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Variant: NM_000277.1(PAH):c.601C>T (p.His201Tyr)

Version: 1.0

CA229643

102752 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 31fc727e-9400-49e3-9c17-63e7b2fb8748
Approved on: 2019/11/10
Published on: 2020/1/25

HGVS expressions

NM_000277.1(PAH):c.601C>T (p.His201Tyr)
NM_000277.1:c.601C>T
NC_000012.12:g.102855241G>A
CM000674.2:g.102855241G>A
NC_000012.11:g.103249019G>A
CM000674.1:g.103249019G>A
NC_000012.10:g.101773149G>A
NG_008690.1:g.67362C>T
NG_008690.2:g.108170C>T
ENST00000553106.6:c.601C>T
ENST00000307000.7:c.586C>T
ENST00000549111.5:n.697C>T
ENST00000553106.5:c.601C>T
NM_000277.2:c.601C>T
NM_001354304.1:c.601C>T
NM_000277.3:c.601C>T
NM_001354304.2:c.601C>T

Likely Pathogenic

Met criteria codes 3

PM2 PM3_Strong PP4_Moderate

Not Met criteria codes 3

PP3 PM1 PM5

Evidence Links 2

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.601C>T (p.His201Tyr) variant in PAH has been reported in multiple individuals with PAH deficiency (BH4 deficiency excluded). (PP4_Moderate; PMID: 16198137). This variant is at a ow frequency in controls (3.964e-6 in gnomAD; PM2). This variant was detected with known pathogenic variants IVS10nt546 (PMID: 9521426) and R158Q (PMID: 16198137; PM3_strong). Computational evidence is conflicting.

In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM2, PM3_strong.

Met criteria codes

PM2	✔	3.964e-6 in gnomAD; Low frequency in control population database
PM3_Strong	✔	In trans with IVS10nt546 (PMID: 9521426) and R158Q (PMID: 16198137), Both Pathogenic in ClinVar Patient 44 Genotype H201Y/R158Q (VarID 587, Pathogenic in ClinVar) PubMed:16198137 Patient F99: Genotype H201Y/IVS10nt546 (VarID:607, Pathogenic); Phenotype non-PKU HPA. PubMed:9521426
PP4_Moderate	✔	Seen in 2 patient with HPA and BH4 defects were ruled out (PMID: 16198137) All patients born in Lombardy (Italy) between January 2000 and December 2004, and affected by HPA (107 patients) were classiffed after BH4 loading test, analysis of urinary pterins, and determination of DHPR activity in blood, and investigated for BH4-responsiveness. Patient 44 Genotype H201Y/R158Q; Phenotype MHP (plasma phe 120–360 □umol/L). PubMed:16198137 Patient F99: Genotype H201Y/IVS10nt546; Phenotype non-PKU HPA. The occurrence of defects involving homeostasis or synthesis of the phenylalanine hydroxylase cofactor (BH4) was ruled out by dosing the urinary pterins as well as by identification of mutations in the PAH gene. PubMed:9521426

Not Met criteria codes

PP3	✖	Conflicting predictions: Tolerated in SIFT, Damaging in MutationTaster
PM1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✖	p.His201Arg (VarID 102753) Clinical significance not provided in ClinVar

Curation History

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