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.538G>A (p.Glu180Lys)

Version: 1.1

CA10584590

245711 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 63dea6d6-388c-4d5b-a692-7a92656a24d8
Approved on: 2024/8/5
Published on: 2024/8/5

HGVS expressions

NM_000546.5:c.538G>A
NM_000546.5(TP53):c.538G>A (p.Glu180Lys)
NC_000017.11:g.7675074C>T
CM000679.2:g.7675074C>T
NC_000017.10:g.7578392C>T
CM000679.1:g.7578392C>T
NC_000017.9:g.7519117C>T
NG_017013.2:g.17477G>A
ENST00000503591.2:c.538G>A
ENST00000508793.6:c.538G>A
ENST00000509690.6:c.142G>A
ENST00000514944.6:c.259G>A
ENST00000604348.6:c.517G>A
ENST00000269305.9:c.538G>A
ENST00000269305.8:c.538G>A
ENST00000359597.8:c.538G>A
ENST00000413465.6:c.538G>A
ENST00000420246.6:c.538G>A
ENST00000445888.6:c.538G>A
ENST00000455263.6:c.538G>A
ENST00000504290.5:c.142G>A
ENST00000504937.5:c.142G>A
ENST00000505014.5:n.794G>A
ENST00000509690.5:c.142G>A
ENST00000510385.5:c.142G>A
ENST00000514944.5:c.259G>A
ENST00000574684.1:n.46G>A
ENST00000610292.4:c.421G>A
ENST00000610538.4:c.421G>A
ENST00000610623.4:c.61G>A
ENST00000615910.4:c.505G>A
ENST00000617185.4:c.538G>A
ENST00000618944.4:c.61G>A
ENST00000619186.4:c.61G>A
ENST00000619485.4:c.421G>A
ENST00000620739.4:c.421G>A
ENST00000622645.4:c.421G>A

ENST00000635293.1:c.421G>A
NM_001126112.2:c.538G>A
NM_001126113.2:c.538G>A
NM_001126114.2:c.538G>A
NM_001126115.1:c.142G>A
NM_001126116.1:c.142G>A
NM_001126117.1:c.142G>A
NM_001126118.1:c.421G>A
NM_001276695.1:c.421G>A
NM_001276696.1:c.421G>A
NM_001276697.1:c.61G>A
NM_001276698.1:c.61G>A
NM_001276699.1:c.61G>A
NM_001276760.1:c.421G>A
NM_001276761.1:c.421G>A
NM_001276695.2:c.421G>A
NM_001276696.2:c.421G>A
NM_001276697.2:c.61G>A
NM_001276698.2:c.61G>A
NM_001276699.2:c.61G>A
NM_001276760.2:c.421G>A
NM_001276761.2:c.421G>A
NM_000546.6:c.538G>A
NM_001126112.3:c.538G>A
NM_001126113.3:c.538G>A
NM_001126114.3:c.538G>A
NM_001126115.2:c.142G>A
NM_001126116.2:c.142G>A
NM_001126117.2:c.142G>A
NM_001126118.2:c.421G>A
NM_001276695.3:c.421G>A
NM_001276696.3:c.421G>A
NM_001276697.3:c.61G>A
NM_001276698.3:c.61G>A
NM_001276699.3:c.61G>A
NM_001276760.3:c.421G>A
NM_001276761.3:c.421G>A

Likely Pathogenic

Met criteria codes 4

PM2_Supporting PS4 PP3 PS3_Moderate

Not Met criteria codes 12

BP4 BA1 PS1 PS2 PP1 PP4 PM1 PM5 PM6 BS1 BS4 BS3

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.538G>A variant in TP53 is a missense variant predicted to cause substitution of glutamic acid by lysine at amino acid 180 (p.Glu180Lys). This variant has been reported in 12 unrelated families meeting Revised Chompret criteria and reported in 1 individual with a HER2+ breast cancer. Based on this evidence, this variant scores 7 total points meeting the TP53 VCEP phenotype scoring criteria of 4-7.5 points. (PS4; PMIDs: 35974385, 33178583, 25584008, 8118819; Internal lab contributors: SCV000629836.7, SCV000581143.5, SCV000292772.10). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). In vitro assays performed in yeast and/or human cell lines showed partially functional transactivation and loss of growth suppression activity indicating that this variant impacts protein function (PS3_Moderate; PMIDs: 12826609, 30224644, 29979965). Computational predictor scores (BayesDel = 0.262; Align GVGD = Class C55) are above recommended thresholds (BayesDel > 0.16 and an Align GVGD Class of > 15), evidence that correlates with impact to TP53 via protein change (PP3). In summary, this variant meets the criteria to be classified as Likely Pathogenic for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: PS4; PM2_Supporting, PS3_Moderate; PP3. (Bayesian Points: 8; VCEP specifications version 2.0; 7/24/2024)

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PS4	✔	This variant has been reported in 12 unrelated families meeting Revised Chompret criteria and reported in 1 individual with a HER2+ breast cancer. Based on this evidence, this variant scores 7 total points meeting the TP53 VCEP phenotype scoring criteria of 4-7.5 points. (PS4; PMIDs: 35974385, 33178583, 25584008, 8118819; Internal lab contributors: SCV000629836.7, SCV000581143.5, SCV000292772.10).
PP3	✔	Computational predictor scores (BayesDel = 0.262; Align GVGD = Class C55) are above recommended thresholds (BayesDel > 0.16 and an Align GVGD Class of > 15), evidence that correlates with impact to TP53 via protein change (PP3).
PS3_Moderate	✔	In vitro assays performed in yeast and/or human cell lines showed partially functional transactivation and loss of growth suppression activity indicating that this variant impacts protein function (PS3_Moderate; PMIDs: 12826609, 30224644, 29979965).

Not Met criteria codes

BP4	✖	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
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
PP1	✖	

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

PP4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1		✖	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		✖	2 different missense variants (c.540G>T, p.Glu180Asp and c.540G>C, p.Glu180Asp) in the same codon have been reported (ClinVar Variation IDs: 1521256, 1509915). 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).
PM6		✖	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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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000546.5(TP53):c.538G>A (p.Glu1…	Likely Pathogenic	Li-Fraumeni Syndrome	2024-08-05	1.1	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.538G>A (p.Glu1…	Likely Pathogenic	Li-Fraumeni Syndrome	2020-01-24	1.0	-	TP53

Showing 1 to 2 of 2 rows

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