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Variant: NM_000546.5(TP53):c.1120G>C (p.Gly374Arg)

Version: 2.0

CA000677

230269 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 3cfae801-62ea-44b2-a4e9-c7993942151c
Approved on: 2024/8/5
Published on: 2024/8/5

HGVS expressions

NM_000546.5(TP53):c.1120G>C (p.Gly374Arg)
NM_000546.5:c.1120G>C
NC_000017.11:g.7669671C>G
CM000679.2:g.7669671C>G
NC_000017.10:g.7572989C>G
CM000679.1:g.7572989C>G
NC_000017.9:g.7513714C>G
NG_017013.2:g.22880G>C
ENST00000503591.2:c.1120G>C
ENST00000508793.6:c.1120G>C
ENST00000509690.6:c.724G>C
ENST00000514944.6:c.841G>C
ENST00000604348.6:c.1099G>C
ENST00000269305.9:c.1120G>C
ENST00000269305.8:c.1120G>C
ENST00000359597.8:c.994-3427G>C
ENST00000413465.6:c.782+4510G>C
ENST00000420246.6:c.*227G>C
ENST00000445888.6:c.1120G>C
ENST00000455263.6:c.*139G>C
ENST00000504290.5:c.*139G>C
ENST00000504937.5:c.724G>C
ENST00000510385.5:c.*227G>C
ENST00000576024.1:c.73G>C
ENST00000610292.4:c.1003G>C
ENST00000610538.4:c.*139G>C
ENST00000610623.4:c.*139G>C
ENST00000615910.4:c.1087G>C
ENST00000617185.4:c.*227G>C
ENST00000618944.4:c.*227G>C
ENST00000619186.4:c.643G>C
ENST00000619485.4:c.1003G>C
ENST00000620739.4:c.1003G>C
ENST00000622645.4:c.*227G>C
ENST00000635293.1:c.983+938G>C
NM_001126112.2:c.1120G>C
NM_001126113.2:c.*139G>C

NM_001126114.2:c.*227G>C
NM_001126115.1:c.724G>C
NM_001126116.1:c.*227G>C
NM_001126117.1:c.*139G>C
NM_001126118.1:c.1003G>C
NM_001276695.1:c.*139G>C
NM_001276696.1:c.*227G>C
NM_001276697.1:c.643G>C
NM_001276698.1:c.*227G>C
NM_001276699.1:c.*139G>C
NM_001276760.1:c.1003G>C
NM_001276761.1:c.1003G>C
NM_001276695.2:c.*139G>C
NM_001276696.2:c.*227G>C
NM_001276697.2:c.643G>C
NM_001276698.2:c.*227G>C
NM_001276699.2:c.*139G>C
NM_001276760.2:c.1003G>C
NM_001276761.2:c.1003G>C
NM_000546.6:c.1120G>C
NM_001126112.3:c.1120G>C
NM_001126113.3:c.*139G>C
NM_001126114.3:c.*227G>C
NM_001126115.2:c.724G>C
NM_001126116.2:c.*227G>C
NM_001126117.2:c.*139G>C
NM_001126118.2:c.1003G>C
NM_001276695.3:c.*139G>C
NM_001276696.3:c.*227G>C
NM_001276697.3:c.643G>C
NM_001276698.3:c.*227G>C
NM_001276699.3:c.*139G>C
NM_001276760.3:c.1003G>C
NM_001276761.3:c.1003G>C

Benign

Met criteria codes 3

BP4 BS2 BS3

Not Met criteria codes 15

PS1 PS2 PS3 PS4 PM1
PM5 PM2 BA1 PVS1 BP7
BS1 BS4 PP1 PP3 PP4

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.1120G>C variant in TP53 is a missense variant predicted to cause substitution of Glycine by Arginine at amino acid 374 (p.Gly374Arg). This variant has been observed in at least 8 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, Internal lab contributors: SCV000273745.6). 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 (PMIDs: 12826609, 29979965, 30224644) (BS3). Computational predictor scores (BayesDel = -0.0546; Align GVGD Class 0) 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). 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, BS3, BP4_moderate. (Bayesian Points: -10; VCEP specifications version 2.0; 7/24/2024)

Met criteria codes

BP4	✔	BP4_MODERATE Computational predictor scores (BayesDel = -0.0546; Align GVGD Class 0) 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).
BS2	✔	This variant has been observed in at least 8 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, Internal lab contributors: SCV000273745.6).
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 (PMIDs: 12826609, 29979965, 30224644) (BS3)

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
PS3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4	✖	This variant received a total of 0 points across 73 unrelated probands. However, PS4 cannot be applied because current literature and internal lab data do not include cases meeting either LFS classic or Chompret criteria. Variant was also not found in women with breast cancer HER2+ diagnosed before 40 years old. (PS4 not met).
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	✖	3 different missense variants (c.1121G>T, p.Gly347Val ; c.1120G>T, p.Gly347Cys, and c.1120G>A, p.Gly374Ser) in the same codon have been reported (ClinVar Variation IDs: 1797938, 665996, 141583). 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).

PM2		✖	The highest population minor allele frequency in gnomAD v41.0 is 0.00006680 (5/74852 alleles) in the African/African American population (PM2, BS1, and BA1 are not met).
BA1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4	ℹ	✖	This variant has been reported not to segregate with phenotype (BS4; Internal lab contributors).
PP1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4	ℹ	✖	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.1120G>C (p.Gly…	Benign	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.1120G>C (p.Gly…	Likely Benign	Li-Fraumeni Syndrome	2020-01-24	1.0	-	TP53

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