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Variant: NM_000277.1(PAH):c.1180G>C (p.Asp394His)

Version: 1.0

CA229371

102545 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: fbd336f7-b6dc-43c0-8ae5-479035f47b66
Approved on: 2020/8/17
Published on: 2021/11/21

HGVS expressions

NM_000277.1(PAH):c.1180G>C (p.Asp394His)
NM_000277.1:c.1180G>C
NC_000012.12:g.102843665C>G
CM000674.2:g.102843665C>G
NC_000012.11:g.103237443C>G
CM000674.1:g.103237443C>G
NC_000012.10:g.101761573C>G
NG_008690.1:g.78938G>C
NG_008690.2:g.119746G>C
ENST00000553106.6:c.1180G>C
ENST00000307000.7:c.1165G>C
ENST00000549247.6:n.939G>C
ENST00000551114.2:n.842G>C
ENST00000553106.5:c.1180G>C
ENST00000635477.1:c.284G>C
ENST00000635528.1:n.695G>C
NM_000277.2:c.1180G>C
NM_001354304.1:c.1180G>C
NM_000277.3:c.1180G>C
NM_001354304.2:c.1180G>C

Likely Pathogenic

Met criteria codes 4

PP3 PM2 PM3 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.1180G>C (p.Asp394His) variant in PAH has been reported in multiple individuals with PAH deficiency (BH4 deficiency excluded, PMID: 8889590, 21147011, 31355225). This variant is absent in population databases. This variant was detected with pathogenic variants IVS10-11G>A (PMID: 8889590); IVS11nt1g>c (IVS11+1G>C, PMID: 10947211). Computational evidence support a deleterious effect. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM2, PM3, PP3.

Met criteria codes

PP3	✔	Predicted deleterious in SIFT, Polyphen2, MutationTaster, REVEL=0.913
PM2	✔	Absent from ExAC, gnomAD, 1000G, ESP
PM3	✔	D394H detected with IVS10-11G>A (Pathogenic in ClinVar) parental analysis not reported PMID: 8889590; IVS11nt1g>c (IVS11+1G>C?) parental analysis not reported PMID: 10947211; c.355C > T, p.P119S (LP/US) Parents were investigated to confirm carrier status. PMID: 31355225 Patient with classical PKU has D394H with IVS10nt-11g>a (VarID 607, Pathogenic in ClinVar) on the second chromosome. PubMed:8889590
PP4_Moderate	✔	D394H seen in PKU patients. BH4 deficiency excluded by assessment of PAH gene and genes of the BH4 synthesis/recycling pathways (PTS and QDPR). PMID: 8889590, PMID: 21147011, PMID: 31355225 Forty-five unrelated hyperphenylalaninemic patients were genotyped. A G>C transversion in codon 394 in exon 11, causing the replacement of His for Asp, was found in a Turkish patient with classical PKU. The patient carries the IVS10nt-11g>a mutation on the second chromosome. PubMed:8889590 588 hyperphenylalaninemic patients were investigated. Assessment included PAH gene and genes of the BH4 synthesis/recycling pathways (PTS and QDPR). D394H seen in 2 patients. PubMed:21147011

Not Met criteria codes

PM5	✖	D394Y (VarID 120262) likely pathogenic per 1 submission in ClinVar

Curation History

Showing 1 to 1 of 1 rows

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