

Variant: *NM_000277.2(PAH):c.193A>G (p.Ile65Val)*

Version: 1.0

CA229478 [↗](#)

102622 (ClinVar) [↗](#)

Gene: PAH ([HGNC:5053](#))

Condition: phenylketonuria ([MONDO:0009861](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: 738623d6-eeb6-46ce-bebb-1ece2e0347ea

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HGVS expressions

NM_000277.2:c.193A>G

NM_000277.2(PAH):c.193A>G (p.Ile65Val)

NC_000012.12:g.102894894T>C

CM000674.2:g.102894894T>C

NC_000012.11:g.103288672T>C

CM000674.1:g.103288672T>C

NC_000012.10:g.101812802T>C

NG_008690.1:g.27709A>G

NG_008690.2:g.68517A>G

ENST00000553106.6:c.193A>G

ENST00000307000.7:c.178A>G

ENST00000546844.1:c.193A>G

ENST00000548677.2:n.280A>G

ENST00000548928.1:n.115A>G

ENST00000549111.5:n.289A>G

ENST00000550978.6:c.177A>G

ENST00000551337.5:c.193A>G

ENST00000551988.5:n.282A>G

ENST00000553106.5:c.193A>G

ENST00000635500.1:n.161A>G

NM_000277.1:c.193A>G

NM_001354304.1:c.193A>G

NM_000277.3:c.193A>G

NM_001354304.2:c.193A>G

Pathogenic

Met criteria codes **5**

PM3_Strong

PP3

PM5

PM2

PP4_Moderate

Evidence Links **0**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.193A>G (p.Ile65Val) variant in PAH has been reported in multiple individuals with mild PKU and mild hyperphenylalaninaemia (BH4 deficiency excluded). (PP4_Moderate; PMID: 12501224). This variant is at extremely low frequency: gnomAD MAF 0.00003 (PM2). This variant was detected with multiple pathogenic variants: p.R261Q, IVS12+1G>A (PMID: 12501224); c.168+5G>C (PMID: 22526846); p.Y386C (PMID: 26210745); p.EX6-96A>G (PMID: 30050108). Multiple lines of computational evidence support a deleterious effect (PP3). Another missense change at the same amino acid residue is pathogenic (p.Ile65Thr). In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM2, PM3_strong, PM5, PP3.

Met criteria codes

PM3_Strong			Detected with R261Q and IVS12+1G>A (pathogenic in ClinVar, parental testing not reported) PMID: 12501224; c.168+5G>C (P 7 submitters, parental analysis not reported) PMID: 22526846; p.Y386C c.1157A>G (P 3 submitters); p.G239S c.715G>A (no int in ClinVar). parental testing not reported PMID: 26210745; p.EX6-96A>G (P 8 submitters). validation tests on parents were performed PMID: 30050108. 3.0 points total
PP3			Multiple lines of computational evidence support a deleterious effect: SIFT, PolyPhen-2, MutationTaster. REVEL= 0.795.
PM5			p.Ile65Thr pathogenic by 13 submitters
PM2			extremely low frequency: gnomAD MAF 0.00003
PP4_Moderate			I65V reported in 3 patients: 1 with mild HPA, 2 with mild PKU. BH4 deficiency excluded. PMID: 12501224

Curation History

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