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Variant: NM_000277.3(PAH):c.611A>G (p.Tyr204Cys)

Version: 1.0

CA229653

590 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 533dfef9-f4fd-434d-8d70-23d08956adf3
Approved on: 2021/3/26
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HGVS expressions

NM_000277.3:c.611A>G
NM_000277.3(PAH):c.611A>G (p.Tyr204Cys)
NC_000012.12:g.102855231T>C
CM000674.2:g.102855231T>C
NC_000012.11:g.103249009T>C
CM000674.1:g.103249009T>C
NC_000012.10:g.101773139T>C
NG_008690.1:g.67372A>G
NG_008690.2:g.108180A>G
ENST00000553106.6:c.611A>G
ENST00000307000.7:c.596A>G
ENST00000549111.5:n.707A>G
ENST00000553106.5:c.611A>G
NM_000277.1:c.611A>G
NM_000277.2:c.611A>G
NM_001354304.1:c.611A>G
NM_001354304.2:c.611A>G

Pathogenic

Met criteria codes 4

PP4_Moderate PM2 PM3_Very Strong PP3

Evidence Links 0

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.611A>G (p.Tyr204Cys) variant in PAH has been reported in multiple individuals with Classic PKU and MHP (BH4 deficiency excluded). (PMID: 15503242). This variant has a MAF (0.00016) in gnomAD. This variant creates a fully active, novel 5′ donor splice site which results in an aberrantly spliced mRNA with a 96-nt deletion at the 3′-end of exon 6 PMID: 8990021 (aka Ex6-96A>G). Multiple lines of computational evidence support a deleterious effect. This variant was detected in trans with multiple pathogenic variants including: p.R111* (2); c.442-1G>A; p.R158W; p.L255S; p.P281L; p.K363Nfs*37; p.V399V; p.R408W; p.R241C (2); p.R243Q; p.R261Q (2); p.S349A;

p.R413P; p.A434D (2) (PMID: 26322415). In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM2, PP4_Moderate, PM3_very-strong, PP3.

Met criteria codes

PP4_Moderate	✔	Detected in multiple patients with classical PKU and MHP. Urinary pterin analysis and DHPR assay excluded 6-pyruvoyl- tetrahydropterin synthase (PTPS) deficiencies. PMID: 15503242
PM2	✔	MAF = 0.00016 in gnomAD
PM3_Very Strong	✔	Detected in trans with R111* (2) c.442-1G>A R158W L255S P281L K363Nfs*37 V399V R408W R241C (2) R243Q R261Q (2) S349A R413P A434D (2) PMID: 26322415 >4 points
PP3	✔	Predicted deleterious in SIFT (D), PolyPhen2 (P), Mutation Taster (A), REVEL=0.782

Curation History

Showing 1 to 1 of 1 rows

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