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Variant: NM_000277.3(PAH):c.969+1G>A

Version: 1.0

CA229878

102914 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 340b253a-4f3c-45ed-aef4-8e02574c8109
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HGVS expressions

NM_000277.3:c.969+1G>A
NM_000277.3(PAH):c.969+1G>A
NC_000012.12:g.102846894C>T
CM000674.2:g.102846894C>T
NC_000012.11:g.103240672C>T
CM000674.1:g.103240672C>T
NC_000012.10:g.101764802C>T
NG_008690.1:g.75709G>A
NG_008690.2:g.116517G>A
ENST00000553106.6:c.969+1G>A
ENST00000307000.7:c.954+1G>A
ENST00000549247.6:n.728+1G>A
ENST00000551114.2:n.631+1G>A
ENST00000553106.5:c.969+1G>A
ENST00000635477.1:c.74-2463G>A
ENST00000635528.1:n.484+1G>A
NM_000277.1:c.969+1G>A
NM_000277.2:c.969+1G>A
NM_001354304.1:c.969+1G>A
NM_001354304.2:c.969+1G>A

Likely Pathogenic

Met criteria codes 4

PVS1_Strong PM3_Supporting PM2 PP4

Evidence Links 0

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The PAH variant c.969+1G>A (IVS9+1G>A) is a null variant (donor site) located in exon number 9 of the PAH gene. Loss of function in the PAH gene is a known mechanism of disease. Four null variants in exon 9 of the PAH gene have been reported. This variant is predicted to

alter a region that is critical to protein function (13 pathogenic non-nonsense variants in the skipped exon have been reported). Exon skipping is not predicted to disrupt the reading frame. According to TraP in silico splicing prediction, this alteration is probably damaging (TraP score 0.968). HSF (-32.06% variation) and MaxEnt (-86.2% variation) agree that this alteration of the WT donor site most probably affects splicing. The PAH variant c.969+1G>A (IVS9+1G>A) was reported with the PAH pathogenic variant c.1222C>T (p.Arg408Trp) (ClinVar ID: 577) in a European patient with classical PKU (serum Phe levels above 1200µmol/L). Cofactor deficiency was excluded by the BH4 test (PMID: 10679941) and in a patient from Iran with classical PKU (serum Phe levels above 1200µmol/L) (PMID: 26413448). This variant is absent in the gnomAD, ExAC, and PAGE population databases. In summary, this variant meets the criteria to be classified as likely pathogenic. PAH-specific ACMG/AMP criteria applied: PM2, PM3_Supporting, PP4, and PVS1_Strong.

Met criteria codes

PVS1_Strong	✔	The PAH variant c.969+1G>A (IVS9+1G>A) is a null variant (donor site) located in exon number 9 of the PAH gene. Loss of function in the PAH gene is a known mechanism of disease. Four null variants in exon 9 of the PAH gene have been reported. This variant is predicted to alter a region that is critical to protein function (13 pathogenic non-nonsense variants in the skipped exon have been reported). Exon skipping is not predicted to disrupt the reading frame. According to TraP in silico splicing prediction, this alteration is probably damaging (TraP score 0.968). HSF (-32.06% variation) and MaxEnt (-86.2% variation) agree that this alteration of the WT donor site most probably affects splicing. Exon 9 forms part of the PAH catalytic domain (which spans residues 143-410) and includes the Ser310 residue, which along with the Arg408 residue forms a hydrogen-bonding network that anchors the oligomerization and catalytic domains of PAH, supporting tetramerization; in addition, Arg408 forms hydrogen bonds with the carbonyl oxygens of the (exon 9) Leu308 and Leu311 residues (PMID: 18538294). Exon 9 also contains residues Ala313, Pro314, Asp315, and Tyr317, which along with Arg252 form a network which is key for active site spatial orientation (PMID: 18538294). It contains recurrent Pathogenic (per ClinGen PAH panel) non-truncating mutations such as c.916A>G (p.Ile306Val), c.926C>T (p.Ala309Val), and c.940C>T (p.Pro314Ser) (see PMID: 24882081; PMID: 23457044; PMID: 22005392), which result in reduced activity versus wild-type enzyme (<30%). Thus, loss of exon 9 is expected to substantially diminish PAH activity. Therefore, PVS1_Strong will be applied if Exon 9 is lost.
PM3_Supporting	✔	The PAH variant c.969+1G>A (IVS9+1G>A) was reported with the PAH pathogenic variant c.1222C>T (p.Arg408Trp) (ClinVar ID: 577) in a European patient with classical PKU (serum Phe levels above 1200µmol/L). Cofactor deficiency was excluded by the BH4 test PM3 Points: 1*0.5= 0.5 (PMID: 10679941)
PM2	✔	This variant is absent in the gnomAD, ExAC , and PAGE population databases.
PP4	✔	The PAH variant c.969+1G>A (IVS9+1G>A) was reported in two patients with classical PKU (serum Phe levels >1200µmol/L). One patient was from Europe (PMID: 10679941), and the other patient was from Iran (PMID: 26413448).

Curation History

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