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Variant: NM_000277.1(PAH):c.1243G>A (p.Asp415Asn)

CA114364

617 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: d8d2e477-0bfe-4136-9489-617a94f7fda6
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HGVS expressions

NM_000277.1(PAH):c.1243G>A (p.Asp415Asn)
NM_000277.1:c.1243G>A
NC_000012.12:g.102840472C>T
CM000674.2:g.102840472C>T
NC_000012.11:g.103234250C>T
CM000674.1:g.103234250C>T
NC_000012.10:g.101758380C>T
NG_008690.1:g.82131G>A
NG_008690.2:g.122939G>A
NM_000277.2:c.1243G>A
NM_001354304.1:c.1243G>A
NM_000277.3:c.1243G>A
ENST00000307000.7:c.1228G>A
ENST00000551114.2:n.905G>A
ENST00000553106.5:c.1243G>A
ENST00000635477.1:n.347G>A
ENST00000635528.1:n.758G>A

Pathogenic

Met criteria codes 3

PM2 PM3_Very Strong PP4_Moderate

Not Met criteria codes 3

PM5 PS3 PP3

Evidence Links 4

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.1243G>A (p.Asp415Asn) variant in PAH has been reported in 3 patients with Hyperphenylalaninemia (BH4 deficiency excluded). (PP4_Moderate; PMID: 1358789). This variant has an extremely low allele frequency (0.0001097 in gnomAD) (PM2; http://gnomad.broadinstitute.org). This variant was detected in trans with R408W, F39L, Y414C, IVS10-11G>A (Pathogenic in ClinVar)

(PM3_Very-strong; PMID: 1358789; PMID: 12501224; PMID: 18299955). 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

PM2	✔	Extremely low frequency in ExAC and GnomAD (MAF=0.00036) and absent from 1000G and ESP
PM3_Very Strong	✔	D415N detected in trans with R408W, F39L, Y414C, IVS10-11G>A (all Pathogenic) PMID: 1358789; PMID: 12501224; PMID: 18299955 D415N was found in trans with R408W (VarID 577, Pathogenic) in 1 HPA patient. PubMed:1358789 Patient genotype: IVS10 - 11G>A (VarID607, Pathogenic) + D415N PubMed:18299955 Patient 4: F39L (VarID 605, Pathogenic)/D415N; Patient 5:Y414C (VarID 593, Pathogenic)/D415N. PubMed:12501224
PP4_Moderate	✔	D415N was found in 3 patients with HPA. Pterines and dihydropteridine reductase activity was assessed. Upgraded per ClinGen PAH EP PMID: 1358789 Haplotype analysis at the PAH locus was performed in 17 Danish families with non-PKU HPA, revealing compound heterozygosity in all individuals. Three children had inherited a G-to-A transition at codon 415 in exon 12 of the PAH gene, resulting in the substitution of asparagine for aspartate. Pterines in the urine were determined by HPLC, and dihydropteridine reductase activity in cultured fibroblasts. PubMed:1358789

Not Met criteria codes

PM5	✖	Only variant in this codon in ClinVar
PS3	✖	Conflicting evidence of 2 in vitro expression: 100-128% activity of wt in mammalian system and 72+/-19% in e. coli We have used two heterologous in vitro expression systems (a mammalian cell-free transcription-translation system and the pET system of Escherichia coli) to examine 34 mutations that have been associated with PAH deficiency in the Danish population. D415N had PAH enzyme activity of 128/100% of wt in the pcDNA3/IVT system and 72+/-19 in the pET/E. coli system. PubMed:11161839
PP3	✖	Conflicting predictions of pathogenicity: benign in SIFT/Polyphen, damaging in FATHMM

Curation History

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