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.284C>T (p.Pro95Leu)

Version: 1.0

CA000383

189403 (ClinVar)

Gene: PTEN (HGNC:5728)
Condition: PTEN hamartoma tumor syndrome (MONDO:0017623)
Inheritance Mode: Autosomal dominant inheritance
UUID: 43eee6bc-e0e1-4ce0-8d9a-b838428c1884
Approved on: 2019/6/25
Published on: 2019/7/23

HGVS expressions

NM_000314.6(PTEN):c.284C>T (p.Pro95Leu)
NM_000314.6:c.284C>T
NC_000010.11:g.87933043C>T
CM000672.2:g.87933043C>T
NC_000010.10:g.89692800C>T
CM000672.1:g.89692800C>T
NC_000010.9:g.89682780C>T
NG_007466.2:g.74605C>T
ENST00000700029.2:c.284C>T
ENST00000710265.1:c.284C>T
ENST00000472832.3:c.284C>T
ENST00000688158.2:n.1019C>T
ENST00000688922.2:c.*114C>T
ENST00000700021.1:c.239C>T
ENST00000700022.1:c.284C>T
ENST00000700029.1:c.118C>T
ENST00000706954.1:c.284C>T
ENST00000706955.1:c.*319C>T
ENST00000686459.1:c.284C>T
ENST00000688158.1:c.*395C>T
ENST00000688308.1:c.284C>T
ENST00000688922.1:c.205C>T
ENST00000693560.1:c.803C>T
ENST00000371953.8:c.284C>T
ENST00000371953.7:c.284C>T
ENST00000498703.1:n.110C>T
ENST00000610634.1:c.182C>T
NM_000314.5:c.284C>T
NM_001304717.2:c.803C>T
NM_001304718.1:c.-467C>T
NM_000314.7:c.284C>T
NM_001304717.5:c.803C>T
NM_001304718.2:c.-467C>T
NM_000314.8:c.284C>T

Pathogenic

Met criteria codes 5

PS4_Supporting PP2 PM6 PM2 PS3

Not Met criteria codes 21

PP1 PP3 PP4 PM1 PM3 PM5 PM4 BA1 BS2 BS1 BS4 BS3 PS1 PS2 BP4 BP3 BP1 BP2 PVS1 BP5 BP7

Evidence Links 7

Expert Panel

PTEN VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

PTEN VCEP

PTEN c.284C>T (p.Pro95Leu) meets criteria to be classified as pathogenic for PTEN Hamartoma Tumor syndrome in an autosomal dominant manner using modified ACMG criteria (PMID 30311380). Please see a summary of the rules and criteria codes in the "PTEN ACMG Specifications Summary" document (assertion method column). PS3: Phosphatase activity <50% of wild type (PMID 21828076, PMID 29706350) PM2: Absent in large sequenced populations (PMID 27535533). PM6: Assumed de novo, but without confirmation of paternity and maternity in a patient with the disease and no family history. (internal laboratory contributor ClinVar Organization ID 26957) 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. PS4_P: Proband(s) with phenotype specificity score of 1-1.5. (internal laboratory contributor ClinVar Organization ID 26957)

Met criteria codes

PS4_Supporting ✔

Heald B et al. in a prospective series of PTEN mutation carriers reported subject 1515 has having > 50 hamartomas. The Herman Laboratory Nationwide Children's Hospital reported clinical data into Clinvar. The patient had macrocephaly (+6.4 SD) and > 40 colon polyps and 15 were > 1cm and all were juvenile polyps. It is unclear whether this patient is the same as the patient reported in Heald B et al. Tan et. al reported individual 20 as meeting relaxed International Consortium operational criteria for PTHS. Could meet PS4_S but need more phenotype information. Entry by MPerpich. KS: GeneDx internal data: male child with macrocephaly, penile freckling, developmental delay and pediatric proband score = 7. This case is also de novo, and reaches 1 phenotype specificity point. A second case of a female in her 40's with breast cancer and 3 colon polyps (adenomatous and hyperplastic). PTEN study data: Very likely this is the same patient as Heald et al., OFC = 60 cm, GI hamartomas (6), and GI poylps NOS (44), and CC score = 22.

PubMed:21194675
Macrocephaly (+6.4 SD); Colonoscopy with >40 polyps throughout the colon, 15 were >1cm, all were jevenile type.
PubMed:28526761
Likely is the same patient as Heald et al. and Tan et al. PubMed:25669429
Variant identified in 2 individuals in study. PubMed:21659347
PubMed:20600018

PP2 ✔

KS agrees.

PM6 ✔

Internal case from GeneDx: male child with macrocephaly, developmental delay and penile freckling (pediatric proband specificity score = 7).

PM2		✔	Variant is not present in gnomAD. KS agrees.
PS3	ℹ	✔	Escudero et al. (2011) demonstrated a high percentage of PIP3+ cells (similar to vector), no growth rescue and reduced PTEN activity in figure 4. Miguel et al. (2018) classified variant as truncation-like with a G score of -3.414242736. MPerpich entry. KS agrees. Matreyek results not available.

PubMed:29706350
PubMed:21828076

Not Met criteria codes

PP1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4		✖	Included under PS4.
PM1	ℹ	✖	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	✖	ClinVar entry for Pro95Thr, however that variant not is reported in the literature. Likely will not meet likely pathogenic/pathogenic at this time. May be reasonable to re-evaluate in future.
PM4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4	ℹ	✖	

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
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
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
PVS1	✖	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

Curation History

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