

Variant: *NM\_000284.3(PDHA1):c.1132C>T (p.Arg378Cys)*

Version: 1.0

CA323094 [↗](#)

214936 (ClinVar) [↗](#)

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

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

**Inheritance Mode:** X-linked inheritance

**UUID:** ce28d7f7-3561-4601-9603-7bb8aa198a9e

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### *HGVS expressions*

**NM\_000284.3:c.1132C>T**

**NM\_000284.3(PDHA1):c.1132C>T (p.Arg378Cys)**

NC\_000023.11:g.19359612C>T

CM000685.2:g.19359612C>T

NC\_000023.10:g.19377730C>T

CM000685.1:g.19377730C>T

NC\_000023.9:g.19287651C>T

NG\_016781.1:g.20720C>T

NG\_021184.1:g.160650G>A

ENST00000355808.10:c.1153C>T

ENST00000379805.4:c.\*824C>T

ENST00000417819.6:c.1216C>T

ENST00000423505.6:c.1246C>T

ENST00000481733.2:n.927C>T

ENST00000696704.1:c.\*464C>T

ENST00000696705.1:c.\*587C>T

ENST00000422285.7:c.1132C>T

ENST00000379804.1:c.289C>T

ENST00000379806.9:c.1246C>T

ENST00000422285.6:c.1132C>T

ENST00000478795.1:n.571C>T

ENST00000540249.5:c.1039C>T

ENST00000545074.5:c.1153C>T

NM\_001173454.1:c.1246C>T

NM\_001173455.1:c.1153C>T

NM\_001173456.1:c.1039C>T

NM\_000284.4:c.1132C>T

NM\_001173454.2:c.1246C>T

NM\_001173455.2:c.1153C>T

NM\_001173456.2:c.1039C>T

**Pathogenic**

Met criteria codes **5**

PM6\_Strong

PP3

PP4

PM2

PM5

Expert Panel

Mitochondrial Diseases VCEP [↗](#)

Criteria Specification Information **!**

Not Met criteria codes 7

PVS1 BS1 PS1 PP1 BA1  
PM1 PM4

[Criteria Specifications for this VCEP](#)

Evidence Links 1

Evidence submitted by expert panel

***Mitochondrial Diseases VCEP***

The c.1132C>T (p.R378C) variant in PDHA1 has been reported in multiples males and females with pyruvate dehydrogenase deficiency and is one of the more common pathogenic variants seen in this cohort (PMID: 22896851). It has been seen in at least three individuals with decreased pyruvate dehydrogenase activity (PP4; Patient 6 in PMID: 8962591; Subject M-7 in PMID: 20002461; Subject 35-2 in PMID: 10679936). This variant has been identified as a de novo occurrence (unconfirmed parental relationships) in at least 4 unrelated individuals with pyruvate dehydrogenase deficiency [PM6\_Strong; utilized ClinGen SVI de novo scoring guidance (phenotype consistent but not highly specific); PMID: 10679936, subject 35-2; PMID: 20002461, subject M-7; PMID: 21914562, subject AM8; PMID: 21914562, subject AF22]. Of note, to our knowledge, there are no reports of this variant being inherited from a healthy mother, however it is important to note that not all cases reported in the literature had mothers who were tested. This variant is absent from gnomAD v2.1.1 (PM2). Another missense variant at this position [c.1133G>A, p.R378H] has been reported in at least six other probands (PM5; PMIDs: 8032855 - 1 case, 7887409 - 2 cases, 9409363 - 3 cases) and is a known pathogenic variant. The computational predictor REVEL gives a score of 0.907, 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 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, PM5, PM6\_strong, PP3, PP4.

**Met criteria codes**

|                                                                                                                                                        |                                                                                     |                                                                                     |                                                                                                                                                                                                                                                         |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PM6_Strong                                                                                                                                             |  |  | Utilized ClinGen SVI de novo scoring guidance (phenotype consistent but not highly specific); TOTAL 2 = 0.5 (PMID: 10679936, subject 35-2) + 0.5 (PMID: 20002461, subject M-7) + 0.5 (PMID: 21914562, subject AM8) + 0.5 (PMID: 21914562, subject AF22) |
| PP3                                                                                                                                                    |  |  | The computational predictor REVEL gives a score of 0.907, which is above the threshold of 0.75, evidence that correlates with impact to PDHA1 function (PP3).                                                                                           |
| PP4                                                                                                                                                    |  |  | At least three patients with this variant displayed decreased pyruvate dehydrogenase activity (PP4; Patient 6 in PMID: 8962591; Subject M-7 in PMID: 20002461; Subject 35-2 in PMID: 10679936).                                                         |
| Low E1a and E1b on immunoblotting <a href="#">PubMed:8962591</a>  |                                                                                     |                                                                                     |                                                                                                                                                                                                                                                         |
| PM2                                                                                                                                                    |  |  | This variant is absent from gnomAD v2.1.1 (PM2).                                                                                                                                                                                                        |
| PM5                                                                                                                                                    |  |  | Another missense variant [c.1133G>A, p.R378H] has been reported in at least six other probands (PMIDs: 8032855 - 1 case, 7887409 - 2 cases, 9409363 - 3 cases) and is a known pathogenic variant.                                                       |

**Not Met criteria codes**

|             |                                                                                   |                                                                                   |                                                                                                                            |
|-------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|
| <b>PVS1</b> |     |     | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| <b>BS1</b>  |  |  | Absent                                                                                                                     |
| <b>PS1</b>  |  |  | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| <b>PP1</b>  |  |  | No large families reported to date                                                                                         |
| <b>BA1</b>  |  |  | Absent                                                                                                                     |
| <b>PM1</b>  |                                                                                   |  | Not located in domains outlined in specifications                                                                          |
| <b>PM4</b>  |  |  | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |

| Curation History  |  |  |
|----------------------------------------------------------------------------------------------------|--|--|
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| Showing 1 to 1 of 1 rows                                                                           |  |  |
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