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_000277.2(PAH):c.662A>G (p.Glu221Gly)

Version: 1.0

CA229677

609 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: dfac2ff9-0b20-422d-a189-df2e2ff04e34
Approved on: 2020/5/22
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HGVS expressions

NM_000277.2:c.662A>G
NM_000277.2(PAH):c.662A>G (p.Glu221Gly)
NC_000012.12:g.102855180T>C
CM000674.2:g.102855180T>C
NC_000012.11:g.103248958T>C
CM000674.1:g.103248958T>C
NC_000012.10:g.101773088T>C
NG_008690.1:g.67423A>G
NG_008690.2:g.108231A>G
ENST00000553106.6:c.662A>G
ENST00000307000.7:c.647A>G
ENST00000549111.5:n.758A>G
ENST00000553106.5:c.662A>G
NM_000277.1:c.662A>G
NM_001354304.1:c.662A>G
NM_000277.3:c.662A>G
NM_001354304.2:c.662A>G

Likely Pathogenic

Met criteria codes 4

PM3 PM2 PP3 PP4_Moderate

Evidence Links 3

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.662A>G (p.Glu221Gly) variant in PAH has been reported in multiple individuals with mild PKU (BH4 deficiency excluded) and MHP. (PMID: 1679030 8860005 10947211). It was detected in trans with pathogenic variant L48S and in the homozygous state. This variant has extremely low frequency in ExAC (0.00001) and gnomAD (0.000004064). Computational evidence support a deleterious effect. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM2, PM3, PP3.

Met criteria codes

PM3	✔	E221G found in trans with L48S, which is Pathogenic in ClinVar PubMed:10947211 Glu221Gly found in trans with Leu48Ser in a Turkish patient with PKU. L48S is classified as Pathogenic in ClinVar (VarID 608). PubMed:1679030
PM2	✔	Extremely low frequency in ExAC (0.00001) and gnomAD (0.000004064)
PP3	✔	Predicted deleterious by SIFT, Polyphen, MutationTaster
PP4_Moderate	✔	E221G seen in 2 unrelated PKU patients. Cofactor deficiency was ruled out in 1 patient. Upgraded per ClinGen PAHEP. PMID: 1679030 PMID: 8860005 PMID: 10947211 Turkish patient with classic phenylketonuria, The Leu48Ser amino acid substitution and the Glu221Gly substitutions were found. The Glu221Gly mutation has only been detected within patient E1 and his father. Patient was tested for cofactor deficiency within 1 month of life. PubMed:1679030 6 independent Costa Rican PKU families with at least 1 affected child, all classified as having classical PKU per Guttler criteria. E221G was found in 1 patient/allele. PubMed:8860005

Curation History

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