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Variant: NM_001354304.1:c.470G>C

CA16020797

619162 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: a2d92aa7-5fed-4ba2-be23-93c6b25c50cb
Approved on: 2018-12-10
Published on: 2018-12-10

HGVS expressions

NM_001354304.1:c.470G>C
ENST00000553106.6:c.470G>C
ENST00000307000.7:c.455G>C
ENST00000549111.5:n.566G>C
ENST00000551988.5:n.530+10827G>C
ENST00000553106.5:c.470G>C
NM_000277.1:c.470G>C
NM_000277.2:c.470G>C
NM_000277.3:c.470G>C
NM_001354304.2:c.470G>C
NC_000012.12:g.102866635C>G
CM000674.2:g.102866635C>G
NC_000012.11:g.103260413C>G
CM000674.1:g.103260413C>G
NC_000012.10:g.101784543C>G
NG_008690.1:g.55968G>C
NG_008690.2:g.96776G>C

Uncertain Significance

Met criteria codes 3

PP3 PM5 PM2

Not Met criteria codes 1

PS3

Evidence Links 1

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.470G>C (p.Arg157Thr) variant in PAH has not been reported in an affected patient to our knowledge. The reference in BioPKU (Carter KC, 1998) does not include this variant. The p.R157T mutant is listed as having 5% of wt PAH activity in vitro (BioPKU), but this likely corresponds to the p.R157N variant (PMID: 9450897). The p.Arg157Asn variant at the same amino acid is interpreted as pathogenic in ClinVar (VarID 590772). p.Arg157Thr is absent from ExAC, gnomAD, 1000G, and ESP. It is predicted deleterious in SIFT, Polyphen-2,

MutationTaster, and REVEL=0.95. In summary, this variant meets criteria to be classified as uncertain significance for PAH. PAH-specific ACMG/AMP criteria applied: PM2, PM5, PP3.

Met criteria codes

PP3	✔	Predicted deleterious in SIFT, Polyphen2, MutationTaster. REVEL=0.95.
PM5	✔	R157N is pathogenic by McGill https://www.ncbi.nlm.nih.gov/clinvar/variation/590772/
PM2	✔	Absent from ExAC, gnomAD, 1000G, ESP

Not Met criteria codes

PS3	✖	From PAHvdb: R157T mutant has 5% PAH activity calculated as average of data obtained in eukaryotic cell systems. This data applies to variant R157N (PMID: 9450897), as comfirmed by Dr. Blau (email correspondence 2/2021 ("You are right. 5% belongs to p.Arg157Asn.") c.470G>A;c.471A>C (R157N) in pcDNA3/human kidney cells A293 had 5% PAH enzyme activity PubMed:9450897

Curation History

Showing 1 to 2 of 2 rows

See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_001354304.1:c.470G>C	Uncertain Significance	Phenylketonuria	2021-05-14	2.0	-	PAH
View	NM_000277.1:c.470G>C	Likely Pathogenic	Phenylketonuria	2021-02-14	1.0	-	PAH

Showing 1 to 2 of 2 rows

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