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# *Variant: NM_000314.6(PTEN):c.740T>C (p.Leu247Ser)*

Version: 1.1

*CA16044135*

*223142 (ClinVar)*

**Gene**: PTEN (HGNC:5728)
**Condition**: PTEN hamartoma tumor syndrome (MONDO:0017623)
**Inheritance Mode**: Autosomal dominant inheritance
**UUID:** 33e47859-5909-4f34-ac6c-c5bf41ab8544
**Approved on**: 2023/8/4
**Published on**: 2023/10/19

## *HGVS expressions*

**NM_000314.6(PTEN):c.740T>C (p.Leu247Ser)**
**NM_000314.6:c.740T>C**
NC_000010.11:g.87957958T>C
CM000672.2:g.87957958T>C
NC_000010.10:g.89717715T>C
CM000672.1:g.89717715T>C
NC_000010.9:g.89707695T>C
NG_007466.2:g.99520T>C
ENST00000700029.2:c.740T>C
ENST00000710265.1:c.740T>C
ENST00000472832.3:c.740T>C
ENST00000688158.2:n.1475T>C
ENST00000688922.2:c.*570T>C
ENST00000700021.1:c.695T>C
ENST00000700022.1:c.*79T>C
ENST00000700023.1:n.1898T>C
ENST00000700024.1:n.2132T>C
ENST00000700025.1:n.1509T>C
ENST00000700026.1:n.377T>C
ENST00000700029.1:c.574T>C
ENST00000706954.1:c.740T>C
ENST00000706955.1:c.*775T>C
ENST00000686459.1:c.*326T>C
ENST00000688158.1:c.*851T>C
ENST00000688308.1:c.740T>C
ENST00000688922.1:c.661T>C
ENST00000693560.1:c.1259T>C
ENST00000371953.8:c.740T>C
ENST00000371953.7:c.740T>C
ENST00000472832.2:c.167T>C
NM_000314.5:c.740T>C
NM_001304717.2:c.1259T>C
NM_001304718.1:c.149T>C
NM_000314.7:c.740T>C
NM_001304717.5:c.1259T>C
NM_001304718.2:c.149T>C
NM_000314.8:c.740T>C

**Likely Pathogenic**

**Met criteria codes** 5

PM6_Strong | PS3_Moderate | PP2 | PP3 | PM2_Supporting

**Not Met criteria codes** 21

PVS1 | BA1 | BP5 | BP7 | BP4 | BP3 | BP1 | BP2 | BS2 | BS1 | BS4 | BS3 | PP1 | PP4 | PM1 | PM3 | PM5 | PM4 | PS1 | PS2 | PS4

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 3.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

***PTEN VCEP***

**PTEN c.740T>C (p.Leu247Ser) 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). PM2_Supporting: Absent in large sequenced populations (PMID: 27535533). PM6_Strong: One proband with presumed de novo occurrence (maternity/paternity not confirmed) for a patient with highly specific phenotype. (PMIDs: 28086757 and 29752200) 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. PS3_Moderate: Functional studies showing a damaging effect on protein function. Phosphatase activity ≤ -1.11 per Mighell et al. 2018 (PMID: 29706350). This variant: score of -1.669765892. PP3: REVEL score > 0.7 (this variant: score=0.918).**

**Met criteria codes**

| | | |
|---|---|---|
| **PM6_Strong** | ✔ | Negishi et al reported that patient #5 had variant as confirmed de novo event (PMID: 28086757; Please note: Kato et al reported the same patient in PMID: 29752200). Added the upweight to PM6_Strong due to the 4.9mo female who had an OFC of 4.3 SD and developmental delay. Proband specificity score is 5. |
| **PS3_Moderate** | ✔ | Per new PTEN VCEP guidelines, PS3_M can be applied for functional scores in the hypomorphic range in Mighell et al. 2018. |
| **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 of 0.918 (>0.7) |
| **PM2_Supporting** | ✔ | Variant not found in gnomAD. |

**Not Met criteria codes**

| | | | |
|---|---|---|---|
| **PVS1** | | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| **BA1** | | ✖ | 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 |
| **BP7** | | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| **BP4** | | ✖ | 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** | | ✖ | 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 |
| **BS2** | | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| **BS1** | | ✖ | 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 |
| **BS3** | | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| **PP1** | | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| **PP4** | | ✖ | Patient #5 described in paper by Negishi et al is a 4.9mo female who has an OFC of 4.3 SD and developmental delay. Proband specificity score is 5 so PP4 can be applied. - JM agree but added to PS4 instead of PP4.<br><br>Patient #5 proband specificity score is 5. PubMed:28086757 |
| **PM1** | | ✖ | |

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

| | | | |
|---|---|---|---|
| **PM3** | | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| **PM5** | ℹ | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| **PM4** | ℹ | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| **PS1** | ℹ | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| **PS2** | ℹ | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| **PS4** | ℹ | ✖ | Proband specificity score of 5 for child = 1 point. PS4 weight was removed here and combined with PM6 to upweight to PM6_Strong. See PM6_Strong.<br><br>Per M. Perpich: Patient #5 described in paper by Negishi et al is a 4.9mo female who has an OFC of 4.3 SD and developmental delay. Proband specificity score is 5 so PP4 can be applied. PubMed:28086757 |

## Curation History

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