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Variant: NM_175914.5(HNF4A):c.498T>A (p.Cys166Ter)

Version: 1.0

CA409106015

520675 (ClinVar)

Gene: HNF4A (HGNC:3172)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Autosomal dominant inheritance
UUID: 526caa15-7563-4817-be67-acdbd940c164
Approved on: 2024/5/9
Published on: 2024/5/9

HGVS expressions

NM_175914.5(HNF4A):c.498T>A (p.Cys166Ter)
NM_175914.5:c.498T>A
NC_000020.11:g.44414578T>A
CM000682.2:g.44414578T>A
NC_000020.10:g.43043218T>A
CM000682.1:g.43043218T>A
NC_000020.9:g.42476632T>A
NG_009818.1:g.63778T>A
ENST00000316673.9:c.498T>A
ENST00000316099.10:c.564T>A
ENST00000619550.5:c.538T>A
ENST00000683148.1:n.540T>A
ENST00000683657.1:n.1688T>A
ENST00000316099.9:c.564T>A
ENST00000316099.8:c.564T>A
ENST00000316673.8:c.498T>A
ENST00000372920.1:c.*331T>A
ENST00000415691.2:c.564T>A
ENST00000443598.6:c.564T>A
ENST00000457232.5:c.498T>A
ENST00000609795.5:c.498T>A
ENST00000619550.4:c.489T>A
NM_000457.4:c.564T>A
NM_001030003.2:c.498T>A
NM_001030004.2:c.498T>A
NM_001258355.1:c.543T>A
NM_001287182.1:c.489T>A
NM_001287183.1:c.489T>A
NM_001287184.1:c.489T>A
NM_175914.4:c.498T>A
NM_178849.2:c.564T>A
NM_178850.2:c.564T>A
NM_001030003.3:c.498T>A
NM_001030004.3:c.498T>A
NM_001258355.2:c.543T>A
NM_001287182.2:c.489T>A
NM_001287184.2:c.489T>A

NM_178849.3:c.564T>A
NM_178850.3:c.564T>A
NM_000457.5:c.564T>A
NM_000457.6:c.564T>A
NM_001287183.2:c.489T>A

Likely Pathogenic

Met criteria codes 2

PVS1 PM2_Supporting

Not Met criteria codes 1

PS4

Evidence Links 0

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for HNF4A Version 2.0.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.498T>A variant in the hepatocyte nuclear factor 4-alpha gene, HNF4A, results in a premature termination at codon 166 (p.(Cys166Ter)) of NM_175914.5. This variant, located in biologically-relevant exon 5 of 10, is predicted to lead to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1; PMID: 23348805). This variant is absent in gnomAD v2.1.1 (PM2_Supporting). It was identified in two unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (ClinVar ID: 520675). In summary, c.498T>A meets the criteria to be classified as likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 2.0.0, approved 10/11/2023): PVS1, PM2_Supporting).

Met criteria codes

PVS1	✔	This variant, located in biologically-relevant exon 5 of 10, is predicted to lead to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1; PMID: 23348805).
PM2_Supporting	✔	This variant is absent in gnomAD v2.1.1 (PM2_Supporting).

Not Met criteria codes

PS4	✖	This variant was identified in two unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (ClinVar ID: 520675).

Curation History

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