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.396G>C (p.Lys132Asn)

Version: 1.1

CA16603044

376624 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: d817c4c8-1df0-4998-acec-3488a11fc4b0
Approved on: 2022-03-18
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HGVS expressions

NM_000546.5:c.396G>C
NM_000546.5(TP53):c.396G>C (p.Lys132Asn)
NC_000017.11:g.7675216C>G
CM000679.2:g.7675216C>G
NC_000017.10:g.7578534C>G
CM000679.1:g.7578534C>G
NC_000017.9:g.7519259C>G
NG_017013.2:g.17335G>C
ENST00000503591.2:c.396G>C
ENST00000508793.6:c.396G>C
ENST00000509690.6:c.-1G>C
ENST00000514944.6:c.117G>C
ENST00000604348.6:c.376-1G>C
ENST00000269305.9:c.396G>C
ENST00000269305.8:c.396G>C
ENST00000359597.8:c.396G>C
ENST00000413465.6:c.396G>C
ENST00000420246.6:c.396G>C
ENST00000445888.6:c.396G>C
ENST00000455263.6:c.396G>C
ENST00000504290.5:c.-1G>C
ENST00000504937.5:c.-1G>C
ENST00000505014.5:n.652G>C
ENST00000508793.5:c.396G>C
ENST00000509690.5:c.-1G>C
ENST00000510385.5:c.-1G>C
ENST00000514944.5:c.117G>C
ENST00000604348.5:c.376-1G>C
ENST00000610292.4:c.279G>C
ENST00000610538.4:c.279G>C
ENST00000610623.4:c.-82G>C
ENST00000615910.4:c.363G>C
ENST00000617185.4:c.396G>C
ENST00000618944.4:c.-82G>C
ENST00000619186.4:c.-82G>C
ENST00000619485.4:c.279G>C
ENST00000620739.4:c.279G>C

ENST00000622645.4:c.279G>C
ENST00000635293.1:c.279G>C
NM_001126112.2:c.396G>C
NM_001126113.2:c.396G>C
NM_001126114.2:c.396G>C
NM_001126115.1:c.-1G>C
NM_001126116.1:c.-1G>C
NM_001126117.1:c.-1G>C
NM_001126118.1:c.279G>C
NM_001276695.1:c.279G>C
NM_001276696.1:c.279G>C
NM_001276697.1:c.-82G>C
NM_001276698.1:c.-82G>C
NM_001276699.1:c.-82G>C
NM_001276760.1:c.279G>C
NM_001276761.1:c.279G>C
NM_001276695.2:c.279G>C
NM_001276696.2:c.279G>C
NM_001276697.2:c.-82G>C
NM_001276698.2:c.-82G>C
NM_001276699.2:c.-82G>C
NM_001276760.2:c.279G>C
NM_001276761.2:c.279G>C
NM_000546.6:c.396G>C
NM_001126112.3:c.396G>C
NM_001126113.3:c.396G>C
NM_001126114.3:c.396G>C
NM_001126115.2:c.-1G>C
NM_001126116.2:c.-1G>C
NM_001126117.2:c.-1G>C
NM_001126118.2:c.279G>C
NM_001276695.3:c.279G>C
NM_001276696.3:c.279G>C
NM_001276697.3:c.-82G>C
NM_001276698.3:c.-82G>C
NM_001276699.3:c.-82G>C
NM_001276760.3:c.279G>C
NM_001276761.3:c.279G>C

Likely Pathogenic

Met criteria codes 4

PS3 PM1 PP3_Moderate PM2_Supporting

Not Met criteria codes 13

PS1 PS2 PS4 PP1 PM6 PM5 BA1 BS2 BS1 BS4 BS3 BP4 BP2

Evidence Links 4

Expert Panel

TP53 VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

TP53 VCEP

Transactivation assays show a low functioning allele according to Kato, et al. and there is evidence of a dominant negative effect and loss of function according to Giacomelli, et al. (PS3; PMID: 12826609, 30224644). This variant has a BayesDel score > 0.16 and Align GVGD (Zebrafish) is Class 65 (PP3_Moderate). This variant has >10 observations as a somatic hotspot variant in tumors (PM1; cancerhotspots.org v(2)). This variant is absent in the gnomAD cohort (PM2_Supporting; http://gnomad.broadinstitute.org). In summary, TP53 c.396G>C (p.Lys132Asn) meets criteria to be classified as likely pathogenic for Li-Fraumeni syndrome. ACMG/AMP criteria applied, as specified by the TP53 Variant Curation Expert Panel: PS3, PP3_Moderate, PM1, PM2_Supporting.

Met criteria codes

PS3	✔	Experimental studies show this variant to be non-functional (Kato 2003) and to demonstrate both dominant negative effect (DNE) and loss of function (LOF) (Dearth 2007, Giacomelli 2018 and Kotler 2018). Evidence for LOF PubMed:29979965 Evidence of LOF and DNE PubMed:16861262 Shows DNE and LOF PubMed:30224644 Shows variant to be non-functional. PubMed:12826609
PM1	✔	Not in hot spot codon but seen in 30 tumor samples on cancerhotspots.org.
PP3_Moderate	✔	aGVGD class C65 and BayesDel >0.16. Strength modified as described by VCEP.
PM2_Supporting	✔	Absent from population databases.

Not Met criteria codes

PS1	✖	c.396G>T (p.Lys132Asn) has also been seen (ClinVar ID: 634773) but has not been evaluated by TP53 VCEP and is currently designated a VUS by Invitae
PS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4	✖	No published case reports of germline variant in the literature. Identified at least once in an unpublished case of a young female with rhabdomyosarcoma (parents not tested) not meeting classic LFS or Chompret criteria.
PP1	✖	No known segregation information.
PM6	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✖	NM_000546.5(TP53):c.395A>T (p.Lys132Met) ClinVar ID: 376629 (Not evaluated by VCEP; VUS by Invitae) NM_000546.5(TP53):c.395A>C (p.Lys132Thr) ClinVar ID: 376627 (Not evaluated by VCEP; LP by somatic entries

only) NM_000546.5(TP53):c.395A>G (p.Lys132Arg) ClinVar ID: 376625 (Not evaluated by VCEP; VUS by Invitae) NM_000546.5(TP53):c.394A>C (p.Lys132Gln) ClinVar ID: 376628 (Not evaluated by VCEP; LP by somatic entries only) NM_000546.5(TP53):c.394A>G (p.Lys132Glu) ClinVar ID; 376626 (Not evaluated by VCEP; conflicting VUS (Invitae)/ LP (Ambry) interpretations

BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2	✖	Not seen in FLOSSIES database or in individuals age 60+ in the literature.
BS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4	✖	No known segregation information.
BS3	✖	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
BP2	✖	No reported incidences.

Curation History

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