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.734T>C (p.Val245Ala)

Version: 1.0

CA114372

632 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 0129bef0-6e1d-4f6b-8e4e-2c05721902af
Approved on: 2018-09-28
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HGVS expressions

NM_000277.2:c.734T>C
NM_000277.2(PAH):c.734T>C (p.Val245Ala)
NC_000012.12:g.102852923A>G
CM000674.2:g.102852923A>G
NC_000012.11:g.103246701A>G
CM000674.1:g.103246701A>G
NC_000012.10:g.101770831A>G
NG_008690.1:g.69680T>C
NG_008690.2:g.110488T>C
NM_000277.1:c.734T>C
NM_001354304.1:c.734T>C
NM_000277.3:c.734T>C
ENST00000307000.7:c.719T>C
ENST00000549247.6:n.493T>C
ENST00000553106.5:c.734T>C

Pathogenic

Met criteria codes 3

PP4_Moderate PM5 PM3_Very Strong

Not Met criteria codes 3

PS3 PP3 PM2

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: PM5: V245L Pathogenic; PP4_Moderate: Seen in at least 7 MHP patients. Exclusion of a defect in tetrahydrobiopterin metabolism. Upgraded per ClinGen Metabolic Workgroup. (PMID:7981714; PMID:9298832; PMID:9634518); PM3_VeryStrong: V245A detected with IVS-12nt1, R252W, L194P (both P/LP), R408W (Path). Upgraded per ClinGen SVI Workgroup (PMID:7981714; PMID:9298832; PMID:8088845). 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: (PM5, PP4_Moderate, PM3_VeryStrong).

Met criteria codes

PP4_Moderate	✔	Seen in at least 7 MHP patients. Exclusion of a defect in tetrahydrobiopterin metabolism. Upgraded per ClinGen Metabolic Workgroup. Seven centers in France, Italy, Belgium, Germany, and Denmark participated in this collaborative study. In all patients, hyperphenylalaninemia had been detected by national mass screening programs, and PAH deficiency had been assessed after exclusion of a defect in tetrahydrobiopterin metabolism. V245A was seen in 7 MHP patients from 3 different centers. Patients who have phenylalanine levels <600 mmol/liter on a normal diet were classified as having MHP. PubMed:9634518 One non-PKU HPA patient (F) carries two novel mutations. One is a T-to-C transition at codon 245 in exon 7, resulting in the replacement of valine by alanine (V245A). Serum Phe level 237 umol/liter. PubMed:7981714 Genomic DNA was isolated from total blood of 34 MHP and eight mild PKU probands from unrelated Polish families. V245A was detected in 2 patients (serum Phe levels 442, 394). PubMed:9298832
PM5	✔	V245L Pathogenic
PM3_Very Strong	✔	V245A detected with IVS-12nt1, R252W, L194P (both P/LP), R408W (Path). Upgraded per ClinGen SVI Workgroup Patient F: V245A/L194P (VarID 102742, P/LP) PubMed:7981714 V245A seen in 2 patients. Once with R252W (varID 584, P/LP). Once with R408W (VarID 577, Pathogenic) PubMed:9298832 Patient K Genotype: V245A/IVS-12nt1. Patient L: V245A/R408W. Patient M: V245A/Y414C PubMed:8088845

Not Met criteria codes

PS3	✖	V245A has PAH enzyme activities 63;39 (% of wt). 50% stated in PAHdb/BioPKU Two heterologous in vitro expression systems (cell-free rabbit reticulocyte lysates) to assess the residual activities and oligomeric compositions. V245A had PAH enzyme activities 63;39 (% of wt, pcDNA3/IVT). PubMed:11161839
PP3	✖	Conflicting predictions of pathogenicity: Tolerated in SIFT, Damaging in Polyphen2, MutationTaster.
PM2	✖	ExAC MAF: 0.00114

Curation History

Showing 1 to 1 of 1 rows