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.372C>A (p.Cys124Ter)

Version: 1.1

CA397844214

458537 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: a9d7558a-f941-4cec-95c8-682dafc6ca40
Approved on: 2024/8/5
Published on: 2024/8/5

HGVS expressions

NM_000546.5:c.372C>A
NM_000546.5(TP53):c.372C>A (p.Cys124Ter)
NC_000017.11:g.7675997G>T
CM000679.2:g.7675997G>T
NC_000017.10:g.7579315G>T
CM000679.1:g.7579315G>T
NC_000017.9:g.7520040G>T
NG_017013.2:g.16554C>A
ENST00000503591.2:c.372C>A
ENST00000508793.6:c.372C>A
ENST00000509690.6:c.-21-761C>A
ENST00000514944.6:c.96+385C>A
ENST00000604348.6:c.372C>A
ENST00000269305.9:c.372C>A
ENST00000269305.8:c.372C>A
ENST00000359597.8:c.372C>A
ENST00000413465.6:c.372C>A
ENST00000420246.6:c.372C>A
ENST00000445888.6:c.372C>A
ENST00000455263.6:c.372C>A
ENST00000503591.1:c.372C>A
ENST00000505014.5:n.628C>A
ENST00000508793.5:c.372C>A
ENST00000509690.5:c.-21-761C>A
ENST00000514944.5:c.96+385C>A
ENST00000604348.5:c.372C>A
ENST00000610292.4:c.255C>A
ENST00000610538.4:c.255C>A
ENST00000615910.4:c.340+28C>A
ENST00000617185.4:c.372C>A
ENST00000619485.4:c.255C>A
ENST00000620739.4:c.255C>A
ENST00000622645.4:c.255C>A
ENST00000635293.1:c.255C>A
NM_001126112.2:c.372C>A
NM_001126113.2:c.372C>A
NM_001126114.2:c.372C>A

NM_001126118.1:c.255C>A
NM_001276695.1:c.255C>A
NM_001276696.1:c.255C>A
NM_001276760.1:c.255C>A
NM_001276761.1:c.255C>A
NM_001276695.2:c.255C>A
NM_001276696.2:c.255C>A
NM_001276760.2:c.255C>A
NM_001276761.2:c.255C>A
NM_000546.6:c.372C>A
NM_001126112.3:c.372C>A
NM_001126113.3:c.372C>A
NM_001126114.3:c.372C>A
NM_001126118.2:c.255C>A
NM_001276695.3:c.255C>A
NM_001276696.3:c.255C>A
NM_001276760.3:c.255C>A
NM_001276761.3:c.255C>A

Pathogenic

Met criteria codes 3

PM2_Supporting PVS1 PS2

Not Met criteria codes 6

PP4 PM6 PM1 BS3 PS3 PS4

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.372C>A (p.Cys124Ter) is a TP53 nonsense variant upstream of p.Lys351. The variant is predicted to undergo nonsense-mediated decay (PVS1; PMID: 22233476). This variant has been identified as a de novo occurrence with unconfirmed parental relationships in 2 individuals with LFS-associated cancers totaling 4 phenotype points (PS2; PMID: 22233476, 32658383). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). 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: PVS1, PS2, PM2_Supporting. (Bayesian Points: 13; VCEP specifications version 2.0; 7/24/2024).

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PVS1	✔	The NM_000546.6 c.372C>A (p.Cys124Ter) is a TP53 nonsense variant upstream of p.Lys351. The variant is predicted to undergo nonsense-mediated decay (PVS1; PMID: 22233476).

PS2		✔	This variant has been identified as a de novo occurrence with unconfirmed parental relationships in 2 individual(s) with an LFS-associated cancer totaling 4 phenotype points (PS2; PMID: 22233476, 32658383).

Not Met criteria codes

PP4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6		✖	This evidence code is not currently applicable for TP53 VCEP curations.
PM1		✖	This variant does not reside within a region of TP53 that is defined as a mutational hotspot or critical functional domain by the ClinGen TP53 VCEP (PM1 not met).
BS3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4		✖	This variant received a total of 1 point across 2 unrelated probands. However, PS4 cannot be applied because individuals are counted towards de novo code PS2. (PS4 not met; PMIDs: 22233476, 32658383).

Curation History

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