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Variant: NM_000277.3(PAH):c.113_115TCT[1] (p.Phe39del)

Version: 1.0

CA229364

188933 (ClinVar)

Gene: PAH
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 334b8b62-50b5-4fb6-8ee6-0934740e8038
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HGVS expressions

NM_000277.3:c.113_115TCT[1]
NM_000277.3(PAH):c.113_115TCT[1] (p.Phe39del)
NC_000012.12:g.102912844_102912846del
CM000674.2:g.102912844_102912846del
NC_000012.11:g.103306622_103306624del
CM000674.1:g.103306622_103306624del
NC_000012.10:g.101830752_101830754del
NG_008690.1:g.9760_9762del
NG_008690.2:g.50568_50570del
ENST00000553106.6:c.116_118del
ENST00000307000.7:c.101_103del
ENST00000546844.1:c.116_118del
ENST00000548677.2:n.203_205del
ENST00000548928.1:n.38_40del
ENST00000549111.5:n.212_214del
ENST00000550978.6:c.100_102del
ENST00000551337.5:c.116_118del
ENST00000551988.5:n.205_207del
ENST00000553106.5:c.116_118del
ENST00000635500.1:n.84_86del
NM_000277.1:c.116_118del
NM_000277.2:c.116_118del
NM_001354304.1:c.116_118del
NM_000277.3:c.116_118del
NM_001354304.2:c.116_118del

Pathogenic

Met criteria codes 5

PS3_Supporting PP4_Moderate PM3_Strong PM2_Supporting PM4

Evidence Links 8

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

This c.113_115TCTdel (p.Phe39del) variant is also known as c.115_117delTTC (p.Phe39del) in the literature. This variant in PAH was reported in 3 Chinese patients with PAH deficiency (PMID: 26503515). DHPR activity, biopterin and/or pteridine analysis was performed to rule out other causes of hyperphenylalaninemia. This variant was documented in 5 patients with PAH deficiency with a pathogenic or likely pathogenic variant in trans (PMID: 16256386, 23500595, 26542770, 29102225, 12655550). This variant is present in European (non-Finnish) populations at a frequency of 0.000035 (gnomAD), and in European (non-Finnish) populations at a frequency of 0.000045 (ExAC). This variant changes the protein length from an in-frame deletion in a non-repetitive region. Functional analysis of this variant found that it is associated with approximately 20% residual enzyme activity (PMID: 11161839; 17935162). In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM2_supporting, PP4_moderate, PM4, PS3-supporting, PM3_strong.

Met criteria codes

PS3_Supporting ✔

Functional analysis of this variant (referred to as c.115_117delTTC) found that it is associated with approximately 20% residual enzyme activity (PMID: 11161839; 17935162).

Functional analysis of this variant (referred to as c.115_117delTTC in this paper) found that it is associated with approximately 20% residual enzyme activity. PubMed:11161839

Functional analysis of this variant (referred to as c.115_117delTTC in this paper) found that it is associated with approximately 20% residual enzyme activity. PubMed:17935162

PP4_Moderate ✔

This variant was documented twice in Northern Chinese patients and once in Southern Chinese patients with PAH deficiency (PMID: 26503515). Tetrahydrobiopterin (BH4) deficiency was excluded through a BH4 loading test, urinary pterin analysis, DHPR activity assay.

This variant was documented twice in Northern Chinese and once in Southern Chinese PKU patients (PMID: 26503515). It was not specific whether the two alleles counted in Northern China were form a homozygous or compound heterozygous patient. Subjects in this study were diagnosed through neonatal screening program or by clinical presentation. Phenylalanine plasma concentrations >120 µmol/L were reported for all subjects. Tetrahydrobiopterin (BH4) deficiency was excluded through a BH4 loading test, urinary pterin analysis, DHPR activity assay. PubMed:26503515

PM3_Strong ✔

This variant was documented in 5 patients with PAH deficiency with a pathogenic or likely pathogenic variant in trans (PMID: 16256386, 23500595, 26542770, 29102225, 12655550).

This variant was documented in one Spanish patient with mild PKUwith the likely pathogenic p.R68S variant in trans (PMID: 23500595). Parental analysis was not performed to confirm compound heterozygosity. PubMed:23500595
Documented in 1 Lithuanian patient with Severe PKU with the pathogenic c.1066-11G>A (IVS10-11G>A) variant in trans. Parental analysis was not performed to confirm compound heterozygosity. PubMed:12655550
This variant was detected in one Chinese patient diagnosed with Classic PKU, who was homozygous for the variant. PubMed:16256386
This variant was documented in 1 hyperphenylalaninemia (HPA) patient with the pathogenic c.117C>G variant in trans. Parental analysis was not performed to confirm compound heterozygosity. PubMed:29102225
This variant was documented in 1 patient with mild hyperphenylalaninemia, with the likely pathogenic c.532G>A variant in trans. The phenotype was based on Phe tolerance and pre-treatment Phe levels, and the patient was lost

to follow-up at the age of 3 months; at that time, the patient was clinically MHP with no diet requirements. Parental testing confirmed that the c.532G>A variant was in trans. PubMed:26542770

PM2_Supporting		✔	Present in European (non-Finnish) populations at a frequency of 0.000035 (gnomAD v2.1.1)
PM4		✔	Protein length changes from in-frame deletion in a non-repetitive region

Curation History

Showing 1 to 1 of 1 rows

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