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: 2024-08-05
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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

PS3 PM1 PM2_Supporting PS4_Supporting PP4_Moderate

Not Met criteria codes 12

PS1 PS2 PP1 PP3 PM5 PVS1 BA1 BS1 BS4 BS3 BS2 BP4

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

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).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
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).

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
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).
PVS1		✖	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
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

Curation History

Showing 1 to 3 of 3 rows