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Variant: NM_000277.1(PAH):c.935G>A (p.Gly312Asp)

Version: 1.0

CA229857

102901 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: d7f480cd-9e8f-47a8-b380-d7698998cae2
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HGVS expressions

NM_000277.1(PAH):c.935G>A (p.Gly312Asp)
NM_000277.1:c.935G>A
NC_000012.12:g.102846929C>T
CM000674.2:g.102846929C>T
NC_000012.11:g.103240707C>T
CM000674.1:g.103240707C>T
NC_000012.10:g.101764837C>T
NG_008690.1:g.75674G>A
NG_008690.2:g.116482G>A
ENST00000553106.6:c.935G>A
ENST00000307000.7:c.920G>A
ENST00000549247.6:n.694G>A
ENST00000551114.2:n.597G>A
ENST00000553106.5:c.935G>A
ENST00000635477.1:c.74-2498G>A
ENST00000635528.1:n.450G>A
NM_000277.2:c.935G>A
NM_001354304.1:c.935G>A
NM_000277.3:c.935G>A
NM_001354304.2:c.935G>A

Likely Pathogenic

Met criteria codes 4

PP3 PM3 PM2 PP4_Moderate

Evidence Links 1

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The NM_000277.1(PAH):c.935G>A (p.Gly312Asp) variant is a missense variant in exon 9/13 of PAH. It has been reported in at least 3 PKU cases in presumed trans with other Pathogenic variants (PM3; 1.5 points total), in two of whom BH4 deficiency was excluded

(PP4_Moderate). It has been previously reported in presumed trans with the p.R241C variant (Pathogenic per ClinGen PAH VCEP) in two cases with mild PKU (plasma Phe 600–1200 µmol/L) and BH4 deficiency excluded (PMID: 30459323). It has also been reported in presumed trans with the p. R408W variant (Pathogenic by ClinGen PAH VCEP) in a patient with classic PKU and with undefined BH4 responsiveness. The variant is absent from ethnically diverse control databases, including gnomAD/ExAC, 1000 Genomes, and ESP (PM2). The variant is predicted damaging by multiple in-silico missense predictors, including REVEL (REVEL score 0.958) (PP3). Classification: Likely Pathogenic Supporting Criteria: PM2; PM3; PP4_Moderate; PP3

Met criteria codes

PP3	✔	All computational evidence support a deleterious effect. REVEL=0.958
PM3	✔	It has been reported in at least 3 PKU cases in presumed trans with other Pathogenic variants (PM3; 1.5 points total), in two of whom BH4 deficiency was excluded (PP4_Moderate). It has been previously reported in presumed trans with the p.R241C variant (Pathogenic per ClinGen PAH VCEP) in two cases with mild PKU (plasma Phe 60–1200 µmol/L) and BH4 deficiency excluded (PMID: 30459323). It has also been reported in presumed trans with the p. R408W variant (Pathogenic by ClinGen PAH VCEP) in a patient with classic PKU and with undefined BH4 responsiveness Single patient reported G312D/R408W with undefined BH4 responsiveness and classic PKU **PubMed:24350308**
PM2	✔	Not found in any pop database.
PP4_Moderate	✔	It has been reported in at least 3 PKU cases in presumed trans with other Pathogenic variants (PM3; 1.5 points total), in two of whom BH4 deficiency was excluded (PP4_Moderate). It has been previously reported in presumed trans with the p.R241C variant (Pathogenic per ClinGen PAH VCEP) in two cases with mild PKU (plasma Phe 60–1200 µmol/L) and BH4 deficiency excluded (PMID: 30459323). It has also been reported in presumed trans with the p. R408W variant (Pathogenic by ClinGen PAH VCEP) in a patient with classic PKU and with undefined BH4 responsiveness. Single patient reported G312D/R408W with undefined BH4 responsiveness and classic PKU **PubMed:24350308**

Curation History

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