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Variant: NM_000277.3(PAH):c.586_608del (p.Ser196fs)

Version: 1.0

CA229634

102743 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 3c726e17-eac3-4375-af90-eceffdbcb7df
Approved on: 2020/7/24
Published on: 2020/7/24

HGVS expressions

NM_000277.3(PAH):c.586_608del (p.Ser196fs)
NM_000277.3:c.586_608del
NC_000012.12:g.102855235_102855257del
CM000674.2:g.102855235_102855257del
NC_000012.11:g.103249013_103249035del
CM000674.1:g.103249013_103249035del
NC_000012.10:g.101773143_101773165del
NG_008690.1:g.67347_67369del
NG_008690.2:g.108155_108177del
ENST00000553106.6:c.586_608del
ENST00000307000.7:c.571_593del
ENST00000549111.5:n.682_704del
ENST00000553106.5:c.586_608del
NM_000277.1:c.586_608del
NM_000277.2:c.586_608del
NM_001354304.1:c.586_608del
NM_001354304.2:c.586_608del

Pathogenic

Met criteria codes 4

PM3 PM2 PVS1 PP4_Moderate

Evidence Links 1

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.586_608del (p.Ser196fs) frameshift variant in PAH is predicted to undergo nonsense-mediated decay. This variant was reported in a Spanish patient with classic PKU in trans with pathogenic variant p.Arg261Gln. A defect in the synthesis or regeneration in the pathways of 6R-BH4 was ruled out by analyzing urinary pterin levels and by measuring the dihydropteridine reductase activity (PMID 27121329). This variant was also reported in another Spanish patient with moderate PKU and identified with the pathogenic variant p.I65T (PMID

15464430). This variant is absent from gnomAD. In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PVS1, PM2, PM3, and PP4 moderate.

Met criteria codes

PM3	✔	Detected in trans with pathogenic variant p.Arg261Gln. Segregation analysis was done (PMID 27121329). Heterozygous with pathogenic variant p.I65T and Mendelian inheritance was confirmed in all cases by DGGE or sequencing analysis. (PMID 15464430). PubMed:27121329
PM2	✔	Absent from gnomAD.
PVS1	✔	Frameshift variant, predicted to undergo NMD, not located in last exon or last 50bp of preliminary exon. Coding exon number 6 out of 13 coding exons (6 out of total exons)
PP4_Moderate	✔	Reported in a Spanish patient with classic PKU. A defect in the synthesis or regeneration in the pathways of 6R-BH4 was ruled out by analyzing urinary pterin levels as well as by measuring the dihydropteridine reductase activity (PMID 27121329). Reported in a second Spanish patient with moderate PKU. Urinary pterin analysis and DHPR activity measurements excluded a BH4 deficiency in these cases (PMID 15464430).

Curation History

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