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Variant: NM_000277.2(PAH):c.512G>C (p.Gly171Ala)

Version: 1.0

CA229599

102717 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: fa47c3ea-0e75-4e80-a83e-19d3fb7b4e99
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HGVS expressions

NM_000277.2(PAH):c.512G>C (p.Gly171Ala)
NM_000277.2:c.512G>C
NC_000012.12:g.102855330C>G
CM000674.2:g.102855330C>G
NC_000012.11:g.103249108C>G
CM000674.1:g.103249108C>G
NC_000012.10:g.101773238C>G
NG_008690.1:g.67273G>C
NG_008690.2:g.108081G>C
ENST00000553106.6:c.512G>C
ENST00000307000.7:c.497G>C
ENST00000549111.5:n.608G>C
ENST00000551988.5:n.533G>C
ENST00000553106.5:c.512G>C
NM_000277.1:c.512G>C
NM_001354304.1:c.512G>C
NM_000277.3:c.512G>C
NM_001354304.2:c.512G>C

Likely Pathogenic

Met criteria codes 5

PP3_Moderate | PM3_Supporting | PP4_Moderate | PM2_Supporting | PS3_Supporting

Evidence Links 4

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.512G>C (p.Gly171Ala) variant in PAH has been reported in multiple individuals with PAH deficiency (BH4 deficiency excluded). (PP4_Moderate; PMID: 7833954, 9634518); detected with IVSI0nt546 (aka c.1066-11G>A PMID: 7833954). This variant is absent in population databases (PM2_supporting). This variant produces 27% enzyme activity as compared to wild type PAH (PMID: 10479481)

Computational evidence supports a damaging effect (REVEL=0.947). In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PS3_supporting, PP4_Moderate, PM2_supporting, PP3_moderatePM3_supporting.

Met criteria codes

PP3_Moderate	✔	Deleterious effect predicted in SIFT, Polyphen2, MutationTaster, REVEL=0.947.
PM3_Supporting	✔	Detected with IVSl0nt546 (PMID: 7833954). this is c.1066-11G>A (P) per Ref https://pubmed.ncbi.nlm.nih.gov/1301187/ 0.5 points Patient genotype: G171A / IVSl0nt546. parental DNA not available. PubMed:7833954
PP4_Moderate	✔	G171A detected in a patient with MHP, defect in tetrahydrobiopterin metabolism was excluded. 2 reports may be of the same patient (PMID: 7833954, 9634518). G171A was detected in a French patient with mild variant PKU. BH4 deficiency not reported to be ruled out. PubMed:7833954 G171A detected in a patient with MHP. In all patients, hyperphenylalaninemia had been detected by national mass screening programs, and PAH deficiency had been assessed after exclusion of a defect in tetrahydrobiopterin metabolism. PubMed:9634518
PM2_Supporting	✔	Absent from ExAC, gnomAD, 1000G, ESP
PS3_Supporting	✔	27% enzyme activity (PMID: 29653233, PMID: 10479481) analyzed three novel naturally occurring PAH gene variants: p.Glu178Lys (c.532G>A), p.Val245Met (c.733G>A) and p.Ser250Phe (c.749C>T). Vectors expressing the corresponding PAH variants were generated for expression in E. coli and in HEK293T cells. The RNA expression of the three PAH variants was measured by quantitative reverse transcription polymerase chain reaction (RT-qPCR). The mutant PAH protein levels were determined by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), western blot and enzyme-linked immunosorbent assay (ELISA). The transcription of the three PAH variants was similar to the wild type PAH gene in HEK293T cells. In contrast, the levels of mutant PAH proteins decreased significantly compared to the wild type control, in both E. coli and HEK293T cells. PubMed:29653233 20-40% enzyme activity, 12 variants tested, none benign PubMed:10479481

Curation History

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