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(PAH):c.688G>A (p.Val230Ile)

CA286506

102784 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 08c0af15-2212-42d9-841c-0a5e84d6838d
Approved on: 2018-08-12
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HGVS expressions

NM_000277.1(PAH):c.688G>A (p.Val230Ile)
NM_000277.1:c.688G>A
NC_000012.12:g.102855154C>T
CM000674.2:g.102855154C>T
NC_000012.11:g.103248932C>T
CM000674.1:g.103248932C>T
NC_000012.10:g.101773062C>T
NG_008690.1:g.67449G>A
NG_008690.2:g.108257G>A
NM_000277.2:c.688G>A
NM_001354304.1:c.688G>A
NM_000277.3:c.688G>A
ENST00000307000.7:c.673G>A
ENST00000549111.5:n.784G>A
ENST00000553106.5:c.688G>A

Likely Pathogenic

Met criteria codes 2
PM3_Very Strong | PP4_Moderate

Not Met criteria codes 4
PM2 | PM5 | PS3 | PP3

Evidence Links 5

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: PP4_Moderate: V2301 seen in 1 patient with PAH deficiency. BH4 deficiency ruled out. Upgraded per ClinGen Metabolism WG. (PMID:8268925); PM3_VeryStrong: Detected in trans with IVS 10-11G>A, L48S, R408W, E390G). Upgraded per ClinGen SVI Workgroup. (PMID:15943553; PMID:21147011). In summary this variant meets criteria to be classified as likely pathogenic for phenylketonuria in an autosomal recessive manner based on the ACMG/AMP criteria applied as specified by the PAH Expert Panel: (PP4_Moderate, PM3_VeryStrong).

Met criteria codes

PM3_Very Strong	✔	Detected in trans with IVS 10-11G>A, L48S, R408W, E390G). Upgraded per ClinGen SVI Workgroup. V230I found in 6 patients with PKU: 2 mHPA patients in trans with IVS10-11G>A (varID 607, Pathogenic); 1 mPKU patient in trans with p.L48S (varID 608, Pathogenic); 1 mHPA patient in trans with p.R408W (varID 577, Pathogenic); 1 mHPA patient in trans with p.E390G (varID 625, Pathogenic/LP); 1 mHPA patient in trans with IVS2+5G>C. PubMed:21147011 R158Q/V230I present in one patient with classical PKU (seen with V245V/IVS3nt-22ct/IVS5nt-54a>g); G272X/V230I present in one patient showing HPA phenotype (seen with V245V/E280 > Q280) PubMed:15943553
PP4_Moderate	✔	V2301 seen in 1 patient with PAH deficiency. BH4 deficiency ruled out. Upgraded per ClinGen Metabolism WG. Subjects included 53 unrelated patients presenting with blood phenylalanine levels persistently above 150 umol/l. The criteria for inclusion were: normal serum tyrosine, normal urinary excresion of biopterin and neopterin, and no indication of acquired hyperphenylalaninemia. V230I was found on 1 chromosome. PubMed:8268925

Not Met criteria codes

PM2	✖	MAF=0.00266 in gnomAD
PM5	✖	V230G, no clinical significance provided
PS3	✖	In vitro studies in 2 expression systems show reduced activity of V230I mutant, 52-72% of wt. We have used two heterologous in vitro expression systems (a mammalian cell-free transcription-translation system and the pET system of Escherichia coli). V230I showed pcDNA3/IVT: 72;53% of wt and 52% in pET/E. coli. Could not detect any tetrameric forms of enzymes carrying V230I. PubMed:11161839 Reference to residual in vitro activity of V230I mutant with 63% of wt activity. PubMed:17924342
PP3	✖	Conflicting interpretations of pathogenicity (tolerated in SIFT, benign in PolyPhen2, Damaging in MutationTaster

Curation History

Showing 1 to 1 of 1 rows

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