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_000277.2(PAH):c.718T>G (p.Phe240Val)

Version: 2.0

CA229713

102801 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 91df5c40-1e87-49a7-b02e-2cb85486ce49
Approved on: 2024/11/17
Published on: 2024/11/18

HGVS expressions

NM_000277.2(PAH):c.718T>G (p.Phe240Val)
NM_000277.2:c.718T>G
NC_000012.12:g.102852939A>C
CM000674.2:g.102852939A>C
NC_000012.11:g.103246717A>C
CM000674.1:g.103246717A>C
NC_000012.10:g.101770847A>C
NG_008690.1:g.69664T>G
NG_008690.2:g.110472T>G
ENST00000553106.6:c.718T>G
ENST00000307000.7:c.703T>G
ENST00000549247.6:n.477T>G
ENST00000553106.5:c.718T>G
NM_000277.1:c.718T>G
NM_001354304.1:c.718T>G
NM_000277.3:c.718T>G
NM_001354304.2:c.718T>G

Likely Pathogenic

Met criteria codes 3

PP3_Strong PM2_Supporting PM5_Supporting

Not Met criteria codes 1

PM1

Evidence Links 1

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.718T>G (p.Phe240Val) variant in PAH has not been reported in the literature detected in an affected patient to our knowledge. This variant has a Pop Max allele frequency of [0.00001271] for [ENF] chromosomes by gnomAD v4.1.0, which is lower than the ClinGen PAH threshold (≤ 0.0002) and therefore meets PM2_Supporting. A deleterious effect is predicted in SIFT, Polyphen-2, MutationTaster, and REVEL=0.978. A different likely pathogenic missense change (p.Phe240Ser) has been seen before. In summary, this variant meets criteria to be classified as Likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM2_supporting, PP3_strong, PM5_supporting.

Met criteria codes

PP3_Strong	✔	Predicted deleterious in SIFT, Polyphen2, MutationTaster. REVEL=0.978
PM2_Supporting	✔	The Pop Max allele frequency is [0.00001271] for [ENF] chromosomes by gnomAD v4.1.0, which is lower than the ClinGen PAH threshold (≤ 0.0002) and therefore meets PM2_Supporting.
PM5_Supporting	✔	F240S is LP by PAH VCEP

Not Met criteria codes

PM1	✖	Close to active site area as well as several Phe's - stacks onto Phe294. Disrupted on substitution to Val. PMID: 10527663 Close to active site area as well as several Phe's - stacks onto Phe294. Disrupted on substitution to Val. **PubMed:10527663**

Curation History

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