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Variant: NM_000277.1:c.859C>G

CA6748814

619164 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 381aa0a0-283a-47df-a1b8-0180f05e3d16
Approved on: 2018-12-09
Published on: 2018-12-10

HGVS expressions

NM_000277.1:c.859C>G
NC_000012.12:g.102851740G>C
CM000674.2:g.102851740G>C
NC_000012.11:g.103245518G>C
CM000674.1:g.103245518G>C
NC_000012.10:g.101769648G>C
NG_008690.1:g.70863C>G
NG_008690.2:g.111671C>G
NM_000277.2:c.859C>G
NM_001354304.1:c.859C>G
NM_000277.3:c.859C>G
ENST00000307000.7:c.844C>G
ENST00000549247.6:n.618C>G
ENST00000551114.2:n.521C>G
ENST00000553106.5:c.859C>G
ENST00000635477.1:n.20C>G

Likely Pathogenic

Met criteria codes 3

PM2 PP4_Moderate PM3_Strong

Not Met criteria codes 1

PP3

Evidence Links 2

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.859C>G (p.Leu287Val) variant in PAH is found with low allele frequency in population databases (3.0e-5). It has been identified in trans with pathogenic variants in two individuals in the literature (P281L and A300S, PMID: 12409276), and in one of those patients a defect in BH4 metabolism was excluded as a cause of elevated phenylalanine (PMID: 16198137). . In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM2, PM3.

Met criteria codes

PM2	✔	Allele Frequency: 0.00003
PP4_Moderate	✔	BH4 defect excluded in all patients (Fiori) PMID: 16198137 BH4 defect excluded in all patients, single patient with mild Hyperphe (Phe=167.40umol/L) PubMed:16198137
PM3_Strong	✔	281L (Pathogenic)(PMID: 12409276), and A300S (pathogenic)(PMID: 16198137) Single patient in trans with P281L, classic PKU PubMed:12409276 Single patient with MHP, in trans with A300S PubMed:16198137

Not Met criteria codes

PP3	✖	Provean=neutral, SIFT=damaging. REVEL=0.822

Curation History

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