

Variant: *NM_000277.2(PAH):c.143T>C (p.Leu48Ser)*

Version: 1.0

CA251539 [↗](#)

608 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: d9c8f867-8d78-48cd-8299-827206594d17

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HGVS expressions

NM_000277.2:c.143T>C

NM_000277.2(PAH):c.143T>C (p.Leu48Ser)

NC_000012.12:g.102912816A>G

CM000674.2:g.102912816A>G

NC_000012.11:g.103306594A>G

CM000674.1:g.103306594A>G

NC_000012.10:g.101830724A>G

NG_008690.1:g.9787T>C

NG_008690.2:g.50595T>C

NM_000277.1:c.143T>C

NM_001354304.1:c.143T>C

NM_000277.3:c.143T>C

ENST00000307000.7:c.128T>C

ENST00000546844.1:c.143T>C

ENST00000548677.2:n.230T>C

ENST00000548928.1:n.65T>C

ENST00000549111.5:n.239T>C

ENST00000550978.6:n.127T>C

ENST00000551337.5:c.143T>C

ENST00000551988.5:n.232T>C

ENST00000553106.5:c.143T>C

ENST00000635500.1:n.111T>C

Pathogenic

Met criteria codes 5

PS3

PP1

PP3

PM3

PP4_Moderate

Not Met criteria codes 1

PM2

Evidence Links 5

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information !

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

Phenylketonuria VCEP

The c.143T>C (p.Leu48Ser) variant in PAH has been reported multiple individuals with mild and classic PKU (BH4 deficiency excluded). (PP4_Moderate; PMID: 26322415, 16879198, 1679030). This variant has a frequency that is higher than the suggested cutoff for PM2 by the PAH VCEP (MAF=0.00026). This variant has 39% residual activity (PS3, PMID: 17935162). This variant was detected in trans with p.G247R (LP, 2 submitters) PM3, PMID: 26322415). Computational prediction tools and conservation analysis suggest that this variant may impact the protein (PP3). Cosegregation with PKU in 2 siblings for 2 unrelated families was reported (PMID: 23430547). In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PS3, PM3, PP1, PP3.

Met criteria codes

PS3		p.L48S, c.143T>C has 39% residual activity PMID: 17935162
Table 1: p.L48S, c.143T>C has 39% residual activity PubMed:17935162		
PP1		Cosegregation with PKU in 2 siblings for 2 unrelated families PMID: 23430547
Siblings (Patient 17 and 18) with classic PKU and genotype p.[L48S];[S231F]. Siblings (Patient 13 and 14) with mild PKU and homozygous genotype. PubMed:23430547		
PP3		Multiple lines of computational evidence support a deleterious effect (SIFT, PolyPhen2, MutationTaster, REVEL=0.97)
PM3		detected in trans with p.G247R (LP, 2 submitters) PMID: 26322415
Patient genotype: c.[143T>C];[739G>C], p.[L48S];[G247R] (LP, 2 submitters). All mutations identified in patients were confirmed by analyzing parental DNA. When mutation loci were detected in patients, the same locus of the parental sample was amplified by PCR and analyzed by Sanger automated sequencing. PubMed:26322415		
PP4_Moderate		Detected in multiple patients with PKU (mild and classic). Bh4 deficiency excluded. PMID: 26322415, PMID: 16879198, PMID: 1679030
L48S was detected on 1 allele. All patients fulfilled the diagnostic criteria of PKU, with a blood phenylalanine concentration >2 mg/dl. BH4 deficiency was excluded by analysis of urinary pterins and dihydropteridine reductase activity in erythrocytes. PubMed:26322415		
Using both polymerase chain reaction-restriction fragment length polymorphism and 'broad-range' denaturing-gradient gel electrophoresis/DNA sequencing analysis, 19 disease-causing mutations were identified, corresponding to mutation detection rate of 97%. The most frequent ones were L48S (21%). We found that the most frequent mutation, L48S, was exclusively associated with the classical (severe) PKU phenotype. PubMed:16879198		
Detected in a Turkish patient with classic PKU. PubMed:1679030		

Not Met criteria codes

PM2		MAF=0.00026 in gnomAD is higher than PAH VCEP threshold (<0.0002) for PM2
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