Variant: NM_000277.3(PAH):c.1194A>G (p.Lys398=)

Version: 1.0

CA229376

102550 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 70f8e388-4b46-4ba3-bfb6-102e901314c8
Approved on: 2020-09-12
Published on: 2020-09-12

HGVS expressions

NM_000277.3:c.1194A>G
NM_000277.3(PAH):c.1194A>G (p.Lys398=)
NC_000012.12:g.102843651T>C
CM000674.2:g.102843651T>C
NC_000012.11:g.103237429T>C
CM000674.1:g.103237429T>C
NC_000012.10:g.101761559T>C
NG_008690.1:g.78952A>G
NG_008690.2:g.119760A>G
ENST00000553106.6:c.1194A>G
ENST00000307000.7:c.1179A>G
ENST00000549247.6:n.953A>G
ENST00000551114.2:n.856A>G
ENST00000553106.5:c.1194A>G
ENST00000635477.1:c.298A>G
ENST00000635528.1:n.709A>G
NM_000277.1:c.1194A>G
NM_000277.2:c.1194A>G
NM_001354304.1:c.1194A>G
NM_001354304.2:c.1194A>G

Likely Pathogenic

Met criteria codes 4

PM3_Strong PP4_Moderate PP3 PM2

Not Met criteria codes 1

PM5

Evidence Links 3

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.1194A>G (p.Lys398Lys) variant in PAH has been reported in 1in 2 Chinese patients with moderate/classic PKU and BH4 deficiency excluded. (PMIDs: 25894915, 28982351; PP4_Moderate). Both patients were compound heterozygotes with pathogenic variants R413P and R241C confirmed in trans (PM3_Strong). This variant is present at an extremely low frequency with a MAF of 0.00005438 in the gnomAD East Asian population. (PM2). There is consensus of computational predictors that there is potential alteration of splicing via activation of a cryptic splice site near the end of exon 11.In summary, this variant meets criteria to be classified as Likely Pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM2, PM3_Strong, PP3, PP4_Moderate.

Met criteria codes

PM3_Strong	✔	Two compound heterozygotes have been reported (PMID: 28982351 and PMID: 25894915) with pathogenic variants R413P and R241C confirmed in trans. PubMed:28982351
PP4_Moderate	✔	PMID: 25894915 and PMID: 28982351 - K398K detected in 2 Chinese patients with moderate/classic PKU and BH4 deficiency excluded. PubMed:25894915 PubMed:10394930
PP3	✔	HSF (87.18>97.27=>11.57%), MaxEntScan (6.6>10.51=> 59.24%) and SpliceAI (0.82) agree that there is activation of a cryptic splice site near the end of exon 11. Furthermore, the activated cryptic donor site is stronger than the nearby canonical site (HSF 87, MaxEntScan 6) and SplicAI predicts loss of the canonical donor site (0.5). Overall, there is consensus for potential alteration of splicing which would cause a 5bp deletion and frameshift.
PM2	✔	The variant is present at an extremely low frequency with an overall allele frequency in gnomAD of 0.000003979 and a MAF of 0.00005438 (1/18390 alleles) in the East Asian population.

Not Met criteria codes

PM5	✖	At same codon as c.1194A>C (p.K398N) curated as VUS by ClinGen PAH VCEP

Curation History

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