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Variant: NM_000277.2(PAH):c.183C>G (p.Asn61Lys)

Version: 1.0

CA229471

102618 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: dbe38cd4-53be-42c3-ae3f-db3b6e57552d
Approved on: 2020/4/10
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HGVS expressions

NM_000277.2(PAH):c.183C>G (p.Asn61Lys)
NM_000277.2:c.183C>G
NC_000012.12:g.102894904G>C
CM000674.2:g.102894904G>C
NC_000012.11:g.103288682G>C
CM000674.1:g.103288682G>C
NC_000012.10:g.101812812G>C
NG_008690.1:g.27699C>G
NG_008690.2:g.68507C>G
ENST00000553106.6:c.183C>G
ENST00000307000.7:c.168C>G
ENST00000546844.1:c.183C>G
ENST00000548677.2:n.270C>G
ENST00000548928.1:n.105C>G
ENST00000549111.5:n.279C>G
ENST00000550978.6:c.167C>G
ENST00000551337.5:c.183C>G
ENST00000551988.5:n.272C>G
ENST00000553106.5:c.183C>G
ENST00000635500.1:n.151C>G
NM_000277.1:c.183C>G
NM_001354304.1:c.183C>G
NM_000277.3:c.183C>G
NM_001354304.2:c.183C>G

Likely Pathogenic

Met criteria codes 3

PM2 PM3_Strong PP4_Moderate

Not Met criteria codes 1

PP3

Evidence Links 2

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.183C>G (p.Asn61Lys) variant in PAH has been reported in 3 individuals with mild hyperphenylalaninaemia and mild PKU (BH4 deficiency excluded). (PMID: 10234516, 27121329). This variant is at extremely low frequency in ExAC: MAF=0.00017. This variant was detected with pathogenic variants p.R176L, IVS1nt5G>T (c.60+5G>T) and IVS10-11G>A (PMID: 10234516, 27121329). Computational evidence is conflicting. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM2, PM3_strong.

Met criteria codes

PM2	✔	Extremely low frequency in ExAC: MAF=0.00017
PM3_Strong	✔	Detected with R176L (P 7 submitters) and IVS1nt5G>T (c.60+5G>T, P 6 submitters) (PMID: 10234516 The Mendelian inheritance was confirmed when parental samples were available by DGGE or restriction enzyme digestion) and in trans with IVS10-11G>A (PMID: 27121329) (segregation analysis was done) PubMed:27121329 N61K (c.183C>G) detected in 2 patients: Genotypes N61K/IVS1nt5, and N61K/R176L (VarID631, Pathogenic). PubMed:10234516
PP4_Moderate	✔	N61K (c.183C>G) detected in 3 patients with MHP. BH4 defects excluded. PMID: 10234516, 27121329 Analysed 195 PKU patients by DGGE analysis. Patients were considered as having hyperphenylalaninaemia when the serum phenylalanine levels at diagnosis were higher than 120 ímol/L and after exclusion of a defect in tetrahydrobiopterin metabolism. N61K (c.183C>G) detected in 2 patients with MHP. PubMed:10234516

Not Met criteria codes

PP3	✖	computational evidence conflicting: SIFT (T/D), PolyPhen-2 (P,D), MutationTaster (D), REVEL=0.815

Curation History

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