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_000277.1:c.697T>A

CA16020843

619163 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: b990f0f7-2c1b-428d-bfec-28ed05f717f4
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HGVS expressions

NM_000277.1:c.697T>A
NC_000012.12:g.102855145A>T
CM000674.2:g.102855145A>T
NC_000012.11:g.103248923A>T
CM000674.1:g.103248923A>T
NC_000012.10:g.101773053A>T
NG_008690.1:g.67458T>A
NG_008690.2:g.108266T>A
NM_000277.2:c.697T>A
NM_001354304.1:c.697T>A
NM_000277.3:c.697T>A
ENST00000307000.7:c.682T>A
ENST00000549111.5:n.793T>A
ENST00000553106.5:c.697T>A

Pathogenic

Met criteria codes 5

PP4_Moderate PM3_Strong PM2 PS3 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.697T>A (p.Phe233Ile) variant in PAH has been reported in 2 unrelated patients with PKU (BH4 deficiency excluded) and was detected with known pathogenic variants p.R408W and p.V245A. (PP4_Moderate, PM3_Strong; PMID: 23764561). This variant is absent in population databases (PM2). This variant showed no specific activity in functional assay and no response to chaperone co-expression (PS3; PMID: 28653649). Computational prediction tools and conservation analysis suggest this 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, PS3, PM3_strong, PM2, PP3.

Met criteria codes

PP4_Moderate	✔	p.F233I was detected in two unrelated PKU patients. BH4 deficiency was excluded. PMID: 23764561 We investigated the mutation spectrum of the phenylalanine hydroxylase gene (PAH) in a cohort of patients from 135 Slovak PKU families. We identified the novel missense mutation: p.F233I. Patients with BH4 deficiency were excluded from molecular analysis. PubMed:23764561
PM3_Strong	✔	p.F233I was detected in two apparently unrelated patients in compound heterozygosity with p.R408W (VarID 577, Pathogenic) and p.V245A (Pathogenic) PMID: 23764561 Mutation p.F233I was detected in two apparently unrelated patients in compound heterozygosity with p.R408W (VarID 577, Pathogenic) and p.V245A (Pathogenic) respectively. PubMed:23764561
PM2	✔	Absent from ExAC, gnomAD, 1000G, ESP
PS3	✔	Showed no specific activity in functional assay and no response to chaperone co-expression. PMID: 28653649 In this study, in silico prediction and in vitro prokaryotic and eukaryotic expression systems were used to functionally characterize five PAH missense variants (including p.F233I). p.F233I was classified as deleterious mutations since it showed no specific activity in functional assay and no response to chaperone co-expression. Protein levels of the PAH variant was very low when expressed in HepG2 cells. PubMed:28653649
PP3	✔	Deleterious effect predicted in SIFT, Polyphen2, MutationTaster. REVEL=0.92

Curation History

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