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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
UUID: 98acfed4-de66-4a8c-b6ba-bc9a67cd4189
Approved on: 2021-04-20
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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
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NM_001126117.1:c.315G>A
NM_001126118.1:c.594G>A
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NM_001276698.1:c.234G>A
NM_001276699.1:c.234G>A
NM_001276760.1:c.594G>A
NM_001276761.1:c.594G>A
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NM_001276760.2:c.594G>A
NM_001276761.2:c.594G>A
NM_000546.6:c.711G>A
NM_001126112.3:c.711G>A
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NM_001126117.2:c.315G>A
NM_001126118.2:c.594G>A
NM_001276695.3:c.594G>A
NM_001276696.3:c.594G>A
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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

PP1_Moderate PM6_Supporting PS3 PS4 PM1

Not Met criteria codes 8

BP4 BS1 BS3 BS2 PP3 PM5 PM2 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.

Met criteria codes

PP1_Moderate	✔	6 meioses in across 2 families (NIH, Invitae)
PM6_Supporting	✔	Assumed de novo in female with breast cancer in 30s (0.5 pts; GeneDx)
PS3	✔	Nonfunctional by Kato; LOF by Kotler; LOF+DNE by Giacomelli
PS4	✔	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
PM1	✔	55/64 samples on cancerhotspots.com

Not Met criteria codes

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

Curation History

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