723A>T
NM_001276696.3:c.723A>T
NM_001276697.3:c.363A>T
NM_001276698.3:c.363A>T
NM_001276699.3:c.363A>T
NM_001276760.3:c.723A>T
NM_001276761.3:c.723A>T

Pathogenic

Met criteria codes 5

PM1_Supporting PM2_Supporting PP3_Moderate PP4_Moderate PS3

Not Met criteria codes 8

PP1 BA1 BS2 BS1 BS4 BP4 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 2.4.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

TP53 VCEP

The NM_000546.6: c.840A>T variant in TP53 is a missense variant predicted to cause substitution of arginine by serine at amino acid 280 (p.Arg280Ser). Although this variant has been observed in a hypodiploid ALL case, to our knowledge, this variant has not been reported in individuals meeting classical LFS or Chompret criteria (PS4 not met; PMIDs: 23334668, 26580448, 29489754, 32000721, 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 contributors). This variant has an allele frequency of 0.00000062 (1/1613914 alleles) across gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00003) for PM2_Supporting, and therefore meets this criterion (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 = 0.519515; Align GVGD = Class 65) 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 8 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: PP4_Moderate, PM2_Supporting, PS3, PP3_Moderate, PM1_Supporting. (Bayesian Points: 10; VCEP specifications version 2.4)

Met criteria codes

PM1_Supporting	✔	This variant has 8 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).
PM2_Supporting	✔	This variant has an allele frequency of 0.00000062 (1/1613914 alleles) across gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00003) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting).
PP3_Moderate	✔	Computational predictor scores (BayesDel = 0.519515; Align GVGD = Class 65) 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).
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 contributors).
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
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
BP4	✖	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; PMIDs: 23334668, 26580448, 29489754, 32000721, Internal lab contributors).

Curation History

Showing 1 to 1 of 1 rows

See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000546.6(TP53):c.840A>T (p.Arg2...	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

Showing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.