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.392C>T (p.Thr131Ile)

CA000442

39669 (ClinVar)

Gene: PTEN (HGNC:5728)
Condition: PTEN hamartoma tumor syndrome (MONDO:0017623)
Inheritance Mode: Autosomal dominant inheritance
UUID: 78613fd1-ded6-4249-b54d-0894617cf17d
Approved on: 2018-11-28
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HGVS expressions

NM_000314.6(PTEN):c.392C>T (p.Thr131Ile)
NM_000314.6:c.392C>T
NM_000314.5:c.392C>T
NM_001304717.2:c.911C>T
NM_001304718.1:c.-359C>T
NM_000314.7:c.392C>T
NM_001304717.5:c.911C>T
NM_001304718.2:c.-359C>T
ENST00000371953.7:c.392C>T
ENST00000498703.1:n.218C>T
ENST00000610634.1:c.290C>T
NC_000010.11:g.87933151C>T
CM000672.2:g.87933151C>T
NC_000010.10:g.89692908C>T
CM000672.1:g.89692908C>T
NC_000010.9:g.89682888C>T
NG_007466.2:g.74713C>T

Pathogenic

Met criteria codes 5

PM2 PM6_Strong PS4_Moderate PS3 PP2

Not Met criteria codes 18

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

Evidence Links 6

Expert Panel

PTEN VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

PTEN VCEP

PTEN c.392C>T (p.Thr131Ile) 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) PM6_S: Two probands with presumed de novo occurrence (maternity/paternity not confirmed) in a patient with the disease and no family history. (PMID 23160955, 23335809 author communication) PM2: Absent in large sequenced populations (PMID 27535533). PS4_M: Probands with phenotype specificity score of 2-3.5. (PMID 23160955, 23335809) 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.

Met criteria codes

PM2	✔	Absent in gnomAD
PM6_Strong	✔	De novo variant identified in Cauc male with autism, non-verbal IQ=50. OFC 57.8 cm at or under 4 yrs old. At least +5SD, z-score +4.7 per article. Pt in study via Simons Simplex Collection. Pt ID 14433.p1. Pt tested via exome but parents tested targeted only. PubMed:23160955 Info unpublished, but per Dr. Longy, parents of pt 74 are unaffected and both negative for variant. PubMed:23335809 Reported de novo variant in child with macrocephaly and autism; variant absent in a sibling, affected status unknown. Pts recruited from National Database for Autism research BUT study ID (14 433) way too similar to O'Roak, appears to be same individual. PubMed:28250423
PS4_Moderate	✔	JM: bumped up to PS4_moderate with 2 total phenotype points (1 for Bubien, 1 for O'Roak) Identified in child with extreme macrocephaly and autism. See de novo section. 1 point. Patient was reported as male with speech delay, low verbal and non-verbal IQ PubMed:23160955 Identified in pts 73/74 (child and parent). Child is proband pt 73, had macrocephaly (55.5cm) and MR/autism/ADD. Parent had targeted testing, history of macrocephaly (62cm) , polyps (pseudo polyps and lymphoid hyperplasia), benign thyroid (MNG) and breast disease (mild fibrocystic mastopathy). Reached out to Dr. Longy for details: Dear Jessica, Thank for your note. I confirm that patient 73 is the son of patient 74. Patient 73: born in 2002, observed in 2005 (3 years old). Macrocephaly: 55.5 cm (+4DS); delay in acquisitions and attention deficit. Patient 74: born In 1974, observed in 2005 (31 years old). Macrocephaly: 62 cm; colonoscopy in 2007 showing pseudo polyps with lymphoid hyperplasia, unoperated thyroid goiter and mild fibrocystic mastopathy. To note that the father and the mother of patient 74 , phenotypically normal, are non-carrier of the PTEN T131I. To note also that I was contacted by William Foulkes in 2015 because he had to follow a boy with the same mutation and autism disorder. PubMed:23335809
PS3	✔	Variant categorized as "WT-like" on VAMPseq high throughput assay assessing protein abundance as a measure of stability. PubMed:29785012 Variant demonstrated loss of phosphatase activity on in vitro assay, also showed lack of growth rescue capability. PubMed:21828076 Variant in hypomorphic range (score -1.91) on high-throughput phosphatase assay PubMed:29706350
PP2	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Not Met criteria codes

PM5	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1	✖	Absent in gnomAD
BS1	✖	Absent in gnomAD
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
BS2	✖	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
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
PVS1	✖	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	✖	De novo variant identified in Cauc male with autism, non-verbal IQ=50. OFC 57.8 cm at or under 4 yrs old. At least +5SD, z-score +4.7 per article. Pt in study via Simons Simplex Collection. Pt ID 14433.p1. Pt tested via exome but parents tested targeted only. PubMed:23160955 Info unpublished, but per Dr. Longy, parents of pt 74 are unaffected and both negative for variant. PubMed:23335809

Reported de novo variant in child with macrocephaly and autism; variant absent in a sibling, affected status unknown. Pts recruited from National Database for Autism research BUT study ID (14 433) way too similar to O'Roak, appears to be same individual. PubMed:28250423

PP3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4	✖	Individual 73 has macrocephaly (55.5cm) and ADD/autism which provides a CC score of 5 or 1 point or PP4. Moved to PS4. See explanation PubMed:23335809
PP1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

Showing 1 to 1 of 1 rows

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