

Variant: NM_000314.6(PTEN):c.104T>G (p.Met35Arg)

Version: 1.0

CA000268 [↗](#)

7825 (ClinVar) [↗](#)

Gene: PTEN ([HGNC:5728](#))

Condition: PTEN hamartoma tumor syndrome ([MONDO:0017623](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: 2374c339-e2d7-4496-9d9a-d33c1abd8dce

Approved on: 2018/7/25

Published on: 2019/7/23

HGVS expressions

NM_000314.6:c.104T>G

NM_000314.6(PTEN):c.104T>G (p.Met35Arg)

NC_000010.11:g.87894049T>G

CM000672.2:g.87894049T>G

NC_000010.10:g.89653806T>G

CM000672.1:g.89653806T>G

NC_000010.9:g.89643786T>G

NG_007466.2:g.35611T>G

ENST00000700029.2:c.104T>G

ENST00000710265.1:c.104T>G

ENST00000472832.3:c.104T>G

ENST00000688158.2:n.899+13611T>G

ENST00000688922.2:c.104T>G

ENST00000700021.1:c.104T>G

ENST00000700022.1:c.104T>G

ENST00000706954.1:c.104T>G

ENST00000706955.1:c.*139T>G

ENST00000686459.1:c.104T>G

ENST00000688158.1:c.*275+13611T>G

ENST00000688308.1:c.104T>G

ENST00000693560.1:c.623T>G

ENST00000371953.8:c.104T>G

ENST00000371953.7:c.104T>G

ENST00000462694.1:n.106T>G

ENST00000610634.1:c.2T>G

NM_000314.5:c.104T>G

NM_001304717.2:c.623T>G

NM_001304718.1:c.-602T>G

NM_000314.7:c.104T>G

NM_001304717.5:c.623T>G

NM_001304718.2:c.-602T>G

NM_000314.8:c.104T>G

Pathogenic

Met criteria codes 4

PM2PS2PS3PP2

Not Met criteria codes 22

PM1PM3PM5PM4PM6BS2BS1BS4BS3PVS1PS1PS4BP5BP7BP4BP3BP1BP2BA1PP1PP3PP4

Evidence Links 3

Expert Panel

PTEN VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

PTEN VCEP		
PTEN c.104T>G (p.Met35Arg) 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. (PMID 9425889) PS3: Phosphatase activity <50% of wild type. (PMID 21828076, 25875300) 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		
PM2		variant not in gnomAD or other databases (MP) Per Felicia, I agree
PS2		Per Olschwang S et al, the genotypes at 8 highly polymorphic microsatellite loci in the parents and patient confirmed mendelian inheritance. Sequencing of exon 2 amplified from the DNAs of both parents revealed only codon 35 for methionine, demonstrating that codon 35 of arginine was a de novo mutation (FH). Per Expert Panel review, PS2 applies as opposed to PM6 (JM). Parents of patient with variant were tested and did not have variant. No proof of paternity documented/mentioned. PubMed:9425889
PS3		I agree (FH) Figure 6(A) demonstrates functional assessment of PTEN mutations in relation to PHTS hereditary syndromes. M35R shows approx 95% PIP3 positive cells and shows WT at 0%. Evidence of inhibited dephosphorylation. Might be useful to look at supplementary data (table S1). I could not find the supplementary table. PubMed:21828076 Figure 2: functional analysis of PTEN tumor suppressor function in vivo on a panel of N-terminal PTEN mutations including M35R. Shown in 2B, 2C and table 1, there is increased nuclear localization on a PTEN WT background when tested on mammalian COS-7 cells. A partial inhibition of nuclear accumulation was observed on a PTEN 1-375 background. PIP3 phosphatase activity was assessed next using S. cerevisiae heterologous reconstitution system. Fig 2D, 2E, Table 2, M35R totally abrogated PTEN activity in the yeast model. Figure 2D shows no galactose activity indicating non-functioning PTEN. PubMed:25875300
PP2		I Agree (FH)

Not Met criteria codes

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
PM6			Parents of patient G710 were negative for variant. I disagree with PM6 (FH) Parents of patient with variant were tested and did not have variant. No proof of paternity documented/mentioned. PubMed:9425889 
BS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			variant not in gnomAD or other databases (MP) Per Felicia, I agree
BS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3			I agree (FH)
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
PS4			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			I Agree (FH)
BP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1			variant not in gnomAD or other databases (MP) Per Felicia, I agree
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			I agree (FH)

Curation History 		
    		
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