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Variant: NM_000277.1(PAH):c.1169A>G (p.Glu390Gly)

CA114367

625 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 4917956e-57f9-44fe-959a-f93a579f02f2
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HGVS expressions

NM_000277.1:c.1169A>G
NM_000277.1(PAH):c.1169A>G (p.Glu390Gly)
NC_000012.12:g.102843676T>C
CM000674.2:g.102843676T>C
NC_000012.11:g.103237454T>C
CM000674.1:g.103237454T>C
NC_000012.10:g.101761584T>C
NG_008690.1:g.78927A>G
NG_008690.2:g.119735A>G
NM_000277.2:c.1169A>G
NM_001354304.1:c.1169A>G
NM_000277.3:c.1169A>G
ENST00000307000.7:c.1154A>G
ENST00000549247.6:n.928A>G
ENST00000551114.2:n.831A>G
ENST00000553106.5:c.1169A>G
ENST00000635477.1:n.273A>G
ENST00000635528.1:n.684A>G

Pathogenic

Met criteria codes 4

PP3 PM2 PM3_Very Strong PP4_Moderate

Not Met criteria codes 1

PS3

Evidence Links 3

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.1169A>G (p.Glu390Gly) variant in PAH has been reported on at least 47 alleles, most often with Mild Hyperphenylalaninemia. (BH4 deficiency excluded). (PP4_Moderate; PMID: 8088845; PMID: 21147011). This variant has an extremely low allele frequency (MAF=0.00018

in gnomAD) (PM2; http://gnomAD.broadinstitute.org). This variant was detected in trans with IVS-12nt1, L333F (Pathogenic in ClinVar) + 8 homozygotes (PM3_Very-strong; PMID: 10479481; PMID: 21147011; PMID: 8088845). Computational prediction tools and conservation analysis suggest that the c.1169A>G variant may impact the protein (PP3). In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM3_Very-strong

Met criteria codes

PP3	✔	Predicted deleterious in SIFT, PolyPhen2, MutationTaster (automatic) and PROVEAN
PM2	✔	Extremely low frequency in ExAC, gnomAD (MAF 0.00018), 1000G, ESP
PM3_Very Strong	✔	E390G in trans with IVS-12nt1, L333F (Pathogenic in ClinVar) + 8 homozygotes PMID: 10479481; PMID: 21147011; PMID: 8088845 compound heterozygosity: L333F (VarID624, Pathogenic)/ E390G **PubMed:10479481** Found in Patient V: E390G/IVS-12nt1 (VarID 576) pathogenic in ClinVar **PubMed:8088845** 8 homozygotes reported **PubMed:21147011**
PP4_Moderate	✔	E390G seen on at least 47 alleles (PMID: 8088845; PMID: 21147011), most often associated with MHP. BH4 deficiencies ruled out in 1 study. Upgraded per ClinGen PAHEP Patient V: E390G/IVS-12nt1, median serum Phe 550 uM (270-820). **PubMed:8088845** 588 hyperphenylalaninemic patients were investigated. Assessment of the PAH gene and genes of the BH4 synthesis/recycling pathways (PTS, and QDPR). E390G was found on 46 alleles, most often associated with MHP (blood Phe <600 µmol/L). **PubMed:21147011**

Not Met criteria codes

PS3	✖	In vitro PAH activity ~70% of wt PAH activity in COS cell homogenates following transient expression of wild- type and mutant cDNA constructs. E390G mutant had 70% activity. **PubMed:10479481** E390G PAH activity reported as 72.5% of wt when recombinantly expressed in eukaryotic cell system **PubMed:21147011**

Curation History

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