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Variant: NM_000277.3(PAH):c.533A>T (p.Glu178Val)

Version: 1.0

CA229611

102728 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 3dea04d4-9b44-473c-b491-d7568f3f774a
Approved on: 2024-09-06
Published on: 2024-09-06

HGVS expressions

NM_000277.3(PAH):c.533A>T (p.Glu178Val)
NM_000277.3:c.533A>T
NC_000012.12:g.102855309T>A
CM000674.2:g.102855309T>A
NC_000012.11:g.103249087T>A
CM000674.1:g.103249087T>A
NC_000012.10:g.101773217T>A
NG_008690.1:g.67294A>T
NG_008690.2:g.108102A>T
ENST00000553106.6:c.533A>T
ENST00000307000.7:c.518A>T
ENST00000549111.5:n.629A>T
ENST00000551988.5:n.554A>T
ENST00000553106.5:c.533A>T
NM_000277.1:c.533A>T
NM_000277.2:c.533A>T
NM_001354304.1:c.533A>T
NM_001354304.2:c.533A>T

Likely Pathogenic

Met criteria codes 4

PM5 PP3_Moderate PS3_Supporting PM2_Supporting

Evidence Links 1

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen Phenylketonuria Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for PAH Version 2.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.533A>T (p.Glu178Val) variant in PAH has not been reported in the literature/in a patient to our knowledge. This variant is absent in population databases. Computational evidence support a deleterious effect (REVEL= 0.866. Functional studies of this variant have been reported to BioPKU: mutant in vitro expression in COS cells reportedly had 18% enzyme activity as compared to wild type. Another missense change at this amino acid (p.Glu178Gly) is classified as pathogenic. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PS3_supporting, PM2_supporting, PM5, PP3_moderate.

Met criteria codes

PM5	✔	p.Glu178Gly is Pathogenic by 6 submitters and PAH VCEP
PP3_Moderate	✔	REVEL = 0.866
PS3_Supporting	✔	Expressed in vitro in COS host cells, 18% enzyme activity as compared to wild type. PMID: 10980574 We present the interpretation of the effect of mutations on PAH activity, based on the available three-dimensional structural information of PAH of 120 mutations associated with PKU that include the 104 ‘classified’ PKU mutations and all the mutations where the corresponding mutant PAH protein has been expressed in vitroCOS host cells, 18% enzyme activity as compared to wild type. Mutations of polar surface residues to hydrophobic ones destabilise the folded state of the protein (mutations T92I and E178V). PubMed:10980574
PM2_Supporting	✔	Absent from controls in gnomAD v2.1.1

Curation History

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