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Variant: NM_000277.1(PAH):c.638T>C (p.Leu213Pro)

CA273109

92747 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 1adb5216-c67d-4ebf-8b37-89b36d1f2625
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HGVS expressions

NM_000277.1(PAH):c.638T>C (p.Leu213Pro)
NM_000277.1:c.638T>C
NC_000012.12:g.102855204A>G
CM000674.2:g.102855204A>G
NC_000012.11:g.103248982A>G
CM000674.1:g.103248982A>G
NC_000012.10:g.101773112A>G
NG_008690.1:g.67399T>C
NG_008690.2:g.108207T>C
NM_000277.2:c.638T>C
NM_001354304.1:c.638T>C
NM_000277.3:c.638T>C
ENST00000307000.7:c.623T>C
ENST00000549111.5:n.734T>C
ENST00000553106.5:c.638T>C

Pathogenic

Met criteria codes 4

PP4_Moderate PM2 PM3_Very Strong PP3

Evidence Links 4

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.638T>C (p.Leu213Pro) variant in PAH has been reported in in 4 patients with PAH deficiency (BH4 deficiency excluded). (PP4_Moderate; PMID: 8659548; PMID: 19292873; PMID: 21147011). This variant is absent from large population studies (PM2; http://exac.broadinstitute.org). This variant was detected in trans with c.1066-11G>A, E390G, D415N, R261X.(Pathogenic in ClinVar) (PM3_Very-strong; PMID: 19292873; PMID: 21147011; PMID: 8632937). Computational prediction tools and conservation analysis suggest that the c.638T>C variant may impact the protein (PP3). In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM3_Very-strong

Met criteria codes

PP4_Moderate	✔	Found in 4 patients: (Phe levels 240 umol/L, 1936 uM, mHPA). BH4 deficiency excluded in 2 patients. Upgraded per ClinGen PAHEP PMID: 8659548; PMID: 19292873; PMID: 21147011 588 hyperphenylalaninemic patients were investigated. Assessment included PAH gene and genes of the BH4 synthesis/recycling pathways (PTS and QDPR). Seen on 2 alleles in 2 patients with mHPA. PubMed:21147011 We sequenced the entire gene for phenylalanine hydroxylase in 51 unrelated hyperphenylalaninemia patients from Southern Italy. Patient 42 had L213P variant with c.1066-11G>A, pretreatment Phe level was 1936 uM, HPA I phenotype PubMed:19292873 One hundred forty-nine patients en- rolled in the Maternal PKU Collaborative Study were subjects for clinical and molecular investigations. PAH gene mutations associated with phenylketonuria (PKU) or mild hyperphenylalaninemia (MHP) were identified on 279 of 294 independent mutant chromosomes. Patient 1/1101/ENO-10, 2nd mutation not found, Phe level=240 umol/L, MHP, English/Mexican ethnicity. PubMed:8659548
PM2	✔	Not found in ExAC, gnomAD, 1000G, or ESP
PM3_Very Strong	✔	Detected in trans with c.1066-11G, E390G, D415N, R261X. P/LP in ClinVar PMID: 19292873; PMID: 21147011; PMID: 8632937 PAH Genotype: L213P/R261X (VarID 610, Pathogenic) PubMed:8632937 Detected in 2 patients: p.L213P/p.E390G (VarID 625 P/LP) and p.L213P/p.D415N (VarID 617, Pathogenic). PubMed:21147011 L213P in trans with c.1066-11G>A ((Pathogenic in ClinVar, VarID 607) PubMed:19292873
PP3	✔	Deleterious effect predicted in SIFT, Polyphen2, MutationTaster

Curation History

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