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Variant: NM_000277.1:c.47_48insCT

Version: 1.0

CA891862634

805802 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: c7b4b798-e2b4-431a-bd0d-2d7c903d2c57
Approved on: 2019/2/26
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HGVS expressions

NM_000277.1:c.47_48insCT
NC_000012.12:g.102917083_102917084insAG
CM000674.2:g.102917083_102917084insAG
NC_000012.11:g.103310861_103310862insAG
CM000674.1:g.103310861_103310862insAG
NC_000012.10:g.101834991_101834992insAG
NG_008690.1:g.5519_5520insCT
NG_008690.2:g.46327_46328insCT
ENST00000553106.6:c.47_48insCT
ENST00000307000.7:c.-101_-100insCT
ENST00000546844.1:c.47_48insCT
ENST00000547319.1:n.358_359insCT
ENST00000549111.5:n.143_144insCT
ENST00000550978.6:c.31_32insCT
ENST00000551337.5:c.47_48insCT
ENST00000551988.5:n.136_137insCT
ENST00000553106.5:c.47_48insCT
ENST00000635500.1:n.29-4186_29-4185insCT
NM_000277.2:c.47_48insCT
NM_001354304.1:c.47_48insCT
NM_000277.3:c.47_48insCT
NM_001354304.2:c.47_48insCT

Pathogenic

Met criteria codes 4

PVS1 PM2 PP4_Moderate PM3_Strong

Evidence Links 2

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The PAH: c.47_48dupCT variant is a frameshift variant occurring in exon 1 of 13 in the canonical transcript of PAH, a gene fulfilling the most recent criteria for LOF being a known disease mechanism (see PMID: 30192042) (PVS1). The variant has been previously reported in trans with the known pathogenic L48S allele in 1 Israeli case with classic PKU (PMID: 18299955; PMID: 18294361) as assessed by plasma Phe levels; BH4 deficiency was excluded. It was also noted in 3 Turkish probands: in two, it was found in trans with the p.R243X allele, and in one, it was found in trans with the p.R261Q allele (PMID: 21147011); all three cases had classic as assessed by plasma Phe levels and BH4 deficiency was excluded by genetic testing. Thus PM3_Strong and PP4_Moderate apply. It is absent from control databases including ethnically matched individuals, including gnomAD/ExAC, 1000 Genomes, and ESP (PM2).

Met criteria codes

PVS1	✔	The PAH: c.47_48dupCT variant is a frameshift variant occurring in exon 1 of 13 in the canonical transcript of PAH, a gene fulfilling the most recent criteria for LOF being a known disease mechanism (see PMID: 30192042) (PVS1).
PM2	✔	Variant is absent from control databases including ethnically matched individuals, including gnomAD/ExAC, 1000 Genomes, ESP, and the Greater Middle East Variome (PM2).
PP4_Moderate	✔	The variant has been previously reported in trans with the known pathogenic L48S allele in 1 Israeli case with classic PKU (PMID: 18299955; PMID: 18294361) as assessed by plasma Phe levels; BH4 deficiency was excluded. It was also noted in 3 Turkish probands: in two, it was found in trans with the p.R243X allele, and in one, it was found in trans with the p.R261Q allele (PMID: 21147011); all three cases had classic as assessed by plasma Phe levels and BH4 deficiency was excluded by genetic testing. Thus PM3_Strong and PP4_Moderate apply. PubMed:21147011 PubMed:18299955
PM3_Strong	✔	The variant has been previously reported in trans with the known pathogenic L48S allele in 1 Israeli case with classic PKU (PMID: 18299955; PMID: 18294361) as assessed by plasma Phe levels; BH4 deficiency was excluded. It was also noted in 3 Turkish probands: in two, it was found in trans with the p.R243X allele, and in one, it was found in trans with the p.R261Q allele (PMID: 21147011); all three cases had classic as assessed by plasma Phe levels and BH4 deficiency was excluded by genetic testing. Thus PM3_Strong and PP4_Moderate apply. It was also noted in 3 Turkish probands: in two, it was found in trans with the p.R243X allele, and in one, it was found in trans with the p.R261Q allele (PMID: 21147011); all three cases had classic as assessed by plasma Phe levels and BH4 deficiency was excluded by genetic testing. PubMed:21147011 The variant has been previously reported in trans with the known pathogenic L48S allele in 1 Israeli case with classic PKU (PMID: 18299955; PMID: 18294361) as assessed by plasma Phe levels; BH4 deficiency was excluded. PubMed:18299955

Curation History

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