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Variant: NM_000277.2(PAH):c.745C>T (p.Leu249Phe)

CA273356

102821 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 6807a54c-cde9-445c-b30f-9d4a3fbbdc85
Approved on: 2018-08-12
Published on: 2018-12-10

HGVS expressions

NM_000277.2:c.745C>T
NM_000277.2(PAH):c.745C>T (p.Leu249Phe)
NC_000012.12:g.102852912G>A
CM000674.2:g.102852912G>A
NC_000012.11:g.103246690G>A
CM000674.1:g.103246690G>A
NC_000012.10:g.101770820G>A
NG_008690.1:g.69691C>T
NG_008690.2:g.110499C>T
NM_000277.1:c.745C>T
NM_001354304.1:c.745C>T
NM_000277.3:c.745C>T
ENST00000307000.7:c.730C>T
ENST00000549247.6:n.504C>T
ENST00000553106.5:c.745C>T

Pathogenic

Met criteria codes 4

PP3 PM2 PP4_Moderate PM3_VeryStrong

Not Met criteria codes 2

PM5 PS3

Evidence Links 3

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

PAH-specific ACMG/AMP criteria applied: PM2: Absent from 1000G, ESP. Extremely low frequency in ExAC and gnomAD (0.00004065); PP3: Deleterious effect predicted in SIFT, Polyphen2, MutationTaster. REVEL=0.981; PP4_Moderate: L249F was seen 3 times in HPA patients associated with 2 different haplotypes. DHPR defeciency was excluded. Upgraded per ClinGen Metabolic workgroup. (PMID:8533759); PM3_VeryStrong: Seen with R261X, A309V, V388M, R261Q. All Pathogenic/Likely Pathogenic in ClinVar. Upgraded per ClinGen SVI Workgroup (PMID:21871829; PMID:24765287). In summary this variant meets criteria to be classified as pathogenic for phenylketonuria in

an autosomal recessive manner based on the ACMG/AMP criteria applied as specified by the PAH Expert Panel: (PM2, PP3, PP4_Moderate, PM3_VeryStrong).

Met criteria codes

PP3	✔	Deleterious effect predicted in SIFT, Polyphen2, MutationTaster. REVEL=0.981
PM2	✔	Absent from 1000G, ESP. Extremely low frequency in ExAC and gnomAD (0.00004065)
PP4_Moderate	✔	L249F was seen 3 times in HPA patients associated with 2 different haplotypes. DHPR defeciency was excluded. Upgraded per ClinGen Metabolic workgroup. A total of 121 Northern Irish families with HPA (111 with PKU and10 with MHP) were investigated, including virtually all patients born after 1972. Dihydrobiopterinreductase deficiency was excluded. L249F was seen 3 times, with 2 different haplotypes (at least 2 different families). PubMed:8533759
PM3_Very Strong	✔	Seen with R261X, A309V, V388M, R261Q. All Pathogenic/Likely Pathogenic in ClinVar. Upgraded per ClinGen SVI Workgroup The diagnosis was confirmed through molecular analysis of the patient as well as the parents. Genetic analysis showed that she is compound heterozygous for the following mutations: p.L249F and p.R261Q (VarID 582, P/LP). The father carries the first mutation and the mother the second. PubMed:24765287 L249F found with p.R261X (Pathogenic) in Patient 47. p.A309V (Path/LP) in Patient 48, p.V388M (Pathogenic) in Patient 49. PubMed:21871829

Not Met criteria codes

PM5	✖	L249H, no assertion provided
PS3	✖	51% enzyme activity in BioPKU

Curation History

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