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Variant: NM_000277.3(PAH):c.121C>T (p.Leu41Phe)

Version: 1.0

CA229401

102569 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: a983e8b6-878e-4027-bcec-c47d9fbc5201
Approved on: 2020/6/1
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HGVS expressions

NM_000277.3:c.121C>T
NM_000277.3(PAH):c.121C>T (p.Leu41Phe)
NC_000012.12:g.102912838G>A
CM000674.2:g.102912838G>A
NC_000012.11:g.103306616G>A
CM000674.1:g.103306616G>A
NC_000012.10:g.101830746G>A
NG_008690.1:g.9765C>T
NG_008690.2:g.50573C>T
ENST00000553106.6:c.121C>T
ENST00000307000.7:c.106C>T
ENST00000546844.1:c.121C>T
ENST00000548677.2:n.208C>T
ENST00000548928.1:n.43C>T
ENST00000549111.5:n.217C>T
ENST00000550978.6:c.105C>T
ENST00000551337.5:c.121C>T
ENST00000551988.5:n.210C>T
ENST00000553106.5:c.121C>T
ENST00000635500.1:n.89C>T
NM_000277.1:c.121C>T
NM_000277.2:c.121C>T
NM_001354304.1:c.121C>T
NM_001354304.2:c.121C>T

Pathogenic

Met criteria codes 4

PP4_Moderate PM3 PM2 PS3

Not Met criteria codes 2

PM5 PP3

Evidence Links 3

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.121C>T (p.Leu41Phe) variant in PAH has been reported in 2 individuals with mild PKU (BH4 deficiency excluded). (PMID: 21147011, 8268925). This variant is absent in population databases. This variant has 10% enzyme activity PMID: 21953985. This variant was detected with IVS10-11G>A (PMID: 21147011) and R261Q (PMID: 8268925)). Computational prediction tools are conflicting. In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PS3, PM2, PM3.

Met criteria codes

PP4_Moderate	✔	L41F seen in 2 patients with mild PKU. BH4 deficiency excluded in 1 patient. PMID: 21147011 PMID: 8268925 588 hyperphenylalaninemic patients were investigated. Assessment included PAH gene and genes of the BH4 synthesis/recycling pathways (PTS and QDPR). L41F seen in 1 patient with mild PKU. PubMed:21147011 In this study, we conducted a systematic analysis of 53 patients from the Sicilian population. L41F seen in 1 patient with mild PKU. PubMed:8268925
PM3	✔	Detected with IVS10-11G>A (PMID: 21147011) and R261Q (PMID: 8268925), parental analysis not reported L41F seen in trans with IVS10-11G>A (VarID 607, Pathogenic in ClinVar) PubMed:21147011 L41F seen in trans with R261Q (VarID 582, Pathogenic/LP in ClinVar) in 1 patient with mild PKU. PubMed:8268925
PM2	✔	Absent from ExAC, gnomAD, 1000G, ESP
PS3	✔	10% enzyme activity PMID: 21953985 expression in COS-7 cells showed total activity of 10%, 91% protein level, mRNA level of 88% PubMed:21953985

Not Met criteria codes

PM5	✖	L41P has no interpretation in ClinVar
PP3	✖	Conflicting predictions of pathogenicity: tolerated in SIFT, deleterious in PolyPhen2, MutationTaster

Curation History

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