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

Version: 1.0

*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
**Approved on**: 2025-04-04
**Published on**: 2025-05-05

## *HGVS expressions*

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

PP2 PP3 PM5 PM2_Supporting PS3_Moderate

**Not Met criteria codes** 3

PS4 PP1 PP4

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 (PMID 30311380). 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 (≤ -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** | ✔ | Missense |
| **PP3** | ✔ | REVEL score (0.966) > 0.7 |
| **PM5** | ✔ | BLOSUM score for focal variant (V>F: -1) ≤ 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_Supporting** | ✔ | Absent in gnomAD v2 and v4 |
| **PS3_Moderate** | ✔ | Data from Mighell et al. is now eligible for PS3_Moderate (see update below).<br><br>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 ≤ -1.11) PubMed:29706350 |

**Not Met criteria codes**

| | | |
|---|---|---|
| **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, trichillemmomas in face, high philtrum, gum hypertrophy, tongue papillomas, papillomas in mucosa CC score = 22;

| | | | |
|---|---|---|---|
| **PP1** | ℹ | ✖ | 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, trichillemmomas 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. |

Curation History

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