The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000277.2(PAH):c.712A>C (p.Thr238Pro)

Version: 1.0

CA229705

102796 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: adefc5ed-7d59-4119-8b3d-07dcdc504c09
Approved on: 2020/10/23
Published on: 2020/10/23

HGVS expressions

NM_000277.2(PAH):c.712A>C (p.Thr238Pro)
NM_000277.2:c.712A>C
NC_000012.12:g.102852945T>G
CM000674.2:g.102852945T>G
NC_000012.11:g.103246723T>G
CM000674.1:g.103246723T>G
NC_000012.10:g.101770853T>G
NG_008690.1:g.69658A>C
NG_008690.2:g.110466A>C
ENST00000553106.6:c.712A>C
ENST00000307000.7:c.697A>C
ENST00000549247.6:n.471A>C
ENST00000553106.5:c.712A>C
NM_000277.1:c.712A>C
NM_001354304.1:c.712A>C
NM_000277.3:c.712A>C
NM_001354304.2:c.712A>C

Likely Pathogenic

Met criteria codes 4
PM3 PM2 PP3 PP4

Not Met criteria codes 1
PM5

Evidence Links 2

Expert Panel
Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.712A>C (p.Thr238Pro) variant in PAH has been reported in 2 individuals with PKU, detected with pathogenic variants p.R408W (PMID: 1363786) and p.R158Q (PMID: 11295882). This variant is absent in population databases. Computational evidence supports a deleterious effect. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4, PM2, PM3, PP3.

Met criteria codes

PM3	✔	T238P identified with R408W, pathogenic in ClinVar. Further DNA analysis in this family traced the mutation to a haplotype 4 PKU allele and confirmed Mendelian inheritance. PMID: 1363786; R158Q, parental analysis not reported PMID: 11295882 Patient D10-3: T238P/R408W (VarID 577, Pathogenic) PubMed:1363786 PubMed:11295882
PM2	✔	Absent from ExAC, gnomAD, 1000G, ESP
PP3	✔	Deleterious effect predicted by SIFT, Polyphen2, MutationTaster. REVEL=0.972
PP4	✔	T238P identified in a patient with classical PKU from West Germany/Bulgaria. BH4 deficiency not excluded. PMID: 1363786 Complete sequence analysis of 194 human phenylalanine hydroxylase genes from PKU patients originating from West Germany and Bulgaria revealed 13 different mutations within exon 7 of the gene. T238P: ACT>CCT was seen on 1 allele of a patient with classical PKU. PubMed:1363786

Not Met criteria codes

PM5	✖	p.T238A is likely pathogenic by PAH VCEP in ClinVar (no other submitters)

Curation History

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