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.977G>A (p.Trp326Ter)

Version: 1.0

CA229887

579 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 60780d1e-de33-4990-88af-58b2b28a5fdd
Approved on: 2020/4/13
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HGVS expressions

NM_000277.2(PAH):c.977G>A (p.Trp326Ter)
NM_000277.2:c.977G>A
NC_000012.12:g.102844424C>T
CM000674.2:g.102844424C>T
NC_000012.11:g.103238202C>T
CM000674.1:g.103238202C>T
NC_000012.10:g.101762332C>T
NG_008690.1:g.78179G>A
NG_008690.2:g.118987G>A
ENST00000553106.6:c.977G>A
ENST00000307000.7:c.962G>A
ENST00000549247.6:n.736G>A
ENST00000551114.2:n.639G>A
ENST00000553106.5:c.977G>A
ENST00000635477.1:c.81G>A
ENST00000635528.1:n.492G>A
NM_000277.1:c.977G>A
NM_001354304.1:c.977G>A
NM_000277.3:c.977G>A
NM_001354304.2:c.977G>A

Pathogenic

Met criteria codes 4

PM3_Very Strong | PVS1 | PM2 | PP4_Moderate

Evidence Links 2

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.977G>A (p.Trp326Ter) is a variant in PAH is a null variant (nonsense variant) in a gene where LOF is a known mechanism of disease, leading to premature truncation and NMD (PVS1). It is present at extremely low frequencies in ethnically diverse control databases

(gnomAD AF 0.00000399; PAH PM2 cutoff: <0.0002) (PM2). It has been identified in at least five PKU cases in whom BH4 deficiency was excluded (PP4_Moderate), in four cases in trans with known pathogenic variants (PM3_VeryStrong). It has been identified in at least two Chinese classic PKU cases (PMID: 261600; PMID: 1301927; PMID: 28982351), in trans with the known pathogenic (per PAH VCEP) p.Y356X and p.R243Q variants; as a single heterozygous variant in a Chinese classic PKU case with BH4 deficiency excluded (PMID: 24705691); in trans with the known pathogenic (per PAH VCEP) p.R261Q variant in one Slovak case with classic PKU with BH4 deficiency said to be excluded (PMID: 23764561); one Chinese proband with mild hyperphenylalanemia in trans with c.1197A>T (p.V399V) (PMID: 25456745). It is also listed Pathogenic in ClinVar by three labs (variant ID 579). Classification: Pathogenic Supporting Criteria: PVS1, PM2; PM3_VeryStrong; PP4_Moderate

Met criteria codes

PM3_Very Strong	✔	It has been identified in at least five PKU cases in whom BH4 deficiency was excluded (PP4_Moderate), in four cases in trans with known pathogenic variants (PM3_VeryStrong). It has been identified in at least two Chinese classic PKU cases (PMID: 261600; PMID: 1301927; PMID: 28982351), in trans with the known pathogenic (per PAH VCEP) p.Y356X and p.R243Q variants; as a single heterozygous variant in a Chinese classic PKU case with BH4 deficiency excluded (PMID: 24705691); in trans with the known pathogenic (per PAH VCEP) p.R261Q variant in one Slovak case with classic PKU with BH4 deficiency said to be excluded (PMID: 23764561); one Chinese proband with mild hyperphenylalanemia in trans with c.1197A>T (p.V399V) (PMID: 25456745). It is also listed Pathogenic in ClinVar by three labs (variant ID 579). Single patient with HPA PubMed:25456745
PVS1	✔	Nonsense variant (p.W326X)
PM2	✔	not found in any pop database
PP4_Moderate	✔	It has been identified in at least five PKU cases in whom BH4 deficiency was excluded (PP4_Moderate), in four cases in trans with known pathogenic variants (PM3_VeryStrong). It has been identified in at least two Chinese classic PKU cases (PMID: 261600; PMID: 1301927; PMID: 28982351), in trans with the known pathogenic (per PAH VCEP) p.Y356X and p.R243Q variants; as a single heterozygous variant in a Chinese classic PKU case with BH4 deficiency excluded (PMID: 24705691); in trans with the known pathogenic (per PAH VCEP) p.R261Q variant in one Slovak case with classic PKU with BH4 deficiency said to be excluded (PMID: 23764561); one Chinese proband with mild hyperphenylalanemia in trans with c.1197A>T (p.V399V) (PMID: 25456745). It is also listed Pathogenic in ClinVar by three labs (variant ID 579). BH4 defect excluded PubMed:24705691 BH4 defect excluded PubMed:25456745

Curation History

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