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:c.755G>C

Version: 1.0

CA16020854

932252 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: c746efb0-6516-407e-bad0-a2cc5b62fb0b
Approved on: 2020/3/15
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HGVS expressions

NM_000277.1:c.755G>C
NC_000012.12:g.102852902C>G
CM000674.2:g.102852902C>G
NC_000012.11:g.103246680C>G
CM000674.1:g.103246680C>G
NC_000012.10:g.101770810C>G
NG_008690.1:g.69701G>C
NG_008690.2:g.110509G>C
ENST00000553106.6:c.755G>C
ENST00000307000.7:c.740G>C
ENST00000549247.6:n.514G>C
ENST00000553106.5:c.755G>C
NM_000277.2:c.755G>C
NM_001354304.1:c.755G>C
NM_000277.3:c.755G>C
NM_001354304.2:c.755G>C

Likely Pathogenic

Met criteria codes 5

PM3 PM5 PM2 PP3 PP4_Moderate

Evidence Links 2

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.755G>C (p.Arg252Pro) variant in PAH has been reported in multiple individuals with PKU (BH4 deficiency excluded, PMID: 21307867). This variant is absent in population databases. This variant was detected in trans with pathogenic variant p.Arg243Gln (PMID: 29316886). Computational evidence supports a deleterious effect. Other missense variants at the p.Arg252 amino acid are pathogenic (p.Arg252Gln/Trp/Gly). In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM2, PM3, PM5, PP3.

Met criteria codes

PM3	✔	Detected in trans with p.Arg243Gln (P 10 submitters) variable sites in patient genes were aligned with the corresponding sites from the respective parents. PMID: 29316886 PubMed:29316886
PM5	✔	p.Arg252Gln/Trp/Gly pathogenic
PM2	✔	Absent from controls in ExAC, gnomAD, 1000 Genomes, or ESP
PP3	✔	Predicted deleterious in SIFT, PolyPhen2, MutationTaster. REVEL=0.966
PP4_Moderate	✔	PMID 21307867: 5 alleles of p.Arg252Pro in a cohort of Japanese PKU patients. Serum phenylalanine level higher than 0.18mM. analysis of dihydropteridine reductase activity in red blood cells, biopterin loading test and/or pteridine analysis in urine. In Table 2, listed 5 alleles of p.Arg252Pro in a cohort of Japanese PKU patients. PubMed:21307867

Curation History

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