The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000277.1(PAH):c.782G>A (p.Arg261Gln)

Version: 1.0

CA251528

582 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 9e4b6d0e-936a-4cbe-a237-e66213b685d4
Approved on: 2018-08-13
Published on: 2019-04-05

HGVS expressions

NM_000277.1:c.782G>A
NM_000277.1(PAH):c.782G>A (p.Arg261Gln)
NC_000012.12:g.102852875C>T
CM000674.2:g.102852875C>T
NC_000012.11:g.103246653C>T
CM000674.1:g.103246653C>T
NC_000012.10:g.101770783C>T
NG_008690.1:g.69728G>A
NG_008690.2:g.110536G>A
NM_000277.2:c.782G>A
NM_001354304.1:c.782G>A
NM_000277.3:c.782G>A
ENST00000307000.7:c.767G>A
ENST00000549247.6:n.541G>A
ENST00000553106.5:c.782G>A

Pathogenic

Met criteria codes 4

PP4_Moderate | PM3_Very Strong | PP3 | PS3

Not Met criteria codes 1

PM2

Evidence Links 3

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

PAH-specific ACMG/AMP criteria applied: PP3: tools predict damaging; PS3: 15.5-30% activity (PMID:2014036; PMID:25596310); PM3_VeryStrong: L48S, R408W, S349P, R243X (PMID:25596310; PMID:17935162); PP4_Moderate: (PMID:25596310). In summary this variant meets criteria to be classified as pathogenic for phenylketonuria in an autosomal recessive manner based on the ACMG/AMP criteria applied as specified by the PAH Expert Panel: (PP3, PS3, PM3_VeryStrong, PP4_Moderate).

Met criteria codes

PP4_Moderate	✔	Table 2_Residual PAH activity and optimal enzymatic working range of PAH proteins_R261Q in trans with L48S or R408W known PATH var; or R261 homo pt also seen in this table with increased Phe level, reduced residual enzyme activity; BH4 level levels showed in this table as well. (this paper provided us with PM3, PS2 and PP4_M) PubMed:25596310
PM3_Very Strong	✔	L48S, R408W, S349P, R243X Table 2_Residual PAH activity and optimal enzymatic working range of PAH proteins_R261Q in trans with L48S or R408W known PATH var; or R261 homo pt also seen in this table with increased Phe level, reduced residual enzyme activity. PubMed:25596310 The BIOPKUdb comprises genotypes information from 315 BH4-responsive patients. Patient genotypes mentioned: p.R261Q/ p.L48S, p.R261Q/p.R53H (VarID 102601, VUS/LB); p.R261Q/ p.S349P (VarID 615 P/LP), p.R261Q/p.R243X (VarID 588, P). PubMed:17935162
PP3	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3	✔	15.5-30% activity PAH enzyme activity of a patients with phenylketonuria was 15.5% activity of WT (Table S4). This paper also reports a high number of homozygous and compound heterozygous patients PubMed:25596310 R261Q mutant PAH activity measurement resulted in a 30% of the WT activity (Table 1) PubMed:2014036

Not Met criteria codes

PM2	✖	gnomAD MAF 0.00039

Curation History

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