The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000314.8(PTEN):c.476G>A (p.Arg159Lys)

Version: 1.0

CA377482801

646006 (ClinVar)

Gene: PTEN (HGNC:5728)
Condition: PTEN hamartoma tumor syndrome (MONDO:0017623)
Inheritance Mode: Autosomal dominant inheritance
UUID: 4cd22c47-1e9d-469a-8faf-fd5b3fcf863e
Approved on: 2025/10/3
Published on: 2025/10/27

HGVS expressions

NM_000314.8:c.476G>A
NM_000314.8(PTEN):c.476G>A (p.Arg159Lys)
NC_000010.11:g.87933235G>A
CM000672.2:g.87933235G>A
NC_000010.10:g.89692992G>A
CM000672.1:g.89692992G>A
NC_000010.9:g.89682972G>A
NG_007466.2:g.74797G>A
ENST00000700029.2:c.476G>A
ENST00000710265.1:c.476G>A
ENST00000472832.3:c.476G>A
ENST00000688158.2:n.1211G>A
ENST00000688922.2:c.*306G>A
ENST00000700021.1:c.431G>A
ENST00000700022.1:c.476G>A
ENST00000700029.1:c.310G>A
ENST00000706954.1:c.476G>A
ENST00000706955.1:c.*511G>A
ENST00000686459.1:c.476G>A
ENST00000688158.1:c.*587G>A
ENST00000688308.1:c.476G>A
ENST00000688922.1:c.397G>A
ENST00000693560.1:c.995G>A
ENST00000371953.8:c.476G>A
ENST00000371953.7:c.476G>A
ENST00000498703.1:n.302G>A
ENST00000610634.1:c.374G>A
NM_000314.5:c.476G>A
NM_000314.6:c.476G>A
NM_001304717.2:c.995G>A
NM_001304718.1:c.-275G>A
NM_000314.7:c.476G>A
NM_001304717.5:c.995G>A
NM_001304718.2:c.-275G>A

Pathogenic

Met criteria codes 6

PS3_Moderate PM6_Strong PS4_Moderate PM2_Supporting PP2 PP3

Not Met criteria codes 2

PM5 BS2

Evidence Links 0

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.476G>A (p.Arg159Lys) meets criteria to be classified as Pathogenic for PTEN hamartoma tumor syndrome in a autossomal dominant manner under ACMG criteria for PTEN gene v3 (PMID:30311380). Please see a summary of the rules and criteria codes in the "PTEN ACMG Specifications Summary" document (assertion method column). PS3_M: Phosphatase activity <-1.11 per Mighell et al. 2018 (PMID: 29706350). PP2: PTEN classified as a gene with missense variants that have low rate of benign missense variation and where missense variants are common mechanisms of disease. PP3: REVEL score (0.961) greater than 0.7. PM2_P: Variant absent on gnomad (v4). PM6_S: Assumed de novo case with strong PTEN-specific phenotype in patient (reported with extreme macrocephaly, autism and developmental delay, and seizures (Pediatric score +5) (internal laboratory contributor). PS4_M: Pediatric patient reported in Tuli et al. (PMID: 34184188) to have neonatal overgrowth, macrocephaly (+5.6 SD), developmental delay and periventricular leukomalacia.(Pediatric score +5. +1 proband point). Pediatric patient reported with developmental delay, macrocephaly and polymicrogyria. (Pediatric score +6, +1 proband point) (Internal laboratory contributor).

Met criteria codes

PS3_Moderate	✔	Phosphatase activity <-1.11 per Mighell et al. 2018 (PMID: 29706350).
PM6_Strong	✔	Assumed de novo pediatric patient with highly specific phenotype: macrocephaly, autism and developmental delay, and seizures (Pediatric score +5, meets PS4 criteria). (internal laboratory contributor).
PS4_Moderate	✔	Pediatric patient reported in Tuli et al. (PMID: 34184188) to have neonatal overgrowth, macrocephaly (+5.6 SD), developmental delay and periventricular leukomalacia. (Pediatric score +5. +1 proband point). Pediatric patient reported with developmental delay, macrocephaly and polymicrogyria. (Pediatric score +6, +1 proband point) (Internal laboratory contributor).
PM2_Supporting	✔	Variant absent on gnomad (v4).
PP2	✔	PTEN classified as a gene with missense variants that have low rate of benign missense variation and where missense variants are common mechanisms of disease.
PP3	✔	REVEL score (0.961) greater than 0.7.

Not Met criteria codes

PM5	✖	Novel missense change at amino acid position where different missense change has been deemed likely pathogenic. PTEN c.477G>T (p.Arg159Ser) classified as likely pathogenic by Clingen PTEN Variant Curation Panel. BLOSUM 62 score for Arg/Lys change greater than Arg/Ser change, due to this weight for PM5_M is not applied.
BS2	✖	Observed in one unaffected individual without homozygous status confirmed. (internal communication)

Curation History

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