

Variant: NM_175914.5(HNF4A):c.778G>T (p.Asp260Tyr)

Version: 1.0

CA409107542 [↗](#)

549555 (ClinVar) [↗](#)

Gene: HNF4A ([HGNC:3172](#))

Condition: monogenic diabetes ([MONDO:0015967](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: 3fb9eb15-e6c5-41be-bbdb-c0a4ec44d279

Approved on: 2024/9/26

Published on: 2024/9/26

HGVS expressions

NM_175914.5:c.778G>T

NM_175914.5(HNF4A):c.778G>T (p.Asp260Tyr)

NC_000020.11:g.44419828G>T

CM000682.2:g.44419828G>T

NC_000020.10:g.43048468G>T

CM000682.1:g.43048468G>T

NC_000020.9:g.42481882G>T

NG_009818.1:g.69028G>T

ENST00000316673.9:c.778G>T

ENST00000316099.10:c.844G>T

ENST00000619550.5:c.818G>T

ENST00000683148.1:n.820G>T

ENST00000683657.1:n.1968G>T

ENST00000316099.9:c.844G>T

ENST00000316099.8:c.844G>T

ENST00000316673.8:c.778G>T

ENST00000372920.1:c.*611G>T

ENST00000415691.2:c.844G>T

ENST00000443598.6:c.844G>T

ENST00000457232.5:c.778G>T

ENST00000609795.5:c.778G>T

ENST00000619550.4:c.769G>T

NM_000457.4:c.844G>T

NM_001030003.2:c.778G>T

NM_001030004.2:c.778G>T

NM_001258355.1:c.823G>T

NM_001287182.1:c.769G>T

NM_001287183.1:c.769G>T

NM_001287184.1:c.769G>T

NM_175914.4:c.778G>T

NM_178849.2:c.844G>T

NM_178850.2:c.844G>T

NM_001030003.3:c.778G>T

NM_001030004.3:c.778G>T

NM_001258355.2:c.823G>T

NM_001287182.2:c.769G>T

NM_001287184.2:c.769G>T

NM_178849.3:c.844G>T
NM_178850.3:c.844G>T
NM_000457.5:c.844G>T
NM_000457.6:c.844G>T
NM_001287183.2:c.769G>T

Likely Pathogenic

Met criteria codes 5

PP4_Moderate PS4_Moderate PP3
PP1_Moderate PM2_Supporting

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.778G>T variant in the hepatocyte nuclear factor 4 alpha gene, HNF4A, causes an amino acid change of aspartate to tyrosine at codon 260 (p.(Asp260Tyr)) of NM_175914.5. This variant is absent from gnomAD v2.1.1 (PM2_Supporting). This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.912, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant was identified in 5 unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4_Moderate; internal lab contributors). This variant was identified in an individual with a clinical history highly specific for HNF4A-monogenic diabetes (MODY probability calculator result >50%, negative genetic testing for HNF1A, and antibody negative) (PP4_Moderate; internal lab contributors). This variant was segregated with diabetes, with three informative meioses in two families (PP1_Moderate; internal lab contributors). In summary, c.778G>T 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): PS4_moderate, PP1_moderate, PP4_moderate, PM2_supporting, PP3.

Met criteria codes

PP4_Moderate			This variant was identified in an individual with a clinical history highly specific for HNF4A-monogenic diabetes (MODY probability calculator result >50%, negative genetic testing for HNF1A, and antibody negative) (PP4_Moderate; internal lab contributors).
PS4_Moderate			This variant was identified in 5 unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4_Moderate; internal lab contributors).
PP3			This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.912, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PP1_Moderate			This variant was segregated with diabetes, with three informative meioses in two families (PP1_Moderate; internal lab contributors).

PM2_Supporting  

This variant is absent from gnomAD v2.1.1 (PM2_Supporting). gnomAD v4.1.0, absent

Curation History

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