

Variant: *NM_000284.4(PDHA1):c.214C>T (p.Arg72Cys)*

Version: 1.0

CA320653 [↗](#)

214938 (ClinVar) [↗](#)

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

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

Inheritance Mode: X-linked inheritance

UUID: d5172594-7221-4b8d-a69c-d1e5ea5ad636

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HGVS expressions

NM_000284.4:c.214C>T

NM_000284.4(PDHA1):c.214C>T (p.Arg72Cys)

NC_000023.11:g.19350033C>T

CM000685.2:g.19350033C>T

NC_000023.10:g.19368151C>T

CM000685.1:g.19368151C>T

NC_000023.9:g.19278072C>T

NG_016781.1:g.11141C>T

ENST00000355808.10:c.214C>T

ENST00000379805.4:c.214C>T

ENST00000417819.6:c.298C>T

ENST00000423505.6:c.328C>T

ENST00000696704.1:c.214C>T

ENST00000696705.1:c.214C>T

ENST00000422285.7:c.214C>T

ENST00000355808.9:c.214C>T

ENST00000379805.3:c.214C>T

ENST00000379806.9:c.328C>T

ENST00000417819.5:c.298C>T

ENST00000422285.6:c.214C>T

ENST00000423505.5:c.328C>T

ENST00000492364.1:n.316C>T

ENST00000540249.5:c.214C>T

ENST00000545074.5:c.214C>T

NM_000284.3:c.214C>T

NM_001173454.1:c.328C>T

NM_001173455.1:c.214C>T

NM_001173456.1:c.214C>T

NM_001173454.2:c.328C>T

NM_001173455.2:c.214C>T

NM_001173456.2:c.214C>T

Likely Pathogenic

Met criteria codes **4**

PP3

PP4

PM6

PM2

Expert Panel

Mitochondrial Diseases VCEP [↗](#)

Not Met criteria codes 2

BA1

BS1

Evidence Links 0

Criteria Specification Information !

[Criteria Specifications for this VCEP](#)

Evidence submitted by expert panel

The c.214C>T (p.R72C) variant in PDHA1 has been reported in multiples males with pyruvate dehydrogenase deficiency with phenotypes ranging from childhood onset Leigh syndrome spectrum (PMID: 8664900) to living into adulthood with ataxia, neuropathy, and dystonia (PMID: 21914562). We did not come across any affected female case reports in this extensive literature review. This variant has been reported to be inherited from a healthy mother (PMID: 10679936; case 3-4) and there have been several de novo case reports, as well. Indeed, this variant has been identified as a de novo occurrence (unconfirmed parental relationships) in at least three unrelated individuals with pyruvate dehydrogenase deficiency [PM6; Utilized ClinGen SVI de novo scoring guidance (phenotype consistent but not highly specific); PMID: 10679936, case 3-2; PMID: 10679936, case 3-3; PMID: 21914562, case AM23]. Additionally, this variant has been seen in at least one other individual with documented decreased pyruvate dehydrogenase activity (PP4; Patient 3 in PMID: 15384102 had Leigh syndrome and decreased total PDH complex activity (in native and DCA-activated states) in fibroblast cell line (<3rd percentile of controls). This variant is absent from gnomAD v2.1.1 (PM2). The computational predictor REVEL gives a score of 0.955, which is above the threshold of 0.75, evidence that correlates with impact to PDHA1 function (PP3). In summary, this variant meets criteria to be classified as likely pathogenic for pyruvate dehydrogenase deficiency inherited in an X-linked manner. This classification was approved by the NICHD U24 Mitochondrial Disease Variant Curation Expert Panel on May 20, 2020. PDHA1-specific ACMG/AMP criteria applied: PM2, PM6, PP3, PP4.

Met criteria codes

PP3			The computational predictor REVEL gives a score of 0.955, which is above the threshold of 0.75, evidence that correlates with impact to PDHA1 function.
PP4			This variant has been seen in at least one other individual with documented decreased pyruvate dehydrogenase activity (PP4; Patient 3 in PMID: 15384102 had Leigh syndrome and decreased total PDH complex activity (in native and DCA-activated states) in fibroblast cell line (<3rd percentile of controls) - see Table II.
PM6			This variant has been identified as a de novo occurrence (unconfirmed parental relationships) in at least three unrelated individuals with pyruvate dehydrogenase deficiency - Utilized ClinGen SVI de novo scoring guidance (phenotype consistent but not highly specific); TOTAL 1.5 [0.5 (PMID: 10679936, case 3-2) + 0.5 (PMID: 10679936, case 3-3) + (PMID: 21914562, case AM23)]
PM2			This variant is absent from gnomAD v2.1.1.

Not Met criteria codes

BA1			Absent
BS1			Absent

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