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Variant: NM_000277.3(PAH):c.529G>C (p.Val177Leu)

Version: 1.0

CA229610

102727 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: db42ee8e-361d-4756-8504-caeaf67f6741
Approved on: 2019/9/22
Published on: 2021/4/9

HGVS expressions

NM_000277.3(PAH):c.529G>C (p.Val177Leu)
NM_000277.3:c.529G>C
NC_000012.12:g.102855313C>G
CM000674.2:g.102855313C>G
NC_000012.11:g.103249091C>G
CM000674.1:g.103249091C>G
NC_000012.10:g.101773221C>G
NG_008690.1:g.67290G>C
NG_008690.2:g.108098G>C
ENST00000553106.6:c.529G>C
ENST00000307000.7:c.514G>C
ENST00000549111.5:n.625G>C
ENST00000551988.5:n.550G>C
ENST00000553106.5:c.529G>C
NM_000277.1:c.529G>C
NM_000277.2:c.529G>C
NM_001354304.1:c.529G>C
NM_001354304.2:c.529G>C

Pathogenic

Met criteria codes 3

PM3_Very Strong | PM2 | PP4_Moderate

Not Met criteria codes 1

PP3

Evidence Links 9

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.529G>C (p.Val177Leu) variant in PAH has been reported in multiple individuals with PAH deficiency (BH4 deficiency excluded). (PP4_Moderate). This variant has an extremely low allele frequency (Pop Max MAF=0.00005 ENF) in gnomAD (PM2). This variant was

detected with pathogenic variants: F39L, L48S, F39del, R408W, R261Q, F55fs, R158Q, Trp187*. Parental testing not reported. PMID: 8659548, PMID: 16879198, PMID: 19609714, PMID: 23430918, PMID: 22391997, PMID: 22513348, PMID: 26666653 (PM3_very-strong. Computational prediction tools and conservation analysis do not agree. In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM3_very-strong, PM2.

Met criteria codes

PM3_Very Strong	✔	Detected with pathogenic variants F39L, L48S, F39del, R408W, R261Q, F55fs, R158Q, Trp187*. Parental testing not reported. PMID: 8659548, PMID: 16879198, PMID: 19609714, PMID: 23430918, PMID: 22391997, PMID: 22513348, PMID: 26666653 Patient 50: p.R158Q/p.V177L. parental testing not reported. PubMed:22513348 p.V177L: p.R408W. parental testing not reported. PubMed:23430918 [V177L]+[F39del]. parental testing not reported. PubMed:19609714 Allele 2: F39L Parental testing not reported. PubMed:8659548 Patient 5, Allele 2: p.R261Q. Patient 8, Allele 2: p.F55fs. parental testing not reported. PubMed:22391997 c. [529G>C]; [561G>A] p.[Val177Leu];[Trp187*]. parental testing not reported. PubMed:26666653 L48S+V177L. parental testing not reported. PubMed:16879198
PM2	✔	Pop Max MAF=0.00005 ENF in gnomAD
PP4_Moderate	✔	Detected in multiple patients with PAH deficiency. BH4 deficiency excluded in one report. PMID: 22526846 Detected on 1 allele from a hyperphenylalaninemic female. Patient A/3098/RCR-10, Phe level 400 (MHP) PubMed:8659548 p.V177L (c.529G>C) was detected in this cohort. Elevated phenylalanine concentrations were detected by newborn screening and confirmed by quantitative analysis of plasma amino acids. Analysis of urinary pterins and dihydropterine reductase assays were performed to exclude BH4 deficiency (Nenad Blau, Zurich, Switzerland). PubMed:22526846 183 patients from six Dutch university medical centres. Detected in the cohort. PubMed:23842451

Not Met criteria codes

PP3	✖	Conflicting predictions: SIFT-D; PolyPhen2-B; MutationTaster-D

Curation History

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