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Variant: NM_000277.1(PAH):c.929C>A (p.Ser310Tyr)

Version: 1.0

CA229854

102898 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 98fab9fa-47b3-47c6-9bd9-1d833f7e4ee4
Approved on: 2025/10/12
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HGVS expressions

NM_000277.1(PAH):c.929C>A (p.Ser310Tyr)
NM_000277.1:c.929C>A
NC_000012.12:g.102846935G>T
CM000674.2:g.102846935G>T
NC_000012.11:g.103240713G>T
CM000674.1:g.103240713G>T
NC_000012.10:g.101764843G>T
NG_008690.1:g.75668C>A
NG_008690.2:g.116476C>A
ENST00000553106.6:c.929C>A
ENST00000307000.7:c.914C>A
ENST00000549247.6:n.688C>A
ENST00000551114.2:n.591C>A
ENST00000553106.5:c.929C>A
ENST00000635477.1:c.74-2504C>A
ENST00000635528.1:n.444C>A
NM_000277.2:c.929C>A
NM_001354304.1:c.929C>A
NM_000277.3:c.929C>A
NM_001354304.2:c.929C>A

Pathogenic

Met criteria codes 6

PM3 PM5 PP4_Moderate PP3_Strong PM2_Supporting PS3_Supporting

Evidence Links 2

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Phenylketonuria Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for PAH Version 2.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The NM_000277.1(PAH):c.929C>A (p.Ser310Tyr) variant is a missense variant in exon 9/13 in PAH. The variant has been found to result in <1% of wild-type PAH enzyme activity in cDNA and Intinc systems (PMID: 18590700), and has been found to result in high molecular weight aggregates without residual enzyme activity (PMID: 18538294) (PS3_supporting). It has been previously reported in a patient with mild hyperphenylalanemia in trans with p.F55L (Pathogenic/Likely Pathogenic in ClinVar); BH4 deficiency was excluded by analysis of urinary pterins and dihydropteridine reductase activity in erythrocytes (PMID: 12501224) (PM3; PP4_Moderate). The variant is absent from ethnically diverse control databases, including gnomAD/ExAC, 1000 Genomes, and ESP (PM2_supporting). The variant is predicted damaging by multiple in-silico missense predictors, including REVEL (REVEL score 0.991) (PP3_strong). Classification: Pathogenic Supporting Criteria: PS3_supporting; PM2_supporting; PM3; PP4_Moderate; PP3_strong

Met criteria codes

PM3	✔	It has been previously reported in a patient with mild hyperphenylalanemia in trans with p.F55L (Pathogenic/Likely Pathogenic in ClinVar); BH4 deficiency was excluded by analysis of urinary pterins and dihydropteridine reductase activity in erythrocytes (PMID: 12501224) (PM3; PP4_Moderate). Patient #7 S310Y/F55L (pathogenic per clinVar) – with BH4 responsive mild hyperphe (>600umol/L @dx) S310Y is novel in this paper **PubMed:12501224**
PM5	✔	p.Ser310Phe Pathogenic by PAH VCEP
PP4_Moderate	✔	It has been previously reported in a patient with mild hyperphenylalanemia in trans with p.F55L (Pathogenic/Likely Pathogenic in ClinVar); BH4 deficiency was excluded by analysis of urinary pterins and dihydropteridine reductase activity in erythrocytes (PMID: 12501224) (PM3; PP4_Moderate). BH4 defect excluded in all patients with urine pterins and DHPR activity. **PubMed:12501224**
PP3_Strong	✔	All predictive software agree on damaging effect REVEL = 0.991
PM2_Supporting	✔	Not found in any population databases
PS3_Supporting	✔	Ho, 2008. Both standard cDNA and intinic systems suggest this variant has <1% enzyme activity. PMID: 18590700 PAH activity analysis. Site directed mutagenesis, transfected COS-1 cells. Enzyme activity measured as conversion of L-[14C]phe to L-[14C]tyr. Use both standard cDNA expression system and a new Intinic plasmid system which incorporates intronic sequences. Both systems predict <1% enzyme activity for this variant. **PubMed:18590700**

Curation History

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