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Variant: NM_000284.4(PDHA1):c.910C>T (p.Arg304Ter)

Version: 1.0

CA321113

214935 (ClinVar)

Gene: PDHA1 (HGNC:5160)
Condition: pyruvate dehydrogenase deficiency (MONDO:0019169)
Inheritance Mode: X-linked inheritance
UUID: c64dd2fc-6007-48b6-9877-33bf2b72f75e
Approved on: 2021/4/2
Published on: 2021/5/6

HGVS expressions

NM_000284.4:c.910C>T
NM_000284.4(PDHA1):c.910C>T (p.Arg304Ter)
NC_000023.11:g.19358926C>T
CM000685.2:g.19358926C>T
NC_000023.10:g.19377044C>T
CM000685.1:g.19377044C>T
NC_000023.9:g.19286965C>T
NG_016781.1:g.20034C>T
NG_021184.1:g.161336G>A
ENST00000355808.10:c.931C>T
ENST00000379805.4:c.*602C>T
ENST00000417819.6:c.994C>T
ENST00000423505.6:c.1024C>T
ENST00000481733.2:n.705C>T
ENST00000696704.1:c.*242C>T
ENST00000696705.1:c.*365C>T
ENST00000422285.7:c.910C>T
ENST00000379804.1:c.67C>T
ENST00000379806.9:c.1024C>T
ENST00000422285.6:c.910C>T
ENST00000478795.1:n.349C>T
ENST00000481733.1:n.338C>T
ENST00000540249.5:c.817C>T
ENST00000545074.5:c.931C>T
NM_000284.3:c.910C>T
NM_001173454.1:c.1024C>T
NM_001173455.1:c.931C>T
NM_001173456.1:c.817C>T
NM_001173454.2:c.1024C>T
NM_001173455.2:c.931C>T
NM_001173456.2:c.817C>T

Pathogenic

Met criteria codes 4

PM6_Supporting PP4 PM2 PVS1

Expert Panel

Mitochondrial Diseases VCEP

Not Met criteria codes 7

PM4 BA1 BS2 BS1 PS1 PS2 BP5

Evidence Links 0

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Mitochondrial Diseases VCEP

The c.910C>T; p. R304X variant in the PDHA1 gene is a nonsense mutation resulting in truncation >50bp upstream of the last exon-exon junction in PDHA1 and is predicted to undergo nonsense mediated decay (PVS1). While this mutation occurs in a hotspot domain (aa position R304, phosphorylation loop region), it is predicted to undergo nonsense mediated decay so PM1 was not scored. This variant is absent from population databases (PM2). This variant has been reported once in the literature in an 8-day old patient with neonatal lactic acidosis, microcephaly, hypotonia and psychomotor delay (PMID: 21914562). The variant was not seen in patient's mother, but maternity was not confirmed (PM6_supporting). Blood pyruvate was significantly elevated at 0.84mM with a lactate/pyruvate ratio of 19, which the PDHA1 Curation Expert Panel agreed was supportive of pathogenicity (PP4). In summary, this variant meets criteria to be classified as a pathogenic of PDHA1- related pyruvate dehydrogenase deficiency in an X-linked manner. PDHA1-specific ACMG/AMP criteria applied: (PVS1, PM2, PM6_supporting, PP4). This was reviewed with the PDHA1 expert panel on 2/16/2021 and approved on 03/10/2021.

Met criteria codes

PM6_Supporting	✔	PMID: 21914562 = 0.5 points (patient AF8). De novo per report in this article. However, neither SNP analysis nor exome sequencing were performed to confirm maternity.
PP4	✔	In PMID: 21914562, patient AF8's serum pyruvate was reportedly 0.84 mM with a lactate of 16 mM
PM2	✔	Absent from gnomAD query date 2/15/2021
PVS1	✔	Located in exon 10/11, several downstream variants are listed as pathogenic in ClinVar. This variant is greater than 50bp upstream of last exon to exon junction per LOVD database

Not Met criteria codes

PM4	✖	This is not an in-frame deletion/insertion, but a nonsense mutation so PM4 is not applicable
BA1	✖	Absent from gnomAD query date 2/15/2021
BS2	✖	Not reported in gnomAD, query date 2/15/2021
BS1	✖	Absent from gnomad query date 2/15/2021
PS1	✖	There are no other mutations at aa position p.R304 in ClinVar that have been evaluated by the mitochondrial disease expert panel.

PS2		✖	No de novo cases reported to date with maternity and paternity confirmed through either SNP analysis or trio exome
BP5		✖	No such case found

Curation History

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