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Variant: NM_000277.2(PAH):c.500A>T (p.Asn167Ile)

CA220584

92743 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: a49cb655-9cb0-4fac-959d-26d4290227d6
Approved on: 2018-08-28
Published on: 2018-12-10

HGVS expressions

NM_000277.2(PAH):c.500A>T (p.Asn167Ile)
NM_000277.2:c.500A>T
NC_000012.12:g.102866605T>A
CM000674.2:g.102866605T>A
NC_000012.11:g.103260383T>A
CM000674.1:g.103260383T>A
NC_000012.10:g.101784513T>A
NG_008690.1:g.55998A>T
NG_008690.2:g.96806A>T
NM_000277.1:c.500A>T
NM_001354304.1:c.500A>T
NM_000277.3:c.500A>T
ENST00000307000.7:c.485A>T
ENST00000549111.5:n.596A>T
ENST00000551988.5:n.530+10857A>T
ENST00000553106.5:c.500A>T

Likely Pathogenic

Met criteria codes 3

PP4_Moderate | PM3_Strong | PM2

Not Met criteria codes 1

PP3

Evidence Links 4

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

PAH-specific ACMG/AMP criteria applied: PM2: Extremely low frequency in ExAC (MAF=0.00003). Absent from gnomAD, 1000G, ESP; PP4_Moderate: Found in a French patient with HPA and 2 unrelated UK patients. BH4 deficiencies not assessed/reported. Seen in 1 German patient, Cofactor deficiency was excluded by the BH4 test. 1 Spanish patient, a defect in the synthesis or regeneration pathways of 6R-BH4 was ruled out by analyzing urinary pterin levels and measuring dihydropteridine reductase activity. (PMID:26666653; PMID:9012412; PMID:10679941); PM3_Strong: Patient 664 with genotype N167I/Rl58Q (Pathogenic in ClinVar). Detected with G272X and R408W, known

pathogenic variants. (PMID:24368688; PMID:26666653). In summary this variant meets criteria to be classified as likely pathogenic for phenylketonuria in an autosomal recessive manner based on the ACMG/AMP criteria applied as specified by the PAH Expert Panel: (PM2, PP4_Moderate, PM3_Strong).

Met criteria codes

PP4_Moderate	✔	Found in a French patient with HPA and 2 unrelated UK patients. BH4 deficiencies not assessed/reported. Seen in 1 German patient, Cofactor deficiency was excluded by the BH4 test. 1 Spanish patient, a defect in the synthesis or regeneration pathways of 6R-BH4 was ruled out by analyzing urinary pterin levels and measuring dihydropteridine reductase activity. PKU patients from four centers in three countries of Great Britain were studied. N167I was found in 2 unrelated patients. PubMed:9012412 A total of 302 PKU or HPA patients in 290 families were analyzed. Cofactor deficiency was excluded by the BH4 test. N167I seen in 1 patient. PubMed:10679941 364 hyperphenylalaninemic patients from 20 French Centers for Inborn Errors of Metabolism. p.Asn167Ile was found in compound heterozygous patient carrying a second null mutation. PubMed:26666653
PM3_Strong	✔	Patient 664 with genotype N167I/RI58Q (Pathogenic in ClinVar). Detected with G272X and R408W, known pathogenic variants. Patient 7: N167I/R408W PubMed:24368688 Genotype: c. [500A > T] (p.Asn167Ile); [1066-11G > A]. PubMed:26666653
PM2	✔	Extremely low frequency in ExAC (MAF=0.00003). Absent from gnomAD, 1000G, ESP

Not Met criteria codes

PP3	✖	Conflicting predictions of pathogenicity: Damaging in SIFT, MutationTaster, Benign in Polyphen, REVEL=0.645.

Curation History

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