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Variant: NM_000277.3(PAH):c.442G>A (p.Gly148Ser)

Version: 1.0

CA229551

102680 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: b741dc6c-848d-40ed-83d7-1446a4bfbaa1
Approved on: 2019/12/22
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HGVS expressions

NM_000277.3:c.442G>A
NM_000277.3(PAH):c.442G>A (p.Gly148Ser)
NC_000012.12:g.102866663C>T
CM000674.2:g.102866663C>T
NC_000012.11:g.103260441C>T
CM000674.1:g.103260441C>T
NC_000012.10:g.101784571C>T
NG_008690.1:g.55940G>A
NG_008690.2:g.96748G>A
ENST00000553106.6:c.442G>A
ENST00000307000.7:c.427G>A
ENST00000549111.5:n.538G>A
ENST00000551988.5:n.530+10799G>A
ENST00000553106.5:c.442G>A
NM_000277.1:c.442G>A
NM_000277.2:c.442G>A
NM_001354304.1:c.442G>A
NM_001354304.2:c.442G>A

Likely Pathogenic

Met criteria codes 4

PP3 PP4 PM3 PM2

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.442G>A (p.Gly148Ser) has been reported in three individuals with PHA deficiency (Phe levels >120 µM). One patient from the Northeastern region of the US, (PMID: 8659548)(PMID:10429004), one patient from Europe (PMID: 10679941), and one patient from the Campania Region in Southern Italy with mild PKU (Phe between 600 and 1200 µM) (PMID: 17096675). The variant c.442G>A (p.Gly148Ser) was document with the pathogenic variant c.194T>C (p.Ile65Thr)(ClinVar ID: 636), and with the pathogenic variant c.473G>A

(p.Arg158Gln)(ClinVar ID: 587) (PMID: 8535445). According to gnomAD, this variant is present at a low allele frequency in population databases, with the highest reported frequency in the African population (0.00006). In silico modeling predicts that this missense variant is damaging by SIFT, probably damaging by Polyphen 2 and disease causing by Mutation Taster. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM2, PM3, PP3, and PP4 .

Met criteria codes

PP3	✔	Predicted to be damaged by SIFT, probably damaging by Polyphen 2 and disease-causing by Mutation Taster.
PP4	✔	The PAH variant c.442G>A (p.Gly148Ser) has been reported in three individuals with PHA deficiency (Phe levels >120 µM). One patient from the Northeastern region of the US, (PMID: 8659548)(PMID:10429004), one patient from Europe (PMID: 10679941), and one patient from the Campania Region in Southern Italy with mild PKU (Phe between 600 and 1200 µM) (PMID: 17096675). PubMed:8659548 PubMed:10679941 PubMed:17096675
PM3	✔	The variant c.442G>A (p.Gly148Ser) was document with the pathogenic variant c.194T>C (p.Ile65Thr)(ClinVar ID: 636) in a family with a phenotype of moderate + normal retardation, and with the pathogenic variant c.473G>A (p.Arg158Gln)(ClinVar ID: 587) in a family with a moderate retardation phenotype. The families belong to a study of 4 families with untreated PKU in Australia.(PMID: 8535445). PubMed:8535445
PM2	✔	According to gnomAD, this variant is present at a low allele frequency in population databases, with the highest reported frequency in the African population (0.00006).

Curation History

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