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_000277.3(PAH):c.686dup (p.Asp229fs)

Version: 1.0

CA891843538

576828 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 80f0708e-fa2a-4625-be82-9937dbc9ae51
Approved on: 2023/3/16
Published on: 2023/3/16

HGVS expressions

NM_000277.3:c.686dup
NM_000277.3(PAH):c.686dup (p.Asp229fs)
NC_000012.12:g.102855156dup
CM000674.2:g.102855156dup
NC_000012.11:g.103248934dup
CM000674.1:g.103248934dup
NC_000012.10:g.101773064dup
NG_008690.1:g.67447dup
NG_008690.2:g.108255dup
ENST00000553106.6:c.686dup
ENST00000307000.7:c.671dup
ENST00000549111.5:n.782dup
ENST00000553106.5:c.686dup
NM_000277.1:c.686dup
NM_000277.2:c.686dup
NM_001354304.1:c.686dup
NM_001354304.2:c.686dup

Pathogenic

Met criteria codes 3

PM2 PVS1 PP4

Not Met criteria codes 1

PM3

Evidence Links 0

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specification: *ClinGen PAH Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.686dup (p.Asp229fs) variant in PAH is a frameshift variant predicted to cause termination at amino acid 283 resulting in nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism. It has been detected as homozygous in a patient with classic PKU (PMID: 28915855). This variant is absent in population databases. In summary, this variant meets criteria to be classified as Pathogenic for PAH deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen PAH VCEP: PM2, PP4, PVS1

Met criteria codes

PM2	✔	Absent from controls in gnomAD, ExAC, 1000 Genomes, or ESP
PVS1	✔	This is a frameshift variant with termination predicted at amino acid 283 resulting in NMD. Coding exon number 6 out of 13 coding exons (6 out of total exons)
PP4	✔	Detected in one patient with classic PKU. Neonatal phenylalanine screening levels were >20mg/dl (normal <20mg/dl). (PMID: 28915855)

Not Met criteria codes

PM3	✖	Phase unconfirmed for the homozygous patient (PMID: 28915855)

Curation History

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