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.1040C>A (p.Ala347Asp)

Version: 2.0

CA000022

43587 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: d4905d59-9322-441b-9ed0-ea2304d97a65
Approved on: 2024/8/5
Published on: 2024/8/5

HGVS expressions

NM_000546.5:c.1040C>A
NM_000546.5(TP53):c.1040C>A (p.Ala347Asp)
NC_000017.11:g.7670669G>T
CM000679.2:g.7670669G>T
NC_000017.10:g.7573987G>T
CM000679.1:g.7573987G>T
NC_000017.9:g.7514712G>T
NG_017013.2:g.21882C>A
ENST00000503591.2:c.1040C>A
ENST00000508793.6:c.1040C>A
ENST00000509690.6:c.644C>A
ENST00000514944.6:c.761C>A
ENST00000604348.6:c.1019C>A
ENST00000269305.9:c.1040C>A
ENST00000269305.8:c.1040C>A
ENST00000359597.8:c.993+2866C>A
ENST00000413465.6:c.782+3512C>A
ENST00000420246.6:c.*147C>A
ENST00000445888.6:c.1040C>A
ENST00000455263.6:c.*59C>A
ENST00000504290.5:c.*59C>A
ENST00000504937.5:c.644C>A
ENST00000510385.5:c.*147C>A
ENST00000576024.1:c.54-979C>A
ENST00000610292.4:c.923C>A
ENST00000610538.4:c.*59C>A
ENST00000610623.4:c.*59C>A
ENST00000615910.4:c.1007C>A
ENST00000617185.4:c.*147C>A
ENST00000618944.4:c.*147C>A
ENST00000619186.4:c.563C>A
ENST00000619485.4:c.923C>A
ENST00000620739.4:c.923C>A
ENST00000622645.4:c.*147C>A
ENST00000635293.1:c.923C>A
NM_001126112.2:c.1040C>A
NM_001126113.2:c.*59C>A

NM_001126114.2:c.*147C>A
NM_001126115.1:c.644C>A
NM_001126116.1:c.*147C>A
NM_001126117.1:c.*59C>A
NM_001126118.1:c.923C>A
NM_001276695.1:c.*59C>A
NM_001276696.1:c.*147C>A
NM_001276697.1:c.563C>A
NM_001276698.1:c.*147C>A
NM_001276699.1:c.*59C>A
NM_001276760.1:c.923C>A
NM_001276761.1:c.923C>A
NM_001276695.2:c.*59C>A
NM_001276696.2:c.*147C>A
NM_001276697.2:c.563C>A
NM_001276698.2:c.*147C>A
NM_001276699.2:c.*59C>A
NM_001276760.2:c.923C>A
NM_001276761.2:c.923C>A
NM_000546.6:c.1040C>A
NM_001126112.3:c.1040C>A
NM_001126113.3:c.*59C>A
NM_001126114.3:c.*147C>A
NM_001126115.2:c.644C>A
NM_001126116.2:c.*147C>A
NM_001126117.2:c.*59C>A
NM_001126118.2:c.923C>A
NM_001276695.3:c.*59C>A
NM_001276696.3:c.*147C>A
NM_001276697.3:c.563C>A
NM_001276698.3:c.*147C>A
NM_001276699.3:c.*59C>A
NM_001276760.3:c.923C>A
NM_001276761.3:c.923C>A

Pathogenic

Met criteria codes 4

PM2_Supporting PP1_Moderate PS3 PS4

Not Met criteria codes 10

PP3 PP4 PM1 PM5 BA1 BS2 BS1 BP4 PS1 PS2

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.1040C>A variant in TP53 is a missense variant predicted to cause substitution of alanine by aspartic acid at amino acid 347 (p.Ala347Asp). This variant has been reported in 4 unrelated families meeting Classic/Revised Chompret criteria reported in 1 individuals under the age of 40 diagnosed with a HER2+ breast cancer. Based on this evidence, this variant scores 4 total points meeting the TP53 VCEP phenotype scoring criteria of 4-7.5 points. (PS4; PMID: 27496084, Internal lab contributors).The variant has been reported to segregate with LFS-associated cancers in 13 meioses in 1 family (PP1_Moderate; Internal contributor: National Cancer Institute). 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: 37067901, 12826609, 30224644, 29979965). 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, PP1_Moderate, PM2_Supporting, PS3. (Bayesian Points: 11; VCEP specifications version 2.0; 7/24/2024)

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PP1_Moderate	✔	The variant has been reported to segregate with LFS-associated cancers in 13 meioses in 1 family (PP1_Moderate; Internal contributor: National Cancer Institute).
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: 37067901, 12826609, 30224644, 29979965).
PS4	✔	This variant has been reported in 4 unrelated families meeting Classic/Revised Chompret criteria reported in 1 individuals under the age of 40 diagnosed with a HER2+ breast cancer. Based on this evidence, this variant scores 4 total points meeting the TP53 VCEP phenotype scoring criteria of 4-7.5 points. (PS4; PMID: 27496084, Internal lab contributors).

Not Met criteria codes

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, the computational splicing predictor SpliceAI gives a score of 0.00, predicting 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
PM1	✖	This variant does not reside within a region of TP53 that is defined as a mutational hotspot by the ClinGen TP53 VCEP (PM1 not met)
PM5	✖	3 different missense variants (p.Ala347Val; p.Ala347Ser; p.Ala347Thr) in the same codon have been reported (ClinVar Variation IDs: 422725, 1773570, 662690). However, these variants have not yet met the criteria to be classified as pathogenic or likely pathogenic by the ClinGen TP53 VCEP’s specifications (PM5 not met).
BA1	✖	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
BS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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, the computational splicing predictor SpliceAI gives a score of 0.00, predicting that the variant has no impact on splicing (score threshold ≤ 0.10) (PP3 and BP4 not met).
PS1	✖	None
PS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000546.5(TP53):c.1040C>A (p.Ala…	Pathogenic	Li-Fraumeni Syndrome	2024-08-05	2.0	ClinGen TP53 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TP53 Version 2.0.0	TP53
View	NM_000546.5(TP53):c.1040C>A (p.Ala…	Likely Pathogenic	Li-Fraumeni Syndrome	2022-03-18	1.1	-	TP53
View	NM_000546.5(TP53):c.1040C>A (p.Ala…	Likely Pathogenic	Li-Fraumeni Syndrome	2020-01-24	1.0	-	TP53

Showing 1 to 3 of 3 rows

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