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Variant: NM_000277.1(PAH):c.1197A>T (p.Val399=)

Version: 1.0

CA229379

601 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 2e857d40-9a55-4adc-a5f1-92f85b42ab6a
Approved on: 2018-07-28
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HGVS expressions

NM_000277.1:c.1197A>T
NM_000277.1(PAH):c.1197A>T (p.Val399=)
NC_000012.12:g.102843648T>A
CM000674.2:g.102843648T>A
NC_000012.11:g.103237426T>A
CM000674.1:g.103237426T>A
NC_000012.10:g.101761556T>A
NG_008690.1:g.78955A>T
NG_008690.2:g.119763A>T
NM_000277.2:c.1197A>T
NM_001354304.1:c.1197A>T
NM_000277.3:c.1197A>T
ENST00000307000.7:c.1182A>T
ENST00000549247.6:n.956A>T
ENST00000551114.2:n.859A>T
ENST00000553106.5:c.1197A>T
ENST00000635477.1:n.301A>T
ENST00000635528.1:n.712A>T

Pathogenic

Met criteria codes 4

PS3 PM3 PM2 PP4_Moderate

Not Met criteria codes 1

PM5

Evidence Links 2

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.1197A>T (p.Val399=) variant in PAH has been reported on 7 alleles of PKU patients (BH4 deficiency excluded). (PP4_Moderate; PMID: 23271928; PMID: 11214902). This variant has an extremely low allele frequency (0.000004064) in gnomAD (PM2; http://gnomAD.broadinstitute.org). This variant induces post-transcriptional skipping of exon 11 (PS3; PMID: 11214902). This variant was

detected in trans with R408W (Pathogenic in ClinVar) (PM3; PMID: 11214902). In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate

Met criteria codes

PS3	✔	c.1197A/T substitution in the PAH gene induces post-transcriptional skipping of exon 11. PMID: 11214902 Illegitimate PAH transcripts from lymphoblast cultures of a phenylketonuria (PKU) patient heterozygous for c.1197A/T were analyzed by RT-PCR. mRNAs with an exon 11 deletion were revealed. Sequence analysis of the RT-PCR products indicates that virtually all PAH transcripts from the maternal allele with the c. 1197A/T substitution do not contain exon 11. PAH minigenes with or without the substitution were constructed and transfected to a human hepatoma cell line. Analysis of the transcription products by S1 nuclease mapping clearly indicated that exon 11 skipping was directly associated with the c.1197A/T substitution. PubMed:11214902
PM3	✔	c.1197A/T detected in trans with R408W (Pathogenic in ClinVar) PMID: 11214902 phenylketonuria (PKU) patient compound heterozygous for c.1197A/T and R408W (paternal allele). R408W (varID 577) is Pathogenic in ClinVar (9 submitters) PubMed:11214902
PM2	✔	Absent from controls in ExAC, 1000G, ESP; 0.000004064 in gnomAD
PP4_Moderate	✔	C.1197A>T was found on 7 alleles of PKU patients. BH4 deficiency was excluded. Upgraded per ClinGen Metabolic WG PMID: 23271928; PMID: 11214902 phenylketonuria (PKU) patient heterozygous for c.1197A/T PubMed:11214902 Fifty-nine unrelated children with PKU. The patients (30 males, 29 females) were identified during treatment at the Neonatal Screening Center of the Shanxi Province Women and Childrens Hospital in Taiyuan and came from various regions of Shanxi province. All 59 cases exhibited significant clinical manifestations of PKU and fulfilled the diagnostic criteria for PKU, with blood phenylalanine concentrations > 20 mg/dL. Urinary pterin analysis and blood neopterin dihydropteridine reductase assays were used to exclude tetrahydrobiopterin deficiency. c. 1197A > T was found on 6 alleles PubMed:23271928

Not Met criteria codes

PM5	✖	V399A (VarID 120263) is Likely Pathogenic in ClinVar based on 1 submitter, no summary evidence or supporting observations

Curation History

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