

Variant: NM_000546.6(TP53):c.21T>A (p.Asp7Glu)

Version: 1.1

CA000076 [↗](#)

140782 (ClinVar) [↗](#)

Gene: TP53 ([HGNC:7157](#))
Condition: Li-Fraumeni syndrome ([MONDO:0018875](#))
Inheritance Mode: Autosomal dominant inheritance
UUID: 8af93002-92ef-4bc7-a260-86d8e8baf34f
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HGVS expressions

NM_000546.6(TP53):c.21T>A (p.Asp7Glu)
NM_000546.6:c.21T>A
NC_000017.11:g.7676574A>T
CM000679.2:g.7676574A>T
NC_000017.10:g.7579892A>T
CM000679.1:g.7579892A>T
NC_000017.9:g.7520617A>T
NG_017013.2:g.15977T>A
ENST00000503591.2:c.21T>A
ENST00000508793.6:c.21T>A
ENST00000509690.6:c.-21-1338T>A
ENST00000514944.6:c.21T>A
ENST00000604348.6:c.21T>A
ENST00000269305.9:c.21T>A
ENST00000269305.8:c.21T>A
ENST00000359597.8:c.21T>A
ENST00000413465.6:c.21T>A
ENST00000420246.6:c.21T>A
ENST00000445888.6:c.21T>A
ENST00000455263.6:c.21T>A
ENST00000503591.1:c.21T>A
ENST00000505014.5:n.160T>A
ENST00000508793.5:c.21T>A
ENST00000509690.5:c.-21-1338T>A
ENST00000514944.5:c.21T>A
ENST00000604348.5:c.21T>A
ENST00000610292.4:c.-214T>A
ENST00000610538.4:c.-97T>A
ENST00000615910.4:c.21T>A
ENST00000617185.4:c.21T>A
ENST00000619485.4:c.-97T>A
ENST00000620739.4:c.-97T>A
ENST00000622645.4:c.-97T>A
ENST00000635293.1:c.-97T>A
NM_000546.5:c.21T>A
NM_001126112.2:c.21T>A
NM_001126113.2:c.21T>A

NM_001126114.2:c.21T>A
NM_001126118.1:c.-214T>A
NM_001276695.1:c.-97T>A
NM_001276696.1:c.-97T>A
NM_001276760.1:c.-97T>A
NM_001276761.1:c.-97T>A
NM_001276695.2:c.-97T>A
NM_001276696.2:c.-97T>A
NM_001276760.2:c.-97T>A
NM_001276761.2:c.-97T>A
NM_001126112.3:c.21T>A
NM_001126113.3:c.21T>A
NM_001126114.3:c.21T>A
NM_001126118.2:c.-214T>A
NM_001276695.3:c.-97T>A
NM_001276696.3:c.-97T>A
NM_001276760.3:c.-97T>A
NM_001276761.3:c.-97T>A

Likely Benign

Met criteria codes 3

BS3 BP4 PM2_Supporting

Not Met criteria codes 13

BS1 BS4 BS2 PS1 PS2 PS3
PS4 BA1 PP1 PP3 PP4
PM1 PM5

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.21T>A variant in TP53 is a missense variant predicted to cause substitution of Aspartic acid by Glutamic acid at amino acid 7 (p.Asp7Glu). 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). Computational predictor scores (BayesDel = -0.0153; Align GVGD Class C0 are below the recommended thresholds (BayesDel ≤ -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_moderate). This variant has an allele frequency of 0.000001859 (3/1613882 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). 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: BS3, BP4_moderate, PM2_Supporting (Bayesian Points: -5; VCEP specifications version 2.0; 7/24/2024).

Met criteria codes

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			BP4_MODERATE Computational predictor scores (BayesDel = -0.0153; Align GVGD Class C0) are below the recommended thresholds (BayesDel ≤ -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_Moderate).
PM2_Supporting			This variant has an allele frequency of 0.000001859 (3/1613882 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).

Not Met criteria codes

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
BS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1			The same amino acid change, resulting from a different nucleotide change c.21T>G (ClinVar Variation ID 485049), has been reported. However, the variant has not yet been curated to determine if it would be classified as pathogenic or likely pathogenic by the ClinGen TP53 VCEP’s specifications (PS1 not evaluated).
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			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
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
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			2 different missense variants with equal or lesser impact (c.19G>A; p.Asp7Asn and c.19G>C; p.Asp7His) in the same codon have been reported (ClinVar Variation ID 1784158 and 142689). 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).

Curation History 	
    	
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