

Variant: *NM_000284.4(PDHA1):c.506C>T (p.Ala169Val)*

Version: 1.0

CA323959 [↗](#)

214941 (ClinVar) [↗](#)

Gene: PDHA1 ([HGNC:5160](#))

Condition: pyruvate dehydrogenase deficiency ([MONDO:0019169](#))

Inheritance Mode: X-linked inheritance

UUID: dc5261dd-3db5-4b9d-a01b-0c4006234082

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HGVS expressions

NM_000284.4:c.506C>T

NM_000284.4(PDHA1):c.506C>T (p.Ala169Val)

NC_000023.11:g.19353169C>T

CM000685.2:g.19353169C>T

NC_000023.10:g.19371287C>T

CM000685.1:g.19371287C>T

NC_000023.9:g.19281208C>T

NG_016781.1:g.14277C>T

ENST00000355808.10:c.527C>T

ENST00000379805.4:c.506C>T

ENST00000417819.6:c.590C>T

ENST00000423505.6:c.620C>T

ENST00000696704.1:c.418+1762C>T

ENST00000696705.1:c.419-1322C>T

ENST00000422285.7:c.506C>T

ENST00000355808.9:c.527C>T

ENST00000379805.3:c.506C>T

ENST00000379806.9:c.620C>T

ENST00000422285.6:c.506C>T

ENST00000479146.1:n.341C>T

ENST00000540249.5:c.506C>T

ENST00000545074.5:c.527C>T

NM_000284.3:c.506C>T

NM_001173454.1:c.620C>T

NM_001173455.1:c.527C>T

NM_001173456.1:c.506C>T

NM_001173454.2:c.620C>T

NM_001173455.2:c.527C>T

NM_001173456.2:c.506C>T

Pathogenic

Met criteria codes **5**

PS2 PP3 PP4 PM2 PM1

Not Met criteria codes **5**

BS1 BS2 PS1 BA1 PM5

Expert Panel

Mitochondrial Diseases VCEP [↗](#)

Criteria Specification Information **!**

Evidence submitted by expert panel

Mitochondrial Diseases VCEP

The c.506C>T variant in the PDHA1 gene is a missense mutation occurring in a hotspot domain (aa position A169, located in α β heterodimer interface (PM1). This variant is absent from population databases (PM2). This variant has been reported in three individuals in the literature with presentations consistent with PDHA1-related disease. These three cases include two assumed de novo cases (PMID: 20002461 and PMID: 21914562), and one maternity confirmed de novo case via exome sequencing in PMID: 31683770 (PS2). PMID: 20002461 Western Blot studies showed reduced E1a, and Imbard et al 2011 PDC studies indicate activity <3rd percentile in fibroblasts (PP4). In silico predictors suggest a deleterious effect (REVEL score - 0.946; PP3). 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: (PM1, PM2, PS2, PP3, PP4). This was reviewed with the PDHA1 expert panel on 4/6/2021 and approved on 4/6/2021.

Met criteria codes

PS2			Utilized ClinGen SVI de novo scoring guidance (phenotype consistent but not highly specific); TOTAL = 2.0 = [0.5 (Patient M-1 in PMID: 20002461) + 0.5 (Patient AF15 in PMID: 21914562)+1.0 (Patient Pt20 in PMID: 31683770); exome sequencing performed to confirm maternity]
PP3			Predicted deleterious (REVEL SCORE 0.946)
PP4			E1a activity decreased in Quintana et al 2010 on Western Blot. PDC activity <3rd percentile in Imbard et al 2011 in fibroblasts
PM2			Absent from gnomAD 4/3/2021
PM1			located in α β heterodimer interface

Not Met criteria codes

BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2			not seen in gnomAD, nor reported in mother's of reported patient's to date
PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PM5

No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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