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_000546.5(TP53):c.641A>G (p.His214Arg)*

Version: 2.0

*CA16040595*

*376615 (ClinVar)*

**Gene**: TP53 (HGNC:7157)
**Condition**: Li-Fraumeni syndrome (MONDO:0018875)
**Inheritance Mode**: Autosomal dominant inheritance
**UUID:** b36419d2-274a-4464-b4c9-c0ff2471c0d9
**Approved on**: 2024/8/5
**Published on**: 2024/8/5

## *HGVS expressions*

**NM_000546.5:c.641A>G**
**NM_000546.5(TP53):c.641A>G (p.His214Arg)**
NC_000017.11:g.7674890T>C
CM000679.2:g.7674890T>C
NC_000017.10:g.7578208T>C
CM000679.1:g.7578208T>C
NC_000017.9:g.7518933T>C
NG_017013.2:g.17661A>G
ENST00000503591.2:c.641A>G
ENST00000508793.6:c.641A>G
ENST00000509690.6:c.245A>G
ENST00000514944.6:c.362A>G
ENST00000604348.6:c.620A>G
ENST00000269305.9:c.641A>G
ENST00000269305.8:c.641A>G
ENST00000359597.8:c.641A>G
ENST00000413465.6:c.641A>G
ENST00000420246.6:c.641A>G
ENST00000445888.6:c.641A>G
ENST00000455263.6:c.641A>G
ENST00000504290.5:c.245A>G
ENST00000504937.5:c.245A>G
ENST00000505014.5:n.897A>G
ENST00000509690.5:c.245A>G
ENST00000510385.5:c.245A>G
ENST00000514944.5:c.362A>G
ENST00000574684.1:n.67+163A>G
ENST00000610292.4:c.524A>G
ENST00000610538.4:c.524A>G
ENST00000610623.4:c.164A>G
ENST00000615910.4:c.608A>G
ENST00000617185.4:c.641A>G
ENST00000618944.4:c.164A>G
ENST00000619186.4:c.164A>G
ENST00000619485.4:c.524A>G
ENST00000620739.4:c.524A>G
ENST00000622645.4:c.524A>G

ENST00000635293.1:c.524A>G
NM_001126112.2:c.641A>G
NM_001126113.2:c.641A>G
NM_001126114.2:c.641A>G
NM_001126115.1:c.245A>G
NM_001126116.1:c.245A>G
NM_001126117.1:c.245A>G
NM_001126118.1:c.524A>G
NM_001276695.1:c.524A>G
NM_001276696.1:c.524A>G
NM_001276697.1:c.164A>G
NM_001276698.1:c.164A>G
NM_001276699.1:c.164A>G
NM_001276760.1:c.524A>G
NM_001276761.1:c.524A>G
NM_001276695.2:c.524A>G
NM_001276696.2:c.524A>G
NM_001276697.2:c.164A>G
NM_001276698.2:c.164A>G
NM_001276699.2:c.164A>G
NM_001276760.2:c.524A>G
NM_001276761.2:c.524A>G
NM_000546.6:c.641A>G
NM_001126112.3:c.641A>G
NM_001126113.3:c.641A>G
NM_001126114.3:c.641A>G
NM_001126115.2:c.245A>G
NM_001126116.2:c.245A>G
NM_001126117.2:c.245A>G
NM_001126118.2:c.524A>G
NM_001276695.3:c.524A>G
NM_001276696.3:c.524A>G
NM_001276697.3:c.164A>G
NM_001276698.3:c.164A>G
NM_001276699.3:c.164A>G
NM_001276760.3:c.524A>G
NM_001276761.3:c.524A>G

**Pathogenic**

**Met criteria codes** 5

PS4_Supporting PP4_Moderate PM2_Supporting PS3 PM1

**Not Met criteria codes** 12

PVS1 BS1 BS4 BS3 BS2 BP4 PS1 PS2 BA1 PP1 PP3 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.641A>G variant in TP53 is a missense variant predicted to cause substitution of histidine by arginine at amino acid 214 (p.His214Arg). This variant has been reported in 2 unrelated families meeting Revised Chompret criteria. Based on this evidence, this variant scores 1 total point meeting the TP53 VCEP phenotype scoring criteria of 1-1.5 points. (PS4_Supporting; PMID: 20522432; Internal lab contributor: SCV000581129.5). 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 contributor: SCV000581129.5). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). In vitro assays performed in yeast and human cell lines showed non-functional transactivation and loss of growth suppression activity indicating that this variant impacts protein function (PMIDs: 12826609, 30224644, 29979965) (PS3). This variant has 35 somatic occurrences for the same amino acid change in cancerhotspots.org (v2) sufficient to be defined as a mutational hotspot by the Clingen TP53 VCEP (≥ 10 somatic occurrences, PMID: 30311369) (PM1). 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: PS4_Supporting, PP4_Moderate, PM2_Supporting, PS3, PM1. (Bayesian Points: 10; VCEP specifications version 2.0; 7/24/2024)**

**Met criteria codes**

| | | |
|---|---|---|
| **PS4_Supporting** | ✔ | This variant has been reported in 2 unrelated families meeting Revised Chompret criteria. Based on this evidence, this variant scores 1 total point meeting the TP53 VCEP phenotype scoring criteria of 1-1.5 points. (PS4_Supporting; PMID: 20522432; Internal lab contributor: SCV000581129.5). |
| **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 contributor: SCV000581129.5). |
| **PM2_Supporting** | ✔ | This variant is absent from gnomAD v4.1.0 (PM2_Supporting). |
| **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 (PMIDs: 12826609, 30224644, 29979965) (PS3). |
| **PM1** | ✔ | This variant has 35 somatic occurrences for the same amino acid change in cancerhotspots.org (v2) sufficient to be defined as a mutational hotspot by the Clingen TP53 VCEP (≥ 10 somatic occurrences, PMID: 30311369) (PM1). |

**Not Met criteria codes**

| | | |
|---|---|---|
| **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 |
| **BS2** | ✖ | 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 |
| **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 |
| **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** | ✖ | The results from the computational predictors BayesDel and AlignGVGD do not agree, providing no evidence that correlates with a damaging or benign impact on TP53 function via protein change. Additionally, the computational splicing predictor SpliceAI gives a score of 0.06, predicting that the variant has no impact on splicing (score threshold ≤ 0.10) (PP3 and BP4 not met). |
| **PM5** | ✖ | 5 different missense variants (p.His214Gln; p.His214Pro; p.His214Leu; p.His214Tyr; p.His214Asn) in the same codon have been reported (ClinVar Variation IDs: 140943, 643078, 376616, 1053808, 230254). However, these variants have not yet met the criteria to be classified as pathogenic or likely pathogenic by the ClinGen TP53 VCEP's specifications (PM5 not met). |

Curation History

Showing 1 to 3 of 3 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.