

Variant: *NM_000277.1:c.686A>G*

Version: 1.0

CA16020839 [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 09de0d52-2b52-43a4-b23e-0c282bea2795

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HGVS expressions

NM_000277.1:c.686A>G

NC_000012.12:g.102855156T>C

CM000674.2:g.102855156T>C

NC_000012.11:g.103248934T>C

CM000674.1:g.103248934T>C

NC_000012.10:g.101773064T>C

NG_008690.1:g.67447A>G

NG_008690.2:g.108255A>G

ENST00000553106.6:c.686A>G

ENST00000307000.7:c.671A>G

ENST00000549111.5:n.782A>G

ENST00000553106.5:c.686A>G

NM_000277.2:c.686A>G

NM_001354304.1:c.686A>G

NM_000277.3:c.686A>G

NM_001354304.2:c.686A>G

Likely Pathogenic

Met criteria codes **5**

PM2_Supporting

PS3_Supporting

PP3_Moderate

PP4

PM3_Supporting

Evidence Links **2**

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.686A>G (p.Asp229Gly) variant in PAH has been reported in 1 individual with PAH deficiency, detected with pathogenic variant p.R408W (PMID: 23357515). This variant is absent in population databases. Computational evidence supports a deleterious effect

(REVEL=0.922). Functional studies show the p.Asp229Gly mutant had 0% residual activity as compared to WT PAH activity and decreased protein levels (PMID: 31208052). In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PS3_supporting, PP4, PM2_supporting, PM3_supporting, PP3_moderate.

Met criteria codes

PM2_Supporting			Absent from ExAC, gnomAD, 1000G, ESP
PS3_Supporting			p.Asp229Gly had 0% residual activity as compared to WT PAH activity and was calculated as a mean of nine independent functional assays. Western blot analysis revealed decreased protein levels of each tested PAH mutant cultivated under both conditions compared to WT PAH. The overall results were calculated from three independent Western blot analyses performed from three independent PAH expressions in HepG2 cells. PMID: 31208052 The p.Asn167Tyr, p.Thr200Asn, p.Asp229Gly, p.Gly239Ala, p.Phe263Ser, p.Ala342Pro, and p.Ile406Met PAH variants were expressed in prokaryotic and eukaryotic expression systems and assayed in vitro to investigate their specific activity, oligomeric pattern, and the mutant PAH protein stability in the presence of sepiapterin, which is the BH4 precursor, as well as GroEL/ES bacterial chaperones. p.Asp229Gly had 0% residual activity as compared to WT PAH activity and was calculated as a mean of nine independent functional assays. Western blot analysis revealed decreased protein levels of each tested PAH mutant cultivated under both conditions compared to WT PAH. The overall results were calculated from three independent Western blot analyses performed from three independent PAH expressions in HepG2 cells. PubMed:31208052
PP3_Moderate			Deleterious effect predicted in SIFT, Polyphen2, MutationTaster. REVEL=0.922
PP4			Seen in 1 patient with Non-PKU HPA (Phe between 120 and 600 µmol/L). BH4 deficiency not excluded. PMID: 23357515 665 unrelated Czech HPA patients. c.686A>G, p.(Asp229Gly) seen on 1 allele of a Non-PKU HPA patient ((Phe between 120 and 600 µmol/L). PubMed:23357515
PM3_Supporting			Detected with R408W, Pathogenic in ClinVar, parental analysis not reported PMID: 23357515 Seen in 1 Non-PKU HPA patient with the genotype p.[Asp229Gly];[Arg408Trp]. PubMed:23357515

Curation History

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