The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000277.2(PAH):c.1033G>T (p.Ala345Ser)

Version: 1.0

CA286497

102484 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 9bd06960-5c2f-4ce6-a141-0f0702afd6cf
Approved on: 2020-06-05
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HGVS expressions

NM_000277.2:c.1033G>T
NM_000277.2(PAH):c.1033G>T (p.Ala345Ser)
NC_000012.12:g.102844368C>A
CM000674.2:g.102844368C>A
NC_000012.11:g.103238146C>A
CM000674.1:g.103238146C>A
NC_000012.10:g.101762276C>A
NG_008690.1:g.78235G>T
NG_008690.2:g.119043G>T
ENST00000553106.6:c.1033G>T
ENST00000307000.7:c.1018G>T
ENST00000549247.6:n.792G>T
ENST00000551114.2:n.695G>T
ENST00000553106.5:c.1033G>T
ENST00000635477.1:c.137G>T
ENST00000635528.1:n.548G>T
NM_000277.1:c.1033G>T
NM_001354304.1:c.1033G>T
NM_000277.3:c.1033G>T
NM_001354304.2:c.1033G>T

Pathogenic

Met criteria codes 4

PP3 PP4 PM2 PM3_Very Strong

Not Met criteria codes 2

PM1 PM5

Evidence Links 2

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.1033G>T (p.Ala345Ser) variant in PAH has been reported in multiple individuals with PAH deficiency. (PMID: 24368688, 17502162, 3430918). This variant has an extremely low allele frequency (MAF=0.00008) in gnomAD. It was detected with multiple pathogenic variants: p.R408W (in trans, PMID: 24368688); c.1045T>C, c.194T>C (PMID: 17502162); p.F39del, c.47_48delCT (aka c.43_44CT), c.1066-11G>A (PMID: 23430918); p.E280K, p.L348V, p.Y414C (PMID: 31623983). Multiple lines of computational evidence support a deleterious effect. In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM3_VS, PM2, PP3, PP4.

Met criteria codes

PP3	✔	Predicted deleterious by MutationTaster, Sift, PolyPhen, and REVEL (0.96).
PP4	✔	Seen in an individual with HPA, second mutation R408W. BH4 deficiency not reportedly assessed. PMID: 24368688, PMID: 17502162, exclusion criteria: Clinical diagnosis of primary BH4 deficiency PMID: 23430918
		Seen in an individual with HPA, whose two siblings also had PKU but with a different genotype (shared the R408W allele). PubMed:24368688
PM2	✔	Seen in low freq in gnomAD (MAF=0.00008) and absent in 1000 Genomes and ESP.
PM3_Very Strong	✔	second allele R408W. Pathogenic in Clinvar (Var ID=577). confirmed by parental testing. PMID: 24368688; c.1045T>C (P-5 submitters); c.194T>C (2 patients, P-11 submitters) parental analysis not performed PMID: 17502162 p.F39del (P 5 submiters), c.47_48delCT (aka c.43_44CT, P 3 submitters), c.1066-11G>A (P 7 submitters) parental analysis not performed PMID: 23430918; p.E280K (P 9 submitters), p.L348V (P 8 submitters), p.Y414C (P 14 submitters) parental analysis not reported PMID: 31623983 (5 pts)
		Seen in an individual with PKU, second allele R408W. Pathogenic in Clinvar (Var ID=577). PubMed:24368688

Not Met criteria codes

PM1	✖	located in catalytic domain
		located in catalytic domain PubMed:23430918
PM5	✖	A345T likely pathogenic in Clinvar (Var ID= 102483)

Curation History

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