The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000277.1(PAH):c.965C>G (p.Ala322Gly)

Version: 1.0

CA114363

616 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 1e763c4e-db5b-4224-9bd2-80ebcfb5d37d
Approved on: 2019/9/27
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HGVS expressions

NM_000277.1:c.965C>G
NM_000277.1(PAH):c.965C>G (p.Ala322Gly)
NC_000012.12:g.102846899G>C
CM000674.2:g.102846899G>C
NC_000012.11:g.103240677G>C
CM000674.1:g.103240677G>C
NC_000012.10:g.101764807G>C
NG_008690.1:g.75704C>G
NG_008690.2:g.116512C>G
ENST00000553106.6:c.965C>G
ENST00000307000.7:c.950C>G
ENST00000549247.6:n.724C>G
ENST00000551114.2:n.627C>G
ENST00000553106.5:c.965C>G
ENST00000635477.1:c.74-2468C>G
ENST00000635528.1:n.480C>G
NM_000277.2:c.965C>G
NM_001354304.1:c.965C>G
NM_000277.3:c.965C>G
NM_001354304.2:c.965C>G

Likely Pathogenic

Met criteria codes 3

PP3 PP4 PM3_Strong

Not Met criteria codes 2

PM2 PS3

Evidence Links 2

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.965C>G (p.Ala322Gly) variant in PAH has been reported in 4 individuals with mild hyperphenylalaninemia (BH4 deficiency not excluded). (PP4; PMID: 12501224). This variant has an allele frequency higher than the PAH VCEP PM2 threshold (MAF=0.00044). This variant was detected with p.R408W in 3 individuals (Pathogenic in ClinVar) and with p.R252W in 1 individual (PM3_strong; PMID: 12501224). Computational evidence supports a deleterious effect. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4, PM3-strong, PP3.

Met criteria codes

PP3	✔	All lines of computational evidence support a deleterious effect on function. REVEL=0.862
PP4	✔	4 patients have this allele, all with mild hyperphe (PMID: 1301200) A322G / R408Q –300umol/L A322G / R408W – 250umol/L A322G / R408W – 360umol/L A322G / R252W – 250umol/L 4 patients have this allele, all with mild hyperphe A322G / R408Q –300umol/L PubMed:1301200
PM3_Strong	✔	3 patients A322G / R408W (pathogenic) – sequence analysis of parental samples performed in all affected families. 1 patient A322G / R252W Two missense mutations causing mild HPA associated with haplotype 12 88 swedish families. 93 children picked up by NBS A322G / R408Q –300uM/L A322G / R408W – 250uM/L A322G / R408W – 360uM/L A322G / R252W – 250uM/L PubMed:1301200

Not Met criteria codes

PM2	✖	Highest MAF 0.00044 (gnomAD), not found in other databases. Higher than PAH VCEP cutoff of <0.0002.
PS3	✖	Discussed in ClinGen Metabolism workgroup. Due to discrepancy observed between cDNA systems, it was decided to not use this evidence as part of variant classification. 03/28/2017 AT PAH cDNA inserted into polylinker site of human expression vector pRc/CMV. Muta-Gene Phagemid Mutagenesis Kit to generate A322G variant. COS-1 cells transfected. PAH Enzyme activity measured as conversion of L-[14C]phe to L-[14C]tyr. A322G variant demonstrated to have 75% residual enzyme activity. PubMed:1301200 PAH activity analysis. QuikChange site directed mutagenesis, transfected COS-1 cells. Enzyme activity measured as conversion of L-[14C]phe to L-[14C]tyr. Use both standard cDNA expression system (pPAH-cDNA under control of SV40 promoter) and a new Intinic plasmid system which incorporates intronic sequences (similar vector backbone with exon 9 flanked by its introns). Standard cDNA method demonstrates 48% residual enzyme activity for A322G, and intinic system demonstrates 96% residual enzyme activity. PubMed:18590700

Curation History

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