Variant: NM_001126112.2(TP53):c.329G>C (p.Arg110Pro)

Version: 1.0

CA10580948

233627 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: b7f8a84e-5a46-4d96-b19e-9b58d882b2b6
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HGVS expressions

NM_001126112.2:c.329G>C
NM_001126112.2(TP53):c.329G>C (p.Arg110Pro)
NC_000017.11:g.7676040C>G
CM000679.2:g.7676040C>G
NC_000017.10:g.7579358C>G
CM000679.1:g.7579358C>G
NC_000017.9:g.7520083C>G
NG_017013.2:g.16511G>C
ENST00000503591.2:c.329G>C
ENST00000508793.6:c.329G>C
ENST00000509690.6:c.-21-804G>C
ENST00000514944.6:c.96+342G>C
ENST00000604348.6:c.329G>C
ENST00000269305.9:c.329G>C
ENST00000269305.8:c.329G>C
ENST00000359597.8:c.329G>C
ENST00000413465.6:c.329G>C
ENST00000420246.6:c.329G>C
ENST00000445888.6:c.329G>C
ENST00000455263.6:c.329G>C
ENST00000503591.1:c.329G>C
ENST00000505014.5:n.585G>C
ENST00000508793.5:c.329G>C
ENST00000509690.5:c.-21-804G>C
ENST00000514944.5:c.96+342G>C
ENST00000604348.5:c.329G>C
ENST00000610292.4:c.212G>C
ENST00000610538.4:c.212G>C
ENST00000615910.4:c.329G>C
ENST00000617185.4:c.329G>C
ENST00000619485.4:c.212G>C
ENST00000620739.4:c.212G>C
ENST00000622645.4:c.212G>C
ENST00000635293.1:c.212G>C
NM_000546.5:c.329G>C
NM_001126113.2:c.329G>C
NM_001126114.2:c.329G>C

NM_001126118.1:c.212G>C
NM_001276695.1:c.212G>C
NM_001276696.1:c.212G>C
NM_001276760.1:c.212G>C
NM_001276761.1:c.212G>C
NM_001276695.2:c.212G>C
NM_001276696.2:c.212G>C
NM_001276760.2:c.212G>C
NM_001276761.2:c.212G>C
NM_000546.6:c.329G>C
NM_001126112.3:c.329G>C
NM_001126113.3:c.329G>C
NM_001126114.3:c.329G>C
NM_001126118.2:c.212G>C
NM_001276695.3:c.212G>C
NM_001276696.3:c.212G>C
NM_001276760.3:c.212G>C
NM_001276761.3:c.212G>C

Pathogenic

Met criteria codes 5

PM1 PM2_Supporting PS4_Supporting PS3 PS2_Moderate

Not Met criteria codes 13

PP1 PP3 PP4 PM5 PM6 BA1 BS2 BS1 BS4 BS3 PS1 BP4 BP2

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.329G>C variant in TP53 is a missense variant predicted to cause substitution of arginine by proline at amino acid 110 (p.Arg110Pro). This variant has been reported in 2 unrelated families meeting Revised Chompret criteria and reported in 1 individual under the age of 40 diagnosed with a HER2+ breast cancer. Based on this evidence, this variant scores 1.5 total points meeting the TP53 VCEP phenotype scoring criteria of 1-1.5 points. (PS4_Supporting; PMIDs: 30455982, 23894400; Internal lab contributors). This variant has been identified as a de novo occurrence with confirmed parental relationships in 1 individual with a moderately LFS-associated cancer totaling 2 phenotype points (PS2_Moderate; PMID: 29070607). 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). This variant has 11 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: PS3, PM1, PS2_Moderate, PM2_Supporting, PS4_Supporting. (Bayesian Points: 10; VCEP specifications version 2.3)

Met criteria codes

PM1	✔	This variant has 11 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 and reported in 1 individual under the age of 40 diagnosed with a HER2+ breast cancer. Based on this evidence, this variant scores 1.5 total points meeting the TP53 VCEP phenotype scoring criteria of 1-1.5 points. (PS4_Supporting; PMIDs: 30455982, 23894400; Internal lab contributors).
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).
PS2_Moderate	✔	This variant has been identified as a de novo occurrence with confirmed parental relationships in 1 individual with a moderately LFS-associated cancer totaling 2 phenotype points (PS2_Moderate; PMID: 29070607).

Not Met criteria codes

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, SpliceAI predicts that the variant has no impact on splicing (score threshold ≤ 0.10) (PP3 and BP4 not met).
PP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✖	1 missense variants in the same codon have been reported (p.Arg110Leu) that is classified as Pathogenic and has lower Grantham score than the variant in question. (PM5 not applied).
PM6	✖	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 cancer free 60+ females in literature or FLOSSIES.
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
PS1		✖	The same amino acid change, resulting from a different nucleotide change c.329_330delinsCC (ClinVar Variation ID: 641505). This variant is considered Pathogenic by one submitter. However, this other variant has not yet been officially curated by the ClinGen TP53 VCEP's specifications (PS1 not met).
BP4		✖	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, SpliceAI predicts that the variant has no impact on splicing (score threshold ≤ 0.10) (PP3 and BP4 not met).
BP2		✖	Observed at 40% AF in an 80+ yo male w/ pancreatic cancer, possible heme malignancy, and additional TP53 truncating variant subject to NMD, phase unknown, also 40% AF

Curation History

Showing 1 to 1 of 1 rows