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Variant: NM_000277.3:c.125AAG[2]

Version: 1.0

CA229435

102594 (ClinVar)

Gene: PAH
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 66040e6b-c53f-45a8-b99a-5edda3733787
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HGVS expressions

NM_000277.3:c.125AAG[2]
NC_000012.12:g.102912832_102912834del
CM000674.2:g.102912832_102912834del
NC_000012.11:g.103306610_103306612del
CM000674.1:g.103306610_103306612del
NC_000012.10:g.101830740_101830742del
NG_008690.1:g.9775_9777del
NG_008690.2:g.50583_50585del
ENST00000553106.6:c.131_133del
ENST00000307000.7:c.116_118del
ENST00000546844.1:c.131_133del
ENST00000548677.2:n.218_220del
ENST00000548928.1:n.53_55del
ENST00000549111.5:n.227_229del
ENST00000550978.6:c.115_117del
ENST00000551337.5:c.131_133del
ENST00000551988.5:n.220_222del
ENST00000553106.5:c.131_133del
ENST00000635500.1:n.99_101del
NM_000277.1:c.131_133del
NM_000277.2:c.131_133del
NM_001354304.1:c.131_133del
NM_000277.3:c.131_133del
NM_001354304.2:c.131_133del

Likely Pathogenic

Met criteria codes 4

PP4_Moderate PM3_Strong PM2_Supporting PM4

Evidence Links 0

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The NM_000277.3:c.125AAG[2] variant in PAH is predicted to cause a change in the length of the protein due to an in-frame deletion of 1 amino acid in a non-repeat region (p.Glu44del) (PM4). This variant has been detected in at least 3 unrelated individuals with PAH deficiency (PMID: 28982351, PMID: 26600521, PMID: 9012412). Of these individuals, one was a compound heterozygote for the variant and a pathogenic variant, p.Arg408Trp, in trans (phase confirmed by parental testing) (PMID: 26600521), and one was a compound heterozygote for the variant and a likely pathogenic variant, p.Met276Arg, in trans (phase confirmed by parental testing) (PMID: 28982351) (2pts total, PM3_Strong). These two individuals had plasma phenylalanine >120 µmol/L and exclusion of a defect of BH4 cofactor metabolism (PMID: 28982351, PMID: 26600521). These two individuals had plasma phenylalanine >120 µmol/L and exclusion of a defect of BH4 cofactor metabolism (PMID: 28982351, PMID: 26600521). The highest population minor allele frequency in gnomAD v2.1.1 is 0.000096 (1/10368 alleles) in the Ashkenazi Jewish population, which is lower than the ClinGen PAH VCEP's threshold for PM2_Supporting (<0.0002), meeting this criterion (PM2_Supporting). There is a ClinVar entry for this variant (Variation ID: 102594, 1 star review status) with one submitter classifying the variant as likely pathogenic and 3 submitters classifying the variant as a variant of uncertain significance. In summary, this variant meets the criteria to be classified as likely pathogenic for PAH deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen PAH Variant Curation Expert Panel (Specifications Version 2.0): PM2_Supporting, PM3_Strong, PM4, PP4_Moderate.

Met criteria codes

PP4_Moderate	✔	These two individuals had plasma phenylalanine >120 µmol/L and exclusion of a defect of BH4 cofactor metabolism (PMID: 28982351, PMID: 26600521).
PM3_Strong	✔	This variant has been detected in at least 3 unrelated individuals with PAH deficiency (PMID: 28982351, PMID: 26600521, PMID: 9012412). Of these individuals, one was a compound heterozygote for the variant and a pathogenic variant, p.Arg408Trp, in trans (phase confirmed by parental testing) (PMID: 26600521), and one was a compound heterozygote for the variant and a likely pathogenic variant, p.Met276Arg, in trans (phase confirmed by parental testing) (PMID: 28982351) (2pts total, PM3_Strong).
PM2_Supporting	✔	These two individuals had plasma phenylalanine >120 µmol/L and exclusion of a defect of BH4 cofactor metabolism (PMID: 28982351, PMID: 26600521). The highest population minor allele frequency in gnomAD v2.1.1 is 0.000096 (1/10368 alleles) in the Ashkenazi Jewish population, which is lower than the ClinGen PAH VCEP's threshold for PM2_Supporting (<0.0002), meeting this criterion (PM2_Supporting).
PM4	✔	The NM_000277.3(PAH):c.125AAG[2] variant in PAH is predicted to cause a change in the length of the protein due to an in-frame deletion of 1 amino acid in a non-repeat region (p.Glu44del) (PM4).

Curation History

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