

*Variant: NM\_001126112.2(TP53):c.711G>A (p.Met237Ile)*

Version: 1.0

CA000349 [↗](#)

142714 (ClinVar) [↗](#)

**Gene:** TP53 ([HGNC:7157](#))

**Condition:** Li-Fraumeni syndrome 1 ([MONDO:0007903](#))

**Inheritance Mode:** Autosomal dominant inheritance

**UID:** 98acfed4-de66-4a8c-b6ba-bc9a67cd4189

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### *HGVS expressions*

**NM\_001126112.2:c.711G>A**

NM\_001126112.2(TP53):c.711G>A (p.Met237Ile)

NC\_000017.11:g.7674252C>T

CM000679.2:g.7674252C>T

NC\_000017.10:g.7577570C>T

CM000679.1:g.7577570C>T

NC\_000017.9:g.7518295C>T

NG\_017013.2:g.18299G>A

ENST00000503591.2:c.711G>A

ENST00000508793.6:c.711G>A

ENST00000509690.6:c.315G>A

ENST00000514944.6:c.432G>A

ENST00000604348.6:c.690G>A

ENST00000269305.9:c.711G>A

ENST00000269305.8:c.711G>A

ENST00000359597.8:c.711G>A

ENST00000413465.6:c.711G>A

ENST00000420246.6:c.711G>A

ENST00000445888.6:c.711G>A

ENST00000455263.6:c.711G>A

ENST00000504290.5:c.315G>A

ENST00000504937.5:c.315G>A

ENST00000509690.5:c.315G>A

ENST00000510385.5:c.315G>A

ENST00000514944.5:c.432G>A

ENST00000610292.4:c.594G>A

ENST00000610538.4:c.594G>A

ENST00000610623.4:c.234G>A

ENST00000615910.4:c.678G>A

ENST00000617185.4:c.711G>A

ENST00000618944.4:c.234G>A

ENST00000619186.4:c.234G>A

ENST00000619485.4:c.594G>A

ENST00000620739.4:c.594G>A

ENST00000622645.4:c.594G>A

ENST00000635293.1:c.594G>A

NM\_000546.5:c.711G>A

NM\_001126113.2:c.711G>A  
NM\_001126114.2:c.711G>A  
NM\_001126115.1:c.315G>A  
NM\_001126116.1:c.315G>A  
NM\_001126117.1:c.315G>A  
NM\_001126118.1:c.594G>A  
NM\_001276695.1:c.594G>A  
NM\_001276696.1:c.594G>A  
NM\_001276697.1:c.234G>A  
NM\_001276698.1:c.234G>A  
NM\_001276699.1:c.234G>A  
NM\_001276760.1:c.594G>A  
NM\_001276761.1:c.594G>A  
NM\_001276695.2:c.594G>A  
NM\_001276696.2:c.594G>A  
NM\_001276697.2:c.234G>A  
NM\_001276698.2:c.234G>A  
NM\_001276699.2:c.234G>A  
NM\_001276760.2:c.594G>A  
NM\_001276761.2:c.594G>A  
NM\_000546.6:c.711G>A  
NM\_001126112.3:c.711G>A  
NM\_001126113.3:c.711G>A  
NM\_001126114.3:c.711G>A  
NM\_001126115.2:c.315G>A  
NM\_001126116.2:c.315G>A  
NM\_001126117.2:c.315G>A  
NM\_001126118.2:c.594G>A  
NM\_001276695.3:c.594G>A  
NM\_001276696.3:c.594G>A  
NM\_001276697.3:c.234G>A  
NM\_001276698.3:c.234G>A  
NM\_001276699.3:c.234G>A  
NM\_001276760.3:c.594G>A  
NM\_001276761.3:c.594G>A

**Pathogenic**

Met criteria codes **5**

PM1 PP1\_Moderate PM6\_Supporting  
PS3 PS4

Not Met criteria codes **8**

PP3 PM5 PM2 BS1 BS3  
BS2 BP4 BA1

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 >10 observations as a somatic hotspot variant in tumors (PM1; cancerhotspots.org v(2)). 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 been reported in 1 proband meeting Classic LFS criteria and 4 probands meeting Chompret criteria (PS4; PMID: 11370630, 25945745, NIH, Invitae, Ambry). This variant was found to co-segregate with disease in multiple affected family members, with 5 or 6 meioses observed (PP1\_Moderate; NIH, Invitae). There is one de novo observation in a proband with breast and thyroid cancer in her 30s without parental confirmation (PM6\_Supporting; GeneDx). In summary, TP53 c.711G>A (p.Met237Ile) meets criteria to be classified as pathogenic for Li-Fraumeni syndrome. ACMG/AMP criteria applied, as specified by the TP53 Variant Curation Expert Panel: PM1, PS3, PS4, PP1\_Moderate, PM6\_Supporting.

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#### Met criteria codes

<b>PM1</b>	✓	55/64 samples on cancerhotspots.com
<b>PP1_Moderate</b>	✓	6 meioses in across 2 families (NIH, Invitae)
<b>PM6_Supporting</b>	✓	Assumed de novo in female with breast cancer in 30s (0.5 pts; GeneDx)
<b>PS3</b>	✓	Nonfunctional by Kato; LOF by Kotler; LOF+DNE by Giacomelli
<b>PS4</b>	✓	NIH: 1 Chompret; 1 classic = 1.5 pts Literature: Chompret = 0.5 pts (PMID:11370630) and Classical = 1 point (PMID: 25945745) Ambry labs: Chompret = 0.5 pts Invitae Lab: Chompret = 0.5 pts 4 total points

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#### Not Met criteria codes

<b>PP3</b>	✗	aGVGD class C0 (benign) but BayesDel 0.4419>0.16 (path)
<b>PM5</b>	✗	M237T (ID: 481069, VUSx2); M327R (ID: 419524, VUSx1); M237K (ID: 376636, LP somatic only); M237V (ID: 182934, VUSx2)
<b>PM2</b>	✗	Present in 1/17692 East Asian alleles in gnomAD (non-cancer); AF = 0.0057%
<b>BS1</b>	✗	Present in 1/17692 East Asian alleles in gnomAD (non-cancer); AF = 0.0057%
<b>BS3</b>	✗	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>BS2</b>	✗	Absent from FLOSSIES. Internal data not received by some ClinVar submitters.
<b>BP4</b>	✗	aGVGD class C0 (benign) but BayesDel 0.4419>0.16 (path)
<b>BA1</b>	✗	Present in 1/17692 East Asian alleles in gnomAD (non-cancer); AF = 0.0057%

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