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_000277.1:c.185T>C

Version: 1.0

CA16020739

872838 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: dde01117-4f4b-4e62-bd5c-a3746780d66d
Approved on: 2020/1/29
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HGVS expressions

NM_000277.1:c.185T>C
NC_000012.12:g.102894902A>G
CM000674.2:g.102894902A>G
NC_000012.11:g.103288680A>G
CM000674.1:g.103288680A>G
NC_000012.10:g.101812810A>G
NG_008690.1:g.27701T>C
NG_008690.2:g.68509T>C
ENST00000553106.6:c.185T>C
ENST00000307000.7:c.170T>C
ENST00000546844.1:c.185T>C
ENST00000548677.2:n.272T>C
ENST00000548928.1:n.107T>C
ENST00000549111.5:n.281T>C
ENST00000550978.6:c.169T>C
ENST00000551337.5:c.185T>C
ENST00000551988.5:n.274T>C
ENST00000553106.5:c.185T>C
ENST00000635500.1:n.153T>C
NM_000277.2:c.185T>C
NM_001354304.1:c.185T>C
NM_000277.3:c.185T>C
NM_001354304.2:c.185T>C

Likely Pathogenic

Met criteria codes 4

PP3 PP4 PM2 PM3

Evidence Links 1

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.185T>C (p.Leu62Pro) variant in PAH has been reported in 1 individual with classic PKU (BH4 deficiency not assessed/reported). (PP4; PMID: 22513348). This variant is absent in population databases (PM2). This variant was detected with p.R408W (Pathogenic in ClinVar) (PM3; PMID: 22513348). Multiple lines of computational evidence support a deleterious effect (PP3). In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4, PM2, PM3, PP3.

Met criteria codes

PP3	✔	Multiple lines of computational evidence support a deleterious effect (SIFT, PolyPhen-2, MutationTaster). REVEL=0.972
PP4	✔	Novel mutation detected in a patient with classic PKU: p.L62P. BH4 deficiencies not assessed/reported. PMID: 22513348 Mutational spectrum of PAH deficiency was investigated in 107 families (90% of the Slovene PKU population). The entire coding region of the PAH gene was analyzed with dHPLC to select the samples where subsequently the automated sequencing analysis was performed. MLPA analysis was performed to identify large deletions, which were later confirmed with long-range PCR. Novel mutation detected in a patient with classic PKU: p.L62P. PubMed:22513348
PM2	✔	Absent from controls in ExAC, gnomAD, 1000 Genomes, or ESP
PM3	✔	Detected with R408W (pathogenic in ClinVar) PMID: 22513348 Patient 38: allele 1:p.L62P, allele 2: R408W. PubMed:22513348

Curation History

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