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Variant: NM_000277.1:c.712A>G

CA16020847

619166 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: b3f081ca-4251-4be7-a9c4-acd5f05fb2e7
Approved on: 2018-12-10
Published on: 2018-12-10

HGVS expressions

NM_000277.1:c.712A>G
NC_000012.12:g.102852945T>C
CM000674.2:g.102852945T>C
NC_000012.11:g.103246723T>C
CM000674.1:g.103246723T>C
NC_000012.10:g.101770853T>C
NG_008690.1:g.69658A>G
NG_008690.2:g.110466A>G
NM_000277.2:c.712A>G
NM_001354304.1:c.712A>G
NM_000277.3:c.712A>G
ENST00000307000.7:c.697A>G
ENST00000549247.6:n.471A>G
ENST00000553106.5:c.712A>G

Likely Pathogenic

Met criteria codes 4

PP4_Moderate PM3 PM2 PP3

Evidence Links 2

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.712A>G (p.Thr238Ala) variant in PAH has been reported in 2 individuals with PKU (BH4 deficiency excluded). (PP4_Moderate; PMID: 23842451, 26503515). This variant is absent in population databases (PM2). This variant was detected with pathogenic variant p.P281L (PM3; PMID: 23842451). Computational evidence support a deleterious effect. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM2, PM3, PP3.

Met criteria codes

PP4_Moderate ✔

			found in 1 Dutch PKU patient (Phe = 549). PMID: 23842451 and Chinese PKU patient (BH4 deficiency assessed) PMID: 26503515
			A total of 796 unrelated patients from 29 separate newborn screening centres of China were enrolled. Biochemical testing data, including plasma phenylalanine (Phe) levels, dihydropteridine reductase activity, urinary biopterin and neopterin ratio, and tetrahydrobiopterin loading, were collected. p.T238A, c.712A>G was detected on 2 alleles. PubMed:26503515 Data were collected from 183 patients who participated in the 48-hour BH4 loading test between November 2009 and December 2010 in six Dutch university medical centres. Only patients above four years of age, requiring a Phe restricted diet, and not pregnant or planning a pregnancy were considered for treatment with BH4. Blood Phe concentrations in dried blood spots were measured by the patients' respective centre laboratory according to standard quantitative methods, with the same method per patient. To calculate the individual mean blood Phe concentration prior to the BH4 introduction, all known values from the year preceding the BH4 loading test were used, with a minimum of four measurements; alternatively, the period was extended to two years or this value was considered missing. T238A was identified in 1 patient with baseline Phe level of 549 PubMed:23842451
PM3		✔	found with P281L (Pathogenic in ClinVar) PMID: 23842451
			Patient genotype: T238A/P281L (VarID 589, Pathogenic in ClinVar) PubMed:23842451
PM2		✔	Absent from ExAC, gnomAD, 1000G, ESP
PP3		✔	Predicted deleterious in SIFT, Polyphen2, mutation taster. REVEL=0.949

Curation History

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