

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

NM_000314.8:c.476G>A

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

PM6_Strong

PS4_Moderate

PP2

PP3

PM2_Supporting

PS3_Moderate

Not Met criteria codes 2

BS2

PM5

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

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).
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_Supporting			Variant absent on gnomad (v4).
PS3_Moderate			Phosphatase activity <-1.11 per Mighell et al. 2018 (PMID: 29706350).

Not Met criteria codes

BS2			Observed in one unaffected individual without homozygous status confirmed. (internal communication)
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.

Curation History



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