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.278A>G (p.His93Arg)

CA000381

7848 (ClinVar)

Gene: PTEN (HGNC:5728)
Condition: PTEN hamartoma tumor syndrome (MONDO:0017623)
Inheritance Mode: Autosomal dominant inheritance
UUID: 902dd050-bb88-4ce6-b98d-dd80cbc3aa5e
Approved on: 2018-11-28
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HGVS expressions

NM_000314.6:c.278A>G
NM_000314.6(PTEN):c.278A>G (p.His93Arg)
NC_000010.11:g.87933037A>G
CM000672.2:g.87933037A>G
NC_000010.10:g.89692794A>G
CM000672.1:g.89692794A>G
NC_000010.9:g.89682774A>G
NG_007466.2:g.74599A>G
NM_000314.5:c.278A>G
NM_001304717.2:c.797A>G
NM_001304718.1:c.-473A>G
NM_000314.7:c.278A>G
NM_001304717.5:c.797A>G
NM_001304718.2:c.-473A>G
ENST00000371953.7:c.278A>G
ENST00000498703.1:n.104A>G
ENST00000610634.1:c.176A>G

Pathogenic

Met criteria codes 6

PS4_Supporting PP2 PS2 PM1 PM2 PS3_Supporting

Not Met criteria codes 17

BP4 BP2 BP7 BP5 BS2 BS1 BS3 BS4 PP3 PP1 PP4 PS1 BA1 PM5 PM4 PM6 PVS1

Evidence Links 11

Expert Panel

PTEN VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

PTEN VCEP

PTEN c.278A>G (p.His93Arg) 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). PS2: De novo (both maternity and paternity confirmed) observation in a patient with the disease and no family history. (internal laboratory contributor(s) ClinVar Organization ID: 26957) PM1: Located at a residue within a catalytic motif as defined by the ClinGen PTEN Expert Panel. PM2: 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. PS3_P: Abnormal in vitro cellular assay or transgenic model with phenotype different from wild type that does not meet PS3. (PMID 26579216, 25647146, 20718038, 21828076, 29373119, 29785012, 29706350) PS4_P: Proband(s) with phenotype specificity score of 1-1.5. (PMID 15805158, internal laboratory contributor(s) ClinVar Organization ID: 26957)

Met criteria codes

PS4_Supporting	✔	0.5 points for internal GDx case, 1 point Butler 2005 case. 1.5 total phenotype specificity points. Present in 4yo Cauc M with extreme macrocephaly (+8 SD), autism/DD, enlarged perivascular spaces. Peds score = 7, 1 PP4. PubMed:15805158
PP2	✔	Applying PP2 because of low rate of benign missense variation.
PS2	✔	1 GDx internal case, confirmed de novo via WES in 4yo Asian M with OFC +3.5-4SD, DD, polymicrogyria, hypotonia. No other exome diagnoses. De novo (paternity but not maternity confirmed by genotyping) in boy with extreme macrocephaly, autism/DD, enlarged perivascular spaces. PubMed:15805158
PM1	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM2	✔	Absent in gnomAD, but present in PAGE below? Discuss.
PS3_Supporting	✔	PS3_supporting applied following functional subgroup discussion. Variant led to catalytic activity of 3% compared to WT as measured by thermostability. PubMed:25647146 Variant looks to have partial phosphatase activity, capable of rescuing cell growth on yeast assay. Would not apply criteria. PubMed:21828076 H93R prefers to bind Phosphatidylserine (PS) ?over PIP3 and has high affinity for plasma membrane; similar to Redfern results. PubMed:22505997 variant abundance in "possibly WT-like" range, indicating no striking impact on protein stability PubMed:29785012 Studies focused on this variant. In U87MG cells, led to 15% of WT phosphatase activity (C124S was totally null) and increased pAKT expression on Western blot. Variant led to enhanced plasma membrane association. Article calls variant "autism-related" but doesn't provide citation for that assertion. PubMed:20718038 Article not yet available; per abstract, variant unable to rescue neuronal hypertrophy in mice (WT able to do so). PubMed:29373119 score 0.03, in "wild type-like" range PubMed:29706350 H93R unable to suppress expression of tyrosine hydroxylase. Variant also led to unstable protein; 80% degraded after 8 hours of cycloheximide tx (WT unchanged). PubMed:26579216

Not Met criteria codes

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, but present in PAGE below? Discuss.
BS3	✖	PS3_supporting applied following functional subgroup discussion.
BS4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	✖	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	✖	0.5 points for internal GDx case, 1 point Butler 2005 case. Moved to PS4. Variant listed in Table S2 with no specific phenotype information, however author overlap and most likely patient overlap. **PubMed:21194675** Reported in pt with eosinophilic colitis and PHTS; also had polyps, but no other helpful phenotype info provided. From CCF cohort. **PubMed:24345843** Present in 4yo Cauc M with extreme macrocephaly (+8 SD), autism/DD, enlarged perivascular spaces. Peds score = 7, 1 PP4. **PubMed:15805158**
PS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1	✖	Absent in gnomAD, but present in PAGE below? Discuss.

PM5	✖	H93Y in HGMD; could work up if needed to see if could help get this to PATH.
PM4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6	✖	Met but don't wish to duplicate de novo evidence, given PS2 also applied. De novo (paternity but not maternity confirmed by genotyping) in boy with extreme macrocephaly, autism/DD, enlarged perivascular spaces. PubMed:15805158
PVS1	✖	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