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_000277.3(PAH):c.205C>T (p.Pro69Ser)

Version: 1.0

CA229486

102628 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 9370fcab-fbf4-4a22-a254-33daee7a31c0
Approved on: 2023/3/16
Published on: 2023/3/16

HGVS expressions

NM_000277.3:c.205C>T
NM_000277.3(PAH):c.205C>T (p.Pro69Ser)
NC_000012.12:g.102894882G>A
CM000674.2:g.102894882G>A
NC_000012.11:g.103288660G>A
CM000674.1:g.103288660G>A
NC_000012.10:g.101812790G>A
NG_008690.1:g.27721C>T
NG_008690.2:g.68529C>T
ENST00000553106.6:c.205C>T
ENST00000307000.7:c.190C>T
ENST00000546844.1:c.205C>T
ENST00000548677.2:n.292C>T
ENST00000548928.1:n.127C>T
ENST00000549111.5:n.301C>T
ENST00000550978.6:c.189C>T
ENST00000551337.5:c.205C>T
ENST00000551988.5:n.294C>T
ENST00000553106.5:c.205C>T
ENST00000635500.1:n.173C>T
NM_000277.1:c.205C>T
NM_000277.2:c.205C>T
NM_001354304.1:c.205C>T
NM_001354304.2:c.205C>T

Likely Pathogenic

Met criteria codes 3

PM3 PM2 PP4_Moderate

Not Met criteria codes 5

PP3 PM1 PM5 PS1 PS3

Evidence Links 0

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specification: *ClinGen PAH Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.205C>T (p.Pro69Ser) variant in PAH has been reported in at least two individuals with PKU without specified Phe levels, including at least one for whom BH4 deficiency has been excluded (PMID: 15503242, PMID: 32668217, PMID: 26503515). p.Pro69Ser has been detected at least twice with p.Arg261Gln, which is classified pathogenic by PAH VCEP, but without documentation of parental testing to establish phase. In-vitro studies show reduced enzyme activity, but not below the PAH VCEP cutoff of 50% (PMID: 16253218). p.Pro69Ser is absent from population databases. Multiple lines of computational evidence yield inconsistent predictions regarding the impact of this substitution. In summary, this variant meets criteria to be classified as likely pathogenic. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM2, PM3.

Met criteria codes

PM3	✔	P69S observed at least twice with R261Q, which is pathogenic according to PAH VCEP (ID 582)
PM2	✔	Absent from 1000G, ESP, gnomAD
PP4_Moderate	✔	Observed with PAH deficiency with BH4 deficiency excluded, but without a documented Phe level and without a known PKU type (PMID: 15503242, PMID: 26503515).

Not Met criteria codes

PP3	✖	Computational predictions yield inconsistent results (predicted tolerated in SIFT, possibly damaging in Polyphen2, disease-causing in MutationTaster, REVEL = 0.673).
PM1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✖	No additional variants at this codon in ClinVar.
PS1	✖	No additional variants at this codon in ClinVar.
PS3	✖	Kim et al. 2006 PMID: 16253218 – in-vitro expression analysis showed mean enzyme activity 52% of wild-type (PS3 not met)

Curation History

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