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.733G>C (p.Val245Leu)

Version: 1.0

CA229724

102810 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: fd61f8d1-cff0-4fe7-a5e3-acd517903539
Approved on: 2020/6/26
Published on: 2023/4/1

HGVS expressions

NM_000277.2(PAH):c.733G>C (p.Val245Leu)
NM_000277.2:c.733G>C
NC_000012.12:g.102852924C>G
CM000674.2:g.102852924C>G
NC_000012.11:g.103246702C>G
CM000674.1:g.103246702C>G
NC_000012.10:g.101770832C>G
NG_008690.1:g.69679G>C
NG_008690.2:g.110487G>C
ENST00000553106.6:c.733G>C
ENST00000307000.7:c.718G>C
ENST00000549247.6:n.492G>C
ENST00000553106.5:c.733G>C
NM_000277.1:c.733G>C
NM_001354304.1:c.733G>C
NM_000277.3:c.733G>C
NM_001354304.2:c.733G>C

Pathogenic

Met criteria codes 5

PM3 PM2 PS3_Supporting PP3 PP4

Evidence Links 3

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.733G>C (p.Val245Leu) variant in PAH has been reported in 3 individuals with PAH deficiency, detected with pathogenic variants p.R408Q and p.A104D (PMID: 8659548, 24368688). This variant has an extremely low allele frequency (0.000008972) in gnomAD. This variant has 13% enzyme activity (PMID: 11161839). Computational prediction tools and conservation analysis support a deleterious effect. In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4, PS3, PM2, PM3, PP3.

Met criteria codes

PM3	✔	Seen with R408Q and A104D in 2 patients. Both pathogenic, parental analysis not reported. PMID: 24368688 Patient 55: R408Q (VarID 612, Pathogenic), Patient 72: A104D (VarID 102650, Pathogenic) PubMed:24368688 V245L seen with N133Ql34fsdel4bp ((398-401)del4bp) PubMed:8659548
PM2	✔	Absent from 1000G, ESP. Extremely low frequency in gnomAD (MAF=0.00001)
PS3_Supporting	✔	PAH activity of 13%. PMID: 11161839 "In vitro expression of 34 naturally occurring mutant variants of phenylalanine hydroxylase" Gjetting et al. PAH enzyme activities (as % of wild-type): pcDNA3/IVT:13;0. pET/E. coli:15 +/- 11. The data for the bacterial expression represent three independent experiments. PubMed:11161839
PP3	✔	Predicted deleterious in SIFT, Polyphen2, MutationTaster. REVEL=0.96.
PP4	✔	V245L seen in 1 classic PKU patient. PMID: 8659548 149 hyperphenylalaninemic females were genotyped. V245L was seen in patient A/1056/BDE-10 with classical PKU. Serum Phe level was 1,840 umol/l. normal blood tyrosine concentrations, and large concentrations of phenylalanine metabolites in urine. PubMed:8659548

Curation History

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