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Variant: NM_000546.6(TP53):c.761T>A (p.Ile254Asn)

Version: 1.0

CA397837760

856299 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: fa49eea4-1941-461d-b4ed-44fa217fb4cc
Approved on: 2025/12/5
Published on: 2025/12/5

HGVS expressions

NM_000546.6(TP53):c.761T>A (p.Ile254Asn)
NM_000546.6:c.761T>A
NC_000017.11:g.7674202A>T
CM000679.2:g.7674202A>T
NC_000017.10:g.7577520A>T
CM000679.1:g.7577520A>T
NC_000017.9:g.7518245A>T
NG_017013.2:g.18349T>A
ENST00000503591.2:c.761T>A
ENST00000508793.6:c.761T>A
ENST00000509690.6:c.365T>A
ENST00000514944.6:c.482T>A
ENST00000604348.6:c.740T>A
ENST00000269305.9:c.761T>A
ENST00000269305.8:c.761T>A
ENST00000359597.8:c.761T>A
ENST00000413465.6:c.761T>A
ENST00000420246.6:c.761T>A
ENST00000445888.6:c.761T>A
ENST00000455263.6:c.761T>A
ENST00000504290.5:c.365T>A
ENST00000504937.5:c.365T>A
ENST00000509690.5:c.365T>A
ENST00000510385.5:c.365T>A
ENST00000610292.4:c.644T>A
ENST00000610538.4:c.644T>A
ENST00000610623.4:c.284T>A
ENST00000615910.4:c.728T>A
ENST00000617185.4:c.761T>A
ENST00000618944.4:c.284T>A
ENST00000619186.4:c.284T>A
ENST00000619485.4:c.644T>A
ENST00000620739.4:c.644T>A
ENST00000622645.4:c.644T>A
ENST00000635293.1:c.644T>A
NM_000546.5:c.761T>A
NM_001126112.2:c.761T>A

NM_001126113.2:c.761T>A
NM_001126114.2:c.761T>A
NM_001126115.1:c.365T>A
NM_001126116.1:c.365T>A
NM_001126117.1:c.365T>A
NM_001126118.1:c.644T>A
NM_001276695.1:c.644T>A
NM_001276696.1:c.644T>A
NM_001276697.1:c.284T>A
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NM_001276699.1:c.284T>A
NM_001276760.1:c.644T>A
NM_001276761.1:c.644T>A
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NM_001276698.2:c.284T>A
NM_001276699.2:c.284T>A
NM_001276760.2:c.644T>A
NM_001276761.2:c.644T>A
NM_001126112.3:c.761T>A
NM_001126113.3:c.761T>A
NM_001126114.3:c.761T>A
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NM_001276761.3:c.644T>A

Pathogenic

Met criteria codes 4

PS2 PS3 PM2_Supporting PP3_Moderate

Not Met criteria codes 14

PS1 PS4 BP7 BP4 PP1 PP4 PM1 PM5 BA1 BS2 PVS1 BS1 BS4 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.761T>A variant in TP53 is a missense variant predicted to cause substitution of isoleucine by asparagine at amino acid 254 (p.Ile254Asn). This variant has been identified as a de novo occurrence with confirmed parental relationships in 1 individual with a strongly LFS-associated cancer totaling 4 phenotype points (PS2; PMID 29070607). This variant has an allele frequency of 6.200e-7 (1/1612836 alleles) across gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00003) for PM2_Supporting and has no more than one allele per non-bottleneck subpopulation (PM2_Supporting). In vitro assays performed in yeast and/or human cell lines showed non-functional transactivation and loss of growth suppression activity indicating that this variant impacts protein function (PS3; PMIDs: 12826609, 30224644, 29979965). Computational predictor scores (BayesDel = 0.5449; Align GVGD = Class 65) are above recommended thresholds (BayesDel > 0.16 and an Align GVGD Class of 65), evidence that correlates with impact to TP53 via protein change (PP3_Moderate). 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: PS2, PM2_Supporting, PS3, PP3_Moderate. (Bayesian Points: 11; VCEP specifications version 2.3).

Met criteria codes

PS2	✔	This variant has been identified as a de novo occurrence with confirmed parental relationships in 1 individual with a strongly LFS-associated cancer totaling 4 phenotype points (PS2; PMID 29070607).
PS3	✔	In vitro assays performed in yeast and/or human cell lines showed non-functional transactivation and loss of growth suppression activity indicating that this variant impacts protein function (PS3; PMIDs: 12826609, 30224644, 29979965).
PM2_Supporting	✔	This variant has an allele frequency of 6.200e-7 (1/1612836 alleles) across gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00003) for PM2_Supporting and has no more than one allele per non-bottleneck subpopulation (PM2_Supporting).
PP3_Moderate	✔	Computational predictor scores (BayesDel = 0.5449; Align GVGD = Class 65) are above recommended thresholds (BayesDel > 0.16 and an Align GVGD Class of 65), evidence that correlates with impact to TP53 via protein change (PP3_Moderate).

Not Met criteria codes

PS1	✖	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
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
PP1	✖	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	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✖	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
PVS1	✖	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

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.761T>A (p.Ile25…	Pathogenic	Li-Fraumeni Syndrome	2025-12-05	1.0	ClinGen TP53 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TP53 Version 2.3.0	TP53

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