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.403T>G (p.Cys135Gly)

Version: 2.0

CA16602989

376563 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: c4a27155-9f6f-4586-8a08-70b96d281243
Approved on: 2024/8/5
Published on: 2024/8/5

HGVS expressions

NM_000546.5:c.403T>G
NM_000546.5(TP53):c.403T>G (p.Cys135Gly)
NC_000017.11:g.7675209A>C
CM000679.2:g.7675209A>C
NC_000017.10:g.7578527A>C
CM000679.1:g.7578527A>C
NC_000017.9:g.7519252A>C
NG_017013.2:g.17342T>G
ENST00000503591.2:c.403T>G
ENST00000508793.6:c.403T>G
ENST00000509690.6:c.7T>G
ENST00000514944.6:c.124T>G
ENST00000604348.6:c.382T>G
ENST00000269305.9:c.403T>G
ENST00000269305.8:c.403T>G
ENST00000359597.8:c.403T>G
ENST00000413465.6:c.403T>G
ENST00000420246.6:c.403T>G
ENST00000445888.6:c.403T>G
ENST00000455263.6:c.403T>G
ENST00000504290.5:c.7T>G
ENST00000504937.5:c.7T>G
ENST00000505014.5:n.659T>G
ENST00000508793.5:c.403T>G
ENST00000509690.5:c.7T>G
ENST00000510385.5:c.7T>G
ENST00000514944.5:c.124T>G
ENST00000604348.5:c.382T>G
ENST00000610292.4:c.286T>G
ENST00000610538.4:c.286T>G
ENST00000610623.4:c.-75T>G
ENST00000615910.4:c.370T>G
ENST00000617185.4:c.403T>G
ENST00000618944.4:c.-75T>G
ENST00000619186.4:c.-75T>G
ENST00000619485.4:c.286T>G
ENST00000620739.4:c.286T>G

ENST00000622645.4:c.286T>G
ENST00000635293.1:c.286T>G
NM_001126112.2:c.403T>G
NM_001126113.2:c.403T>G
NM_001126114.2:c.403T>G
NM_001126115.1:c.7T>G
NM_001126116.1:c.7T>G
NM_001126117.1:c.7T>G
NM_001126118.1:c.286T>G
NM_001276695.1:c.286T>G
NM_001276696.1:c.286T>G
NM_001276697.1:c.-75T>G
NM_001276698.1:c.-75T>G
NM_001276699.1:c.-75T>G
NM_001276760.1:c.286T>G
NM_001276761.1:c.286T>G
NM_001276695.2:c.286T>G
NM_001276696.2:c.286T>G
NM_001276697.2:c.-75T>G
NM_001276698.2:c.-75T>G
NM_001276699.2:c.-75T>G
NM_001276760.2:c.286T>G
NM_001276761.2:c.286T>G
NM_000546.6:c.403T>G
NM_001126112.3:c.403T>G
NM_001126113.3:c.403T>G
NM_001126114.3:c.403T>G
NM_001126115.2:c.7T>G
NM_001126116.2:c.7T>G
NM_001126117.2:c.7T>G
NM_001126118.2:c.286T>G
NM_001276695.3:c.286T>G
NM_001276696.3:c.286T>G
NM_001276697.3:c.-75T>G
NM_001276698.3:c.-75T>G
NM_001276699.3:c.-75T>G
NM_001276760.3:c.286T>G
NM_001276761.3:c.286T>G

Pathogenic

Met criteria codes 5

PP3_Moderate PM1_Supporting PM2_Supporting PP4_Moderate PS3

Not Met criteria codes 12

PP1 PM5 BA1 BS2 BS1 BS4 BS3 BP4 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 2.0.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

TP53 VCEP

The NM_000546.6: c.403T>G variant in TP53 is a missense variant predicted to cause substitution of Cysteine by Glycine at amino acid 135 (p.Cys135Gly). 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, Internal lab contributors: SCV000664432.4). 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 indicating that this variant impacts protein function (PS3; PMID: 12826609, 30224644, 29979965). Computational predictor scores (BayesDel = 0.5991; 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 2 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 2.0; 7/24/2024).

Met criteria codes

PP3_Moderate	✔	Computational predictor scores (BayesDel = 0.5991; 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 2 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 is absent from gnomAD v4.1.0 (PM2_Supporting).
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, Internal lab contributors: SCV000664432.4).
PS3	✔	In vitro assays performed in yeast and/or human cell lines showed non-functional transactivation and loss of growth suppression activity indicating that this variant impacts protein function (PMID: 12826609, 30224644, 29979965) (PS3).

Not Met criteria codes

PP1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✖	5 different missense variants (c.403T>A, p.Cys135Ser;c.403T>C, p.Cys135Arg; c.404G>A, p.Cys135Tyr; c.404G>T, p.Cys135Phe; c.405C>G, p.Cys135Trp) in the same codon have been reported (ClinVar Variation ID 376561, 376559, 141762, 376562, 376560). However, the variants have not yet been curated to determine if they would be classified as pathogenic or likely pathogenic by the ClinGen TP53 VCEP's specifications (PM5 not evaluated).
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
BP4	✖	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
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	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000546.5(TP53):c.403T>G (p.Cys1…	Pathogenic	Li-Fraumeni Syndrome	2024-08-05	2.0	ClinGen TP53 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TP53 Version 2.0.0	TP53
View	NM_000546.5(TP53):c.403T>G (p.Cys1…	Likely Pathogenic	Li-Fraumeni Syndrome	2020-01-24	1.0	-	TP53

Showing 1 to 2 of 2 rows

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