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# *Variant: NM_000546.6(TP53):c.761T>C (p.Ile254Thr)*

Version: 1.1

*CA397837761*

*1759844 (ClinVar)*

**Gene**: TP53 (HGNC:7157)
**Condition**: Li-Fraumeni syndrome (MONDO:0018875)
**Inheritance Mode**: Autosomal dominant inheritance
**UUID:** 0cb63752-afab-4376-95f6-290442c43018
**Approved on**: 2026/1/6
**Published on**: 2026/1/14

## *HGVS expressions*

**NM_000546.6:c.761T>C**
**NM_000546.6(TP53):c.761T>C (p.Ile254Thr)**
NC_000017.11:g.7674202A>G
CM000679.2:g.7674202A>G
NC_000017.10:g.7577520A>G
CM000679.1:g.7577520A>G
NC_000017.9:g.7518245A>G
NG_017013.2:g.18349T>C
ENST00000503591.2:c.761T>C
ENST00000508793.6:c.761T>C
ENST00000509690.6:c.365T>C
ENST00000514944.6:c.482T>C
ENST00000604348.6:c.740T>C
ENST00000269305.9:c.761T>C
ENST00000269305.8:c.761T>C
ENST00000359597.8:c.761T>C
ENST00000413465.6:c.761T>C
ENST00000420246.6:c.761T>C
ENST00000445888.6:c.761T>C
ENST00000455263.6:c.761T>C
ENST00000504290.5:c.365T>C
ENST00000504937.5:c.365T>C
ENST00000509690.5:c.365T>C
ENST00000510385.5:c.365T>C
ENST00000610292.4:c.644T>C
ENST00000610538.4:c.644T>C
ENST00000610623.4:c.284T>C
ENST00000615910.4:c.728T>C
ENST00000617185.4:c.761T>C
ENST00000618944.4:c.284T>C
ENST00000619186.4:c.284T>C
ENST00000619485.4:c.644T>C
ENST00000620739.4:c.644T>C
ENST00000622645.4:c.644T>C
ENST00000635293.1:c.644T>C
NM_000546.5:c.761T>C
NM_001126112.2:c.761T>C

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

**Pathogenic**

**Met criteria codes** 5

PS3 PS4_Moderate PM2_Supporting PP4_Moderate PP3_Moderate

**Not Met criteria codes** 13

PS1 PS2 BP7 BP4 BA1 PP1 PM1 PM5 BS1 BS4 BS3 PVS1 BS2

## 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.761T>C variant in TP53 is a missense variant predicted to cause substitution of isoleucine by threonine at amino acid 254 (p.Ile254Thr). 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, PMID: 34906512, Internal lab contributors). This variant has been reported in 4 unrelated probands meeting Revised Chompret criteria. Based on this evidence, this variant scores 2 total points meeting the TP53 VCEP phenotype scoring criteria of 2-3.5 points. (PS4_Moderate; PMIDs: 25584008, 28369373, Internal lab contributors). This variant is absent from gnomAD v4.1.0 (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 = 0.5982; 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: PP4_Moderate, PS4_Moderate, PM2_Supporting, PS3, PP3_Moderate. (Bayesian Points: 11; VCEP specifications version 2.4)**

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**Met criteria codes**

| | | |
|---|---|---|
| **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). |
| **PS4_Moderate** | ✔ | This variant has been reported in 4 unrelated probands meeting Revised Chompret criteria. Based on this evidence, this variant scores 2 total points meeting the TP53 VCEP phenotype scoring criteria of 2-3.5 points. (PS4_Moderate; PMIDs: 25584008, 28369373, Internal lab contributors). |
| **PM2_Supporting** | ✔ | This variant is absent from gnomAD v4.1.0 (PM2_Supporting). |
| **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, PMID: 34906512, Internal lab contributors). |
| **PP3_Moderate** | ✔ | Computational predictor scores (BayesDel = 0.5982; 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). |

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**Not Met criteria codes**

| | | |
|---|---|---|
| **PS1** | ✖ | 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 |
| **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 |

| | | | |
|---|---|---|---|
| **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 |
| **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 |
| **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 |
| **PVS1** | | ✖ | 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 |

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>C (p.Ile25… | Pathogenic | Li-Fraumeni Syndrome | 2026-01-14 | 1.1 | ClinGen TP53 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TP53 Version 2.4.0 | TP53 |
| View | NM_000546.6(TP53):c.761T>C (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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