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.196G>T (p.Glu66Ter)

Version: 1.0

CA267645

120270 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 43d4908f-6cb4-4058-865a-6c3f58dd5dc0
Approved on: 2019-05-26
Published on: 2019-05-26

HGVS expressions

NM_000277.2:c.196G>T
NM_000277.2(PAH):c.196G>T (p.Glu66Ter)
NC_000012.12:g.102894891C>A
CM000674.2:g.102894891C>A
NC_000012.11:g.103288669C>A
CM000674.1:g.103288669C>A
NC_000012.10:g.101812799C>A
NG_008690.1:g.27712G>T
NG_008690.2:g.68520G>T
NM_000277.1:c.196G>T
NM_001354304.1:c.196G>T
NM_000277.3:c.196G>T
ENST00000307000.7:c.181G>T
ENST00000546844.1:c.196G>T
ENST00000548677.2:n.283G>T
ENST00000548928.1:n.118G>T
ENST00000549111.5:n.292G>T
ENST00000550978.6:n.180G>T
ENST00000551337.5:c.196G>T
ENST00000551988.5:n.285G>T
ENST00000553106.5:c.196G>T
ENST00000635500.1:n.164G>T

Pathogenic

Met criteria codes 4

PM3_Supporting | PVS1 | PM2 | PP4

Evidence Links 1

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.196G>T (p.Glu66Ter) variant in PAH has been previously reported in one proband with classic PKU (PMID: 26666653) (PP4). The proband was heterozygous for the variant and also harbor the pathogenic allele (per ClinGen VCEP) c. 1315+1G>A; however, the phase of the variants was not confirmed via parental testing. (PM3_supporting). The sequence change results in a nonsense variant which occurs in exon 3 of 13 in the in the canonical transcript of PAH, a gene fulfilling the most recent criteria for LOF being a known disease mechanism (see PMID: 30192042) (PVS1). It is absent from control databases (PM2). In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PVS1, PM2, PP4, PM3_supporting.

Met criteria codes

PM3_Supporting	✔	Detected with c.1315+1G>A; however, the manuscript did not specify whether the phase of the variants was confirmed via parental testing. Detected with c.1315+1G>A; however, the manuscript did not specify whether the phase of the variants was confirmed via parental testing. PubMed:26666653
PVS1	✔	The sequence change results in a nonsense variant which occurs in exon 3 of 13 in the in the canonical transcript of PAH, a gene fulfilling the most recent criteria for LOF being a known disease mechanism (see PMID: 30192042) (PVS1).
PM2	✔	It is absent from control databases including ethnically matched individuals, including gnomAD/ExAC, 1000 Genomes, and ESP (PM2).
PP4	✔	The c.196G>T (p.Glu66Ter) variant in PAH has been previously reported in one proband with classic PKU (plasma phenylalanine levels > 1200umol/L) (PMID: 26666653) The c.196G>T (p.Glu66Ter) variant in PAH has been previously reported Likely Pathogenic by one clinical laboratory in ClinVar (see variant ID 120270); the collection method is stated as “literature only” and no further information is provided. With respect to the published literature, it has been previously reported in one proband with classic PKU (defined by the authors as plasma phenylalanine levels > 1200umol/L) (PMID: 26666653) (PP4). The proband was said to be heterozygous for the variant and also harbor the known pathogenic allele (per ClinGen PAH working group classification, see ClinVar ID) c. 1315+1G>A variant; however, the manuscript did not specify whether the phase of the variants was confirmed via parental testing. Thus, at this point, PM3 cannot be applied with full confidence. PubMed:26666653

Curation History

Showing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.