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:c.1262T>G

Version: 1.4

CA16020986

639999 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 502c45ab-1f82-4c1e-ae27-c874a90210e4
Approved on: 2023/10/15
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HGVS expressions

NM_000277.1:c.1262T>G
NC_000012.12:g.102840453A>C
CM000674.2:g.102840453A>C
NC_000012.11:g.103234231A>C
CM000674.1:g.103234231A>C
NC_000012.10:g.101758361A>C
NG_008690.1:g.82150T>G
NG_008690.2:g.122958T>G
ENST00000553106.6:c.1262T>G
ENST00000307000.7:c.1247T>G
ENST00000551114.2:n.924T>G
ENST00000553106.5:c.1262T>G
ENST00000635477.1:c.366T>G
ENST00000635528.1:n.777T>G
NM_000277.2:c.1262T>G
NM_001354304.1:c.1262T>G
NM_000277.3:c.1262T>G
NM_001354304.2:c.1262T>G

Likely Pathogenic

Met criteria codes 4

PP4_Moderate PP3_Strong PM3 PM2_Supporting

Evidence Links 0

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen PAH Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Phenylketonuria VCEP

The NM_000277.3:c.1262T>G (p.Ile421Ser) variant is a missense variant in exon 12/13 of PAH. The variant has been previously reported in an Austrian patient with PKU (plasma Phe 780 umol/L) in confirmed trans with the p.F39L variant (ClinVar Pathogenic (ID 605) and Pathogenic by ClinGen PAH VCEP); BH4 deficiency was excluded by urinary pterins and dihydropterine reductase assays (PMID: 22526846) (PM3; PP4_Moderate). The variant is absent from ethnically diverse control databases, including gnomAD/ExAC, 1000 Genomes, and ESP (PM2_supporting). The variant is predicted damaging by multiple in-silico missense predictors, including REVEL (REVEL score 0.969) (PP3_strong). Classification: Likely Pathogenic Supporting Criteria: PM2_supporting; PM3; PP4_Moderate; PP3_strong

Met criteria codes

PP4_Moderate	✔	Single patient with Phe 780umol/L, Analysis of urinary pterins and dihydropterine reductase assays were performed to exclude BH4 deficiency. PMID: 22526846
PP3_Strong	✔	In silico software agree on deleterious/damaging effect. REVEL=0.969
PM3	✔	Single patient with PKU.[c.1262T>G];[c.117C>G] (pathogenic by PAH VCEP)p.F39L; Family segregation was consistent with autosomal recessive inheritance.
PM2_Supporting	✔	Variant not found in any population database. Absent in gnomAD v2.1.1

Curation History

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