Variant: NM_000546.6(TP53):c.1146del (p.Lys382fs)

Version: 1.0

CA497711354

1408583 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: cbf33d9d-4af0-4b9d-bc0d-163d4df14e20
Approved on: 2025-05-07
Published on: 2025-07-18

HGVS expressions

NM_000546.6:c.1146del
NM_000546.6(TP53):c.1146del (p.Lys382fs)
NC_000017.11:g.7669650del
CM000679.2:g.7669650del
NC_000017.10:g.7572968del
CM000679.1:g.7572968del
NC_000017.9:g.7513693del
NG_017013.2:g.22906del
ENST00000503591.2:c.1146del
ENST00000508793.6:c.1146del
ENST00000509690.6:c.750del
ENST00000514944.6:c.867del
ENST00000604348.6:c.1125del
ENST00000269305.9:c.1146del
ENST00000269305.8:c.1146del
ENST00000359597.8:c.994-3401del
ENST00000413465.6:c.782+4536del
ENST00000420246.6:c.*253del
ENST00000445888.6:c.1146del
ENST00000455263.6:c.*165del
ENST00000504290.5:c.*165del
ENST00000504937.5:c.750del
ENST00000510385.5:c.*253del
ENST00000576024.1:c.99del
ENST00000610292.4:c.1029del
ENST00000610538.4:c.*165del
ENST00000610623.4:c.*165del
ENST00000615910.4:c.1113del
ENST00000617185.4:c.*253del
ENST00000618944.4:c.*253del
ENST00000619186.4:c.669del
ENST00000619485.4:c.1029del
ENST00000620739.4:c.1029del
ENST00000622645.4:c.*253del
ENST00000635293.1:c.983+964del
NM_000546.5:c.1146del
NM_001126112.2:c.1146del

NM_001126113.2:c.*165del
NM_001126114.2:c.*253del
NM_001126115.1:c.750del
NM_001126116.1:c.*253del
NM_001126117.1:c.*165del
NM_001126118.1:c.1029del
NM_001276695.1:c.*165del
NM_001276696.1:c.*253del
NM_001276697.1:c.669del
NM_001276698.1:c.*253del
NM_001276699.1:c.*165del
NM_001276760.1:c.1029del
NM_001276761.1:c.1029del
NM_001276695.2:c.*165del
NM_001276696.2:c.*253del
NM_001276697.2:c.669del
NM_001276698.2:c.*253del
NM_001276699.2:c.*165del
NM_001276760.2:c.1029del
NM_001276761.2:c.1029del
NM_001126112.3:c.1146del
NM_001126113.3:c.*165del
NM_001126114.3:c.*253del
NM_001126115.2:c.750del
NM_001126116.2:c.*253del
NM_001126117.2:c.*165del
NM_001126118.2:c.1029del
NM_001276695.3:c.*165del
NM_001276696.3:c.*253del
NM_001276697.3:c.669del
NM_001276698.3:c.*253del
NM_001276699.3:c.*165del
NM_001276760.3:c.1029del
NM_001276761.3:c.1029del

Likely Pathogenic

Met criteria codes 4

PM2_Supporting PP1 PVS1_Moderate PS4_Moderate

Not Met criteria codes 6

BS1 BS3 PM1 PS3 BA1 PP4

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.1146del (p.Lys382AsnfsTer?) is a TP53 frameshift variant inducing a stop codon read-through. The variant is predicted to escape nonsense mediated decay, targeting a region of unknown function representing <10% of the protein and introducing a C-terminal extension of 28 residues in the protein (PVS1_Moderate). This variant has been reported in 3 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 2 total points meeting the TP53 VCEP phenotype scoring criteria of 2-3.5 points. (PS4_Moderate; Internal lab contributors). The variant has been reported to segregate with LFS-associated cancers in 3-4 meioses in 1 family (PP1; Internal lab contributors). This variant has an allele frequency of 6.196e-7 (1/1614052 alleles) across gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00003) for PM2_Supporting and has no more than one allele per non-bottleneck subpopulation (PM2_Supporting). In summary, this variant meets the criteria to be classified as Likely Pathogenic for Li Fraumeni syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: PVS1_Moderate, PS4_Moderate, PP1, PM2_Supporting. (Bayesian Points: 6; VCEP specifications version 2.3)

Met criteria codes

PM2_Supporting	✔	This variant has an allele frequency of 6.196e-7 (1/1614052 alleles) across gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00003) for PM2_Supporting and has no more than one allele per non-bottleneck subpopulation (PM2_Supporting).
PP1	✔	The variant has been reported to segregate with LFS-associated cancers in 3-4 meioses in 1 family (PP1; Internal lab contributors).
PVS1_Moderate	✔	The NM_000546.6 c.1146del (p.Lys382AsnfsTer?) is a TP53 frameshift variant inducing a stop codon read-through. The variant is predicted to escape nonsense mediated decay, targeting a region of unknown function representing <10% of the protein and introducing a C-terminal extension of 28 residues in the protein (PVS1_Moderate). It's right at the end of the gene and predicted to cause a fs then a protein extension of 28 aa's. Not predicted to be subject to NMD or NSD. Affects <10% of protein and not a functional domain although 3 of the aa's affected are highly conserved but no pathogenic missense variants reported in this region.
PS4_Moderate	✔	This variant has been reported in 3 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 2 total points meeting the TP53 VCEP phenotype scoring criteria of 2-3.5 points. (PS4_Moderate; Internal lab contributors).

Not Met criteria codes

BS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	✖	Additional functional studies are needed for code application (PS3/BS3 not met).
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).
PS3	✖	Additional functional studies are needed for code application (PS3/BS3 not met).
BA1	✖	

No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PP4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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