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(PAH):c.635T>C (p.Leu212Pro)

Version: 1.0

CA229668

102768 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 2eaf4e3c-85c2-49cd-8343-42a8a9e94d1b
Approved on: 2021/7/17
Published on: 2021/9/6

HGVS expressions

NM_000277.1:c.635T>C
NM_000277.1(PAH):c.635T>C (p.Leu212Pro)
NC_000012.12:g.102855207A>G
CM000674.2:g.102855207A>G
NC_000012.11:g.103248985A>G
CM000674.1:g.103248985A>G
NC_000012.10:g.101773115A>G
NG_008690.1:g.67396T>C
NG_008690.2:g.108204T>C
ENST00000553106.6:c.635T>C
ENST00000307000.7:c.620T>C
ENST00000549111.5:n.731T>C
ENST00000553106.5:c.635T>C
NM_000277.2:c.635T>C
NM_001354304.1:c.635T>C
NM_000277.3:c.635T>C
NM_001354304.2:c.635T>C

Likely Pathogenic

Met criteria codes 5

PP3 PP4 PM3 PM2 PS3_Supporting

Not Met criteria codes 1

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.635T>C (p.Leu212Pro) variant in PAH has been reported in multiple individuals with PAH deficiency (PMID: 9781015) detected with pathogenic variants: p.R408W (PMID: 17502162); p.R158Q (PMID: 23430918); c.1066-11G>A (PMID: 26666653). This variant is absent in population databases. In vitro residual activity of the p.L212P mutant enzyme is 17% of wild type, and it also showed reduced protein

expression. Computational prediction tools and conservation analysis support a deleterious effect on the protein. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PS3_supporting, PM2, PM3, PP3, PP4.

Met criteria codes

PP3	✔	Deleterious in SIFT, Polyphen2, MutationTaster
PP4	✔	Found on 1 allele in PKU patient. No patient specific information reported (Phe level, 2nd mutation). BH4 deficiency not investigated. PMID: 9781015
		We successfully analyzed 135 of 141 chromosomes from phenylketonuria (PKU) probands (95.7% of the sample), and eight additional chromosomes from a small number of probands with non-PKU hyperphenylalaninemia (HPA). L212P found on 0.7% of 135 alleles (1 allele). PubMed:9781015
PM3	✔	detected with p.R408W(c.1222C>T) parental analysis not reported PMID: 17502162; p.R158Q parental analysis not reported PMID: 23430918; c.1066-11G>A] parental analysis not reported PMID: 26666653
PM2	✔	Not found in ExAC, gnomAD, 1000G, or ESP
PS3_Supporting	✔	In vitro residual activity of L212P is 17% of wild type. Also showed reduced protein expression. Investigated 8 variants.
		Investigated 8 variants, including c.635T>C (p.L212P). We used an in vitro expression system in combination with liquid chromatography (LC) applied with electrospray ionization tandem mass spectrometry (ESI-MS-MS) for the quantification of tyrosine (Tyr) produced from phenylalanine (Phe) to assess the residual activities. The residual activity expressed as a percentage of the wild-type enzyme activity, was: 17.0 ± 7.0% (p.L212P). All of the PAH variant proteins with rather low activity (p.L212P, p.R270K and p.R261P) also exhibited reduced amounts of PAH protein, compared to wild-type. PubMed:27620137

Not Met criteria codes

PM5	✖	The current variant is the only variant found in this codon in ClinVar.

Curation History

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