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_000314.7(PTEN):c.464A>G (p.Tyr155Cys)

Version: 1.0

CA16613246

404168 (ClinVar)

Gene: PTEN (HGNC:5728)
Condition: PTEN hamartoma tumor syndrome (MONDO:0017623)
Inheritance Mode: Autosomal dominant inheritance
UUID: dab6b7c8-ee3d-4d08-bdd5-ffb0fee948cd
Approved on: 2019/11/22
Published on: 2019/12/11

HGVS expressions

NM_000314.7:c.464A>G
NM_000314.7(PTEN):c.464A>G (p.Tyr155Cys)
NC_000010.11:g.87933223A>G
CM000672.2:g.87933223A>G
NC_000010.10:g.89692980A>G
CM000672.1:g.89692980A>G
NC_000010.9:g.89682960A>G
NG_007466.2:g.74785A>G
ENST00000700029.2:c.464A>G
ENST00000710265.1:c.464A>G
ENST00000472832.3:c.464A>G
ENST00000688158.2:n.1199A>G
ENST00000688922.2:c.*294A>G
ENST00000700021.1:c.419A>G
ENST00000700022.1:c.464A>G
ENST00000700029.1:c.298A>G
ENST00000706954.1:c.464A>G
ENST00000706955.1:c.*499A>G
ENST00000686459.1:c.464A>G
ENST00000688158.1:c.*575A>G
ENST00000688308.1:c.464A>G
ENST00000688922.1:c.385A>G
ENST00000693560.1:c.983A>G
ENST00000371953.8:c.464A>G
ENST00000371953.7:c.464A>G
ENST00000498703.1:n.290A>G
ENST00000610634.1:c.362A>G
NM_000314.5:c.464A>G
NM_000314.6:c.464A>G
NM_001304717.2:c.983A>G
NM_001304718.1:c.-287A>G
NM_001304717.5:c.983A>G
NM_001304718.2:c.-287A>G
NM_000314.8:c.464A>G

Pathogenic

Met criteria codes 5

PS3 PS4 PP2 PM6 PM2

Not Met criteria codes 21

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

Evidence Links 9

Expert Panel

PTEN VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

PTEN VCEP

PTEN c.464A>G (p.Tyr155Cys) 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, 10866302, 29706350) PS4: Probands with phenotype specificity score of 4-15.5 (PMID 23399955, internal laboratory contributors SCV000579967.3, ClinVar Organization ID: 19864) PM6_S: Two probands with presumed de novo occurrence (maternity/paternity not confirmed) in a patient with the disease and no family history. (internal laboratory contributor ClinVar Organization ID: 26957) 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.

Met criteria codes

PS3 ✔

Miguell et al. table shows G score of -2.26881194 which is in the truncation-like range (< -2.13). Han et al. paper demonstrated variant as having no phosphatase activity compared to WT in Figure 2G. Rodriguez-Escudero et al completed a functional assessment of PTEN mutations related to PHTS. They demonstrated in Figure 6A that this variant had PIP3 (+) cells with activity of 100% which was similar to the vector activity. WT showed negligible activity. Phadngam S et al. evaluated ovarian cancer cells and PTEN protein expression. Figure 4C shows a theoretical 3D structure of Y155C and concluded that the presence of this mutation does not alter the structure of PTEN including the phosphatase domain (*discuss with group whether this is negates criteria). Smith et al. evaluated mutational effects that lead to PTEN-ASD and PTEN-cancer phenotypes. Using protein-dynamic structural-network analysis. They assessed the difference in closeness centrality at the network level and identified significant differences compared to WT (figures S5A and S5B). This variant is found in the central core of the protein. *Discuss figure 3 (residue-based betweenness centrality estimation plot) with group. Andres-Pons et al. identified a patient described to meet criteria of PHTS/Cowden with this variant. Yeast functional analysis (table 1) was conducted on this variant and found no reconstitution and low yeast protein expression level. Clinical features of patient could not be located in this paper or referenced papers by the authors.

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PubMed:17942903
Phadngam S et al. evaluated ovarian cancer cells and PTEN protein expression. Figure 4C shows a theoretical 3D structure of Y155C and concluded that the presence of this mutation does not alter the structure of PTEN including the phosphatase domain (*discuss with group whether this is negates criteria). PubMed:27829222
Miguell et al. table shows G score of -2.26881194 which is in the truncation-like range (< -2.13).
PubMed:29706350

Han et al. paper demonstrated variant as having no phosphatase activity compared to WT in Figure 2G.
PubMed:10866302

Rodriguez-Escudero et al completed a functional assessment of PTEN mutations related to PHTS. They demonstrated in Figure 6A that this variant had PIP3 (+) cells with activity of 100% which was similar to the vector activity. WT showed negligible activity. PubMed:21828076

Smith et al. evaluated mutational effects that lead to PTEN-ASD and PTEN-cancer phenotypes. Using protein-dynamic structural-network analysis. They assessed the difference in closeness centrality at the network level and identified significant differences compared to WT (figures S5C and S5D). This variant is found in the central core of the protein. *Discuss figure 3 (residue-based betweenness centrality estimation plot) with group.
PubMed:31006514

PS4		✔	4 phenotype points: 1 from internal Ambry case, 3 from Eng lab patients. Ngeow et al. reported on the prevalence of PTEN mutations in patients with moderate-load colorectal polyps. Supplementary table 2 describes a 66 yo female, individual (7421), as having macrocephaly, hyperplastic polyps, lipoma and benign breast disease. (*ask C.Eng if more clinical data and precise HC is available). Bubien et al. supplementary table lists individual 63 as having mucocutaneous lesions, oral mucosal papillomatosis, facial papules, macrocephaly, GI, GU, acral keratosis, lipomas/vascular, GU, benign thyroid, breast cancer and benign breast disease. Driessen G et al. table E1 describes 6yo and 37 yo males with macrocephaly and DD and macrocephaly. Internal data from Ambry: one case of female breast cancer patient in her 50's with 18 mixed tubular, hyperplastic, inflammatory polyps, Hashimoto's, endometrial polyps, leiomyoma, benign breast papillomas and fibroadenomas (CC score = 13). Less than 25 cut-off. Also male teenage patient with 9 colon polyps (hamartomas or juvenile), goiter and HC of 66-67cm. Peds score = 8 or proband specificity score of 1 point (assuming < age 18) which is compatible with PP4_supporting criteria. An additional case of a child with a HC of 52.5 cm was reported from internal data. Additional data from GeneDx: 1. female child with macrocephaly and hypotonia - assumed de novo (PM6), 2. male child with autism - assumed de novo (PM6), 3. pre-teen female with lipomas and polyps NOS, 4. adult female in her 40's with macrocephaly, AVM, breast ca 40's or younger, uterine fibroids (CC score = 19). Internal Data (Eng C Lab): 1. F, age 76 (consented age 66), OFC = 61cm, fibroadenoma of breast, fibrocystic disease, colon lipoma (1), skin tag CC score: 12; 2. F, age 61 (consented age 53), OFC = 63.5cm, goiter, hashimoto’s, breast ca age 53, intraductal papilloma of br, fibroadenoma, 4 adenomatous polyps, 1 inflammatory polyp, 11 hyperplastic polyps, 8 lower GI polyps (NOS), uterine fibroids, CC score = 22; 3. M, age 12 (consented age 5), OFC = 61.5cm, DD, ASD, dysmorphic, CC score = 7; 4. M, age 7 (consented age 5), OFC = 59cm, fibroadenoma finger, shoulder hemangioma (CC score N/A); 5. F, age 22 (consented age 21), OFC = 61com, thyroid nodule, DD, Fundic gland polyps x 2 (duodenal), 1 hamartomatous polyp (sigmoid), lipoma, papilloma, hemangioma of skin (chest wall), AVM, bilateral renal ca, CC score = 38 PubMed:23399955 PubMed:27531073 PubMed:23335809
PP2		✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6		✔	Additional data from GeneDx: 1. female child with macrocephaly and hypotonia - assumed de novo (PM6), 2. male child with autism - assumed de novo (PM6)
PM2		✔	Variant not reported in gnomAD database.

Not Met criteria codes

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
PP1	✖	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	✖	Ngeow et al. reported on the prevalence of PTEN mutations in patients with moderate-load colorectal polyps. Supplementary table 2 describes a 66 yo female, individual (7421), as having macrocephaly, hyperplastic polyps, lipoma and benign breast disease. (*ask C.Eng if more clinical data and precise HC is available). Ngeow et al. reported on the prevalence of PTEN mutations in patients with moderate-load colorectal polyps. Supplementary table 2 describes a 66 yo female, individual (7421), as having macrocephaly, hyperplastic polyps, lipoma and benign breast disease. (*ask C.Eng if more clinical data and precise HC is available). Internal data from Ambry: one case of female breast cancer patient in her 50's with 18 mixed tubular, hyperplastic, inflammatory polyps, Hashimoto's, endometrial polyps, leiomyoma, benign breast papillomas and fibroadenomas (CC score = 13). Less than 25 cut-off. Also male teenage patient with 9 colon polyps (hamartomas or juvenile), goiter and HC of 66-67cm. Peds score = 8 or proband specificity score of 1 point (assuming < age 18) which is compatible with PP4_supporting criteria. An additional case of a child with a HC of 52.5 cm was reported from internal data. Additional data from GeneDx: 1. female child with macrocephaly and hypotonia - assumed de novo (PM6), 2. male child with autism - assumed de novo (PM6), 3. pre-teen female with lipomas and polyps NOS, 4. adult female in her 40's with macrocephaly, AVM, breast ca 40's or younger, uterine fibroids (CC score = 19). PubMed:23399955
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	✖	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
BA1	✖	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
BS2		✖	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
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

Curation History

Showing 1 to 1 of 1 rows

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