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.320A>T (p.Asp107Val)

Version: 1.0

CA16042748

372481 (ClinVar)

Gene: PTEN (HGNC:5728)
Condition: PTEN hamartoma tumor syndrome (MONDO:0017623)
Inheritance Mode: Autosomal dominant inheritance
UUID: af7069ee-474b-491e-9317-5e91eeba5b76
Approved on: 2019/6/25
Published on: 2019/7/23

HGVS expressions

NM_000314.6(PTEN):c.320A>T (p.Asp107Val)
NM_000314.6:c.320A>T
NC_000010.11:g.87933079A>T
CM000672.2:g.87933079A>T
NC_000010.10:g.89692836A>T
CM000672.1:g.89692836A>T
NC_000010.9:g.89682816A>T
NG_007466.2:g.74641A>T
ENST00000700029.2:c.320A>T
ENST00000710265.1:c.320A>T
ENST00000472832.3:c.320A>T
ENST00000688158.2:n.1055A>T
ENST00000688922.2:c.*150A>T
ENST00000700021.1:c.275A>T
ENST00000700022.1:c.320A>T
ENST00000700029.1:c.154A>T
ENST00000706954.1:c.320A>T
ENST00000706955.1:c.*355A>T
ENST00000686459.1:c.320A>T
ENST00000688158.1:c.*431A>T
ENST00000688308.1:c.320A>T
ENST00000688922.1:c.241A>T
ENST00000693560.1:c.839A>T
ENST00000371953.8:c.320A>T
ENST00000371953.7:c.320A>T
ENST00000498703.1:n.146A>T
ENST00000610634.1:c.218A>T
NM_000314.5:c.320A>T
NM_001304717.2:c.839A>T
NM_001304718.1:c.-431A>T
NM_000314.7:c.320A>T
NM_001304717.5:c.839A>T
NM_001304718.2:c.-431A>T
NM_000314.8:c.320A>T

Pathogenic

Met criteria codes 6

PM6 PM2 PS3 PS4_Moderate PP1 PP2

Not Met criteria codes 20

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

Evidence Links 5

Expert Panel

PTEN VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

PTEN VCEP

PTEN c.320A>T (p.Asp107Val) 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 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. (PMID 25418537) PS4_M: Probands with phenotype specificity score of 2-3.5. (PMID 28526761, PMID 23886400, internal laboratory contributor SCV000490750.2) PP1: Co-segregation with disease in multiple affected family members, with 3 or 4 meioses observed. (PMID 28526761, PMID 23886400, internal laboratory contributor SCV000490750.2) 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

PM6	✔	Variant occurred de novo in a child in the autism simplex cohort; methods appear to have been targeted to known candidate genes, not exome-based, but paper notes "paternity firmly established" via other variant info. May review with team to see whether would wish to apply PM6 or PS2. KS: Agrees and suggests applying PM6. PubMed:25418537
PM2	✔	absent gnomAD. KS agrees.
PS3	✔	KS agrees. Variant showed low protein abundance (score 0.17), PS3 already applied to phosphatase data. PubMed:29785012 Variant showed truncation-like phosphatase activity (score -2.85) PubMed:29706350
PS4_Moderate	✔	1 GDx internal case with peds score = 6, 1 phenotype point; in addition to other lit reports, 2.5 points total, moderate evidence. KS agrees. Proband had glycogenic acanthosis of the esophagus, keratosis of the hands and of the feet and juvenile polyps. He later developed a metastatic and locally advanced rectal cancer and hamartomatous small stomach polyps. minimum CC score = 27, 0.5 phenotype points. Daughter also positive for variant (but age unknown), her hx

includes hamartomatous colon polyps since the age of 10. She was also affected by Hashimoto disease and arteriovenous malformation and showed small facial keratosis. PubMed:23886400

Variant in pt PC0018: 19yo M with extreme macrocephaly, evaluated at age 17yrs (62.5cm, +5.6SD at 17 yrs), autism/ID, thyroid nodules, penile freckling, 1 oral papilloma, clinical dx of CS. Peds score = 13, 1 phenotype point. PubMed:28526761

Seen de novo in 4yo M with autism and macrocephaly +3.44SD, no other features noted. No phenotype points. PubMed:25418537

PP1	✔	3 meioses total (1 Paparo, 1 Hansen-Kiss, 1 GDx internal family) Variant identified in proband described in PS4 section, variant also present in his daughter with hamartomatous colon polyps since the age of 10. She was also affected by Hashimoto disease and arteriovenous malformation and showed small facial keratosis. 1 meiosis. PubMed:23886400 Variant in pt PC0018: M with extreme macrocephaly, evaluated at age 17yrs (62.5cm, +5.6SD at 17 yrs), autism/ID, thyroid nodules, penile freckling, 1 oral papilloma, clinical dx of CS. Variant inherited from mother with macrocephaly (60.5cm), Hashimoto's and thyroid nodules, breast cancer dx @40y, multiple polyps. 1 meiosis. PubMed:28526761
PP2	✔	KS agrees.

Not Met criteria codes

PVS1	✖	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	✖	Variant identified in proband described in PS4 section, variant also present in his daughter with hamartomatous colon polyps since the age of 10. She was also affected by Hashimoto disease and arteriovenous malformation and showed small facial keratosis. 1 meiosis. PubMed:23886400 Variant in pt PC0018: M with extreme macrocephaly, evaluated at age 17yrs (62.5cm, +5.6SD at 17 yrs), autism/ID, thyroid nodules, penile freckling, 1 oral papilloma, clinical dx of CS. Variant inherited from mother with macrocephaly (60.5cm), Hashimoto's and thyroid nodules, breast cancer dx @40y, multiple polyps. 1 meiosis. PubMed:28526761
BS3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5	✖	GeneDx internal data: Patient with PALB2 variant.
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
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	✖		KS: D107N, D107G, D107Y are present in HGMD, however already meets pathogenic so not necessary to work these up.
PM4	✖		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	✖		PubMed:25418537
BA1	✖		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
PP4	✖		incorporated into PS4.

Curation History

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