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Variant: NM_000277.3(PAH):c.283A>T (p.Ile95Phe)

Version: 1.0

CA229507

102645 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: c61fa227-893e-4be0-9e02-2d7c1494af20
Approved on: 2024/9/6
Published on: 2024/9/6

HGVS expressions

NM_000277.3(PAH):c.283A>T (p.Ile95Phe)
NM_000277.3:c.283A>T
NC_000012.12:g.102894804T>A
CM000674.2:g.102894804T>A
NC_000012.11:g.103288582T>A
CM000674.1:g.103288582T>A
NC_000012.10:g.101812712T>A
NG_008690.1:g.27799A>T
NG_008690.2:g.68607A>T
ENST00000553106.6:c.283A>T
ENST00000307000.7:c.268A>T
ENST00000546844.1:c.283A>T
ENST00000548677.2:n.370A>T
ENST00000548928.1:n.205A>T
ENST00000549111.5:n.379A>T
ENST00000550978.6:c.267A>T
ENST00000551337.5:c.283A>T
ENST00000551988.5:n.372A>T
ENST00000553106.5:c.283A>T
NM_000277.1:c.283A>T
NM_000277.2:c.283A>T
NM_001354304.1:c.283A>T
NM_001354304.2:c.283A>T

Likely Pathogenic

Met criteria codes 3

PM3_Strong PP3 PP4

Not Met criteria codes 3

PM1 PM5 PM2

Evidence Links 0

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Phenylketonuria Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for PAH Version 2.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.283A>T (p.Ile95Phe) variant in PAH has been reported in multiple patients with mild and moderate phenylketonuria. It was detected with pathogenic variants: p.R408W (PMID: 10495930); p.R158Q, p.A403V, p.T323del (PMID: 18299955); and p.E280K (PMID: 31623983). This variant has a MAF of 0.00060 in gnomAD in the Ashkenazi Jewish population, which is above our cutoff for PM2 (<0.0002) and below our cutoff for BS1 (>0.002). Computational evidence support a deleterious effect (REVEL=0.658). In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM3_strong, PP3, PP4.

Met criteria codes

PM3_Strong	✔	I95F/R408W, Mendelian inheritance was confirmed. PMID: 10495930; R158Q (P), A403V(P), T323del (P), parental analysis not reported, PMID: 18299955; p.E280K (P by 11 submitters), parental analysis not reported PMID: 31623983; 3.0 pts
PP3	✔	REVEL=0.658
PP4	✔	Reported in multiple patients with mild and moderate PKU, BH4 deficiency not ruled out PMID: 10495930

Not Met criteria codes

PM1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✖	I95T is US by PAH VCEP
PM2	✖	MAF is 0.0004908 (AJ) in gnomAD v4, which is too high for PM2 (<0.0002) and too low for BS1 (>0.002). Reported in an occasional patient INGD (Israeli National Genetic Database) and found in gnomAD uniquely among Ashkenazi Jews (100%) and in a significantly increased frequency (0.10, p<0.005, Carrier frequency of the %). PMID: 29144512

Curation History

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