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Variant: NM_000277.3(PAH):c.204A>T (p.Arg68Ser)

Version: 1.0

CA273113

92738 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 6b7ec948-f2f5-4aeb-8fae-b588b8369c3d
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HGVS expressions

NM_000277.3(PAH):c.204A>T (p.Arg68Ser)
NM_000277.3:c.204A>T
NC_000012.12:g.102894883T>A
CM000674.2:g.102894883T>A
NC_000012.11:g.103288661T>A
CM000674.1:g.103288661T>A
NC_000012.10:g.101812791T>A
NG_008690.1:g.27720A>T
NG_008690.2:g.68528A>T
ENST00000553106.6:c.204A>T
ENST00000307000.7:c.189A>T
ENST00000546844.1:c.204A>T
ENST00000548677.2:n.291A>T
ENST00000548928.1:n.126A>T
ENST00000549111.5:n.300A>T
ENST00000550978.6:c.188A>T
ENST00000551337.5:c.204A>T
ENST00000551988.5:n.293A>T
ENST00000553106.5:c.204A>T
ENST00000635500.1:n.172A>T
NM_000277.1:c.204A>T
NM_000277.2:c.204A>T
NM_001354304.1:c.204A>T
NM_001354304.2:c.204A>T

Pathogenic

Met criteria codes 4

PP3 PM3_Very Strong 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.204A>T (p.Arg68Ser) variant in PAH was reported in a Spanish patient with mild/moderate PKU. A defect in the synthesis or regeneration pathways 6R-BH4 was ruled out by analyzing urinary pterin levels and by measuring the dihydropteridine reductase activity (PMID 27121329). It was detected in trans with several pathogenic variants including p.Ala300Ser, p.Asp415Asn, p.Arg158Gln, and c.1315+1G>A (PMID 27121329, 22841515). This variant was found in low frequency in gnomAD (MAF=0.00016) and was predicted deleterious using in silico data. 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, and PP3.

Met criteria codes

PP3	✔	Predicted deleterious in SIFT, PolyPhen2, Mutation Taster, REVEL=0.897
PM3_Very Strong	✔	Detected in trans with several pathogenic variants including p.Ala300Ser, Asp415Asn , Arg158Gln, and c.1315+1G>A. Additionally, found homozygous (p.[Arg68Ser];[Arg68Ser] (n=2))with mild HPA. Segregation analysis was done in PMID 27121329. Segregation analysis was also in PMID 22841515. PubMed:26666653
PM2	✔	extremely low frequency in gnomAD (MAF=0.00016). Present in European (non-Finnish) populations at a frequency of 0.00007 and all populations at a 0.00004 frequency of (ExAC).
PP4_Moderate	✔	Reported in a Spanish patient with mild/moderate PKU. A defect in the synthesis or regeneration pathways 6R-BH4 was ruled out by analyzing urinary pterin levels as well as by measuring the dihydropteridine reductase activity PMID 27121329 PubMed:23764561

Curation History

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