Variant: NM_000546.6(TP53):c.318C>G (p.Ser106Arg)

Version: 1.0

CA397844688

492752 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 609e5cb1-d182-4f30-aff2-e2d2430efe55
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HGVS expressions

NM_000546.6:c.318C>G
NM_000546.6(TP53):c.318C>G (p.Ser106Arg)
NC_000017.11:g.7676051G>C
CM000679.2:g.7676051G>C
NC_000017.10:g.7579369G>C
CM000679.1:g.7579369G>C
NC_000017.9:g.7520094G>C
NG_017013.2:g.16500C>G
ENST00000503591.2:c.318C>G
ENST00000508793.6:c.318C>G
ENST00000509690.6:c.-21-815C>G
ENST00000514944.6:c.96+331C>G
ENST00000604348.6:c.318C>G
ENST00000269305.9:c.318C>G
ENST00000269305.8:c.318C>G
ENST00000359597.8:c.318C>G
ENST00000413465.6:c.318C>G
ENST00000420246.6:c.318C>G
ENST00000445888.6:c.318C>G
ENST00000455263.6:c.318C>G
ENST00000503591.1:c.318C>G
ENST00000505014.5:n.574C>G
ENST00000508793.5:c.318C>G
ENST00000509690.5:c.-21-815C>G
ENST00000514944.5:c.96+331C>G
ENST00000604348.5:c.318C>G
ENST00000610292.4:c.201C>G
ENST00000610538.4:c.201C>G
ENST00000615910.4:c.318C>G
ENST00000617185.4:c.318C>G
ENST00000619485.4:c.201C>G
ENST00000620739.4:c.201C>G
ENST00000622645.4:c.201C>G
ENST00000635293.1:c.201C>G
NM_000546.5:c.318C>G
NM_001126112.2:c.318C>G
NM_001126113.2:c.318C>G

NM_001126114.2:c.318C>G
NM_001126118.1:c.201C>G
NM_001276695.1:c.201C>G
NM_001276696.1:c.201C>G
NM_001276760.1:c.201C>G
NM_001276761.1:c.201C>G
NM_001276695.2:c.201C>G
NM_001276696.2:c.201C>G
NM_001276760.2:c.201C>G
NM_001276761.2:c.201C>G
NM_001126112.3:c.318C>G
NM_001126113.3:c.318C>G
NM_001126114.3:c.318C>G
NM_001126118.2:c.201C>G
NM_001276695.3:c.201C>G
NM_001276696.3:c.201C>G
NM_001276760.3:c.201C>G
NM_001276761.3:c.201C>G

Pathogenic

Met criteria codes 4

PP4 PS4_Supporting PM2_Supporting PVS1

Not Met criteria codes 8

PP3 PM1 PM5 PS3 BA1 BP4 BS1 BS3

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.318C>G variant in TP53 is a missense variant predicted to cause substitution of serine by arginine at amino acid 106 (p.Ser106Arg). Splicing assay data provides experimental evidence that this variant results in RNA transcript(s) with loss of function (PVS1 (RNA); PMID: 39780207). This variant has been reported in 3 unrelated probands meeting Revised Chompret criteria. Based on this evidence, this variant scores 1.5 total points meeting the TP53 VCEP phenotype scoring criteria of 1-1.5 points (PS4_supporting; PMID: 11518751, Internal lab contributors). 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 contributor). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). In summary, this variant is classified as Pathogenic for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: PVS1 (RNA), PS4_Supporting, PP4, PM2_Supporting (Bayesian Points: 11; VCEP specifications version 2.3).

Met criteria codes

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 contributor).

PS4_Supporting	✔	This variant has been reported in 3 unrelated probands meeting Revised Chompret criteria. Based on this evidence, this variant scores 1.5 total points meeting the TP53 VCEP phenotype scoring criteria of 1-1.5 points (PS4_supporting; PMID: 11518751, Internal lab contributors).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PVS1	✔	Splicing assay data provides experimental evidence that this variant results in RNA transcript(s) with loss of function (PVS1 (RNA); PMID: 39780207).

Not Met criteria codes

PP3	✖	Code not applied as PVS1 is applied. The computational splicing predictor SpliceAI gives a score of 0.85, predicting that the variant has an impact on splicing (score threshold > 0.20) (PP3).
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	✖	Another missense variant (c.317G>T, p.Ser106Ile) in the same codon has been reported (ClinVar Variation ID: 629791). However, this variant does not meet criteria for PM5 code application (PM5 not met).
PS3	✖	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
BP4	✖	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
BS3	✖	In vitro assays performed in yeast and/or human cell lines showed partially functional transactivation, and retained growth suppression activity by all available assays indicating that this variant does not impact protein function (BS3_Supporting; PMIDs: 12826609, 29979965, 30224644, 39774325, 16007150).

Curation History

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