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_000546.5(TP53):c.1136G>A (p.Arg379His)

Version: 2.0

CA10584584

246221 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 9bd50b93-5f12-44c4-81f6-e1a9ced34840
Approved on: 2025/1/16
Published on: 2025/1/16

HGVS expressions

NM_000546.5(TP53):c.1136G>A (p.Arg379His)
NM_000546.5:c.1136G>A
NC_000017.11:g.7669655C>T
CM000679.2:g.7669655C>T
NC_000017.10:g.7572973C>T
CM000679.1:g.7572973C>T
NC_000017.9:g.7513698C>T
NG_017013.2:g.22896G>A
ENST00000503591.2:c.1136G>A
ENST00000508793.6:c.1136G>A
ENST00000509690.6:c.740G>A
ENST00000514944.6:c.857G>A
ENST00000604348.6:c.1115G>A
ENST00000269305.9:c.1136G>A
ENST00000269305.8:c.1136G>A
ENST00000359597.8:c.994-3411G>A
ENST00000413465.6:c.782+4526G>A
ENST00000420246.6:c.*243G>A
ENST00000445888.6:c.1136G>A
ENST00000455263.6:c.*155G>A
ENST00000504290.5:c.*155G>A
ENST00000504937.5:c.740G>A
ENST00000510385.5:c.*243G>A
ENST00000576024.1:c.89G>A
ENST00000610292.4:c.1019G>A
ENST00000610538.4:c.*155G>A
ENST00000610623.4:c.*155G>A
ENST00000615910.4:c.1103G>A
ENST00000617185.4:c.*243G>A
ENST00000618944.4:c.*243G>A
ENST00000619186.4:c.659G>A
ENST00000619485.4:c.1019G>A
ENST00000620739.4:c.1019G>A
ENST00000622645.4:c.*243G>A
ENST00000635293.1:c.983+954G>A
NM_001126112.2:c.1136G>A
NM_001126113.2:c.*155G>A

NM_001126114.2:c.*243G>A
NM_001126115.1:c.740G>A
NM_001126116.1:c.*243G>A
NM_001126117.1:c.*155G>A
NM_001126118.1:c.1019G>A
NM_001276695.1:c.*155G>A
NM_001276696.1:c.*243G>A
NM_001276697.1:c.659G>A
NM_001276698.1:c.*243G>A
NM_001276699.1:c.*155G>A
NM_001276760.1:c.1019G>A
NM_001276761.1:c.1019G>A
NM_001276695.2:c.*155G>A
NM_001276696.2:c.*243G>A
NM_001276697.2:c.659G>A
NM_001276698.2:c.*243G>A
NM_001276699.2:c.*155G>A
NM_001276760.2:c.1019G>A
NM_001276761.2:c.1019G>A
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NM_001126112.3:c.1136G>A
NM_001126113.3:c.*155G>A
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NM_001126115.2:c.740G>A
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NM_001126117.2:c.*155G>A
NM_001126118.2:c.1019G>A
NM_001276695.3:c.*155G>A
NM_001276696.3:c.*243G>A
NM_001276697.3:c.659G>A
NM_001276698.3:c.*243G>A
NM_001276699.3:c.*155G>A
NM_001276760.3:c.1019G>A
NM_001276761.3:c.1019G>A

Likely Benign

Met criteria codes 3

PM2_Supporting BS3 BP4

Not Met criteria codes 13

PS1 PS2 PS3 PS4 BA1 PP1 PP3 PP4 PM1 PM5 BS1 BS4 BS2

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 2.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

TP53 VCEP

The NM_000546.5:c.1136G>A variant in TP53 is a missense variant predicted to cause substitution of arginine by histidine at amino acid 379 (p.Arg379His). In vitro assays performed in yeast and/or human cell lines showed functional transactivation and retained growth suppression activity indicating that this variant does not impact protein function (BS3; PMIDs: 12826609, 29979965, 30224644). This variant has a BayesDel score ≤ -0.008 and Align GVGD (Zebrafish) is Class C0 (BP4_moderate). This variant has an allele frequency of 0.00002671 (2/74876 alleles) in the African/African American population in gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00004) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting). In summary, this variant meets the criteria to be classified as likely benign for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: PM2_supporting, BP4_moderate, BS3. (Bayesian Points: -5; VCEP specifications version 2.0, Date of Approval: 1/16/2025).

Met criteria codes

PM2_Supporting	✔	This variant has an allele frequency of 0.00002671 (2/74876 alleles) in the African/African American population in gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00004) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting).
BS3	✔	In vitro assays performed in yeast and/or human cell lines showed functional transactivation and retained growth suppression activity indicating that this variant does not impact protein function (BS3; PMIDs: 12826609, 29979965, 30224644).
BP4	✔	BP4_MODERATE Computational predictor scores (BayesDel = -0.072; Align GVGD Class 0) are below the recommended thresholds (BayesDel ≤ -0.008 and an Align GVGD Class ≤ 55), evidence that does not predict a damaging effect on TP53 via protein change. SpliceAI predicts that the variant has no impact on splicing. (BP4_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
PS3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4	✖	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
PP1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	✖	

No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PP4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1	ℹ	✖	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	ℹ	✖	3 different missense variants (p.Arg379Leu, p.Arg379Ser, p.Arg379Cys) in the same codon have been reported. However, these variants have not yet met the criteria to be classified as pathogenic or likely pathogenic by the ClinGen TP53 VCEP's specifications (PM5 not met).
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
BS2	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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