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Variant: NM_000546.6(TP53):c.559+5G>A

Version: 1.0

CA645588866

490175 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: bdd477f7-d608-49a9-b461-7036f0a2efe6
Approved on: 2026/1/6
Published on: 2026/1/14

HGVS expressions

NM_000546.6(TP53):c.559+5G>A
NM_000546.6:c.559+5G>A
NC_000017.11:g.7675048C>T
CM000679.2:g.7675048C>T
NC_000017.10:g.7578366C>T
CM000679.1:g.7578366C>T
NC_000017.9:g.7519091C>T
NG_017013.2:g.17503G>A
ENST00000503591.2:c.559+5G>A
ENST00000508793.6:c.559+5G>A
ENST00000509690.6:c.163+5G>A
ENST00000514944.6:c.280+5G>A
ENST00000604348.6:c.538+5G>A
ENST00000269305.9:c.559+5G>A
ENST00000269305.8:c.559+5G>A
ENST00000359597.8:c.559+5G>A
ENST00000413465.6:c.559+5G>A
ENST00000420246.6:c.559+5G>A
ENST00000445888.6:c.559+5G>A
ENST00000455263.6:c.559+5G>A
ENST00000504290.5:c.163+5G>A
ENST00000504937.5:c.163+5G>A
ENST00000505014.5:n.815+5G>A
ENST00000509690.5:c.163+5G>A
ENST00000510385.5:c.163+5G>A
ENST00000514944.5:c.280+5G>A
ENST00000574684.1:n.67+5G>A
ENST00000610292.4:c.442+5G>A
ENST00000610538.4:c.442+5G>A
ENST00000610623.4:c.82+5G>A
ENST00000615910.4:c.526+5G>A
ENST00000617185.4:c.559+5G>A
ENST00000618944.4:c.82+5G>A
ENST00000619186.4:c.82+5G>A
ENST00000619485.4:c.442+5G>A
ENST00000620739.4:c.442+5G>A
ENST00000622645.4:c.442+5G>A

ENST00000635293.1:c.442+5G>A
NM_000546.5:c.559+5G>A
NM_001126112.2:c.559+5G>A
NM_001126113.2:c.559+5G>A
NM_001126114.2:c.559+5G>A
NM_001126115.1:c.163+5G>A
NM_001126116.1:c.163+5G>A
NM_001126117.1:c.163+5G>A
NM_001126118.1:c.442+5G>A
NM_001276695.1:c.442+5G>A
NM_001276696.1:c.442+5G>A
NM_001276697.1:c.82+5G>A
NM_001276698.1:c.82+5G>A
NM_001276699.1:c.82+5G>A
NM_001276760.1:c.442+5G>A
NM_001276761.1:c.442+5G>A
NM_001276695.2:c.442+5G>A
NM_001276696.2:c.442+5G>A
NM_001276697.2:c.82+5G>A
NM_001276698.2:c.82+5G>A
NM_001276699.2:c.82+5G>A
NM_001276760.2:c.442+5G>A
NM_001276761.2:c.442+5G>A
NM_001126112.3:c.559+5G>A
NM_001126113.3:c.559+5G>A
NM_001126114.3:c.559+5G>A
NM_001126115.2:c.163+5G>A
NM_001126116.2:c.163+5G>A
NM_001126117.2:c.163+5G>A
NM_001126118.2:c.442+5G>A
NM_001276695.3:c.442+5G>A
NM_001276696.3:c.442+5G>A
NM_001276697.3:c.82+5G>A
NM_001276698.3:c.82+5G>A
NM_001276699.3:c.82+5G>A
NM_001276760.3:c.442+5G>A
NM_001276761.3:c.442+5G>A

Uncertain Significance

Met criteria codes 3

PM2_Supporting PP4 PVS1_Moderate

Not Met criteria codes 13

BA1 BS2 BS1 BS4 BS3 BP7 BP4 PS2 PS3 PS4 PP1 PP3 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 2.4.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

TP53 VCEP

The NM_000546.6:c.559+5G>A variant in TP53 is an intronic variant which is located in intron 5/10. Splicing assay data provides some experimental evidence that this variant may result in RNA transcript(s) with loss of function, however leakiness and intron retention cannot be ruled out (PVS1_Moderate (RNA); Internal lab contributor). This variant received a total of 0.5 points across 1 proband (PS4 not met; PMIDs, ClinVar SCVs, 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 contributors). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). In summary, this variant meets the criteria to be classified as variant of uncertain clinical significance for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: PVS1_Moderate, PP4, PM2_Supporting. (Bayesian Points: 4; VCEP specifications version 2.4)

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
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 contributors).
PVS1_Moderate	✔	Splicing assay data provides experimental evidence that this variant results in RNA transcript(s) with loss of function (PVS1_Moderate (RNA); Internal lab contributor). Internal lab provider has performed RNA studies but observed leakiness with intro retention. Due to lack of definitive internal data PVS1 conservatively downgraded two strengths from Very Stong to Moderate.

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	✖	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
BS3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7	✖	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
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 0.5 points across 1 proband (PS4 not met; PMIDs, ClinVar SCVs, Internal lab contributors).
PP1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	✖	Met but cannot be applied in combination with PVS1 The computational splicing predictor SpliceAI gives a score of 0.22 acceptor loss, 0.21 donor loss, and 0.56 donor gain, predicting that the variant has an impact on splicing (score threshold > 0.20) (PP3).
PM1	✖	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.559+5G>A	Uncertain Significance	Li-Fraumeni Syndrome	2026-01-14	1.0	ClinGen TP53 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TP53 Version 2.4.0	TP53

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