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_000277.1:c.878T>C

Version: 1.0

CA16020884

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 4f42dda8-77aa-4616-ba24-28556930a2a2
Approved on: 2026/6/17
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HGVS expressions

NM_000277.1:c.878T>C
NC_000012.12:g.102851721A>G
CM000674.2:g.102851721A>G
NC_000012.11:g.103245499A>G
CM000674.1:g.103245499A>G
NC_000012.10:g.101769629A>G
NG_008690.1:g.70882T>C
NG_008690.2:g.111690T>C
ENST00000553106.6:c.878T>C
ENST00000307000.7:c.863T>C
ENST00000549247.6:n.637T>C
ENST00000551114.2:n.540T>C
ENST00000553106.5:c.878T>C
ENST00000635477.1:c.39T>C
NM_000277.2:c.878T>C
NM_001354304.1:c.878T>C
NM_000277.3:c.878T>C
NM_001354304.2:c.878T>C

Likely Pathogenic

Met criteria codes 4

PP4_Moderate PM5_Supporting PP3_Strong PM2_Supporting

Not Met criteria codes 1

PM3

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.878T>C variant in PAH is a missense variant predicted to cause substitution of leucine by serine at amino acid 293 (p.Leu293Ser). At least one patient with this variant displayed plasma phenylalanine concentration persistently above 120umol/L (2mg/dL) AND sequencing of genes in the BH4 cofactor metabolism pathway excluded a defect of BH4 cofactor metabolism, which is highly specific for PAH deficiency (PP4_Moderate, PMID: 21147011). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.968, which meets the threshold of 0.932, evidence that correlates with strong impact to PAH function (PP3_Strong). Another missense variant c.877T>A (p.Leu293Met) [CA16020883] in the same codon has been classified as likely pathogenic for PAH deficiency by the ClinGen PAH Variant Curation Expert Panel (PM5_Supporting). In summary, this variant meets the criteria to be classified as likely pathogenic for autosomal recessive PAH deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen PAH Variant Curation Expert Panel: PP3_strong, PP4_moderate, PM2_supporting, PM5_supporting (PAH VCEP specifications version 2.0.0; approved July 16, 2024).

Met criteria codes

PP4_Moderate	✔	At least one patient with this variant displayed plasma phenylalanine concentration persistently above 120umol/L (2mg/dL) AND sequencing of genes in the BH4 cofactor metabolism pathway to exclude a defect of BH4 cofactor metabolism, which is highly specific for PAH deficiency (PP4_Moderate, PMID: 21147011). 588 hyperphenylalaninemic patients were investigated. Assessment of the PAH gene and genes of the BH4 synthesis/ recycling pathways (PTS, and QDPR). L293S found on 1 allele. **PubMed:21147011**
PM5_Supporting	✔	Another missense variant c.877T>A (p.Leu293Met) [CA16020883] in the same codon has been classified as likely pathogenic for PAH deficiency by the ClinGen PAH Variant Curation Expert Panel (PM5_Supporting).
PP3_Strong	✔	The computational predictor REVEL gives a score of 0.968, which meets the threshold of 0.932, evidence that correlates with strong impact to PAH function (PP3_Strong).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

Not Met criteria codes

PM3	✖	second variant not reported

Curation History

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