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.488A>G (p.Tyr163Cys)

Version: 1.1

CA000240

127814 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 8a807387-daa0-4fb9-86e1-7e5ad3d1217f
Approved on: 2024/8/5
Published on: 2024/8/5

HGVS expressions

NM_000546.5(TP53):c.488A>G (p.Tyr163Cys)
NM_000546.5:c.488A>G
NC_000017.11:g.7675124T>C
CM000679.2:g.7675124T>C
NC_000017.10:g.7578442T>C
CM000679.1:g.7578442T>C
NC_000017.9:g.7519167T>C
NG_017013.2:g.17427A>G
ENST00000503591.2:c.488A>G
ENST00000508793.6:c.488A>G
ENST00000509690.6:c.92A>G
ENST00000514944.6:c.209A>G
ENST00000604348.6:c.467A>G
ENST00000269305.9:c.488A>G
ENST00000269305.8:c.488A>G
ENST00000359597.8:c.488A>G
ENST00000413465.6:c.488A>G
ENST00000420246.6:c.488A>G
ENST00000445888.6:c.488A>G
ENST00000455263.6:c.488A>G
ENST00000504290.5:c.92A>G
ENST00000504937.5:c.92A>G
ENST00000505014.5:n.744A>G
ENST00000508793.5:c.488A>G
ENST00000509690.5:c.92A>G
ENST00000510385.5:c.92A>G
ENST00000514944.5:c.209A>G
ENST00000610292.4:c.371A>G
ENST00000610538.4:c.371A>G
ENST00000610623.4:c.11A>G
ENST00000615910.4:c.455A>G
ENST00000617185.4:c.488A>G
ENST00000618944.4:c.11A>G
ENST00000619186.4:c.11A>G
ENST00000619485.4:c.371A>G
ENST00000620739.4:c.371A>G
ENST00000622645.4:c.371A>G

ENST00000635293.1:c.371A>G
NM_001126112.2:c.488A>G
NM_001126113.2:c.488A>G
NM_001126114.2:c.488A>G
NM_001126115.1:c.92A>G
NM_001126116.1:c.92A>G
NM_001126117.1:c.92A>G
NM_001126118.1:c.371A>G
NM_001276695.1:c.371A>G
NM_001276696.1:c.371A>G
NM_001276697.1:c.11A>G
NM_001276698.1:c.11A>G
NM_001276699.1:c.11A>G
NM_001276760.1:c.371A>G
NM_001276761.1:c.371A>G
NM_001276695.2:c.371A>G
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NM_001276698.2:c.11A>G
NM_001276699.2:c.11A>G
NM_001276760.2:c.371A>G
NM_001276761.2:c.371A>G
NM_000546.6:c.488A>G
NM_001126112.3:c.488A>G
NM_001126113.3:c.488A>G
NM_001126114.3:c.488A>G
NM_001126115.2:c.92A>G
NM_001126116.2:c.92A>G
NM_001126117.2:c.92A>G
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NM_001276697.3:c.11A>G
NM_001276698.3:c.11A>G
NM_001276699.3:c.11A>G
NM_001276760.3:c.371A>G
NM_001276761.3:c.371A>G

Pathogenic

Met criteria codes 7

PM1 PM2_Supporting PP3_Moderate PS4_Supporting PP4_Moderate PS2 PS3

Not Met criteria codes 8

PP1 BA1 BS2 BS1 BS4 BS3 BP4 PS1

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.488A>G variant in TP53 is a missense variant predicted to cause substitution of tyrosine by cysteine at amino acid 163 (p.Tyr163Cys). This variant has been identified as a de novo occurrence with confirmed parental relationships in 1 individual with a strongly-associated LFS-associated cancer totaling 4 phenotype points (PS2; PMID: 19556618). This variant has been reported in 2 additional unrelated families meeting Revised Chompret criteria. Based on this evidence, this variant scores 1 total point meeting the TP53 VCEP phenotype scoring criteria of 1-1.5 points. (PS4_Supporting; PMIDs 21601526, 8164043). 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 contributor: SCV000581096.5). This variant has an allele frequency of 6.196e-7 (1/1613972 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 human cell lines showed non-functional transactivation and loss of growth suppression activity indicating that this variant impacts protein function (PS3; PMIDs: 12826609, 30224644, 29979965). This variant has 54 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 (≥ 10 somatic occurrences) (PM1, PMID: 30311369). Computational predictor scores (BayesDel = 0.54; 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). 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: PS2, PS4_Supporting, PP4_Moderate, PM2_Supporting, PS3, PM1, PP3_Moderate. (Bayesian Points: 16; VCEP specifications version 2.0; 7/24/2024)

Met criteria codes

PM1	✔	This variant has 54 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 (≥ 10 somatic occurrences, PMID: 30311369).
PM2_Supporting	✔	This variant has an allele frequency of 6.196e-7 (1/1613972 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 = 0.54; 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)
PS4_Supporting	✔	This variant has been reported in 2 additional unrelated families meeting Revised Chompret criteria. Based on this evidence, this variant scores 1 total point meeting the TP53 VCEP phenotype scoring criteria of 1-1.5 points. (PS4_Supporting; PMIDs 21601526, 8164043).
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 contributor: SCV000581096.5).
PS2	✔	This variant has been identified as a de novo occurrence with confirmed parental relationships in 1 individual with a strongly-associated LFS-associated cancer totaling 4 phenotype points (PS2; PMID: 19556618).
PS3	✔	In vitro assays performed in yeast and human cell lines showed non-functional transactivation and loss of growth suppression activity indicating that this variant impacts protein function (PS3; PMIDs: 12826609, 30224644, 29979965).

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
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
PS1	✖	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.488A>G (p.Tyr1…	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.488A>G (p.Tyr1…	Pathogenic	Li-Fraumeni Syndrome	2020-01-24	1.0	-	TP53

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