Variant: NM_000277.1(PAH):c.1208C>T (p.Ala403Val)

Version: 1.0

CA273106

92731 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: e8a0e1ef-d616-4dfe-a24e-30a901afa80f
Approved on: 2018-08-10
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HGVS expressions

NM_000277.1:c.1208C>T
NM_000277.1(PAH):c.1208C>T (p.Ala403Val)
NC_000012.12:g.102840507G>A
CM000674.2:g.102840507G>A
NC_000012.11:g.103234285G>A
CM000674.1:g.103234285G>A
NC_000012.10:g.101758415G>A
NG_008690.1:g.82096C>T
NG_008690.2:g.122904C>T
NM_000277.2:c.1208C>T
NM_001354304.1:c.1208C>T
NM_000277.3:c.1208C>T
ENST00000307000.7:c.1193C>T
ENST00000551114.2:n.870C>T
ENST00000553106.5:c.1208C>T
ENST00000635477.1:n.312C>T
ENST00000635528.1:n.723C>T

Pathogenic

Met criteria codes 3

PP4_Moderate PS3 PM3_Very Strong

Not Met criteria codes 3

PP3 PM2 PM5

Evidence Links 3

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: Seen on 3 PKU alleles, BH4 deficiency was ruled out. Upgraded per ClinGen Metabolic WG. (PMID:8268925); PM3_VeryStrong: A403V found with 4 pathogenic variants . Upgraded per ClinGen SVI workgroup. (PMID:9429153); PS3: In vitro A403V mutant protein activity was ~43% wt. (PMID:21820508). 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: (PP4_Moderate, PM3_VeryStrong, PS3).

Met criteria codes

PP4_Moderate	✓	Seen on 3 PKU alleles, BH4 deficiency was ruled out. Upgraded per ClinGen Metabolic WG. 53 patients with persistently elevated blood levels of phenylalanine who met the differential criteria for PAH deficiency. A403V was found on 3 alleles. All patients were presenting with blood phenylalanine levels persistently above 150 /umol/l, and diagnosis of PAH deficiency was made when other potential causes of hyperphenylalaninemia had been ruled out. The criteria for inclusion were: normal serum tyrosine, normal urinary excresion of biopterin and neopterin, and no indication of acquired hyperphenylalaninemia. PubMed:8268925
PS3	✓	In vitro A403V mutant protein activity was ~43% wt. We reproduced a full-length wild-type protein and seven natural full-length PAH variants (p.A403V), and analyzed their biochemical and biophysical behavior. The residual activity of the mutant PAH enzyme, expressed as a percentage of wild-type enzyme activity, was 43± 4% (p.A403V). Using confocal microscopy with the number and brightness technique, we studied the effect of BH4 addition directly in living human cells expressing wild-type PAH or p.A403V. Our results demonstrate that BH4 addition promotes re-establishment of the oligomerization equilibrium, thus indicating that the dimer-to-tetramer shift in pA403V plays a key role in BH4 responsiveness. PubMed:21820508
PM3_Very Strong	✓	A403V found with 4 pathogenic variants . Upgraded per ClinGen SVI workgroup. A403V found in 13 Polish patients in trans with 4 different known pathogenic variants. R408W, R158Q, P281L, IVS10. PubMed:9429153

Not Met criteria codes

PP3	✗	Conflicting predictions: tolerated in SIFT, deleterious in PolyPhen2, MutationTaster
PM2	✗	MAF= 0.00502 in gnomAD
PM5	✗	No other reported variants in this codon

Curation History

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