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Variant: NM_000277.3:c.184del

Version: 1.0

CA16020737

805812 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 6ce4710c-a4cc-4862-bb59-65b80cf308c0
Approved on: 2019/4/4
Published on: 2019/8/16

HGVS expressions

NM_000277.3:c.184del
NC_000012.12:g.102894904del
CM000674.2:g.102894904del
NC_000012.11:g.103288682del
CM000674.1:g.103288682del
NC_000012.10:g.101812812del
NG_008690.1:g.27700del
NG_008690.2:g.68508del
ENST00000553106.6:c.184del
ENST00000307000.7:c.169del
ENST00000546844.1:c.184del
ENST00000548677.2:n.271del
ENST00000548928.1:n.106del
ENST00000549111.5:n.280del
ENST00000550978.6:c.168del
ENST00000551337.5:c.184del
ENST00000551988.5:n.273del
ENST00000553106.5:c.184del
ENST00000635500.1:n.152del
NM_000277.1:c.184del
NM_000277.2:c.184del
NM_001354304.1:c.184del
NM_001354304.2:c.184del

Pathogenic

Met criteria codes 4

PP4 PM2 PM3 PVS1

Evidence Links 2

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.184delC variant in PAH has been previously reported as a heterozygous single variant in one Italian proband with mild HPA (PMID: 17096675) and in trans with the known pathogenic p.A403V allele in an Italian proband (PMID: 18346471). Of note, the two papers share the primary authors, so it is unclear whether this represents one versus two distinct patients. The variant is a 1bp deletion leading to a nonsense variant which occurs in exon 3 of 13 in the in the canonical transcript of PAH, a gene fulfilling the most recent criteria for LOF being a known disease mechanism (see PMID: 30192042) (PVS1). It is absent from control databases including ethnically matched individuals, including gnomAD/ExAC, 1000 Genomes, and ESP (PM2). In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PVS1, PM2, PM3, PP4.

Met criteria codes

PP4	✔	c.184delC was detected in 1 Mild HPA patient. BH4 deficiency not assessed. PMID: 17096675 We studied 126 HPA patients, identified from neonatal screening, Phe serum concentration was measured. The patients were divided into three groups: classic PKU (or HPA I) when Phe >1200 µM (>20 mg/dL); mild PKU (HPA II) when Phe was between 600 and 1200 µM (10-20 mg/dL); and mild HPA (or HPA III) when Phe was between 120 and 600 µM (2–10 mg/dL). c.184delC was detected in 0.7% of Mild HPA patients. PubMed:17096675
PM2	✔	It is absent from control databases including ethnically matched individuals, including gnomAD/ExAC, 1000 Genomes, and ESP (PM2).
PM3	✔	Detected in trans with the known pathogenic p.A403V allele in an Italian proband (PMID: 18346471). PubMed:18346471
PVS1	✔	The variant is a 1bp deletion leading to a nonsense variant which occurs in exon 3 of 13 in the in the canonical transcript of PAH, a gene fulfilling the most recent criteria for LOF being a known disease mechanism (see PMID: 30192042) (PVS1).

Curation History

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