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Variant: NM_000277.3(PAH):c.208T>C (p.Ser70Pro)

Version: 1.0

CA229488

102631 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 12dc078f-4f90-4e29-a304-abfd5153cb71
Approved on: 2022/3/11
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HGVS expressions

NM_000277.3(PAH):c.208T>C (p.Ser70Pro)
NM_000277.3:c.208T>C
NC_000012.12:g.102894879A>G
CM000674.2:g.102894879A>G
NC_000012.11:g.103288657A>G
CM000674.1:g.103288657A>G
NC_000012.10:g.101812787A>G
NG_008690.1:g.27724T>C
NG_008690.2:g.68532T>C
ENST00000553106.6:c.208T>C
ENST00000307000.7:c.193T>C
ENST00000546844.1:c.208T>C
ENST00000548677.2:n.295T>C
ENST00000548928.1:n.130T>C
ENST00000549111.5:n.304T>C
ENST00000550978.6:c.192T>C
ENST00000551337.5:c.208T>C
ENST00000551988.5:n.297T>C
ENST00000553106.5:c.208T>C
ENST00000635500.1:n.176T>C
NM_000277.1:c.208T>C
NM_000277.2:c.208T>C
NM_001354304.1:c.208T>C
NM_001354304.2:c.208T>C

Likely Pathogenic

Met criteria codes 5

PS3_Supporting PM3_Supporting PP4_Moderate PM2 PP3

Not Met criteria codes 2

PM5 PP1

Evidence Links 0

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.208T>C (p.Ser70Pro) variant in PAH has been reported in at least four individuals with hyperphenylalanemia, including at least one for whom BH4 deficiency was excluded (PMID: 9860305, PMID: 21307867). Of these, two were siblings who also had p.Arg241His (PMID: 22330942), which is classified as pathogenic by PAH VCEP (Variation ID: 102804), without documentation of parental testing to establish phase. In-vitro studies show 20% enzyme activity (PMID: 9860305). This variant is absent from population databases. Multiple lines of computational evidence support a deleterious effect. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP3, PP4, PM2, PM3_Supporting, PS3_supporting.

Met criteria codes

PS3_Supporting	✔	Okano et al. 1998 PMID: 9860305 – in vitro PAH activity of mutant PAH cDNA construct in a COS cell expression system showed mean enzyme activity 20% of wild-type. PS3_supp approved for use for this PMID on PAH VCEP call 2/25/22.
PM3_Supporting	✔	Two sibs with p.Ser70Pro and p.Arg241His (classified as Path by PAH VCEP, Variation ID: 102804). However, phase undescribed. Per SVI guidelines "If the phase cannot be determined, it is recommended that at least two different LP/P variants (depending on classifications) are needed to equal the weight of one LP/P co-occurrence confirmed in trans." Only one LP/P variant in this case, as these are two related individuals, so this situation reflects 0.5 points for one (phase unknown) occurrence of Ser70Pro with Arg241His.
PP4_Moderate	✔	p.Ser70Pro observed in association with PAH deficiency with BH4 deficiency excluded, but without documented plasma phenylalanine levels (PMID: 9860305, PMID: 21307867). Plasma Phe levels >120 umol/L without documentation of exclusion of BH4 deficiency (PMID: 22330942).
PM2	✔	Absent from controls in ExAC, gnomAD, 1000 Genomes, or ESP
PP3	✔	Damaging in SIFT, probably damaging in PP-2, disease-causing in MutationTaster, REVEL=0.968

Not Met criteria codes

PM5	✖	c.209C>T(p.Ser70Phe) classified as likely pathogenic by PAH VCEP (Variation ID: 987767). PM5 not met as p.Ser70Phe is likely path and not path.
PP1	✖	Two affected segregations and no unaffected segregations noted. However, parental testing for phase not discussed (PMID: 22330942).

Curation History

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