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Variant: NM_000277.1(PAH):c.653G>T (p.Gly218Val)

Version: 1.0

CA229676

102773 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 434de9b0-5555-467e-ad5d-82a9d79d9f3b
Approved on: 2020/7/9
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HGVS expressions

NM_000277.1(PAH):c.653G>T (p.Gly218Val)
NM_000277.1:c.653G>T
NC_000012.12:g.102855189C>A
CM000674.2:g.102855189C>A
NC_000012.11:g.103248967C>A
CM000674.1:g.103248967C>A
NC_000012.10:g.101773097C>A
NG_008690.1:g.67414G>T
NG_008690.2:g.108222G>T
ENST00000553106.6:c.653G>T
ENST00000307000.7:c.638G>T
ENST00000549111.5:n.749G>T
ENST00000553106.5:c.653G>T
NM_000277.2:c.653G>T
NM_001354304.1:c.653G>T
NM_000277.3:c.653G>T
NM_001354304.2:c.653G>T

Pathogenic

Met criteria codes 5

PM2 PM3_Very Strong PP1 PP3 PP4

Not Met criteria codes 1

PS3

Evidence Links 4

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.653G>T (p.Gly218Val) variant in PAH has been reported in multiple individuals with PAH deficiency (PMID: 8406445, 9781015, 10479481). This variant has an extremely low allele frequency (MAF=0.00004) in gnomAD. It was detected with multiple pathogenic variants: p.R158Q, p.I65T (PMID: 10479481); p.Y414C (PMID: 8632937); c.1066-11G>A, p.Arg270Lys, (PMID: 26666653); p.P281L (PMID:

24368688); p.R408W (PMID: 11032331); p.S349P (PMID: 22841515); c.1223G > A (p.R408Q) (PMID: 29102225). It co-segregated with disease (PKU) in 2 sisters (PMID: 8831077). Computational prediction tools and conservation analysis support a deleterious effect on the protein. In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM3_very-strong, PM2, PP1, PP3, PP4.

Met criteria codes

PM2	✔	Extremely low frequency in gnomAD (MAF=0.00004)
PM3_Very Strong	✔	detected with R158Q and I65T, both pathogenic, parental analysis not reported. PMID: 10479481; Y414C, pathogenic, parental analysis not reported PMID: 8632937; c.1066-11G>A, p.Arg270Lys, pathogenic, parental analysis not confirmed PMID: 26666653; p.P281L, LP, parental analysis not reported PMID: 24368688 R408W, P, parental analysis not reported PMID: 11032331; p.S349P P 6 submitters parental analysis not reported PMID: 22841515; c.1223G > A (R408Q), P, parental analysis not reported PMID: 29102225 4.25 pts 2 patients with G218V, 1 in trans with R158Q (Pathogenic in ClinVar, VarID 587), another in trans with I65T (VarID 636, pathogenic/likely pathogenic in ClinVar). PubMed:10479481
PP1	✔	Reported in 2 sisters with PKU PMID: 8831077
PP3	✔	Predicted to have deleterious effect in SIFT, polyphen2, MutationTaster
PP4	✔	G218V reported in one patient with PKU (serum Phe > 600 umol/l). Other causes of HPA had been ruled out. PMID: 8406445, PMID: 9781015, PMID: 10479481 Reported on 2 alleles in PKU population PubMed:9781015 11 PAH-deficient patients included in this study belong to nine unrelated families and were detected through the French neonatal screening pro- gram. Patients were classified according to their dietary tolerance for phenylalanine and their plasma phenylalanine levels after a standard phenylalanine loading test. 1 patient with G218V/R158Q, with mild PKU. 1 patient with G218V/I65T with mild PKU. Mild PKU characterized by a dietary phenylalanine between 350 and 850 mg/day, plasma phenylalanine levels of 0.6 –1.2 mM, and a residual PAH activity between 1 and 3%. PubMed:10479481 Subjects included PKU patients and family members from 135 unrelated Danish families. Patients were classified as PKU when serum Phe was > 600 umol/l before treatment and when other causes of HPA had been ruled out. G218V was seen on one allele. 2nd mutation not reported. PubMed:8406445

Not Met criteria codes

PS3	✖	In vitro G218V mutant activity 15% of wild type in COS7 cells (Benit, 1999); 101% (Pey 2003); and 25% (Himmelreich 2018) The 11 PAH-deficient patients included in this study belong to nine unrelated families and were detected through the French neonatal screening program. 1 patient with G218V/R158Q, 1 patient with G218V/I65T. Figure 1 shows G218V mutant activity as expressed in COS7 cells as <20% of wild type (mean of 4 assays). PubMed:10479481 Expression analysis was performed in COS cells. G218V associated with near normal levels of residual activity (101% of wt). Expression of PAH mutant proteins in E. coli with and without chaperonin (GroESL) showed ~64% activity relative to w.t. PubMed:12655546

Curation History

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