The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_001276761.1:c.802+1G>A

Version: 2.0

CA397836247

633606 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: e5597807-7124-425a-b33a-5c6af85c5edc
Approved on: 2024/8/5
Published on: 2024/8/5

HGVS expressions

NM_001276761.1:c.802+1G>A
NC_000017.11:g.7673700C>T
CM000679.2:g.7673700C>T
NC_000017.10:g.7577018C>T
CM000679.1:g.7577018C>T
NC_000017.9:g.7517743C>T
NG_017013.2:g.18851G>A
ENST00000503591.2:c.919+1G>A
ENST00000508793.6:c.919+1G>A
ENST00000509690.6:c.523+1G>A
ENST00000514944.6:c.640+1G>A
ENST00000604348.6:c.898+1G>A
ENST00000269305.9:c.919+1G>A
ENST00000269305.8:c.919+1G>A
ENST00000359597.8:c.919+1G>A
ENST00000413465.6:c.782+481G>A
ENST00000420246.6:c.919+1G>A
ENST00000445888.6:c.919+1G>A
ENST00000455263.6:c.919+1G>A
ENST00000504290.5:c.523+1G>A
ENST00000504937.5:c.523+1G>A
ENST00000509690.5:c.523+1G>A
ENST00000510385.5:c.523+1G>A
ENST00000610292.4:c.802+1G>A
ENST00000610538.4:c.802+1G>A
ENST00000610623.4:c.442+1G>A
ENST00000615910.4:c.886+1G>A
ENST00000617185.4:c.919+1G>A
ENST00000618944.4:c.442+1G>A
ENST00000619186.4:c.442+1G>A
ENST00000619485.4:c.802+1G>A
ENST00000620739.4:c.802+1G>A
ENST00000622645.4:c.802+1G>A
ENST00000635293.1:c.802+1G>A
NM_000546.5:c.919+1G>A
NM_001126112.2:c.919+1G>A
NM_001126113.2:c.919+1G>A

NM_001126114.2:c.919+1G>A
NM_001126115.1:c.523+1G>A
NM_001126116.1:c.523+1G>A
NM_001126117.1:c.523+1G>A
NM_001126118.1:c.802+1G>A
NM_001276695.1:c.802+1G>A
NM_001276696.1:c.802+1G>A
NM_001276697.1:c.442+1G>A
NM_001276698.1:c.442+1G>A
NM_001276699.1:c.442+1G>A
NM_001276760.1:c.802+1G>A
NM_001276695.2:c.802+1G>A
NM_001276696.2:c.802+1G>A
NM_001276697.2:c.442+1G>A
NM_001276698.2:c.442+1G>A
NM_001276699.2:c.442+1G>A
NM_001276760.2:c.802+1G>A
NM_001276761.2:c.802+1G>A
NM_000546.6:c.919+1G>A
NM_001126112.3:c.919+1G>A
NM_001126113.3:c.919+1G>A
NM_001126114.3:c.919+1G>A
NM_001126115.2:c.523+1G>A
NM_001126116.2:c.523+1G>A
NM_001126117.2:c.523+1G>A
NM_001126118.2:c.802+1G>A
NM_001276695.3:c.802+1G>A
NM_001276696.3:c.802+1G>A
NM_001276697.3:c.442+1G>A
NM_001276698.3:c.442+1G>A
NM_001276699.3:c.442+1G>A
NM_001276760.3:c.802+1G>A
NM_001276761.3:c.802+1G>A

Pathogenic

Met criteria codes 4

PVS1 PP4_Moderate PM2_Supporting PS4_Moderate

Not Met criteria codes 15

PM1 PM4 BA1 BS2 BS1 BS4 BS3 BP5 BP7 BP4 BP3 PS2 PS3 PP1 PP3

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.919+1G>A is a TP53 variant within the canonical donor site of exon 8. This change is observed to produce aberrant transcripts encoding premature truncations predicted to induce nonsense-mediated decay. (PVS1 (RNA); PMID: 17066464, 31092812). This variant has been reported in 1 proband meeting Classic criteria and 3 unrelated probands meeting Revised Chompret criteria. Based on this evidence, this variant scores 2.5 total points meeting the TP53 VCEP phenotype scoring criteria of 2-3.5 points (PS4_Moderate; PMIDs: 29324801, 31081129, 20805372, ClinVar SCV001382474). At least two individuals with this variant were found to have a variant allele fraction of 5-25%, which is a significant predictor of variant pathogenicity (PP4_Moderate, ClinVar SCV001382474). This variant is absent from gnomAD v3.1.2 (non-cancer) and gnomAD v2.1.1 (non-cancer) (PM2_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: PVS1, PP4_Moderate, PS4_Moderate, PM2_Supporting. (Bayesian Points: 13; VCEP specifications version 2.0; 7/24/2024).

Met criteria codes

PVS1	✔	The NM_000546.6: c.919+1G>A is a TP53 variant within the canonical donor site of exon 8. This change is observed to produce aberrant transcripts encoding premature truncations predicted to induce nonsense-mediated decay. (PVS1 (RNA); PMID: 17066464, 31092812)
PP4_Moderate	✔	At least two individuals with this variant were found to have a variant allele fraction of 5-25%, which is a significant predictor of variant pathogenicity (PP4_Moderate, ClinVar SCV001382474).
PM2_Supporting	✔	This variant has an allele frequency of 0.000001239 (2/1614120 alleles) across gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00003) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting).
PS4_Moderate	✔	This variant has been reported in 1 proband meeting Classic criteria and 3 unrelated probands meeting Revised Chompret criteria. Based on this evidence, this variant scores 2.5 total points meeting the TP53 VCEP phenotype scoring criteria of 2-3.5 points (PS4_Moderate; PMIDs: 33758026, 31081129, 20805372, ClinVar SCV001382474).

Not Met criteria codes

PM1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4	✖	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
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
BP5		✖	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
BP3		✖	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
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

Curation History

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