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Variant: NM_000546.6(TP53):c.1025G>C (p.Arg342Pro)

Version: 1.0

CA337802

215996 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 6596a2a8-f9bc-4bad-b9fb-403dfe19364d
Approved on: 2024/9/6
Published on: 2024/9/6

HGVS expressions

NM_000546.6:c.1025G>C
NM_000546.6(TP53):c.1025G>C (p.Arg342Pro)
NC_000017.11:g.7670684C>G
CM000679.2:g.7670684C>G
NC_000017.10:g.7574002C>G
CM000679.1:g.7574002C>G
NC_000017.9:g.7514727C>G
NG_017013.2:g.21867G>C
ENST00000503591.2:c.1025G>C
ENST00000508793.6:c.1025G>C
ENST00000509690.6:c.629G>C
ENST00000514944.6:c.746G>C
ENST00000604348.6:c.1004G>C
ENST00000269305.9:c.1025G>C
ENST00000269305.8:c.1025G>C
ENST00000359597.8:c.993+2851G>C
ENST00000413465.6:c.782+3497G>C
ENST00000420246.6:c.*132G>C
ENST00000445888.6:c.1025G>C
ENST00000455263.6:c.*44G>C
ENST00000504290.5:c.*44G>C
ENST00000504937.5:c.629G>C
ENST00000510385.5:c.*132G>C
ENST00000576024.1:c.54-994G>C
ENST00000610292.4:c.908G>C
ENST00000610538.4:c.*44G>C
ENST00000610623.4:c.*44G>C
ENST00000615910.4:c.992G>C
ENST00000617185.4:c.*132G>C
ENST00000618944.4:c.*132G>C
ENST00000619186.4:c.548G>C
ENST00000619485.4:c.908G>C
ENST00000620739.4:c.908G>C
ENST00000622645.4:c.*132G>C
ENST00000635293.1:c.908G>C
NM_000546.5:c.1025G>C
NM_001126112.2:c.1025G>C

NM_001126113.2:c.*44G>C
NM_001126114.2:c.*132G>C
NM_001126115.1:c.629G>C
NM_001126116.1:c.*132G>C
NM_001126117.1:c.*44G>C
NM_001126118.1:c.908G>C
NM_001276695.1:c.*44G>C
NM_001276696.1:c.*132G>C
NM_001276697.1:c.548G>C
NM_001276698.1:c.*132G>C
NM_001276699.1:c.*44G>C
NM_001276760.1:c.908G>C
NM_001276761.1:c.908G>C
NM_001276695.2:c.*44G>C
NM_001276696.2:c.*132G>C
NM_001276697.2:c.548G>C
NM_001276698.2:c.*132G>C
NM_001276699.2:c.*44G>C
NM_001276760.2:c.908G>C
NM_001276761.2:c.908G>C
NM_001126112.3:c.1025G>C
NM_001126113.3:c.*44G>C
NM_001126114.3:c.*132G>C
NM_001126115.2:c.629G>C
NM_001126116.2:c.*132G>C
NM_001126117.2:c.*44G>C
NM_001126118.2:c.908G>C
NM_001276695.3:c.*44G>C
NM_001276696.3:c.*132G>C
NM_001276697.3:c.548G>C
NM_001276698.3:c.*132G>C
NM_001276699.3:c.*44G>C
NM_001276760.3:c.908G>C
NM_001276761.3:c.908G>C

Pathogenic

Met criteria codes 6

PM1_Supporting PP1_Strong PS4_Moderate PM2_Supporting PS3 PP3

Not Met criteria codes 12

BA1 BS2 BS1 BS4 BS3 BP4 PVS1 PS1 PS2 PP4 PM5 PM4

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.1025G>C variant in TP53 is a missense variant predicted to cause substitution of arginine by proline at amino acid 342 (p.Arg342Pro). This variant has been reported in 3 unrelated families meeting Classic criteria. Based on this evidence, this variant scores 3 total points meeting the TP53 VCEP phenotype scoring criteria of 2-3.5 points. (PS4_Moderate; PMIDs 25981898, 25226867, 19714490). The variant has been reported to segregate with LFS-associated cancers in ≥ 7 meioses from 3 families (PP1_Strong; PMIDs 25981898, 25226867, 19714490). In vitro assays performed in yeast and/or human cell lines showed non-functional transactivation, loss of growth suppression activity, and impaired tetramer formation indicating that this variant impacts protein function (PS3; PMIDs: 12826609, 30224644, 16007150). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). Computational predictor scores (BayesDel = 0.24; Align GVGD = Class C35) 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 8 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_Strong, PS3, PM2_Supporting, PP3, PM1_Supporting. (Bayesian Points: 13; VCEP specifications version 2.0; 9/6/2024)

Met criteria codes

PM1_Supporting	✔	This variant has 8 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).
PP1_Strong	✔	The variant has been reported to segregate with LFS-associated cancers in ≥ 7 meioses from 3 families (PP1_Strong; PMIDs 25981898, 25226867, 19714490).
PS4_Moderate	✔	This variant has been reported in 3 unrelated families meeting Classic criteria. Based on this evidence, this variant scores 3 total points meeting the TP53 VCEP phenotype scoring criteria of 2-3.5 points. (PS4_Moderate; PMIDs 25981898, 25226867, 19714490).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PS3	✔	In vitro assays performed in yeast and/or human cell lines showed non-functional transactivation, loss of growth suppression activity, and impaired tetramer formation indicating that this variant impacts protein function (PS3; PMIDs: 12826609, 30224644, 16007150).
PP3	✔	Computational predictor scores (BayesDel = 0.24; Align GVGD = Class C35) 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).

Not Met criteria codes

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	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4	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
PS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2	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
PM5	ℹ	✖	3 different missense variants (p.Arg342Leu, p.Arg342Gln, p.Arg342Gly) in the same codon have been reported (ClinVar Variation IDs: 1055894, 233136, 1769035). 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).
PM4		✖	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.1025G>C (p.Arg…	Pathogenic	Li-Fraumeni Syndrome	2024-09-06	1.0	ClinGen TP53 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TP53 Version 2.0.0	TP53

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