

Variant: NM_000314.8(PTEN):c.355G>T (p.Val119Phe)

Version: 1.1

CA377482258 [↗](#)

428193 (ClinVar) [↗](#)

Gene: PTEN ([HGNC:5728](#))

Condition: PTEN hamartoma tumor syndrome ([MONDO:0017623](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: d34e6361-5beb-4bbe-8bea-c9891ddec52e

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HGVS expressions

NM_000314.8(PTEN):c.355G>T (p.Val119Phe)

NM_000314.8:c.355G>T

NC_000010.11:g.87933114G>T

CM000672.2:g.87933114G>T

NC_000010.10:g.89692871G>T

CM000672.1:g.89692871G>T

NC_000010.9:g.89682851G>T

NG_007466.2:g.74676G>T

ENST00000700029.2:c.355G>T

ENST00000710265.1:c.355G>T

ENST00000472832.3:c.355G>T

ENST00000688158.2:n.1090G>T

ENST00000688922.2:c.*185G>T

ENST00000700021.1:c.310G>T

ENST00000700022.1:c.355G>T

ENST00000700029.1:c.189G>T

ENST00000706954.1:c.355G>T

ENST00000706955.1:c.*390G>T

ENST00000686459.1:c.355G>T

ENST00000688158.1:c.*466G>T

ENST00000688308.1:c.355G>T

ENST00000688922.1:c.276G>T

ENST00000693560.1:c.874G>T

ENST00000371953.8:c.355G>T

ENST00000371953.7:c.355G>T

ENST00000498703.1:n.181G>T

ENST00000610634.1:c.253G>T

NM_000314.5:c.355G>T

NM_000314.6:c.355G>T

NM_001304717.2:c.874G>T

NM_001304718.1:c.-396G>T

NM_000314.7:c.355G>T

NM_001304717.5:c.874G>T

NM_001304718.2:c.-396G>T

Likely Pathogenic

Met criteria codes 5

PP2PP3PM5PM2PS3_Moderate

Not Met criteria codes 3

PP1PP4PS4

Evidence Links 1

Expert Panel

PTEN VCEP

Criteria Specification Information

Criteria Specification: ClinGen PTEN Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for PTEN Version 3.1.0

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

PTEN VCEP

PTEN c.355G>T (p.Val119Phe) meets criteria to be classified as likely pathogenic for PTEN Hamartoma Tumor syndrome in an autosomal dominant manner using modified ACMG criteria (ACMG Classification Rules Specified for PTEN Variant Curation version 3.1.0). Please see a summary of the rules and criteria codes in the “PTEN ACMG Specifications Summary” document (assertion method column). PS3_M: Functional studies supportive of a damaging effect on the gene or gene product. Score of this variant = -2.07 ($\leq$ -1.11) on a high throughput phosphatase assay (PMID 29706350). PM5: Missense change at an amino acid residue where a different missense change determined to be pathogenic or likely pathogenic and with equal or lesser BLOSUM62 score has been seen before (ClinVar Variation ID 3256748). PP3: REVEL score > 0.7 (score of this variant = 0.966). PP2: PTEN is defined by the PTEN Expert Panel as a gene that has a low rate of benign missense variation and where missense variants are a common mechanism of disease. PM2_P: Absent in large sequenced populations (PMID 27535533).

Met criteria codes

PP2	<div><div>i</div><div>✓</div></div>	Missense
PP3	<div><div>i</div><div>✓</div></div>	REVEL score (0.966) > 0.7
PM5	<div><div>i</div><div>✓</div></div>	BLOSUM score for focal variant (V>F: -1) $\leq$ BLOSUM score for 1 close match (V>A: 1) recently classified as LP (discussed at 4/4/25 VCEP meeting, pending approval in VCI).
PM2	<div><div></div><div>✓</div></div>	Absent in gnomAD v2 and v4
PS3_Moderate	<div><div>i</div><div>✓</div></div>	<div>Data from Mighell et al. is now eligible for PS3_Moderate (see update below).</div> <div>High throughput functional study to test lipid phosphatase activity using artificial humanized yeast model. The fitness score was -2.067 (true) for this variant which is in hypomorphic/inconclusive range (less than -2.13 would be truncation-like). Update: Based on PTEN VCEP criteria v3.1.0, the Mighell data is now eligible for PS3_M (Phosphatase activity $\leq$ -1.11) <div>PubMed:29706350</div></div>

Not Met criteria codes

PP1	<div><div>i</div><div>✗</div></div>	
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Ambry (1 meiosis): Proband (F) w/ renal ca @ 30s, bilateral breast ca @50s, endo ca @ 50s, HC = 60.96 cm (>95%), skin tags, one lipoma, thyroid nodules, oral lesions, colon polyps (“HP”, path data not available). Family Hx: Sister (pos for variant) w/ breast ca @ 50s, endo & ovarian ca @ 50s, 1 lipoma, HC = 58.42 cm, 6 colon polyps (“HP”); Brother (neg for variant) w/ colon polyps (3 villous adenoma @40s, 2 pre-cancerous @50s), skin lesions (unknown type); Mother (not tested-deceased) w/ breast ca @30s, endo @ 40s, CRC @ 60s. Ambry (external data share): Variant reported to segregate in one family, but variant carrier status not confirmed. Proband (< 10 yo) w/ HC +3.3 SD. Family Hx: Mother (30s) w/ HC +2.2 SD, thyroid goiter; Grandmother (GM) w/ ‘typical PHTS’ according to PTEN specialist (macrocephaly, obese, trichillemomas in face, high philtrum, gum hypertrophy, tongue papillomas, papillomas in mucosa); GM’s sister w/ multinodular struma, bilateral breast ca @ 40s (BRCA1/2 neg), obese, dysmorphic features; GM’s sister’s daughter w/ obese, thyroid problems (removed partially), hyperthyroidemia.

PP4



Ambry #1 Female dx with renal ca in 30s, bilateral breast ca in 50s, endometrial ca in 50s, head circumference 60.96 cm (>95%), skin tags, one lipoma, thyroid nodules, oral lesions, colon polyps (per clinical notes they needed to check path). CC score is too low at 18-24 depending on polyp number. Sister (POSITIVE): breast ca in 50s, endometrial ca in 50s, and ovarian ca in 50s, one lipoma, head circumference 58.42 cm, 6 colon polyps; Brother (NEGATIVE): colon polyps (3 villous adenomas in 40s, 2 pre-cancerous polyps in 50s), skin lesions (unknown type); Mother (not tested--deceased): breast ca in 30s, endometrial ca in 40s, and CRC in 60s.

PS4



Several probands with clinical evidence but not enough to contribute towards classification: Cleveland Clinic (Dr. Lamis Yehia pers comm): F in 40s w/ Macrocephaly (OFC 59 cm), Thyroid nodule, Hashimoto disease, breast fibrocystic disease, Lipoma, Hyperplastic benign polyp, Ovarian cysts, Pulmonary nodule, Oral mucosa papilloma, Uterine fibroids CC score = 19 Ambry (internal): F w/ renal ca @ 30s, bilateral breast ca @50s, endo ca @ 50s, HC = 60.96 cm (>95%), skin tags, one lipoma, thyroid nodules, oral lesions, colon polyps (“HP”, path data not available) CC score = 18. Proband’s sister (pos for variant): breast ca @ 50s, endo & ovarian ca @ 50s, 1 lipoma, HC = 58.42 cm, 6 colon polyps (“HP”) CC score = 15 Ambry (external data share): Proband (< 10 yo) w/ HC +3.3 SD. Family Hx: Mother (30s) w/ HC +2.2 SD, thyroid goiter; Grandmother ‘typical PHTS’ according to PTEN specialist - macrocephaly, obese, trichillemomas in face, high philtrum, gum hypertrophy, tongue papillomas, papillomas in mucosa CC score = 22;

Curation History

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