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Variant: NM_000277.3(PAH):c.136G>A (p.Gly46Ser)

Version: 1.0

CA229439

629 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 6640c833-7378-4d20-bf7f-32178b1c5c6a
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HGVS expressions

NM_000277.3(PAH):c.136G>A (p.Gly46Ser)
NM_000277.3:c.136G>A
NC_000012.12:g.102912823C>T
CM000674.2:g.102912823C>T
NC_000012.11:g.103306601C>T
CM000674.1:g.103306601C>T
NC_000012.10:g.101830731C>T
NG_008690.1:g.9780G>A
NG_008690.2:g.50588G>A
ENST00000553106.6:c.136G>A
ENST00000307000.7:c.121G>A
ENST00000546844.1:c.136G>A
ENST00000548677.2:n.223G>A
ENST00000548928.1:n.58G>A
ENST00000549111.5:n.232G>A
ENST00000550978.6:c.120G>A
ENST00000551337.5:c.136G>A
ENST00000551988.5:n.225G>A
ENST00000553106.5:c.136G>A
ENST00000635500.1:n.104G>A
NM_000277.1:c.136G>A
NM_000277.2:c.136G>A
NM_001354304.1:c.136G>A
NM_001354304.2:c.136G>A

Pathogenic

Met criteria codes 4

PM2 PP4_Moderate PM3_Very Strong PS3

Not Met criteria codes 1

PP3

Evidence Links 4

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The PAH variant c.136G>A (p.Gly46Ser) was detected in four alleles associated with moderate PKU (phenylalanine values of 900-1200 µmol/L). Patients included in the study had serum phenylalanine levels above 150 µmol/L and normal urinary excretion of biopterin and neopterin (PMID: 7556322). The variant c.136G>A (p.Gly46Ser) was documented in trans with seven other PAH pathogenic or likely pathogenic variants in 15 Norwegian patients with mild and classic PKU. Haplotype analysis of index cases and parents was conducted, when necessary siblings were also investigated (PMID: 8829656). PM3_Very Strong (14 points). In vitro, enzyme activity assays demonstrated a residual activity for the PAH variant c.136G>A (p.Gly46Ser) between 26% and 38% compared to the wild type PAH when using the mammalian cell-free transcription-translation system (PMID: 11161839). According to gnomAD, this variant is present at a low allele frequency in population databases, with the highest reported frequency in the European (Non-Finnish) population (0.00015). In silico modeling, predictions are conflicting. According to SIFT this variant is predicted to be tolerated, probably damaging by Polyphen 2-HVAR and disease-causing Automatic by Mutation Taster. In summary, this variant meets the criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM2, PM3_Very Strong, PP4 met_moderate, and PS3.

Met criteria codes

PM2 ✔

According to gnomAD, this variant is present at a low allele frequency in population databases, with the highest reported frequency in the European (Non-Finnish) population (0.00015).

PP4_Moderate ✔

The variant c.136G>A (p.Gly46Ser) was detected in four alleles associated with moderate PKU (phenylalanine values of 900-1200 µmol/L). Patients included in the study had serum phenylalanine levels above 150 µmol/L and normal urinary excretion of biopterin and neopterin (PMID: 7556322).

PubMed:7556322
PubMed:23514811

PM3_Very Strong ✔

The variant c.136G>A (p.Gly46Ser) was documented in trans with seven other PAH pathogenic or likely pathogenic variants in 15 Norwegian patients with mild and classic PKU. Haplotype analysis of index cases and parents was conducted, when necessary siblings were also investigated (PMID: 8829656). PM3_Very Strong (14 points).

PubMed:8829656

PS3 ✔

In vitro, enzyme activity assays demonstrated a residual activity for the PAH variant c.136G>A (p.Gly46Ser) between 26% and 38% compared to the wild type PAH when using the mammalian cell-free transcription-translation system (PMID: 11161839).

The p.Gly46Ser mutation was introduced in the PAH cDNA by site-directed mutagenesis and expressed in three different systems (the pMALEscherichia coli system, the pcDNA3human embryonic kidney (A293) cells, and the pcDNA3RnT coupled in vitro transcription-translation system). The mutant recombinant E. coli fusion protein was recovered in high yield and with a specific activity of the purified tetrameric form, which was higher than the wild-type activity. Since the kinetic properties of the wild-type PAH were essentially similar for the fusion protein and the cleaved fusion protein (Martinez et al., 1995), an intact catalytic potential of the native p.Gly46Ser mutant enzyme is expected. This should provide, even in homozygous patients, a normal hepatic hydroxylation of L-Phe. In vivo studies demonstrated that after transient expression in A293 cells, the amount of the p.Gly46Ser protein was only about 3% of the wild type at equal PAH mRNA levels. The specific activity of the wild-type enzyme in crude extract was 14.5 nmol/min/mg protein, while the activity of the PAHG46S mutant could not be measured precisely due to low PAH protein levels. The fusion protein cleaved by restriction protease factor Xa, as well as the enzyme produced

by in vitro transcription-translation, revealed an abnormal susceptibility to form catalytically inactive high-molecular-mass aggregates of the enzyme. This aggregation, followed by an increased cellular degradation of the p.Gly46Ser mutant enzyme, is compatible with the clinical/metabolic phenotype of the affected homozygous and compound heterozygous patients.(PMID: 8829656) PubMed:8829656

This study used two heterologous in vitro expression systems (a mammalian cell-free transcription-translation system and the pET system of Escherichia coli) to examine 34 mutations that have been associated with PAH deficiency in the Danish population. The residual activity for the PAH variant c.136G>A (p.Gly46Ser) was between 26% and 38% compared to the wild type PAH when using the mammalian cell-free transcription-translation system, and 62% when using the pET system of Escherichia coli. (PMID: 11161839) PubMed:11161839

Not Met criteria codes

PP3	ℹ	✖	In silico modeling, predictions are conflicting. According to SIFT this variant is predicted to be tolerated, probably damaging by Polyphen 2-HVAR and disease-causing Automatic by Mutation Taster.

Curation History

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