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Variant: NM_000277.3(PAH):c.1315+1G>T

Version: 1.0

CA16020993

370074 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 57a0f42f-2e71-4b0b-8079-573f0d5a4840
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HGVS expressions

NM_000277.3:c.1315+1G>T
NM_000277.3(PAH):c.1315+1G>T
NC_000012.12:g.102840399C>A
CM000674.2:g.102840399C>A
NC_000012.11:g.103234177C>A
CM000674.1:g.103234177C>A
NC_000012.10:g.101758307C>A
NG_008690.1:g.82204G>T
NG_008690.2:g.123012G>T
ENST00000553106.6:c.1315+1G>T
ENST00000307000.7:c.1300+1G>T
ENST00000551114.2:n.977+1G>T
ENST00000553106.5:c.1315+1G>T
ENST00000635477.1:c.419+1G>T
ENST00000635528.1:n.830+1G>T
NM_000277.1:c.1315+1G>T
NM_000277.2:c.1315+1G>T
NM_001354304.1:c.1315+1G>T
NM_001354304.2:c.1315+1G>T

Likely Pathogenic

Met criteria codes 3

PM2 PVS1_Strong PP4

Evidence Links 0

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.1315+1G>T variant in PAH is a canonical splice-site variant predicted to lead to skipping of exon 13 (PVS1_Strong). Exon 13 encodes 15 amino acids + stop codon = 3.3% of PAH protein length. Along with Exon 12, Exon 13 forms the oligomerization domain (residues 411–452), which is responsible for the dimerization and tetramerization of the enzyme, important for regulation of PAH activity (e.g., positive

cooperativity by the substrate, L-Phe, and decreasing PAH activity at low L-Phe concentration) (see PMID: 23457044; PMID: 22005392). Exon 13 contains the non-truncating Likely Pathogenic p.A447P (Likely Pathogenic by ClinGen PAH VCEP) and Pathogenic p.A447D variants (Likely Pathogenic by ClinGen PAH VCEP; Pathogenic in ClinVar (ID 102595; 4 submitters, 2 stars). Thus PVS1_Strong will be applied for variants resulting in deletion of this exon. It is absent from ethnically diverse control databases, including gnomAD/ExAC, 1000 Genomes, and ESP (PM2). The variant has been previously reported in one Catalonian PKU case (as determined by abnormal blood Phe levels), without additional information (PMID: 10598814) (PP4). It is also noted in ClinVar (ID 370074), where it is classified as Likely Pathogenic by one lab, with this published reported cited. Classification: Likely Pathogenic Supporting Criteria: PVS1_Strong; PM2; PP4

Met criteria codes

PM2	✔	It is absent from ethnically diverse control databases, including gnomAD/ExAC, 1000 Genomes, and ESP (PM2).
PVS1_Strong	✔	The c.1315+1G>T variant in PAH is a canonical splice-site variant predicted to lead to skipping of exon 13 (PVS1_Strong). Exon 13 encodes 15 amino acids + stop codon = 3.3% of PAH protein length. Along with Exon 12, Exon 13 forms the oligomerization domain (residues 411–452), which is responsible for the dimerization and tetramerization of the enzyme, important for regulation of PAH activity (e.g., positive cooperativity by the substrate, L-Phe, and decreasing PAH activity at low L-Phe concentration) (see PMID: 23457044; PMID: 22005392). Exon 13 contains the non-truncating Likely Pathogenic p.A447P (Likely Pathogenic by ClinGen PAH VCEP) and Pathogenic p.A447D variants (Likely Pathogenic by ClinGen PAH VCEP; Pathogenic in ClinVar (ID 102595; 4 submitters, 2 stars). Thus PVS1_Strong will be applied for variants resulting in deletion of this exon.
PP4	✔	The variant has been previously reported in one Catalonian PKU case (as determined by abnormal blood Phe levels), without additional information (PMID: 10598814) (PP4). It is also noted in ClinVar (ID 370074), where it is classified as Likely Pathogenic by one lab, with this published reported cited.

Curation History

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