Variant: NM_000546.6(TP53):c.659A>G (p.Tyr220Cys)

Version: 1.1

CA000315

127819 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 4795612b-c5d2-4229-a5ec-172fedfbcf55
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HGVS expressions

NM_000546.6:c.659A>G
NM_000546.6(TP53):c.659A>G (p.Tyr220Cys)
NC_000017.11:g.7674872T>C
CM000679.2:g.7674872T>C
NC_000017.10:g.7578190T>C
CM000679.1:g.7578190T>C
NC_000017.9:g.7518915T>C
NG_017013.2:g.17679A>G
ENST00000503591.2:c.659A>G
ENST00000508793.6:c.659A>G
ENST00000509690.6:c.263A>G
ENST00000514944.6:c.380A>G
ENST00000604348.6:c.638A>G
ENST00000269305.9:c.659A>G
ENST00000269305.8:c.659A>G
ENST00000359597.8:c.659A>G
ENST00000413465.6:c.659A>G
ENST00000420246.6:c.659A>G
ENST00000445888.6:c.659A>G
ENST00000455263.6:c.659A>G
ENST00000504290.5:c.263A>G
ENST00000504937.5:c.263A>G
ENST00000505014.5:n.915A>G
ENST00000509690.5:c.263A>G
ENST00000510385.5:c.263A>G
ENST00000514944.5:c.380A>G
ENST00000574684.1:n.67+181A>G
ENST00000610292.4:c.542A>G
ENST00000610538.4:c.542A>G
ENST00000610623.4:c.182A>G
ENST00000615910.4:c.626A>G
ENST00000617185.4:c.659A>G
ENST00000618944.4:c.182A>G
ENST00000619186.4:c.182A>G
ENST00000619485.4:c.542A>G
ENST00000620739.4:c.542A>G
ENST00000622645.4:c.542A>G

ENST00000635293.1:c.542A>G
NM_000546.5:c.659A>G
NM_001126112.2:c.659A>G
NM_001126113.2:c.659A>G
NM_001126114.2:c.659A>G
NM_001126115.1:c.263A>G
NM_001126116.1:c.263A>G
NM_001126117.1:c.263A>G
NM_001126118.1:c.542A>G
NM_001276695.1:c.542A>G
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NM_001276699.1:c.182A>G
NM_001276760.1:c.542A>G
NM_001276761.1:c.542A>G
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NM_001276761.2:c.542A>G
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NM_001126118.2:c.542A>G
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NM_001276696.3:c.542A>G
NM_001276697.3:c.182A>G
NM_001276698.3:c.182A>G
NM_001276699.3:c.182A>G
NM_001276760.3:c.542A>G
NM_001276761.3:c.542A>G

Pathogenic

Met criteria codes 8

PS3 PS4 PP3_Moderate PP1_Strong PS2_Moderate PM2_Supporting PM1 PP4_Moderate

Not Met criteria codes 10

PS1 BP7 BP4 PM6 PM5 BA1 BS1 BS3 BS2 PVS1

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.659A>G variant in TP53 is a missense variant predicted to cause substitution of Tyrosine by Cysteine at amino acid 220 (p.Tyr220Cys). This variant has been reported in 9 unrelated probands and/or families meeting Classic and/or Revised Chompret criteria. Based on this evidence, this variant scores 6.5 total points meeting the TP53 VCEP phenotype scoring criteria of 4-7.5 points. (PS4; PMIDs: 20028212, 9242456, 19101993, 18307025, 20805372, 21761402, 27714481, 10589545, 10432928, 8118819, ClinVar SCV: SCV000183774.8, Internal lab contributors). This variant has been identified as a de novo occurrence with unconfirmed parental relationships in 1 individual with an LFS-associated cancer totaling 2 phenotype points (PS2_Moderate; PMID: 18307025). The variant has been reported to segregate with LFS-associated cancers in ≥ 7 meioses from 5 families (PP1_Strong; PMIDs: 20028212, 1910993, 10432928, 8118819, 27714481). 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, ClinVar GTRs, SCV000183774.8). This variant has an allele frequency of 0.000005932 (7/1179948 alleles) in the European (non-Finnish) population in gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00004) for PM2_Supporting, and therefore meets this criterion (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 (PMIDs: 12826609, 30224644, 29979965) (PS3). This variant has 127 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). Computational predictor scores (BayesDel = 0.5625; Align GVGD = Class C65) 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: PS4, PS2_Moderate, PP1_Strong, PM2_Supporting, PS3, PM1, PP3_Moderate, PP4_Moderate (Bayesian Points: 21 points; 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).
PS4	✔	This variant has been reported in 9 unrelated probands and/or families meeting Classic and/or Revised Chompret criteria. Based on this evidence, this variant scores 6.5 total points meeting the TP53 VCEP phenotype scoring criteria of 4-7.5 points. (PS4; PMIDs: 20028212, 9242456, 19101993, 18307025, 20805372, 21761402, 27714481, 10589545, 10432928, 8118819, ClinVar SCV: SCV000183774.8, Internal lab contributors).
PP3_Moderate	✔	Computational predictor scores (BayesDel = 0.5625; Align GVGD = Class C65) 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).
PP1_Strong	✔	The variant has been reported to segregate with LFS-associated cancers in ≥ 7 meioses from 5 families (PP1_Strong; PMIDs: 20028212, 1910993, 10432928, 8118819, 27714481).
PS2_Moderate	✔	This variant has been identified as a de novo occurrence with unconfirmed parental relationships in 1 individual with an LFS-associated cancer totaling 2 phenotype points (PS2_Moderate; PMID: 18307025).
PM2_Supporting	✔	This variant has an allele frequency of 0.000005932 (7/1179948 alleles) in the European (non-Finnish) population in gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00004) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting).

PM1	✔	This variant has 127 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).
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, ClinVar GTRs, SCV000183774.8).

Not Met criteria codes

PS1	✖	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
PM6	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✖	4 different missense variants (c.659A>C, p.Try220Ser; c.658T>G, p.Tyr220Asp; c.658T>A, p.Tyr220Asn, c.658T>C, p.Tyr220His) in the same codon have been reported (ClinVar Variation IDs: 12383, 376689, 376688, 376687). 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).
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
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
PVS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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