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_000277.2(PAH):c.441+6T>C

Version: 1.0

CA229549

102675 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: f2b9b95a-925c-41bd-8b84-3526e33dfd4c
Approved on: 2020-07-02
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HGVS expressions

NM_000277.2:c.441+6T>C
NM_000277.2(PAH):c.441+6T>C
NC_000012.12:g.102877456A>G
CM000674.2:g.102877456A>G
NC_000012.11:g.103271234A>G
CM000674.1:g.103271234A>G
NC_000012.10:g.101795364A>G
NG_008690.1:g.45147T>C
NG_008690.2:g.85955T>C
ENST00000553106.6:c.441+6T>C
ENST00000307000.7:c.426+6T>C
ENST00000549111.5:n.537+6T>C
ENST00000550978.6:c.431T>C
ENST00000551988.5:n.530+6T>C
ENST00000553106.5:c.441+6T>C
NM_000277.1:c.441+6T>C
NM_001354304.1:c.441+6T>C
NM_000277.3:c.441+6T>C
NM_001354304.2:c.441+6T>C

Uncertain Significance

Met criteria codes 3

PP3 PM2 PP4_Moderate

Not Met criteria codes 1

PM3

Evidence Links 1

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.441+6T>C variant in PAH has been reported before in the homozygous state in a patient with PKU and BH4 deficiency excluded (PMID: 21147011). It is absent in population databases. Multiple lines of computational evidence support a deleterious effect (MaxENT,

Splice AI, dbsSNV Ada, and RF). In summary, this variant meets criteria to be classified as uncertain significance for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM2, PP3.

Met criteria codes

PP3	✔	MaxENT predicts -54.51% variation at WT Donor site; Splice AI=0.76, splice altering; dbsSNV Ada=0.94, deleterious; RF=0.69, deleterious
PM2	✔	Absent from ExAC, gnomAD, 1000G, ESP
PP4_Moderate	✔	IVS4+6C>T is seen in PKU patients. BH4 deficiency was excluded: Assessment included PAH gene and genes of the BH4 synthesis/recycling pathways (PTS and QDPR) PMID: 21147011 588 hyperphenylalaninemic patients were investigated. Assessment included PAH gene and genes of the BH4 synthesis/recycling pathways (PTS and QDPR). IVS4+6T>C was seen in 1 patient in the homozygous state. PubMed:21147011

Not Met criteria codes

PM3	✖	IVS4+6C>T seen in the homozygous state, parental confirmation not reported PMID: 21147011

Curation History

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