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.1060C>A (p.Gln354Lys)

Version: 2.0

CA000816

231485 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 84fd8478-98b3-4da0-a569-c3ef1e09753e
Approved on: 2024/9/6
Published on: 2024/9/6

HGVS expressions

NM_000546.5(TP53):c.1060C>A (p.Gln354Lys)
NM_000546.5:c.1060C>A
NC_000017.11:g.7670649G>T
CM000679.2:g.7670649G>T
NC_000017.10:g.7573967G>T
CM000679.1:g.7573967G>T
NC_000017.9:g.7514692G>T
NG_017013.2:g.21902C>A
ENST00000503591.2:c.1060C>A
ENST00000508793.6:c.1060C>A
ENST00000509690.6:c.664C>A
ENST00000514944.6:c.781C>A
ENST00000604348.6:c.1039C>A
ENST00000269305.9:c.1060C>A
ENST00000269305.8:c.1060C>A
ENST00000359597.8:c.993+2886C>A
ENST00000413465.6:c.782+3532C>A
ENST00000420246.6:c.*167C>A
ENST00000445888.6:c.1060C>A
ENST00000455263.6:c.*79C>A
ENST00000504290.5:c.*79C>A
ENST00000504937.5:c.664C>A
ENST00000510385.5:c.*167C>A
ENST00000576024.1:c.54-959C>A
ENST00000610292.4:c.943C>A
ENST00000610538.4:c.*79C>A
ENST00000610623.4:c.*79C>A
ENST00000615910.4:c.1027C>A
ENST00000617185.4:c.*167C>A
ENST00000618944.4:c.*167C>A
ENST00000619186.4:c.583C>A
ENST00000619485.4:c.943C>A
ENST00000620739.4:c.943C>A
ENST00000622645.4:c.*167C>A
ENST00000635293.1:c.943C>A
NM_001126112.2:c.1060C>A
NM_001126113.2:c.*79C>A

NM_001126114.2:c.*167C>A
NM_001126115.1:c.664C>A
NM_001126116.1:c.*167C>A
NM_001126117.1:c.*79C>A
NM_001126118.1:c.943C>A
NM_001276695.1:c.*79C>A
NM_001276696.1:c.*167C>A
NM_001276697.1:c.583C>A
NM_001276698.1:c.*167C>A
NM_001276699.1:c.*79C>A
NM_001276760.1:c.943C>A
NM_001276761.1:c.943C>A
NM_001276695.2:c.*79C>A
NM_001276696.2:c.*167C>A
NM_001276697.2:c.583C>A
NM_001276698.2:c.*167C>A
NM_001276699.2:c.*79C>A
NM_001276760.2:c.943C>A
NM_001276761.2:c.943C>A
NM_000546.6:c.1060C>A
NM_001126112.3:c.1060C>A
NM_001126113.3:c.*79C>A
NM_001126114.3:c.*167C>A
NM_001126115.2:c.664C>A
NM_001126116.2:c.*167C>A
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NM_001126118.2:c.943C>A
NM_001276695.3:c.*79C>A
NM_001276696.3:c.*167C>A
NM_001276697.3:c.583C>A
NM_001276698.3:c.*167C>A
NM_001276699.3:c.*79C>A
NM_001276760.3:c.943C>A
NM_001276761.3:c.943C>A

Benign

Met criteria codes 4

BS2 BS3 BP4 PM2_Supporting

Not Met criteria codes 11

BA1 BS1 BS4 PS1 PS2 PS3 PS4 PP1 PP3 PP4 PM1

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.1060C>A variant in TP53 is a missense variant predicted to cause substitution of glutamine by lysine at amino acid 354 (p.Gln354Lys). This variant has been observed in 4-7 heterozygous unrelated females from the same data source with no personal history of cancer prior to age 60 years and no personal history of sarcoma at any age (BS2_Moderate; internal lab contributors). This variant has an allele frequency of 0.00001441 (17/1179974 alleles) in the European (non-Finnish) 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 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). Computational predictor scores (BayesDel = -0.28; Align GVGD Class C0) are below the recommended thresholds (BayesDel < 0.16 and > -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). In summary, this variant meets the criteria to be classified as Benign for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: BS2_moderate, BS3, BP4_Moderate, PM2_supporting. (Bayesian Points: -7; VCEP specifications version 2.0; 9/6/2024).

Met criteria codes

BS2	✔	BS2_MODERATE This variant has been observed in 4-7 heterozygous unrelated females from the same data source with no personal history of cancer prior to age 60 years and no personal history of sarcoma at any age (BS2_Moderate; Ambry).
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 = -0.28; Align GVGD Class C0) 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).
PM2_Supporting	✔	This variant has an allele frequency of 0.00001441 (17/1179974 alleles) in the European (non-Finnish) 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).

Not Met criteria codes

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
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
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	✖	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).

Curation History

Showing 1 to 2 of 2 rows

See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000546.5(TP53):c.1060C>A (p.Gln...	Benign	Li-Fraumeni Syndrome	2024-09-06	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.1060C>A (p.Gln...	Likely Benign	Li-Fraumeni Syndrome 1	2021-09-24	1.0	-	TP53

Showing 1 to 2 of 2 rows

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