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Variant: NM_000277.3:c.998T>C

Version: 1.0

CA16020917

1693239 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 601f952f-355c-4c0c-92ee-2746e651b68e
Approved on: 2022/3/13
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HGVS expressions

NM_000277.3:c.998T>C
NC_000012.12:g.102844403A>G
CM000674.2:g.102844403A>G
NC_000012.11:g.103238181A>G
CM000674.1:g.103238181A>G
NC_000012.10:g.101762311A>G
NG_008690.1:g.78200T>C
NG_008690.2:g.119008T>C
ENST00000553106.6:c.998T>C
ENST00000307000.7:c.983T>C
ENST00000549247.6:n.757T>C
ENST00000551114.2:n.660T>C
ENST00000553106.5:c.998T>C
ENST00000635477.1:c.102T>C
ENST00000635528.1:n.513T>C
NM_000277.1:c.998T>C
NM_000277.2:c.998T>C
NM_001354304.1:c.998T>C
NM_001354304.2:c.998T>C

Likely Pathogenic

Met criteria codes 5

PM3_Supporting PP4_Moderate PM5 PM2 PP3

Evidence Links 0

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.998T>C (p.Leu333Pro) variant in PAH has been reported in individuals with PAH deficiency, detected with p.Pro281Leu (Likely pathogenic by PAH VCEP variation ID: 589) with exclusion of BH4 deficiency (PMID: 19394257). In-vitro functional studies are unavailable. This variant is absent from population databases. Multiple lines of computational evidence support a deleterious effect. A different

pathogenic missense change at the same codon, p.Leu333Phe is pathogenic (by PAH VCEP). In summary, this variant meets criteria to be classified as Likely Pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_moderate, PM2, PM5, PM3_supporting.

Met criteria codes

PM3_Supporting	✔	Detected with p.P281L (P/LP) in 2 patients, parental analysis not reported. 0.5 points
PP4_Moderate	✔	Reported in a Croatian patient with PAH deficiency. BH4 deficiency was excluded in all patients by measuring urinary pterins and dried blood dihydropteridine reductase activity. PMID: 19394257
PM5	✔	L333F is P by PAH VCEP
PM2	✔	Absent from controls in ExAC, gnomAD, 1000 Genomes, or ESP
PP3	✔	Predicted deleterious in SIFT, PolyPhen2, MutationTaster. REVEL=0.991

Curation History

Showing 1 to 1 of 1 rows

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