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Variant: NM_000277.3(PAH):c.241A>C (p.Thr81Pro)

Version: 1.0

CA229497

102637 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: ad7aca98-07bd-4231-9217-aa7b9c63201d
Approved on: 2024/11/17
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HGVS expressions

NM_000277.3(PAH):c.241A>C (p.Thr81Pro)
NM_000277.3:c.241A>C
NC_000012.12:g.102894846T>G
CM000674.2:g.102894846T>G
NC_000012.11:g.103288624T>G
CM000674.1:g.103288624T>G
NC_000012.10:g.101812754T>G
NG_008690.1:g.27757A>C
NG_008690.2:g.68565A>C
ENST00000553106.6:c.241A>C
ENST00000307000.7:c.226A>C
ENST00000546844.1:c.241A>C
ENST00000548677.2:n.328A>C
ENST00000548928.1:n.163A>C
ENST00000549111.5:n.337A>C
ENST00000550978.6:c.225A>C
ENST00000551337.5:c.241A>C
ENST00000551988.5:n.330A>C
ENST00000553106.5:c.241A>C
NM_000277.1:c.241A>C
NM_000277.2:c.241A>C
NM_001354304.1:c.241A>C
NM_001354304.2:c.241A>C

Likely Pathogenic

Met criteria codes 5

PM5_Supporting | PP3 | PP4 | PM2_Supporting | PM3_Strong

Evidence Links 0

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.241A>C (p.Thr81Pro) variant in PAH has been reported in at least two individuals with classic PKU, where it was observed without confirmed phase with c.117C>G (p.Phe39Leu) (classified as pathogenic by PAH VCEP Variation ID 605) and c.842+1G>A (classified as pathogenic by PAH VCEP Variation ID 599) (PMID: 8659548, PMID: 9169088, PMID: 11328945). It has also been described without a specified subtype or phase with two additional pathogenic variants: p.R408W (Variation ID: 577, PMID: 23430918); c.822_832del (p.Lys274fs) (Variation ID: 102852, PMID: 23430918). Exclusion of BH4 deficiency was not specified. In-vitro functional studies are unavailable. This variant has extremely low frequency in gnomAD v4.1.0 (MAF=0.000007629). In-silico predictions support pathogenicity of this variant (REVEL=0.74). Another missense variant [c.242C>A (p.Thr81Asn)] in the same codon has been classified as likely pathogenic by the ClinGen Phenylketonuria Variant Curation Expert Panel. In summary, this variant is likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM3_strong, PP4, PM2_supporting, PM5_supporting, PP3.

Met criteria codes

PM5_Supporting	✔	c.242C>A (p.Thr81Asn) classified as likely pathogenic by PAH VCEP (Variation ID: 208180).
PP3	✔	REVEL=0.74
PP4	✔	Observed in two patients with classical PKU with 2nd variants classified as Pathogenic by PAH VCEP and with plasma phenylalanine >120 umol/L but without confirmation of phase or exclusion of BH4 deficiency (PMID: 8659548).
PM2_Supporting	✔	extremely low frequency in gnomAD v4.1.0 (MAF=0.000007629 ENF)
PM3_Strong	✔	Observed in at least three cases along with a second variant classified as path by PAH VCEP, with unconfirmed phase: three times with c.117C>G (p.Phe39Leu) (Variation ID 605, PMID: 8659548, 11328945, 9169088), but unclear if the same or different patients; c.842+1G>A (Variation ID 599, PMID: 8659548); p.R408W (Variation ID: 577, PMID: 23430918); c.822_832del (p.Lys274fs) (Variation ID: 102852, PMID: 23430918). 2.0 points

Curation History

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