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_000314.6(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
Published on: 2018-12-10

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

PS3_Moderate PP2 PP3 PM2_Supporting PS4_Supporting

Not Met criteria codes 21

PVS1 PM6 PM5 PM4 PM1 PM3 BA1 BS2 BS1 BS3 BS4 BP3 BP1 BP4 BP2 BP7 BP5 PS1 PS2 PP4 PP1

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**

Evidence submitted by expert panel

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

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

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)

PM2_Supporting ✔

Absent in large sequenced populations in the gnomAD cohort. (PMID 27535533).

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

Not Met criteria codes

PVS1	✖	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
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
BA1	✖	Absent in gnomAD; coverage looks good.
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
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
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
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

Curation History

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