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Variant: NM_001354304.2:c.603T>G

Version: 1.0

CA16020826

1460083 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: a2bb1b4e-0615-40af-82b6-a85f5ecf503d
Approved on: 2023/3/16
Published on: 2023/3/16

HGVS expressions

NM_001354304.2:c.603T>G
NC_000012.12:g.102855239A>C
CM000674.2:g.102855239A>C
NC_000012.11:g.103249017A>C
CM000674.1:g.103249017A>C
NC_000012.10:g.101773147A>C
NG_008690.1:g.67364T>G
NG_008690.2:g.108172T>G
ENST00000553106.6:c.603T>G
ENST00000307000.7:c.588T>G
ENST00000549111.5:n.699T>G
ENST00000553106.5:c.603T>G
NM_000277.1:c.603T>G
NM_000277.2:c.603T>G
NM_001354304.1:c.603T>G
NM_000277.3:c.603T>G

Likely Pathogenic

Met criteria codes 4
PP3 PP4 PM3 PM2

Not Met criteria codes 1
PM5

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 c.603T>G (p.His201Gln) variant in PAH has been reported in at least one individual with classic PKU (PMID: 20920871), where it was observed in trans with p.Arg243Ter (Variation ID: 588, classified as Pathogenic by the PAH VCEP). In-vitro functional studies are

unavailable. This variant is absent from 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: PM2, PP3, PP4, PM3.

Met criteria codes

PP3	✔	Damaging in SIFT, PP-2, Disease-causing in MutationTaster, REVEL=0.885
PP4	✔	Observed in 1 case with classic PKU (PMID: 30159852, PMID: 20920871), without exclusion of BH4 deficiency or specific information about serum Phe levels.
PM3	✔	One compound heterozygote (with p.Arg243Ter Variation ID: 588, classified as pathogenic by the PAH VCEP) with phase confirmed (PMID: 20920871, PMID: 30159852).
PM2	✔	Absent from controls in ExAC, gnomAD, 1000 Genomes, and ESP.

Not Met criteria codes

PM5	✖	c.601C>T (p.His201Tyr) classified as Likely Pathogenic by PAH VCEP (Variation ID 102752); c.602A>G (p.His201Arg) listed in ClinVar as Likely Pathogenic by other labs, but not classified by PAH VCEP (Variation ID 102753).

Curation History

Showing 1 to 1 of 1 rows

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