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Variant: NM_000277.3(PAH):c.261C>A (p.Ser87Arg)

Version: 1.0

CA114359

583 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: dda7ffed-eb9f-4830-bcc7-6648991bd1af
Approved on: 2026/4/15
Published on: 2026/4/15

HGVS expressions

NM_000277.3:c.261C>A
NM_000277.3(PAH):c.261C>A (p.Ser87Arg)
NC_000012.12:g.102894826G>T
CM000674.2:g.102894826G>T
NC_000012.11:g.103288604G>T
CM000674.1:g.103288604G>T
NC_000012.10:g.101812734G>T
NG_008690.1:g.27777C>A
NG_008690.2:g.68585C>A
ENST00000553106.6:c.261C>A
ENST00000307000.7:c.246C>A
ENST00000546844.1:c.261C>A
ENST00000548677.2:n.348C>A
ENST00000548928.1:n.183C>A
ENST00000549111.5:n.357C>A
ENST00000550978.6:c.245C>A
ENST00000551337.5:c.261C>A
ENST00000551988.5:n.350C>A
ENST00000553106.5:c.261C>A
NM_000277.1:c.261C>A
NM_000277.2:c.261C>A
NM_001354304.1:c.261C>A
NM_001354304.2:c.261C>A

Pathogenic

Met criteria codes 4

PM2_Supporting PS3_Supporting PP4_Moderate PM3_Very Strong

Not Met criteria codes 2

PP3 PM1

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.261C>A variant in PAH is a missense variant predicted to cause substitution of serine by arginine at amino acid 87 (p.Ser87Arg). At least one patient with this variant displayed plasma phenylalanine concentration persistently above 120umol/L (2mg/dL) AND normal urine pterins and normal DHPR activity, which is highly specific for PAH deficiency (PP4_Moderate, PMID: 15464430). This variant has been detected in at least 7 individuals with PAH deficiency who were compound heterozygous for the variant and distinct pathogenic or likely pathogenic variants and 2 of those were confirmed in trans by parental testing (4.0 PM3 points, PMID: 8088845, 10495930, 15464430, 23514811, 26666653, 31623983; PM3_Very-strong). The allele frequency in gnomAD v4.1.0 is 0.0001159, which is lower than the ClinGen PAH Variant Curation Expert Panel threshold (<0.0002) for PM2_Supporting, meeting this criterion (PM2_Supporting). Expression of this variant in a mammalian transcription-translation system showed <50% enzyme activity in vitro with < 10 benign/pathogenic variant controls indicating that this variant impacts protein function (PMID:11161839)(PS3_supporting). The computational predictor REVEL gives a score of 0.633, which is neither above nor below the thresholds predicting a damaging or benign impact on PAH function. In summary, this variant meets the criteria to be classified as Pathogenic for autosomal recessive PAH deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen PAH Variant Curation Expert Panel: PP4_moderate, PS3_supporting, PM2_supporting, PM3_very-strong (PAH VCEP specifications version 2.0.0; approved July 16, 2024).

Met criteria codes

PM2_Supporting	✔	Extremely low frequency in gnomAD v4.1 (AF=0.0001159)
PS3_Supporting	✔	22-28% PAH enzyme activity of wild type (pcDNA3/IVT, mammalian transcription-translation system) PMID: 11161839
PP4_Moderate	✔	Detected in Proband 18811 with Phe 258uM, Urinary pterin analysis and DHPR activity measurements excluded a BH4 deficiency. PMID: 15464430
PM3_Very Strong	✔	Detected in trans with c.1055delG (pathogenic in ClinVar), confirmed by parental testing PMID: 23514811 [1 point]; F39L (Path by VCEP) unknown phase, R408W (Path by VCEP) unknown phase PMID: 8088845 [1 point]; IVS10 (Path by VCEP) unknown phase PMID: 10495930 [0.5 points]; S349P (P/LP) in trans PMID: 15464430 [1 point]; c.1065+1G>A (LP by VCEP) unknown phase PMID: 26666653 [0.25 points]; P281L (LP by VCEP) unknown phase PMID: 31623983 [0.25 points]. 4.0 points

Not Met criteria codes

PP3	✖	REVEL=0.633
PM1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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