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Variant: NM_000277.2(PAH):c.529G>A (p.Val177Met)

CA229609

102726 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 8e00de6f-21da-48a5-9606-f7afe7fbb6e5
Approved on: 2018-12-10
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HGVS expressions

NM_000277.2:c.529G>A
NM_000277.2(PAH):c.529G>A (p.Val177Met)
NC_000012.12:g.102855313C>T
CM000674.2:g.102855313C>T
NC_000012.11:g.103249091C>T
CM000674.1:g.103249091C>T
NC_000012.10:g.101773221C>T
NG_008690.1:g.67290G>A
NG_008690.2:g.108098G>A
NM_000277.1:c.529G>A
NM_001354304.1:c.529G>A
NM_000277.3:c.529G>A
ENST00000307000.7:c.514G>A
ENST00000549111.5:n.625G>A
ENST00000551988.5:n.550G>A
ENST00000553106.5:c.529G>A

Pathogenic

Met criteria codes 5

PP3 PM2 PM5 PP4_Moderate PM3_Strong

Evidence Links 2

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.529G>A (p.Val177Met) variant in PAH was detected in a patient with Mild hyperphenylalaninemia (BH4 deficiency ruled out). PMID: 12501224 It has been detected with known pathogenic variants R408W (PMID: 12501224), and IVS12+1G>A (PMID: 23764561). It is absent from 1000G, ESP, and gnomAD; and at extremely low frequency in ExAC (MAF=0.00003). A deleterious effect is predicted in SIFT, Polyphen-2, MutationTaster, and REVEL=0.89. A different pathogenic missense change has been seen at this amino acid (V177L). In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM3_strong, PM2, PM5, PP4_Moderate, PP3.

Met criteria codes

PP3	✔	Deleterious effect predicted in SIFT, Polyphen-2, MutationTaster. REVEL=0.89
PM2	✔	Absent from 1000G, ESP, gnomAD. Extremely low frequency in ExAC (MAF=0.00003).
PM5	✔	V177L Pathogenic in ClinVar
PP4_Moderate	✔	Detected in a patient with Mild hyperphenylalaninemia. BH4 deficiency ruled out. PMID: 12501224 38 children with various classes of hyperphenylalaninemia stratified according to the plasma phenylalanine concentration before treatment (normal, 30 to 120 µmol per liter). A defect in the synthesis or recycling of tetrahydrobiopterin was excluded by analysis of urinary pterins and dihydropteridine reductase activity in erythrocytes. V177M detected in Patient 9 with Mild hyperphenylalaninemia. PubMed:12501224
PM3_Strong	✔	Detected with R408W (PMID: 12501224), IVS12+1G>A (PMID: 23764561) Family 75 Genotype: IVS4+5G>T/p.V177M; Family 77 Genotype: IVS12+1G>A/p.V177M PubMed:23764561 Patient 9 genotype: V177M/R408W PubMed:12501224

Curation History

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