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_000277.2(PAH):c.1315+1G>A

Version: 1.0

CA251522

576 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: a0e84b26-03d1-42c0-a937-859d45d287e0
Approved on: 2018-08-05
Published on: 2019-08-17

HGVS expressions

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

Pathogenic

Met criteria codes 4

PS3 PVS1 PP4_Moderate PM3

Evidence Links 4

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: PS3: abolishes PAH activity due to protein instability (PMID:17935162; PMID:3615198); PM3: (PMID:24941924); PP4_Moderate: Reported in Galician PAH deficiency population. BH4 deficiency ruled out. (PMID:23500595); PVS1:

Canonical +1 splice site. 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: (PS3, PM3, PP4_Moderate, PVS1).

Met criteria codes

PS3	✔	abolishes PAH activity due to protein instability Identified IVS12+1G>A (described as GT>AT in intron 12) in a PAH cDNA clone isolated from a cDNA library generated from a phenylketonuria (PKU) carrier individual. Expression of this cDNA clone into COS cells results in the deletion of exon 12 and abolishes PAH activity due to protein instability. PubMed:3615198 Reported IVS12+1G>A in a study of 315 patients from the BIOPKUdb. Variant was listed as a BH4-nonresponsive mutation with no residual PAH enzyme activity. PubMed:17935162
PVS1	✔	Canonical +1 splice site
PP4_Moderate	✔	Reported in Galician PAH deficiency population. BH4 deficiency ruled out. Reported IVS12+1G>A in a Galician population of hyperphenylalaninemia (HPA) patients with a frequency of 1%. Variant was listed in Table 1 associated with <1% residual PAH enzyme activity compared to normal; BH4 deficiency ruled out PubMed:23500595
PM3	✔	In trans with a LOF allele; Table 2 Observed phenotype_Classic PKU PubMed:24941924

Curation History

Showing 1 to 1 of 1 rows