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Variant: NM_000277.3(PAH):c.1316-2A>G

Version: 1.0

CA6748680

439226 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 09e65aa4-05ec-4490-92e7-d382834e932a
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HGVS expressions

NM_000277.3:c.1316-2A>G
NM_000277.3(PAH):c.1316-2A>G
NC_000012.12:g.102839220T>C
CM000674.2:g.102839220T>C
NC_000012.11:g.103232998T>C
CM000674.1:g.103232998T>C
NC_000012.10:g.101757128T>C
NG_008690.1:g.83383A>G
NG_008690.2:g.124191A>G
ENST00000553106.6:c.1316-2A>G
ENST00000307000.7:c.1301-2A>G
ENST00000551114.2:n.978-2A>G
ENST00000553106.5:c.1316-2A>G
ENST00000635477.1:c.420-2A>G
ENST00000635528.1:n.831-2A>G
NM_000277.1:c.1316-2A>G
NM_000277.2:c.1316-2A>G
NM_001354304.1:c.1316-2A>G
NM_001354304.2:c.1316-2A>G

Likely Pathogenic

Met criteria codes 3

PVS1_Strong PM2 PP4

Not Met criteria codes 1

PM3

Evidence Links 0

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

This c.1316-2A>G variant in PAH was reported in 1 Han Chinese patient with PAH deficiency (PMID: 28982351). This variant is present in European (non-Finnish) populations at an extremely low frequency in gnomAD (MAF=0.00001), and ExAC (MAF=0.00002). This variant in

the -2 splice acceptor site of intron 12, disrupts the reading frame and is not predicted to undergo nonsense mediated decay (NMD). The exon is present in biologically-relevant transcripts. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PVS1 strong, PM2, PP4.

Met criteria codes

PVS1_Strong	✔	This variant in the -2 splice acceptor site of IVS12 results in exon skipping or use of a cryptic splice site. The variant disrupts the reading frame and is not predicted to undergo nonsense mediated decay (NMD) as it is located in the 3'-most intron. This variant breaks the splice site in IVS12 according to Splice AI (0.99 – splice altering) and TraP (0.6, >97.5%ile, probably damaging).
PM2	✔	This variant was found at an extremely low frequency in European (non-Finnish) populations in gnomAD (MAF=0.00001), and ExAC (MAF=0.00002).
PP4	✔	This variant was documented in 1 Han Chinese patient with PAH deficiency (240µmol/L Phe). Patients with BH4 cofactor deficiency were excluded by BH4 loading. PMID: 28982351

Not Met criteria codes

PM3	✖	Detected in trans in 1 patient with p.Lys363Asn, a variant of uncertain significance in PAH (.25pts). To determine sequence variability, variable sites in patient genes were aligned with the corresponding sites from the respective parents. PMID: 28982351

Curation History

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