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Variant: NM_000277.2(PAH):c.169G>T (p.Glu57Ter)

Version: 1.0

CA267642

120268 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 25d06695-2ddd-4701-bf21-ddb937ad9b51
Approved on: 2019-09-29
Published on: 2019-10-02

HGVS expressions

NM_000277.2:c.169G>T
NM_000277.2(PAH):c.169G>T (p.Glu57Ter)
NC_000012.12:g.102894918C>A
CM000674.2:g.102894918C>A
NC_000012.11:g.103288696C>A
CM000674.1:g.103288696C>A
NC_000012.10:g.101812826C>A
NG_008690.1:g.27685G>T
NG_008690.2:g.68493G>T
ENST00000553106.6:c.169G>T
ENST00000307000.7:c.154G>T
ENST00000546844.1:c.169G>T
ENST00000548677.2:n.256G>T
ENST00000548928.1:n.91G>T
ENST00000549111.5:n.265G>T
ENST00000550978.6:c.153G>T
ENST00000551337.5:c.169G>T
ENST00000551988.5:n.258G>T
ENST00000553106.5:c.169G>T
ENST00000635500.1:n.137G>T
NM_000277.1:c.169G>T
NM_001354304.1:c.169G>T
NM_000277.3:c.169G>T
NM_001354304.2:c.169G>T

Pathogenic

Met criteria codes 3

PP4 PM2 PVS1

Evidence Links 1

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.169G>T (p.Glu57Ter) variant in PAH has been previously reported Likely Pathogenic by one clinical laboratory in ClinVar (see variant ID 120268); 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 636) c.194T>C (p.Ile65Thr); 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. 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 present at extremely low frequencies in control databases including ethnically matched individuals, including gnomAD/ExAC, 1000 Genomes, and ESP: the highest MAF reported is 0.00014 in Other subpopulation in gnomAD, below the 0.0002 allele frequency cutoff for PAH variants (PM2).

Met criteria codes

PP4	✔	The c.169G>T (p.Glu57Ter) variant in PAH has been previously reported Likely Pathogenic by one clinical laboratory in ClinVar (see variant ID 120268); 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 636) c.194T>C (p.Ile65Thr); 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. The c.169G>T (p.Glu57Ter) variant in PAH has been previously reported Likely Pathogenic by one clinical laboratory in ClinVar (see variant ID 120268); 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 636) c.194T>C (p.Ile65Thr); 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
PM2	✔	It is present at extremely low frequencies in control databases including ethnically matched individuals, including gnomAD/ExAC, 1000 Genomes, and ESP: the highest MAF reported is 0.00014 in Other subpopulation in gnomAD, below the 0.0002 allele frequency cutoff for PAH variants (PM2).
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).

Curation History

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