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Variant: NM_000277.1(PAH):c.929C>T (p.Ser310Phe)

Version: 1.0

CA229855

102899 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: e5c4b52f-a15b-42d6-b5d3-64542c26e58e
Approved on: 2023/12/30
Published on: 2023/12/30

HGVS expressions

NM_000277.1:c.929C>T
NM_000277.1(PAH):c.929C>T (p.Ser310Phe)
NC_000012.12:g.102846935G>A
CM000674.2:g.102846935G>A
NC_000012.11:g.103240713G>A
CM000674.1:g.103240713G>A
NC_000012.10:g.101764843G>A
NG_008690.1:g.75668C>T
NG_008690.2:g.116476C>T
ENST00000553106.6:c.929C>T
ENST00000307000.7:c.914C>T
ENST00000549247.6:n.688C>T
ENST00000551114.2:n.591C>T
ENST00000553106.5:c.929C>T
ENST00000635477.1:c.74-2504C>T
ENST00000635528.1:n.444C>T
NM_000277.2:c.929C>T
NM_001354304.1:c.929C>T
NM_000277.3:c.929C>T
NM_001354304.2:c.929C>T

Pathogenic

Met criteria codes 4

PM3_Very Strong | PM2_Supporting | PP3 | PP4_Moderate

Not Met criteria codes 1

BS3

Evidence Links 3

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.929C>T (p.Ser310Phe) variant is a missense variant in exon 9/13 of PAH. The variant has been found to result in <1% of wild-type PAH enzyme activity in a standard cDNA and an Intinc system (PMID: 18590700) (PS3_supporting). It has been found in at least 8 PKU patients, including among those whom BH4 deficiency was excluding and in trans with other Pathogenic or Likely Pathogenic alleles (PM3_VeryStrong (4.75 points); PP4_Moderate). It has been found in 2 alleles in a survey of German PKU patients (PMID: 12655553); in trans with the c.442-1G>A (Pathogenic in ClinVar and by ClinGen PAH VCEP) variant in a Korean patient with moderate PKU (plasma Phe 600-1200 umol/L) with BH4 deficiency excluded by urinary pterin analysis and dihydropteridine reductase (DHPR) assay (PMID: 15503242). It has been found in as a homozygous variant in a Syrian patient with classic PKU (plasma Phe 1262 umol/L) (PMID: 23856132). It has been found in two Chinese patients with classic PKU and BH4 deficiency excluded via analysis of urinary pterins and dihydropteridine reductase activity in erythrocytes: one harbored it in trans with the p.R111* variant (Pathogenic in ClinVar and by ClinGen PAH VCEP) and one in trans with the p.Y356* variant (Pathogenic in ClinVar and by ClinGen PAH VCEP) (PMID: 30050108). It has been found in a Chinese patient with mild hyperphenylalanemia (plasma Phe 120-360 umol/L) in trans with p.R241C (Pathogenic in ClinVar and by ClinGen PAH VCEP); BH4 deficiency was excluded (PMID: 25894915). It has been found in trans with p.F302V (unclassified) in a Chinese patient with mild PKU (plasma Phe 360–1200 µmol/L) and BH4 deficiency excluded (PMID: 30459323). It has been reported in trans with c.1066-3C>T (Pathogenic/Likely Pathogenic in ClinVar and by ClinGen PAH VCEP)in a PKU patient (PMID: 23430918). 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 0.993) (PP3). Classification: Pathogenic Supporting Criteria: PS3_supporting; PM2_supporting; PM3_VeryStrong; PP4_Moderate; PP3

Met criteria codes

PM3_Very Strong ✔

It has been found in at least 8 PKU patients, including among those whom BH4 deficiency was excluding and in trans with other Pathogenic or Likely Pathogenic alleles (PM3_VeryStrong (4.75 points); PP4_Moderate). It has been found in 2 alleles in a survey of German PKU patients (PMID: 12655553); in trans with the c.442-1G>A (Pathogenic in ClinVar and by ClinGen PAH VCEP) variant in a Korean patient with moderate PKU (plasma Phe 600-1200 umol/L) with BH4 deficiency excluded by urinary pterin analysis and dihydropteridine reductase (DHPR) assay (PMID: 15503242). It has been found in as a homozygous variant in a Syrian patient with classic PKU (plasma Phe 1262 umol/L) (PMID: 23856132). It has been found in two Chinese patients with classic PKU and BH4 deficiency excluded via analysis of urinary pterins and dihydropteridine reductase activity in erythrocytes: one harbored it in trans with the p.R111* variant (Pathogenic in ClinVar and by ClinGen PAH VCEP) and one in trans with the p.Y356* variant (Pathogenic in ClinVar and by ClinGen PAH VCEP) (PMID: 30050108). It has been found in a Chinese patient with mild hyperphenylalanemia (plasma Phe 120-360 umol/L) in trans with p.R241C (Pathogenic in ClinVar and by ClinGen PAH VCEP); BH4 deficiency was excluded (PMID: 25894915). It has been found in trans with p.F302V (unclassified) in a Chinese patient with mild PKU (plasma Phe 360–1200 µmol/L) and BH4 deficiency excluded (PMID: 30459323). It has been reported in trans with c.1066-3C>T (Pathogenic/Likely Pathogenic in ClinVar and by ClinGen PAH VCEP)in a PKU patient (PMID: 23430918).

31 unrelated patients and their parents. BH4 defect excluded in all patients. Single patient c.929C>T / C.721C>T (pathogenic in ClinVar) with moderate PKU (level at dx=1102umol/L) with predicted BH4 responsiveness. PubMed:25894915

Molecular basis of PKU in Korean population. 79 unrelated families. Urinary pterin analysis and DHPR assays performed to exclude BH4 defect. Single patient with moderate PKU (600-1200umol/L) IVS4-1G>A (pathogenic) / S310F. PubMed:15503242

PM2_Supporting ✔

No population data in any database

PP3 ✔

All databases agree on damaging effect. REVEL=0.993.

PP4_Moderate ✔

It has been found in at least 8 PKU patients, including among those whom BH4 deficiency was excluding and in trans with other Pathogenic or Likely Pathogenic alleles (PM3_VeryStrong (4.75 points); PP4_Moderate). It has been found

in 2 alleles in a survey of German PKU patients (PMID: 12655553); in trans with the c.442-1G>A (Pathogenic in ClinVar and by ClinGen PAH VCEP) variant in a Korean patient with moderate PKU (plasma Phe 600-1200 umol/L) with BH4 deficiency excluded by urinary pterin analysis and dihydropteridine reductase (DHPR) assay (PMID: 15503242). It has been found in as a homozygous variant in a Syrian patient with classic PKU (plasma Phe 1262 umol/L) (PMID: 23856132). It has been found in two Chinese patients with classic PKU and BH4 deficiency excluded via analysis of urinary pterins and dihydropteridine reductase activity in erythrocytes: one harbored it in trans with the p.R111* variant (Pathogenic in ClinVar and by ClinGen PAH VCEP) and one in trans with the p.Y356* variant (Pathogenic in ClinVar and by ClinGen PAH VCEP) (PMID: 30050108). It has been found in a Chinese patient with mild hyperphenylalanemia (plasma Phe 120-360 umol/L) in trans with p.R241C (Pathogenic in ClinVar and by ClinGen PAH VCEP); BH4 deficiency was excluded (PMID: 25894915). It has been found in trans with p.F302V (unclassified) in a Chinese patient with mild PKU (plasma Phe 360–1200 µmol/L) and BH4 deficiency excluded (PMID: 30459323). It has been reported in trans with c.1066-3C>T (Pathogenic/Likely Pathogenic in ClinVar and by ClinGen PAH VCEP)in a PKU patient (PMID: 23430918).

31 unrelated patients and their parents. BH4 defect excluded in all patients. Single patient c.929C>T / C.721C>T (pathogenic in ClinVar) with moderate PKU (level at dx=1102umol/L) with predicted BH4 responsiveness. PubMed:25894915

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Not Met criteria codes

BS3	✖	The variant has been found to result in <1% of wild-type PAH enzyme activity in a standard cDNA and an Intinc system (PMID: 18590700) (PS3).
		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. Standard cDNA method demonstrates <1% and intinic system demonstrates <1% residual enzyme activity. PubMed:18590700

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000277.1(PAH):c.929C>T (p.Ser31...	Pathogenic	Phenylketonuria	2023-12-30	1.0	-	PAH

Showing 1 to 1 of 1 rows

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