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Variant: NM_000277.1(PAH):c.721C>T (p.Arg241Cys)

CA273357

102803 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: dd8fcc3c-dde1-42d4-a0f2-31bbafa786a5
Approved on: 2018-08-10
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HGVS expressions

NM_000277.1:c.721C>T
NM_000277.1(PAH):c.721C>T (p.Arg241Cys)
NC_000012.12:g.102852936G>A
CM000674.2:g.102852936G>A
NC_000012.11:g.103246714G>A
CM000674.1:g.103246714G>A
NC_000012.10:g.101770844G>A
NG_008690.1:g.69667C>T
NG_008690.2:g.110475C>T
NM_000277.2:c.721C>T
NM_001354304.1:c.721C>T
NM_000277.3:c.721C>T
ENST00000307000.7:c.706C>T
ENST00000549247.6:n.480C>T
ENST00000553106.5:c.721C>T

Pathogenic

Met criteria codes 5

PM2 PM3_Strong PS3 PP3 PP4_Moderate

Not Met criteria codes 1

PM5

Evidence Links 4

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: PM2: Extremely low frequency in ExAC (0.00014) and gnomAD (0.0001301); PP3: Deleterious effect predicted in SIFT, PolyPhen2, MutationTaster; PP4_Moderate: Seen in multiple PKU patients. BH4 deficiency excluded in 2 patients. Upgraded per ClinGen Metabolic Workgroup. (PMID:8222245; PMID:11142755); PM3_Strong: R241C seen once in trans with R413P, and once with R243Q, both pathogenic. Upgraded per ClinGen SVI Workgroup. (PMID:11142755); PS3: In vitro PAH R241C mutant was found to have 25% PAH activity of normal. In vivo phenylalanine breath test measured a decreased level in R241C homozygote. (PMID:15319459;

PMID:7915167). 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: (PM2, PP3, PP4_Moderate, PM3_Strong, PS3).

Met criteria codes

PM2	✔	Extremely low frequency in ExAC (0.00014) and gnomAD (0.0001301)
PM3_Strong	✔	R241C seen once in trans with R413P, and once with R243Q, both pathogenic. Upgraded per ClinGen SVI Workgroup. R241C seen in 2 Japanese MHP patients in trans with R413P (VarID 592, Pathogenic in ClinVar) and R243Q (VarID 591, Pathogenic in ClinVar). PubMed:11142755
PS3	✔	In vitro PAH R241C mutant was found to have 25% PAH activity of normal. In vivo phenylalanine breath test measured a decreased level in R241C homozygote. We performed the phenylalanine breath test as reliable method to determine the BH4 responsiveness. Phenylalanine breath test quantitatively measures the conversion of L-[1-13C] phenylalanine to 13CO2 and is a noninvasive and rapid test. A mild HPA case was homozygote of R241C. The phenylalanine breath test exhibited continuous levels of CRR (cumulative recovery rate) of 2.74% (mild HPA/R241C homozygote), as compared to control subjects (15.4%). PubMed:15319459 For identification of whether the R241C mutation causes PKU, expression analysis was performed in mammalian cells. In dot blot hybridization of serially diluted RNA of transfected cells, the normal and mutant PAH cDNA constructs expressed similar levels of mRNA. The PAH activity of the mutant protein was 25 ± 3% (SD) of normal PAH. The mother and the patient had the R241C mutation as heterozygotes. PubMed:7915167
PP3	✔	Deleterious effect predicted in SIFT, PolyPhen2, MutationTaster
PP4_Moderate	✔	Seen in multiple PKU patients. BH4 deficiency excluded in 2 patients. Upgraded per ClinGen Metabolic Workgroup. A total of 20 unrelated PKU families Urinary excretion of biopterin (B), neopterin (N), N/B ratio, and dihydropteridine reductase activities in erythrocytes were measured in Japanese patients detected by mass screening, to exclude biopterin deficiency. R241C was seen in 2 Japanese MHP patients (pretreatment Phe level 6.7 and 7.5 mg/dl). PubMed:11142755 We analyzed blood samples of 35 patients, R241C was found in a Taiwanese patient. PubMed:8222245

Not Met criteria codes

PM5	✖	R241H (VarID 102804) is Pathogenic in ClinVar based on 3 submitters

Curation History

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