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Variant: NM_000277.3(PAH):c.620A>G (p.Asn207Ser)

Version: 1.0

CA229665

102765 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 83be9c96-02b3-4161-ae5b-30bade6f25c3
Approved on: 2023/7/23
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HGVS expressions

NM_000277.3:c.620A>G
NM_000277.3(PAH):c.620A>G (p.Asn207Ser)
NC_000012.12:g.102855222T>C
CM000674.2:g.102855222T>C
NC_000012.11:g.103249000T>C
CM000674.1:g.103249000T>C
NC_000012.10:g.101773130T>C
NG_008690.1:g.67381A>G
NG_008690.2:g.108189A>G
ENST00000553106.6:c.620A>G
ENST00000307000.7:c.605A>G
ENST00000549111.5:n.716A>G
ENST00000553106.5:c.620A>G
NM_000277.1:c.620A>G
NM_000277.2:c.620A>G
NM_001354304.1:c.620A>G
NM_001354304.2:c.620A>G

Likely Pathogenic

Met criteria codes 4

PP3 PP4 PM3_Strong PM2_Supporting

Not Met criteria codes 1

PM5

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.620A>G variant in PAH is a missense variant predicted to cause substitution of asparagine by serine at amino acid 207 (p.Asn207Ser). This variant has been detected in at least 5 unrelated individuals with PAH deficiency (PMID: 32668217, PMID: 9048935). Of these individuals, one was a compound heterozygote for the variant and a likely pathogenic variant, p.Pro281Leu, in trans (phase

confirmed by parental testing) (PMID: 9048935), and four were compound heterozygotes for the variant and pathogenic variants, p.Ala300Ser, p.Ala403Val, p.Glu390Gly, p.Arg252Gln, in unknown phase (PMID: 32668217) (3pts total, PM3_Strong). One of these individuals had plasma phenylalanine >120 µmol/L without the exclusion of a defect of BH4 cofactor metabolism (PMID: 9048935) (PP4). This variant is absent in gnomAD v2.1.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.77 which is above the threshold of 0.75, evidence that correlates with impact to PAH function (PP3). There is a ClinVar entry for this variant (Variation ID: 102765, 1 star review status) with one submitter classifying the variant as pathogenic, one submitter classifying the variant as likely pathogenic, and one submitter 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, PP3, PP4.

Met criteria codes

PP3	✔	This variant is absent in gnomAD v2.1.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.77 which is above the threshold of 0.75, evidence that correlates with impact to PAH function (PP3).
PP4	✔	One of these individuals had a plasma phenylalanine concentration persistently above 120µmol/L (2mg/dL) without analysis of urine pterins, DHPR activity, or sequencing to exclude defects of BH4 cofactor metabolism (PMID: 9048935)
PM3_Strong	✔	This variant has been detected in at least 5 unrelated individuals with PAH deficiency (PMID: 32668217, PMID: 9048935). Of these individuals, one was a compound heterozygote for the variant and a likely pathogenic variant, p.Pro281Leu, in trans (phase confirmed by parental testing) (PMID: 9048935), and four were compound heterozygotes for the variant and pathogenic variants, p.Ala300Ser, p.Ala403Val, p.Glu390Gly, p.Arg252Gln, in unknown phase (PMID: 32668217) (3pts total, PM3_Strong).
PM2_Supporting	✔	This variant is absent in gnomAD v2.1.1 (PM2_Supporting).

Not Met criteria codes

PM5	✖	A different missense variant at the same amino acid residue, p.Asn207Asp, has been reported in the literature (PMID: 32668217) and in ClinVar (ClinVar ID: 102764); not counted for PM5 since p.Asn207Ser will be counted for PM5 for the p.Asn207Asp variant, thereby preventing circularity.

Curation History

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