

Variant: *NM_000314.6(PTEN):c.722T>C (p.Phe241Ser)*

CA000555 [↗](#)

7850 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 5c047758-6fb8-4f71-9a53-077a7bf9a2c2

Approved on: 2018-11-28

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HGVS expressions

NM_000314.6:c.722T>C

NM_000314.6(PTEN):c.722T>C (p.Phe241Ser)

NC_000010.11:g.87957940T>C

CM000672.2:g.87957940T>C

NC_000010.10:g.89717697T>C

CM000672.1:g.89717697T>C

NC_000010.9:g.89707677T>C

NG_007466.2:g.99502T>C

ENST00000686459.1:c.*308T>C

ENST00000688158.1:c.*833T>C

ENST00000688308.1:c.722T>C

ENST00000688922.1:c.643T>C

ENST00000693560.1:c.1241T>C

ENST00000371953.8:c.722T>C

ENST00000371953.7:c.722T>C

ENST00000472832.2:c.149T>C

NM_000314.5:c.722T>C

NM_001304717.2:c.1241T>C

NM_001304718.1:c.131T>C

NM_000314.7:c.722T>C

NM_001304717.5:c.1241T>C

NM_001304718.2:c.131T>C

NM_000314.8:c.722T>C

NM_000314.8(PTEN):c.722T>C (p.Phe241Ser)

Likely Pathogenic

Met criteria codes 5

PM2_Supporting

PP2

PP3

PS4_Supporting

PS3_Moderate

Not Met criteria codes 21

BA1

BP3

BP1

BP4

BP2

BP7

BP5

BS2

BS1

BS3

BS4

PP4

PP1

PS1

PS2

PM5

PM4

PM1

PM3

PM6

PVS1

Evidence Links 9

Expert Panel

PTEN VCEP [↗](#)

Criteria Specification Information

[↗](#) **Criteria Specification:** ClinGen PTEN Expert Panel
Specifications to the ACMG/AMP Variant Interpretation
Guidelines for PTEN Version 3.0.0

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

PTEN VCEP

NM_000314.8(PTEN):c.722T>C (p.Phe241Ser) variant 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 3.0.0). 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. This variant: score of -2.39943 (≤ -1.11) on a high throughput phosphatase assay (PMID:29706350). PS4_P: Proband(s) with phenotype specificity score of 1-1.5. (PMID:15805158). PM2_P: Absent in large sequenced populations (PMID 27535533). 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. PP3: REVEL score > 0.7 (score=0.858).

Met criteria codes

PM2_Supporting			Absent in large sequenced populations in the gnomAD cohort. (PMID 27535533).
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.
PP3			REVEL score > 0.7 (score=0.858)
PS4_Supporting			Proband(s) with phenotype specificity score of 1-1.5. (PMID:15805158). 2.5yo male with overgrowth, DD, autistic features, extreme macrocephaly (+4-4.5SD) and penile freckling. Peds score = 8, 1 PP4 point. 2.5yo male with overgrowth, DD, autistic features, extreme macrocephaly (+4-4.5SD) and penile freckling. Peds score = 8, 1 PP4 point. PubMed:15805158 
PS3_Moderate			Functional studies supportive of a damaging effect on the gene or gene product. This variant: score of -2.39943 (≤ -1.11) on a high throughput phosphatase assay (PMID:29706350). Variant caused significant reduction (definitely $>50\%$) in phosphatase activity; only had scant rescue of cell growth in yeast assay (result described as +/-, WT +++). PubMed:21828076  Variant demonstrated decreased protein stability and PTEN expression. No significant increase in pAKT or neuronal cells, but authors posit this is due to lack of protein stability. PubMed:25527629  low (lowest) range protein abundance (score 0.17, range 0-1) PubMed:29785012  Variant appeared to impact parvalbumin/somatostatin ratios in mice neuronal cells. Also led to increased soma size. PubMed:25937288  Per abstract, variant failed to rescue neuronal hypertrophy (WT able to do so). Unable to access article, PubMed acting up. PubMed:29373119  truncation-like (lowest) range phosphatase activity (score -2.4, < -2.13 truncation-like) PubMed:29706350  Variant resulted in decreased protein stability. Also appeared to be unable to suppress tyrosine hydroxylase similar to other mutants. PubMed:26579216 

Not Met criteria codes

BA1			Absent in gnomAD; coverage looks good.
BP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1			Applying PP2 because of low rate of benign missense variation.
BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			Absent in gnomAD; coverage looks good.
BS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4			Moved to PS4. 2.5yo male with overgrowth, DD, autistic features, extreme macrocephaly (+4-4.5SD) and penile freckling. Peds score = 8, 1 PP4 point. PubMed:15805158  Variant reported in CCF PTEN study cohort, but no phenotype details provided. PubMed:21194675 
PP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2			

No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PM5			BUT F241L might get to PATH based on de novo observations per Yuen 2017. May need to curate.
PM4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1			Variant not within specified residues to apply criteria.
PM3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History [↗](#)



 

 

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