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Variant: NM_000277.1(PAH):c.1238G>C (p.Arg413Pro)

CA229414

592 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: ce8fbaf1-f9e2-43cc-ac9c-6b77a1fd68a0
Approved on: 2018-08-05
Published on: 2018-12-10

HGVS expressions

NM_000277.1(PAH):c.1238G>C (p.Arg413Pro)
NM_000277.1:c.1238G>C
NC_000012.12:g.102840477C>G
CM000674.2:g.102840477C>G
NC_000012.11:g.103234255C>G
CM000674.1:g.103234255C>G
NC_000012.10:g.101758385C>G
NG_008690.1:g.82126G>C
NG_008690.2:g.122934G>C
NM_000277.2:c.1238G>C
NM_001354304.1:c.1238G>C
NM_000277.3:c.1238G>C
ENST00000307000.7:c.1223G>C
ENST00000551114.2:n.900G>C
ENST00000553106.5:c.1238G>C
ENST00000635477.1:n.342G>C
ENST00000635528.1:n.753G>C

Pathogenic

Met criteria codes 5

PM3 PM2 PS3 PP3 PP4_Moderate

Evidence Links 2

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

PAH-specific ACMG/AMP criteria applied: PS3: In vitro expression of altered protein in COS cells produces severe decrease of PAH activity (<3%); PM2: Extremely low frequency. ExAC MAF=0.00012; PP4_Moderate: Detected in PKU patients, BH4 deficiency excluded; PP3: Predicted deleterious in SIFT, Polyphen-2, MutationTaster. REVEL=0.895; PM3: Detected with V388M (pathogenic) in 2 patients (PMID:9860305; PMID:21307867). In summary this variant meets criteria to be classified as pathogenic for phenylketonuria in an autosomal recessive manner based on the ACMG/AMP criteria applied as specified by the PAH Expert Panel: (PS3, PM2, PP4_Moderate, PP3, PM3).

Met criteria codes

PM3	✔	Detected with V388M (pathogenic) in 2 patients A132V (not in ClinVar) /R413P. Two patients with compound heterozygote mutations of V388M (VarID619, Pathogenic) /R413P. PubMed:21307867 We confirmed that 7 patients were homozygous for R413P by using direct sequencing and demonstrated that the parents were heterozygous carriers for the same mutations as the patients. PubMed:9860305
PM2	✔	Extremely low frequency. ExAC MAF=0.00012
PS3	✔	In vitro expression of altered protein in COS cells produces severe decrease of PAH activity (<3%)
PP3	✔	Predicted deleterious in SIFT, Polyphen-2, MutationTaster. REVEL=0.895
PP4_Moderate	✔	Detected in PKU patients, BH4 deficiency excluded

Curation History

Showing 1 to 1 of 1 rows

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