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_001354304.2:c.1023G>C

Version: 1.0

CA386493436

1810388 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: defe237b-a3d1-4131-beb4-8625d476067b
Approved on: 2022/7/30
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HGVS expressions

NM_001354304.2:c.1023G>C
NC_000012.12:g.102844378C>G
CM000674.2:g.102844378C>G
NC_000012.11:g.103238156C>G
CM000674.1:g.103238156C>G
NC_000012.10:g.101762286C>G
NG_008690.1:g.78225G>C
NG_008690.2:g.119033G>C
ENST00000553106.6:c.1023G>C
ENST00000307000.7:c.1008G>C
ENST00000549247.6:n.782G>C
ENST00000551114.2:n.685G>C
ENST00000553106.5:c.1023G>C
ENST00000635477.1:c.127G>C
ENST00000635528.1:n.538G>C
NM_000277.1:c.1023G>C
NM_000277.2:c.1023G>C
NM_001354304.1:c.1023G>C
NM_000277.3:c.1023G>C

Likely Pathogenic

Met criteria codes 4

PM2 PM3 PP3 PP4

Not Met criteria codes 1

PM5

Evidence Links 0

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

This c.1023 G>C (p.Lys341Asn) variant in PAH was seen in a patient with mPKU in trans with the pathogenic variant p.Ala434Asp (PMID: 28982351). This variant was found at a very low frequency in population databases. Multiple lines of 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: PM3, PM2, PP3, PP4.

Met criteria codes

PM2	✔	Present in European (Finnish) populations at a frequency of 0.0003981 and in European (non-Finnish) populations at a frequency of 0.00001550 (Gnomad). This variant is absent from the population database Exac.
PM3	✔	This variant was detected in trans with the pathogenic variant p.Ala434Asp (PMID: 28982351). points=1.
PP3	✔	Predicted to be damaging (SIFT), probably damaging (PolyPhen2), Disease causing (MutationTaster). REVEL=0.874
PP4	✔	Variant was detected in a patient affected with mPKU. Variable sites in patient genes were aligned with the corresponding sites from the respective parents. This was seen in trans with a pathogenic variant listed in ClinVar. Those with BH4 cofactor deficiency were excluded PMID: 28982351

Not Met criteria codes

PM5	✖	Two other variants of unknown significance (p.K341T) and (p.K341R) have been documented in the VCI at this amino acid residue.

Curation History

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