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Variant: NM_000546.6(TP53):c.490A>G (p.Lys164Glu)

Version: 1.0

CA10584591

246416 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 110ba7a0-1738-4020-82f8-11fb5444da67
Approved on: 2025/6/5
Published on: 2025/7/18

HGVS expressions

NM_000546.6(TP53):c.490A>G (p.Lys164Glu)
NM_000546.6:c.490A>G
NC_000017.11:g.7675122T>C
CM000679.2:g.7675122T>C
NC_000017.10:g.7578440T>C
CM000679.1:g.7578440T>C
NC_000017.9:g.7519165T>C
NG_017013.2:g.17429A>G
ENST00000503591.2:c.490A>G
ENST00000508793.6:c.490A>G
ENST00000509690.6:c.94A>G
ENST00000514944.6:c.211A>G
ENST00000604348.6:c.469A>G
ENST00000269305.9:c.490A>G
ENST00000269305.8:c.490A>G
ENST00000359597.8:c.490A>G
ENST00000413465.6:c.490A>G
ENST00000420246.6:c.490A>G
ENST00000445888.6:c.490A>G
ENST00000455263.6:c.490A>G
ENST00000504290.5:c.94A>G
ENST00000504937.5:c.94A>G
ENST00000505014.5:n.746A>G
ENST00000508793.5:c.490A>G
ENST00000509690.5:c.94A>G
ENST00000510385.5:c.94A>G
ENST00000514944.5:c.211A>G
ENST00000610292.4:c.373A>G
ENST00000610538.4:c.373A>G
ENST00000610623.4:c.13A>G
ENST00000615910.4:c.457A>G
ENST00000617185.4:c.490A>G
ENST00000618944.4:c.13A>G
ENST00000619186.4:c.13A>G
ENST00000619485.4:c.373A>G
ENST00000620739.4:c.373A>G
ENST00000622645.4:c.373A>G

ENST00000635293.1:c.373A>G
NM_000546.5:c.490A>G
NM_001126112.2:c.490A>G
NM_001126113.2:c.490A>G
NM_001126114.2:c.490A>G
NM_001126115.1:c.94A>G
NM_001126116.1:c.94A>G
NM_001126117.1:c.94A>G
NM_001126118.1:c.373A>G
NM_001276695.1:c.373A>G
NM_001276696.1:c.373A>G
NM_001276697.1:c.13A>G
NM_001276698.1:c.13A>G
NM_001276699.1:c.13A>G
NM_001276760.1:c.373A>G
NM_001276761.1:c.373A>G
NM_001276695.2:c.373A>G
NM_001276696.2:c.373A>G
NM_001276697.2:c.13A>G
NM_001276698.2:c.13A>G
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NM_001276699.3:c.13A>G
NM_001276760.3:c.373A>G
NM_001276761.3:c.373A>G

Pathogenic

Met criteria codes 7

PS3 PP1 PP3 PP4 PM1_Supporting PS4_Moderate PM2_Supporting

Not Met criteria codes 10

PS1 PS2 PVS1 BA1 BS1 BS4 BS3 BS2 BP7 BP4

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 2.3.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

TP53 VCEP

The NM_000546.6: c.490A>G variant in TP53 is a missense variant predicted to cause substitution of lysine by glutamic acid at amino acid 164 (p.Lys164Glu). This variant has been reported in 2 unrelated families meeting Classic/Revised Chompret criteria. Based on this evidence this variant scores 2 total points meeting the TP53 VCEP phenotype scoring criteria of 2-3.5 points. (PS4_Moderate; PMIDs: 33138793, 38050059). The variant has been reported to segregate with LFS-associated cancers in 3-4 meioses in 1 family (PP1; PMID: 38050059). At least one individual with this variant was found to have a variant allele fraction of 5-35%, which is a significant predictor of variant pathogenicity (PP4, PMID: 34906512, Internal lab contributors). This variant has an allele frequency of 6.195e-7 (1/1614174 alleles) across gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00003) for PM2_Supporting and has no more than one allele per non-bottleneck subpopulation (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; PMIDs: 12826609, 30224644, 29979965). Computational predictor scores (BayesDel = 0.5572; 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). This variant has 9 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: PS4_Moderate, PP1, PM2_Supporting, PS3, PP3, PP4, PM1_Supporting. (Bayesian Points: 11; VCEP specifications version 2.3)

Met criteria codes

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 (PS3; PMIDs: 12826609, 30224644, 29979965).
PP1	✓	The variant has been reported to segregate with LFS-associated cancers in 3-4 meioses in 1 family (PP1; PMID: 38050059).
PP3	✓	Computational predictor scores (BayesDel = 0.5572; 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).
PP4	✓	At least one individual with this variant was found to have a variant allele fraction of 5-35%, which is a significant predictor of variant pathogenicity (PP4, PMID: 34906512, Internal lab contributors).
PM1_Supporting	✓	This variant has 9 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).
PS4_Moderate	✓	This variant has been reported in 2 unrelated families meeting Classic/Revised Chompret criteria. Based on this evidence this variant scores 2 total points meeting the TP53 VCEP phenotype scoring criteria of 2-3.5 points. (PS4_Moderate; PMIDs: 33138793, 38050059).
PM2_Supporting	✓	This variant has an allele frequency of 6.195e-7 (1/1614174 alleles) across gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00003) for PM2_Supporting and has no more than one allele per non-bottleneck subpopulation (PM2_Supporting).

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
PVS1	✖	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
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
BS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7	✖	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

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000546.6(TP53):c.490A>G (p.Lys1…	Pathogenic	Li-Fraumeni Syndrome	2025-07-18	1.0	ClinGen TP53 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TP53 Version 2.3.0	TP53

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