Variant: NM_000277.2(PAH):c.533A>G (p.Glu178Gly)

Version: 1.1

CA273110

92746 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 9cbb36d6-2daf-4507-b947-3a692ec4d9e7
Approved on: 2025-04-18
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HGVS expressions

NM_000277.2:c.533A>G
NM_000277.2(PAH):c.533A>G (p.Glu178Gly)
NC_000012.12:g.102855309T>C
CM000674.2:g.102855309T>C
NC_000012.11:g.103249087T>C
CM000674.1:g.103249087T>C
NC_000012.10:g.101773217T>C
NG_008690.1:g.67294A>G
NG_008690.2:g.108102A>G
ENST00000553106.6:c.533A>G
ENST00000307000.7:c.518A>G
ENST00000549111.5:n.629A>G
ENST00000551988.5:n.554A>G
ENST00000553106.5:c.533A>G
NM_000277.1:c.533A>G
NM_001354304.1:c.533A>G
NM_000277.3:c.533A>G
NM_001354304.2:c.533A>G

Pathogenic

Met criteria codes 5

PM3_Strong PP3_Moderate PP4_Moderate PM2_Supporting PS3_Supporting

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.533A>G variant in PAH is a missense variant predicted to cause substitution of glutamine by glycine at amino acid 178 (p.Glu178Gly). At least 5 patients with this variant displayed serum Phe levels > 6.5–10 mg/dl which is highly specific for PAH deficiency; BH4 deficiency was excluded (PP4_moderate, PMID: 18299955, PMID:9634518). Of those individuals, 4 probands were compound heterozygous for the variant and a pathogenic variant and 1 proband was compound heterozygous with a likely pathogenic variant (phase unknown, 2.25 points). The population allele frequency in gnomAD v4.1 is 0.00003965 which is lower than the ClinGen PAH VCEP threshold (<0.0002) for PM2_Supporting, meeting this criterion (PM2_Supporting). The results from in silico predictors [REVEL=0.841], predict a damaging effect on PAH function (PP3_moderate). Enzyme activity assay showed 39% residual phenylalanine hydroxylase activity indicating that this variant impacts protein function (PMID:17935162)(PS3_supporting). In summary, this variant meets criteria to be classified as pathogenic for PAH deficiency in an autosomal recessive manner based on the ACMG/AMP criteria applied, as specified by the ClinGen PAH Expert Panel: PM2_supporting, PP3_moderate, PS3_supporting, PP4_Moderate, PM3_Strong (version 2.0, 11/16/2024).

Met criteria codes

PM3_Strong	✔	Detected with 3 pathogenic variants in 4 probands (0.5 points x 4 = 2.0 points) and 1 likely pathogenic variant (P281L) in 1 proband (0.25 points); phase unknown. 2.25 points
PP3_Moderate	✔	REVEL=0.841
PP4_Moderate	✔	Detected in at least 5 patients with serum Phe levels > 6.5–10 mg/dl. BH4 deficiency excluded. PMID: 18299955, PMID: 9634518
PM2_Supporting	✔	Total AF 0.00003965 in gnomAD v4.1
PS3_Supporting	✔	39% residual phenylalanine hydroxylase activity

Curation History

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