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Variant: NM_000277.1(PAH):c.-4165_-407del3759

Version: 1.0

CA281520

638 (ClinVar)

Gene: PAH
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 00b68297-2f63-4952-bc0d-108c6dfecefb
Approved on: 2020/8/28
Published on: 2021/2/11

HGVS expressions

NM_000277.1:c.-4165_-407del3759
NM_000277.1:c.-4165_-407del
NM_000277.1(PAH):c.-4165_-407del3759
NC_000012.12:g.102917538_102921296del
CM000674.2:g.102917538_102921296del
NC_000012.11:g.103311316_103315074del
CM000674.1:g.103311316_103315074del
NC_000012.10:g.101835446_101839204del
NG_008690.1:g.1308_5066del
NG_008690.2:g.42115_45873del
ENST00000546708.5:n.492+2277_493-313del
ENST00000546844.1:c.-95-4071_-95-313del
ENST00000547319.1:n.217-4071_217-313del
ENST00000551337.5:c.-95-4071_-95-313del
ENST00000635500.1:n.29-8398_29-4640del
NM_001354304.1:c.-95-4071_-95-313del
NM_001354304.2:c.-95-4071_-95-313del

Likely Pathogenic

Met criteria codes 4

PP4 PM2 PM3_Strong PS3_Supporting

Evidence Links 2

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.-4165_-407del3759 deletion in PAH has been reported in 3 unrelated individuals/families with PAH deficiency where it was designated as -4173_-407del. (PMID: 11935335). The -4173_-407del nomenclature was based on the translation initiation site, and corresponds to c.-4165_-407del3759 (based on transcription initiation site). This deletion is absent from gnomAD genomes with good coverage. This variant was detected with pathogenic variants: p.R408Q in 2 unrelated patients; p.E286K in 2 patients (pathogenic by PAH VCEP); and p.E76G in 1 patient (PMID: 24401910). Functional evidence suggests that it diminishes PAH gene expression (retained only 1% of the wild-

type CAT activity, PMID: 11935335). In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4, PM2, PM3_strong, PS3_supporting.

Met criteria codes

PP4 ✔

Detected in a patient with nonPKU HPA. The mutation was designated as –4173_-407del to conform with the nomenclature system for human gene mutations (Antonarakis et al. 1998). PMID: 11935335 BH4 deficiency has been ruled out, but method not reported. (PMID: 24401910)

We identified a patient with nonPKU HPA in family W. Classification of PAH deficiency was assigned on the basis of pretreatment phenylalanine levels in blood (Guldberg et al. 1998). A novel 5.1-kb band appeared in the DNA of the proband (Fig.2A, lane P) and his mother (lane M), in addition to the expected 8.8-kb fragment of the normal control (lane N) and the proband's father (lane F). This result suggested the presence of a 3.7-kb deletion in the maternal allele. DNA sequence analysis of phagemid showed that the 5.1-kb mutant fragment carried a 3767-bp deletion of the sequence nt 4020–nt 254 upstream of the RNA initiation site of the PAH gene (Fig. 2B). This sequence corresponded to nt 4173–nt 407 upstream of the PAH initiation codon. The mutation was designated as –4173_-407del to conform with the nomenclature system for human gene mutations (Antonarakis et al. 1998). PubMed:11935335
-4173_-407del detected on 5 chromosomes. BH4 deficiency has been ruled out in these patients. PubMed:24401910

PM2 ✔

absent from gnomAD (genome coverage > 31,000)

PM3_Strong ✔

Detected in trans with E76G (VarID 639, P/LP). Confirmed with parental testing PMID: 11935335. Compound heterozygous with R408Q (VarID 612, P) in 2 unrelated patients. and E286K P by PAH VCEP (2 patients). Parental testing not reported. PMID: 24401910 3 points

The parenthood of the proband was confirmed by DNA fingerprinting. By linkage analysis to the c.1155G/C (L385L) polymorphic marker, the c.227A→G substitution was deduced to be inherited from the father. Thus, the E76G mutation was most likely a de novo mutation that had occurred during spermatogenesis. In addition to proband BF of family W, probands of two other families, X and AU, were also found to carry this deletion and were both compound heterozygote with the other allele carrying the R408Q mutation. PubMed:11935335
5: −4173_−407del+E286K (2 patients). 11:−4173_−407del+E76G (likely same patient as Chen 2002). 14:−4173_−407del+R408Q (2 patients, likely same patients as Chen 2002). PubMed:24401910

PS3_Supporting ✔

The –4173_-407del mutation diminishes PAH gene expression. The –4173_-407del mutation (construct C) retained only 1% of the wild-type CAT activity, compared between constructs carrying the basic PAH promoter (construct A) and the 5′ 9-kb PAH sequence (construct B), the –4173_-407del mutation (construct C) or the deletion of the liver-specific enhancer (construct D). PMID: 11935335

The –4173_-407del mutation diminishes PAH gene expression. CAT activities were compared between constructs carrying the basic PAH promoter (Fig. 6, construct A) and the 5′ 9-kb PAH sequence (construct B) and its derivatives, including one with the –4173_-407del mutation (construct C) or the deletion of the liver-specific enhancer (construct D). Furthermore, the –4173_-407del mutation (construct C) retained only 1% of the wild-type CAT activity suggesting that, in addition to the liver-specific enhancer, there are other cis-elements that lie within the deletion and that participate in the regulation of PAH gene expression. PubMed:11935335

Curation History

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