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Variant: NM_000277.3(PAH):c.281_283TCA[1] (p.Ile95del)

Version: 1.0

CA251535

604 (ClinVar)

Gene: PAH
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 4cfb3ea8-9859-4e41-8ff3-200a9ed28f91
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HGVS expressions

NM_000277.3:c.281_283TCA[1]
NM_000277.3(PAH):c.281_283TCA[1] (p.Ile95del)
NC_000012.12:g.102894806_102894808del
CM000674.2:g.102894806_102894808del
NC_000012.11:g.103288584_103288586del
CM000674.1:g.103288584_103288586del
NC_000012.10:g.101812714_101812716del
NG_008690.1:g.27800_27802del
NG_008690.2:g.68608_68610del
ENST00000553106.6:c.284_286del
ENST00000307000.7:c.269_271del
ENST00000546844.1:c.284_286del
ENST00000548677.2:n.371_373del
ENST00000548928.1:n.206_208del
ENST00000549111.5:n.380_382del
ENST00000550978.6:c.268_270del
ENST00000551337.5:c.284_286del
ENST00000551988.5:n.373_375del
ENST00000553106.5:c.284_286del
NM_000277.1:c.284_286del
NM_000277.2:c.284_286del
NM_001354304.1:c.284_286del
NM_000277.3:c.284_286del
NM_001354304.2:c.284_286del

Pathogenic

Met criteria codes 4

PM2 PM4 PP4_Moderate PM3_Strong

Evidence Links 10

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

This variant was documented in 8 patients diagnosed with PAH deficiency (PMID: 26503515, 30747360, 30050108, 29560316, 18985011). Tetrahydrobiopterin (BH4) deficiency was excluded through a BH4 loading test, urinary pterin analysis, and DHPR activity assay. This variant was detected in trans with a pathogenic or likely pathogenic PAH variant in 2 patients with PKU and 3 patients with hyperphenylalaninemia (PMID: 19292873, 24368688, 25894915, 26666653, 29316886). This variant is present at a frequency below 0.0002 in the population databases ExAC and gnomAD. This variant changes protein length from an in-frame deletion in a non-repeat region. In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM3_strong, PM2, PM4, PP4_moderate.

Met criteria codes

PM2	✔	Present in European (non-Finnish) populations at a frequency of 0.000035 and East Asian populations at a frequency of 0.0000543 (Gnomad). Present in European (non-Finnish) populations at a frequency of 2.997e-05 and East Asian populations at a frequency of 0.000115 (ExAC).
PM4	✔	Protein length changes from in-frame deletion in a non-repeat region.
PP4_Moderate	✔	This variant was documented in 8 patients diagnosed with PAH deficiency (PMID: 26503515, 30747360, 30050108, 29560316). Tetrahydrobiopterin (BH4) deficiency was excluded through a BH4 loading test, urinary pterin analysis, DHPR activity assay (PMID: 26503515, 30747360). Documented in 1 Korean patient diagnosed with classical PKU, with the c.1339G>C variant in trans. Parental analysis was not performed to confirm heterozygosity. PubMed:18985011 This variant was documented in 1 patient diagnosed with classical PKU and 1 patient diagnosed with moderate PKU. All patients were excluded from tetrahydrobiopterin deficiency through a BH4 loading test, a urinary pterin analysis, and a DHPR activity assay on dried blood spot (DBS) samples. PubMed:30747360 This variant was documented twice in Northern Chinese patients with PAH deficiency (PMID: 26503515). In this paper, the variant is referred to as ‘c.279_281delCAT’, which is the same as the ‘c.281_283delTCA’ variant. 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 This variant was documented in 2 patients diagnosed with mild PKU. PubMed:30050108 This variant was documented in 1 hyperphenylalaninemia patient with a homozygous genotype for the PAH variant p.I95del. PubMed:29560316
PM3_Strong	✔	This variant was detected in trans with a pathogenic or likely pathogenic PAH variant in 3 patients with PKU and 3 patients with hyperphenylalaninemia (PMID: 19292873, 24368688, 25894915, 26666653, 29316886). Documented in 1 PKU patient from New South Wales, Australia, who was a compound heterozygote with the likely pathogenic p.S349P variant in trans. Parental analysis was not performed to confirm compound heterozygosity. PubMed:24368688 This variant was documented in a French patient diagnosed with mild hyperphenylalaninemia (MHP, 180 < Phe < 600 µmol/L) who was a compound heterozygote with the pathogenic c.1243G>A variant in trans; this variant was also found in a patient diagnosed with classic PKU (cPKU, Phe > 1200 µmol/L) who was a compound heterozygote with the pathogenic c.441+5G>T variant in trans (PMID: 26666653). In this paper, the variant is referred to as ‘c.284_286delTCA’, which is the same as the ‘c.281_283delTCA’ variant. Parental analysis was not performed to confirm heterozygosity. PubMed:26666653

Documented in 1 Southern Italian patient diagnosed with hyperphenylalaninemia (HPA), who was a compound heterozygote with the likely pathogenic c.165delT variant in trans. Parental analysis was not performed to confirm compound heterozygosity. PubMed:19292873

This variant was documented in a Chinese patient from Jiangsu province diagnosed with mild hyperphenylalaninemia (MHP) who was a compound heterozygote with the likely pathogenic M276K variant in trans (PMID: 25894915). In this paper, the variant is referred to as 'c.284_286delTCA', which is the same as the 'c.281_283delTCA' variant. Parental analysis was performed to confirm heterozygosity. PubMed:25894915

This variant was documented in one Han Chinese patient diagnosed with mild PKU who was a compound heterozygote with the p.Cys217Tyr VUS in trans (PMID: 29316886). Parental analysis was performed to confirm heterozygosity. PubMed:29316886

Curation History

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