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Variant: NM_000546.6(TP53):c.1015G>C (p.Glu339Gln)

Version: 1.0

CA000018

141893 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 45b695a1-6c52-483f-96cd-093976098264
Approved on: 2024/9/6
Published on: 2024/9/6

HGVS expressions

NM_000546.6(TP53):c.1015G>C (p.Glu339Gln)
NM_000546.6:c.1015G>C
NC_000017.11:g.7670694C>G
CM000679.2:g.7670694C>G
NC_000017.10:g.7574012C>G
CM000679.1:g.7574012C>G
NC_000017.9:g.7514737C>G
NG_017013.2:g.21857G>C
ENST00000503591.2:c.1015G>C
ENST00000508793.6:c.1015G>C
ENST00000509690.6:c.619G>C
ENST00000514944.6:c.736G>C
ENST00000604348.6:c.994G>C
ENST00000269305.9:c.1015G>C
ENST00000269305.8:c.1015G>C
ENST00000359597.8:c.993+2841G>C
ENST00000413465.6:c.782+3487G>C
ENST00000420246.6:c.*122G>C
ENST00000445888.6:c.1015G>C
ENST00000455263.6:c.*34G>C
ENST00000504290.5:c.*34G>C
ENST00000504937.5:c.619G>C
ENST00000510385.5:c.*122G>C
ENST00000576024.1:c.54-1004G>C
ENST00000610292.4:c.898G>C
ENST00000610538.4:c.*34G>C
ENST00000610623.4:c.*34G>C
ENST00000615910.4:c.982G>C
ENST00000617185.4:c.*122G>C
ENST00000618944.4:c.*122G>C
ENST00000619186.4:c.538G>C
ENST00000619485.4:c.898G>C
ENST00000620739.4:c.898G>C
ENST00000622645.4:c.*122G>C
ENST00000635293.1:c.898G>C
NM_000546.5:c.1015G>C
NM_001126112.2:c.1015G>C

NM_001126113.2:c.*34G>C
NM_001126114.2:c.*122G>C
NM_001126115.1:c.619G>C
NM_001126116.1:c.*122G>C
NM_001126117.1:c.*34G>C
NM_001126118.1:c.898G>C
NM_001276695.1:c.*34G>C
NM_001276696.1:c.*122G>C
NM_001276697.1:c.538G>C
NM_001276698.1:c.*122G>C
NM_001276699.1:c.*34G>C
NM_001276760.1:c.898G>C
NM_001276761.1:c.898G>C
NM_001276695.2:c.*34G>C
NM_001276696.2:c.*122G>C
NM_001276697.2:c.538G>C
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NM_001276760.2:c.898G>C
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NM_001126113.3:c.*34G>C
NM_001126114.3:c.*122G>C
NM_001126115.2:c.619G>C
NM_001126116.2:c.*122G>C
NM_001126117.2:c.*34G>C
NM_001126118.2:c.898G>C
NM_001276695.3:c.*34G>C
NM_001276696.3:c.*122G>C
NM_001276697.3:c.538G>C
NM_001276698.3:c.*122G>C
NM_001276699.3:c.*34G>C
NM_001276760.3:c.898G>C
NM_001276761.3:c.898G>C

Likely Benign

Met criteria codes 4

PS4_Supporting BS2_Supporting BS3 BP4

Not Met criteria codes 11

PP1 PP3 PP4 PM2 BA1 PM1 BS1 BS4 PS1 PS2 PS3

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.1015G>C variant in TP53 is a missense variant predicted to cause substitution of glutamic acid by glutamine at amino acid 339 (p.Glu339Gln). 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). This variant has been observed in 2 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_Supporting; Ambry lab). This variant has a BayesDel score < 0.16 and Align GVGD (Zebrafish) is Class C0 (BP4). In summary, this variant meets the criteria to be classified as likely benign for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: BS2_supporting, BS3, BP4. (Bayesian Points: -6; VCEP specifications version 2.0; 9/6/2024).

Met criteria codes

PS4_Supporting	✔	This variant has been reported in 2 unrelated probands 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; PMID: 28573494; Internal lab contributor: Laboratoire de Génétique Moléculaire du CHU de Rouen). This code is not applied as variant does not meet PM2_Supporting
BS2_Supporting	✔	This variant has been observed in 2 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_Supporting; Ambry lab).
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	✔	Computational predictor scores (BayesDel = 0.0408311; 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).

Not Met criteria codes

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
PM2	✖	The highest population minor allele frequency in gnomAD v4.1.0 is 0.00004393 (4/91058 alleles) in the South Asian population (PM2, BS1, and BA1 are not met).
BA1	✖	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).

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

Curation History

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