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Variant: NM_001354304.2:c.557C>T

Version: 1.0

CA386296861

1504560 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 7bd5825e-31d6-4e45-9d3d-d8260ccf5971
Approved on: 2026/4/15
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HGVS expressions

NM_001354304.2:c.557C>T
NC_000012.12:g.102855285G>A
CM000674.2:g.102855285G>A
NC_000012.11:g.103249063G>A
CM000674.1:g.103249063G>A
NC_000012.10:g.101773193G>A
NG_008690.1:g.67318C>T
NG_008690.2:g.108126C>T
ENST00000553106.6:c.557C>T
ENST00000307000.7:c.542C>T
ENST00000549111.5:n.653C>T
ENST00000551988.5:n.578C>T
ENST00000553106.5:c.557C>T
NM_000277.1:c.557C>T
NM_000277.2:c.557C>T
NM_001354304.1:c.557C>T
NM_000277.3:c.557C>T

Likely Pathogenic

Met criteria codes 4

PM3_Supporting PP4_Moderate PP3_Moderate PM2_Supporting

Not Met criteria codes 1

PM5

Evidence Links 0

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.557C>T variant in PAH is a missense variant predicted to cause substitution of threonine by isoleucine at amino acid 186 (p.Thr186Ile). At least one patient with this variant displayed plasma phenylalanine concentration persistently above 120umol/L (2mg/dL), which is highly specific for PAH deficiency; PAH VCEP Expert consensus is that BH4 deficiency was sufficiently excluded (PP4_Moderate, PMID: 30459323). This individual was compound heterozygous for the variant and a pathogenic variant (0.5 PM3 points, PM3_supporting). The allele frequency in gnomAD v4.1.0 is 0.000001239, which is lower than the ClinGen PAH Variant Curation Expert Panel threshold (<0.0002) for PM2_Supporting, meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.87, which is above the threshold of 0.773 but below 0.932, evidence that correlates with moderate impact to PAH function (PP3_Moderate). In summary, this variant meets the criteria to be classified as Like;y pathogenic for autosomal recessive PAH deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen PAH Variant Curation Expert Panel: PP3_moderate, PP4_moderate, PM2_supporting, PM3_supporting (PAH VCEP specifications version 2.0.0; approved July 16, 2024).

Met criteria codes

PM3_Supporting	✔	p.(R111*);(T186I), parental analysis not reported. Path by VCEP
PP4_Moderate	✔	Detected in a patient with MHP (Phe 164 µmol/L); Patients with BH4 cofactor deficiency were excluded, but methods not reported. PMID: 30459323.. Expert consensus is to apply as moderate based on methods and narrative (BH4 deficiency sufficiently exluded)
PP3_Moderate	✔	REVEL=0.87
PM2_Supporting	✔	Extremely low frequency in gnomAD v4.1 (AF=0.000001239)

Not Met criteria codes

PM5	✖	No other missense changes in ClinVar

Curation History

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