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Variant: NM_000314.6(PTEN):c.755A>G (p.Asp252Gly)

CA000564

7849 (ClinVar)

Gene: PTEN (HGNC:5728)
Condition: PTEN hamartoma tumor syndrome (MONDO:0017623)
Inheritance Mode: Autosomal dominant inheritance
UUID: d7efe33c-ab88-4472-ad12-90db0ed372bf
Approved on: 2018-07-25
Published on: 2018-12-10

HGVS expressions

NM_000314.6(PTEN):c.755A>G (p.Asp252Gly)
NM_000314.6:c.755A>G
NC_000010.11:g.87957973A>G
CM000672.2:g.87957973A>G
NC_000010.10:g.89717730A>G
CM000672.1:g.89717730A>G
NC_000010.9:g.89707710A>G
NG_007466.2:g.99535A>G
ENST00000686459.1:c.*341A>G
ENST00000688158.1:c.*866A>G
ENST00000688308.1:c.755A>G
ENST00000688922.1:c.676A>G
ENST00000693560.1:c.1274A>G
ENST00000371953.8:c.755A>G
ENST00000371953.7:c.755A>G
ENST00000472832.2:c.182A>G
NM_000314.5:c.755A>G
NM_001304717.2:c.1274A>G
NM_001304718.1:c.164A>G
NM_000314.7:c.755A>G
NM_001304717.5:c.1274A>G
NM_001304718.2:c.164A>G
NM_000314.8:c.755A>G
NM_000314.8(PTEN):c.755A>G (p.Asp252Gly)

Pathogenic

Met criteria codes 6

PS4_Supporting PP2 PP3 PM6_Strong PS3_Moderate PM2_Supporting

Not Met criteria codes 20

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

Expert Panel

PTEN VCEP

Criteria Specification Information

Criteria Specification: *ClinGen PTEN Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for PTEN Version 3.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

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Evidence submitted by expert panel

PTEN VCEP

NM_000314.8(PTEN):c.755A>G (p.Asp252Gly) variant meets criteria to be classified as pathogenic for PTEN Hamartoma Tumor syndrome in an autosomal dominant manner using modified ACMG criteria (ACMG Classification Rules Specified for PTEN Variant Curation version 3.0.0). Please see a summary of the rules and criteria codes in the "PTEN ACMG Specifications Summary" document (assertion method column). PS6_S: One proband with presumed de novo occurrence (maternity/paternity not confirmed) for a patient with highly specific phenotype. (PMID: 23335809). PS3_M: Phosphatase activity ≤ -1.11 per Mighell et al. 2018, PMID: 29706350. 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. PP3: REVEL score > 0.7 (score=0.971) PM2_P: Absent in large sequenced populations OR present at extremely low (<0.00001, 0.001%) allele frequency in the gnomAD cohort. (PMID 27535533). PS4_P: Proband(s) with phenotype specificity score of 1-1.5. (PMID: 23335809).

Met criteria codes

PS4_Supporting	✔	This variant has been reported in one proband meeting pediatric phenotype criteria (Ped Score=5)(PS4_Supporting; Proband with ped score of 5 and phenotype specificity score of 1; Butler et al. 2005 PMID: 15805158).
PP2	✔	Applying PP2 because of low rate of benign missense variation.
PP3	✔	REVEL score of 0.971 (>0.7 - threshold) (FH)
PM6_Strong	✔	Variant reportedly de novo in a patient reported by Bubien et al, 2013 (PMID: 23335809) per personal communication with Dr. Longy and the patient has a peds score of 5, which would be 1 point counting toward PS4, which bumps PM6 up to PM6_Strong. [PM6_Strong may be used for a proband with presumed de novo occurrence for an individual with a highly specific phenotype (meets criteria to count towards PS4)]
PS3_Moderate	✔	Massively parallel functional assay interrogating phosphatase activity in Mighell et al. 2018 (PMID: 29706350) showed reduced phosphatase activity (Column I=TRUE; Column G=-2.1; PS3_Moderate). D252G demonstrated a partially active protein in yeast. PubMed:21828076 Authors demonstrated that wild-type PTEN can rescue the neuronal hypertrophy, while PTEN D252G failed to rescue this hypertrophy. A subset of these mutations lacked nuclear localization, prompting us to examine the role of nuclear PTEN in regulating neuronal growth. We found that nuclear PTEN alone is sufficient to regulate soma size. Furthermore, forced localization of the D252G into the nucleus partially restores regulation of soma size. PubMed:29373119 Variant scored in "hypomorphic" range (-2.1) on high throughput phosphatase assay - would not consider applying criteria. PubMed:29706350 Variant demonstrated decreased protein expression and stability (~60% of WT) when introduced in COS-7 or U87MG cells. PubMed:29706633 Variant demonstrated decreased protein expression, pAKT closer to WT than pos control C124S. Also showed decreased protein stability. PubMed:25527629

PM2_Supporting	✔	This variant is completely absent from gnomAD/ExAC databases (PM2_Supporting).

Not Met criteria codes

PP1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4	✖	Butler MG et al. 2005 PMID: 15805158 Reported in 3.5yo Cauc M with extreme macrocephaly (+7SD) and developmental delay. Mother with normal OFC negative, father with large OFC (61.2 cm) not tested. Peds score = 5. Note: Phenotype specificity has been incorporated into the rule specifications for PS4 Use 2. Reported in pt with mucocutaneous lesions, facial papules, OMP, macrocephaly. If pediatric, minimum peds score = 5. If adult, minimum CC score = 12. Per Dr. Longy, pt was 16yo F, OFC 65cm, and variant occurred de novo. Earns 1 PP4 pt based on this new info. PubMed:23335809 Seen in 3.5yo Cauc M with extreme macrocephaly (+7SD) and developmental delay. Mother with normal OFC negative, father with large OFC (61.2 cm) not tested. Peds score = 5. PubMed:15805158 Present in an individual in either the CCF or OSU PTEN study; no phenotype data provided. Could try to obtain if needed for classification. PubMed:21194675 1 patient fro OSU PTEN study with clinical features of CS/BRRS. Could be patient overlap. PubMed:21659347 Article references Butler et al., 2005 which identified a patient with D252G. No additional patient with D252G reported in this article. PubMed:17286265
PM3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1	✖	Variant not located in specific residues to apply criteria.
PM4	✖	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
BA1	✖	Absent in gnomAD
BS2	✖	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
BS1	✖	Absent in gnomAD

PS2		✖	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
BP2		✖	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		✖	Applying PP2 because of low rate of benign missense variation.
BP4		✖	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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