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Variant: NM_000277.2(PAH):c.694C>T (p.Gln232Ter)

Version: 1.0

CA229696

102788 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 58217aed-93e8-4080-b19a-9bfa3cd9dea4
Approved on: 2020/5/31
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HGVS expressions

NM_000277.2:c.694C>T
NM_000277.2(PAH):c.694C>T (p.Gln232Ter)
NC_000012.12:g.102855148G>A
CM000674.2:g.102855148G>A
NC_000012.11:g.103248926G>A
CM000674.1:g.103248926G>A
NC_000012.10:g.101773056G>A
NG_008690.1:g.67455C>T
NG_008690.2:g.108263C>T
ENST00000553106.6:c.694C>T
ENST00000307000.7:c.679C>T
ENST00000549111.5:n.790C>T
ENST00000553106.5:c.694C>T
NM_000277.1:c.694C>T
NM_001354304.1:c.694C>T
NM_000277.3:c.694C>T
NM_001354304.2:c.694C>T

Pathogenic

Met criteria codes 4

PP4 PM3 PM2 PVS1

Evidence Links 2

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.694C>T (p.Gln232Ter) variant in PAH has been reported in multiple individuals with PKU (PP4; PMID: 30050108). This variant has an extremely low allele frequency (MAF=0.00003; PM2). This variant was detected with known pathogenic variant c.442-1G>A (PM3; PMID: 30050108). This is a null variant (nonsense) in exon 6 of 13 (NMD predicted) of PAH, a gene where loss of function is a known mechanism of disease (PVS1). In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PVS1, PM2, PM3, PP4.

Met criteria codes

PP4	✔	c.694C>T detected on 6 alleles in a PKU Chinese cohort. PMID: 30050108 c.694C>T detected on 6 alleles. 796 unrelated patients were enrolled. Biochemical testing data, including plasma phenylalanine levels, dihydropteridine reductase activity, urinary biopterin and neopterin ratio, and tetrahydrobiopterin loading, were collected. PubMed:30050108 The mutational spectrum of the phenylalanine hydroxylase (PAH) gene has been defined for the Chilean phenylketonuria (PKU) population. Mutation analysis was performed using a combined approach of screening for common European and Oriental mutations and DGGE scanning. A total of 16 different mutations have been identified, including Q232X. PubMed:10408782
PM3	✔	Detected with known pathogenic variant c.442-1G>A (PMID: 30050108) Patient genotype: c.442-1G>A (VarID594, P)/p.Q232* PubMed:30050108
PM2	✔	Extremely low frequency in ExAC, gnomAD, PAGE, and ESP. MAF=0.00003.
PVS1	✔	Null variant (nonsense) in exon 6 of 13 (NMD predicted)

Curation History

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