

Variant: *NM_000277.3(PAH):c.532G>A (p.Glu178Lys)*

Version: 1.0

CA16020812 [↗](#)

928885 (ClinVar) [↗](#)

Gene: PAH ([HGNC:5053](#))

Condition: phenylketonuria ([MONDO:0009861](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: c54336ad-7a33-4a07-895c-275c08ab017c

Approved on: 2021/1/17

Published on: 2021/2/12

HGVS expressions

NM_000277.3:c.532G>A

NM_000277.3(PAH):c.532G>A (p.Glu178Lys)

NC_000012.12:g.102855310C>T

CM000674.2:g.102855310C>T

NC_000012.11:g.103249088C>T

CM000674.1:g.103249088C>T

NC_000012.10:g.101773218C>T

NG_008690.1:g.67293G>A

NG_008690.2:g.108101G>A

ENST00000553106.6:c.532G>A

ENST00000307000.7:c.517G>A

ENST00000549111.5:n.628G>A

ENST00000551988.5:n.553G>A

ENST00000553106.5:c.532G>A

NM_000277.1:c.532G>A

NM_000277.2:c.532G>A

NM_001354304.1:c.532G>A

NM_001354304.2:c.532G>A

Pathogenic

Met criteria codes 4

PP4_Moderate

PM5

PM2

PM3_Strong

Not Met criteria codes 2

PS3

PP3

Evidence Links 5

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information ⓘ

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.532G>A (p.Glu178Lys) variant in PAH has been reported in multiple individuals with PAH deficiency (BH4 deficiency excluded). (PP4_Moderate; PMID: 26503515; PMID: 26542770). This variant has an extremely low allele frequency (PopMax MAF=0.00006, ENF) in

gnomAD (PM2). This variant was detected in trans with F39del (PMID: 26542770) (Pathogenic/Likely Pathogenic in ClinVar by 7 submitters, see ID 188933). It has also been observed with R408W (PMID: 28771436, parental testing not performed) (Pathogenic in ClinVar (ID 577) and by ClinGen PAH VCEP) and IVS4-1G>A (PMID: 29316886, parental testing unclear) (Pathogenic in ClinVar (ID 594) and by ClinGen PAH VCEP). Computational prediction tools and conservation analysis are conflicting. This is a novel missense change at an amino acid residue where a different pathogenic missense change has been seen before (c.533A>G (p.Glu178Gly). In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM3_strong, PM2, PM5

Met criteria codes

PP4_Moderate			<p>Detected in Chinese PKU patient, dihydropteridine reductase activity, urinary biopterin and neopterin ratio, and tetrahydrobiopterin loading were assessed. PMID: 26503515 Detected in a Danish patient with probable MHP. PMID: 26542770</p> <hr/> <p>Patient 4, probably MHP (lost to follow-up). All patients had PKU according to biochemical criteria.</p> <p>PubMed:26542770 </p> <p>A total of 796 unrelated patients from 29 separate newborn screening centres of China were enrolled. These patients were diagnosed at birth either through a neonatal screening program or based on clinical presentation. Demographic data, including age, consanguinity, family history, and geographical origin, and biochemical testing data, including plasma phenylalanine (Phe) levels, dihydropteridine reductase activity, urinary biopterin and neopterin ratio, and tetrahydrobiopterin loading, were collected. One patient had c.532G>A (p.E178K).</p> <p>PubMed:26503515 </p>
PM5			<p>c.533A>G (p.Glu178Gly) Pathogenic by 6 submitters</p>
PM2			<p>MAF=0.00006 in ENF gnomAD population.</p>
PM3_Strong			<p>detected in trans with F39del (PMID: 26542770, Parental testing confirmed that the two mutations identified in the 368 patients all were present in trans.) and R408W (PMID: 28771436, parental testing not performed) and IVS4-1G>A (PMID: 29316886, variable sites in patient genes were aligned with the corresponding sites from the respective parents.)</p> <hr/> <p>detected in trans with F39del. Parental testing confirmed that the two mutations identified in the 368 patients all were present in trans. PubMed:26542770 </p> <p>Patient 496: IVS4-1G□A/p.Glu178Lys. Peripheral blood samples were collected from the patients and parents in each of the 643 core families. To determine sequence variability, variable sites in patient genes were aligned with the corresponding sites from the respective parents. PubMed:29316886 </p> <p>Sample NBS47: c.1222C>T (R408W,P)/c.532G>A. Parental testing not performed. PubMed:28771436 </p>

Not Met criteria codes

PS3			<p>did not affect the transcription of the PAH gene, however, PAH protein synthesis and/or stability was disturbed. PMID: 29653233</p> <hr/> <p>We performed site-directed mutagenesis and in vitro expression (E. coli and HEK293T). The mRNA and protein levels of three variants were compared with that of wild type gene, as well as a common PAH mutation, p.R243Q, which is known to decrease protein expression and enzyme activity (Pey et al., 2003). Table 2: E178K mRNA 0.973 ± 0.181, empty control 0, wt 1.0. The lower expression in mutant groups indicated that PAH protein expression was impaired</p>
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by variants. In general, all four mutations did not affect the transcription of the PAH gene, however, PAH protein synthesis and/or stability was disturbed. Exact numbers or % of wt were not reported. [PubMed:29653233](#)

PP3



SIFT=T, Polyphen2=B, MutationTaster=D. REVEL=0.607

Curation History

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