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Variant: NM_000277.2(PAH):c.1012G>T (p.Asp338Tyr)

Version: 1.0

CA229269

102468 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 2237dbe2-a983-4dcc-8838-57eb31ccb465
Approved on: 2020/11/9
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HGVS expressions

NM_000277.2(PAH):c.1012G>T (p.Asp338Tyr)
NM_000277.2:c.1012G>T
NC_000012.12:g.102844389C>A
CM000674.2:g.102844389C>A
NC_000012.11:g.103238167C>A
CM000674.1:g.103238167C>A
NC_000012.10:g.101762297C>A
NG_008690.1:g.78214G>T
NG_008690.2:g.119022G>T
ENST00000553106.6:c.1012G>T
ENST00000307000.7:c.997G>T
ENST00000549247.6:n.771G>T
ENST00000551114.2:n.674G>T
ENST00000553106.5:c.1012G>T
ENST00000635477.1:c.116G>T
ENST00000635528.1:n.527G>T
NM_000277.1:c.1012G>T
NM_001354304.1:c.1012G>T
NM_000277.3:c.1012G>T
NM_001354304.2:c.1012G>T

Pathogenic

Met criteria codes 3

PP4_Moderate PM3_Very Strong PM2

Not Met criteria codes 2

PP3 PM5

Evidence Links 3

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.1012G>T (p.Asp338Tyr) variant in PAH has been reported in multiple individuals with PAH deficiency (BH4 deficiency excluded, PMID: 27121329, PMID: 21147011). This variant has an extremely low allele frequency in gnomAD (MAF=0.00002). This variant was detected with multiple pathogenic variants: p.P281L (PMID: 16601866); p.F299C (PMID: 7913581); p.I65T (PMID: 17502162); c.1066-11G>A (PMID: 31623983); p.Arg261*, p.Phe55Leu (PMID: 26655635). Multiple lines of computational evidence do not agree on predicted pathogenicity (Deleterious in SIFT, PolyPhen, Polymorphism in MutationTaster). In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM3_very-strong, PM2, PP4_Moderate.

Met criteria codes

PP4_Moderate	✔	D338Y was found in 3 PKU patients. A defect in the synthesis or regeneration pathways of 6R-BH4 was ruled out by analyzing urinary pterin levels as well as by measuring the dihydropteridine reductase activity. PMID: 27121329, PMID: 21147011, PMID: 7913581 Fifty-five PKU probands contributed DNA. A G->T transversion in codon 338 (D338Y) of exon 10 occurred on one French Canadian chromosome, is on Hp4, and abolishes a HinfI site (fig. 1, middle). PubMed:7913581 588 hyperphenylalaninemic patients were investigated. Assessment included PAH gene and genes of the BH4 synthesis/recycling pathways (PTS and QDPR). D338Y was found in one homozygous PKU patient. PubMed:21147011
PM3_Very Strong	✔	D338Y seen in trans with 2 pathogenic variants in 2 PKU patents (P281L, PMID: 16601866; F299C, PMID: 7913581) and with c.194T>C (p.I65T, P) parental analysis not reported PMID: 17502162; c.1066-11G>A (P), p.G352C (VUS) parental analysis not reported PMID: 31623983; p. [Arg261*]; [Asp338Tyr]; p.[Phe55Leu]; [Asp338Tyr] P/LP parental analysis not reported PMID: 26655635 4.0 pts D338Y seen in trans with P281L (VarID 589, Pathogenic in ClinVar) in 1 patient with mild PKU. All the mutations identified were confirmed by analysing parental DNA. PubMed:16601866 Seen in 1 PKU patient. The mother of the proband carries the D338Y mutation; the paternal mutation is F299C (VarID 613, Pathogenic/LP in ClinVar). PubMed:7913581
PM2	✔	Absent in 1000G, ESP. Extremely low frequency in ExAC (0.00001) and gnomAD (MAF=0.00002)

Not Met criteria codes

PP3	✖	Deleterious in SIFT, PolyPhen, Polymorphism in MutationTaster
PM5	✖	Only variant in this codon in ClinVar

Curation History

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