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.472C>T (p.Arg158Trp)

Version: 1.0

CA229570

102693 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: faad1844-5076-4b6f-b671-eeb06035449a
Approved on: 2018-08-10
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HGVS expressions

NM_000277.2:c.472C>T
NM_000277.2(PAH):c.472C>T (p.Arg158Trp)
NC_000012.12:g.102866633G>A
CM000674.2:g.102866633G>A
NC_000012.11:g.103260411G>A
CM000674.1:g.103260411G>A
NC_000012.10:g.101784541G>A
NG_008690.1:g.55970C>T
NG_008690.2:g.96778C>T
NM_000277.1:c.472C>T
NM_001354304.1:c.472C>T
NM_000277.3:c.472C>T
ENST00000307000.7:c.457C>T
ENST00000549111.5:n.568C>T
ENST00000551988.5:n.530+10829C>T
ENST00000553106.5:c.472C>T

Pathogenic

Met criteria codes 5

PS3 PP3 PM2 PM3_Strong PP4_Moderate

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: PM2: Extremely low frequency. ExAC MAF=0.00019.; PP3: Predicted deleterious in SIFT, Polyphen-2, MutationTaster. REVEL=0.939; PS3: 2% mutant enzyme activity in BioPKU; PP4_Moderate: Detected in at least 3 patients with PAH deficiency. BH4 deficiency ruled out in 1 patient. (PMID:1307609; PMID:10429004; PMID:9634518); PM3_Strong: Detected with 3 pathogenic/likely pathogenic variants (PMID:14681498; PMID:23430918). 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, PS3, PP4_Moderate, PM3_Strong).

Met criteria codes

PS3	✔	2% mutant enzyme activity in BioPKU
PP3	✔	Predicted deleterious in SIFT, Polyphen-2, MutationTaster. REVEL=0.939
PM2	✔	Extremely low frequency. ExAC MAF=0.00019.
PM3_Strong	✔	Detected with 3 pathogenic/likely pathogenic variants Table 2. Mutant Genotypes. p.R158W: p.R261P (VarID102832, LP). p.R158W: p.R408W (VarID577, Path). p.I65T (VarID:636, P/LP): p.R158W. PubMed:23430918 In case 2, P407S (VarID102568, clinical significance not provided) was detected in one allele and R158W in the other allele. PubMed:14681498
PP4_Moderate	✔	Detected in at least 3 patients with PAH deficiency. BH4 deficiency ruled out in 1 patient. R158W was detected. 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. PubMed:9634518 A novel Arg158 (CGG)-to-Trp158 (TGG) mutation was identified in exon 5 of the PAH gene in a Chinese PKU patient. PubMed:1307609 R158W was observed in the study. PubMed:10429004

Curation History

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