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Variant: NM_000546.5(TP53):c.523C>T (p.Arg175Cys)

Version: 1.1

CA002442

245851 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: 3699ed0e-e5f6-4457-bee4-961ef507dd2c
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HGVS expressions

NM_000546.5:c.523C>T
NM_000546.5(TP53):c.523C>T (p.Arg175Cys)
NC_000017.11:g.7675089G>A
CM000679.2:g.7675089G>A
NC_000017.10:g.7578407G>A
CM000679.1:g.7578407G>A
NC_000017.9:g.7519132G>A
NG_017013.2:g.17462C>T
ENST00000503591.2:c.523C>T
ENST00000508793.6:c.523C>T
ENST00000509690.6:c.127C>T
ENST00000514944.6:c.244C>T
ENST00000604348.6:c.502C>T
ENST00000269305.9:c.523C>T
ENST00000269305.8:c.523C>T
ENST00000359597.8:c.523C>T
ENST00000413465.6:c.523C>T
ENST00000420246.6:c.523C>T
ENST00000445888.6:c.523C>T
ENST00000455263.6:c.523C>T
ENST00000504290.5:c.127C>T
ENST00000504937.5:c.127C>T
ENST00000505014.5:n.779C>T
ENST00000509690.5:c.127C>T
ENST00000510385.5:c.127C>T
ENST00000514944.5:c.244C>T
ENST00000574684.1:n.31C>T
ENST00000610292.4:c.406C>T
ENST00000610538.4:c.406C>T
ENST00000610623.4:c.46C>T
ENST00000615910.4:c.490C>T
ENST00000617185.4:c.523C>T
ENST00000618944.4:c.46C>T
ENST00000619186.4:c.46C>T
ENST00000619485.4:c.406C>T
ENST00000620739.4:c.406C>T
ENST00000622645.4:c.406C>T

ENST00000635293.1:c.406C>T
NM_001126112.2:c.523C>T
NM_001126113.2:c.523C>T
NM_001126114.2:c.523C>T
NM_001126115.1:c.127C>T
NM_001126116.1:c.127C>T
NM_001126117.1:c.127C>T
NM_001126118.1:c.406C>T
NM_001276695.1:c.406C>T
NM_001276696.1:c.406C>T
NM_001276697.1:c.46C>T
NM_001276698.1:c.46C>T
NM_001276699.1:c.46C>T
NM_001276760.1:c.406C>T
NM_001276761.1:c.406C>T
NM_001276695.2:c.406C>T
NM_001276696.2:c.406C>T
NM_001276697.2:c.46C>T
NM_001276698.2:c.46C>T
NM_001276699.2:c.46C>T
NM_001276760.2:c.406C>T
NM_001276761.2:c.406C>T
NM_000546.6:c.523C>T
NM_001126112.3:c.523C>T
NM_001126113.3:c.523C>T
NM_001126114.3:c.523C>T
NM_001126115.2:c.127C>T
NM_001126116.2:c.127C>T
NM_001126117.2:c.127C>T
NM_001126118.2:c.406C>T
NM_001276695.3:c.406C>T
NM_001276696.3:c.406C>T
NM_001276697.3:c.46C>T
NM_001276698.3:c.46C>T
NM_001276699.3:c.46C>T
NM_001276760.3:c.406C>T
NM_001276761.3:c.406C>T

Uncertain Significance

Met criteria codes 5

PM1 BS3_Supporting PP3_Moderate PS4_Supporting BS2_Supporting

Not Met criteria codes 14

PP1 PS1 PS2 PS3 PM5 PM6 PM2 PVS1 BA1 BP7 BP4 BP2 BS1 BS4

Evidence Links 0

Expert Panel

TP53 VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

TP53 VCEP

This variant has a BayesDel score > 0.16 and Align GVGD (Zebrafish) is Class 65 (PP3_Moderate). This variant is within a codon that is an established hotspot in the TP53 gene (PM1). This variant has been reported in 2 probands meeting Revised Chompret criteria (PS4_Supporting; PMID: 31119730, internal laboratory contributor(SCV000903055.2)). Transactivation assays show partially functional variant according to Kato, et al. and there is no evidence of a dominant negative effect or loss of function according to Giacomelli, et al. (BS3_Supporting; PMID: 12826609, 30224644). This variant has been observed in 5 60+ year old females without a cancer diagnosis (BS2_Supporting; internal laboratory contributor, SCV000833097.4). In summary, the clinical significance of TP53 c.523C>T (p.Arg175Cys) is uncertain for Li-Fraumeni Syndrome. ACMG/AMP criteria applied, as specified by the TP53 Expert Panel: PP3_Moderate; PM1; PS4_Supporting; BS3_Supporting; BS2_Supporting.

Met criteria codes

PM1	✔	Code is scored based on the its location within the hotspot codon 175. Cancer hotspots website describes 8 somatic occurrences (does not reach threshold of 10, as set by the ClinGen TP53 group)
BS3_Supporting	✔	Kato assay = partially functional (median = 72.5) Giacomelli = notDNE_notLOF Kotler = noLOF (score = -2.535)
PP3_Moderate	✔	Multiple lines of computational evidence support a deleterious effect on the gene or gene product. Align-GVGD = Class C65 BayesDel = 0.544256 (score > 0.16, as requested)
PS4_Supporting	✔	Two cases in TCGA: - TCGA-BH-A18I: breast cancer (53) - 0 point - TCGA-06-2563: glioblastoma (72) - 0 point IARC: There are four entries of confirmed germline p.R175C carriers in the IARC database v.R20. - ZA08385-1 (Same entry as PUBMED ID 28724667) - SAR19-15-II-1: squamous cell carcinoma, at the age of 65 years old - 0 point - SAR19-15-IV-1: neuroectodermal tumor, at the age of 9 years old - 0 point - WEB18-3: ovary cancer, at 45 years old. - 0 point Clinvar data: One women affected with breast cancer at late 20s years old. Affecting one breast. Family history not reported. This patient therefore meets Chompret 2015 LFS criteria (early-onset breast cancer (<31yo) irrespective of family history = 0.5 points. (SCV000903055.2). PMID 31119730: Patient with breast cancer diagnosed at 30 years of age = 0.5 points
BS2_Supporting	✔	Variant not found in the FLOSSIES database. Variant found in woman with ovarian cancer at 64. Family history of breast, leukemia, and colon cancers on both sides. Does not meet any clinical criteria. Counts as woman unaffected at 60 (PMID: 22006311). Internal lab with 5 cases of women cancer free by age 60 (SCV000833097.4)

Not Met criteria codes

PP1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1	✖	There is no previous "pathogenic" p.R175C variant with a nucleotide change different than c.523C>T. According to the IARC database, the variant c.523C>T creates a new splice donor site (based on HSF_V2.3)
PS2	✖	No enough evidence

PS3	✖	Variant does not meet this criteria since BS3_Supporting has been scored.
PM5	✖	PM5 not applied once this variant is located within a hotspot (PM1) Other variants in this codon: - Variant p.R175H: widely known as pathogenic - Variants p.R175G: pathogenic/likely pathogenic entries in ClinVar - Variant p.R175L: conflicting interpretations These other variants not yet assessed by VCEP.
PM6	✖	No enough evidence
PM2	✖	Global allele frequency in gnomAD v2.1.1 non-cancer subset = 0.00001492 (4 alleles)
PVS1	✖	Variant is not a null variant
BA1	✖	Global allele frequency in gnomAD v2.1.1 non-cancer subset = 0.00001492 (4 alleles)
BP7	✖	Variant is not synonymous
BP4	✖	Not applied since variant meets PP3_moderate.
BP2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	✖	Global allele frequency in gnomAD v2.1.1 non-cancer subset = 0.00001492 (4 alleles)
BS4	✖	No enough evidence

Curation History

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