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Variant: NM_175914.5(HNF4A):c.3G>A (p.Met1Ile)

Version: 2.0

CA409109842

1299751 (ClinVar)

Gene: HNF4A (HGNC:3172)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Autosomal dominant inheritance
UUID: eb614114-665c-4124-92d9-26b55c1dfc11
Approved on: 2024-04-06
Published on: 2024-04-06

HGVS expressions

NM_175914.5:c.3G>A
NM_175914.5(HNF4A):c.3G>A (p.Met1Ile)
NC_000020.11:g.44355807G>A
CM000682.2:g.44355807G>A
NC_000020.10:g.42984447G>A
CM000682.1:g.42984447G>A
NC_000020.9:g.42417861G>A
NG_009818.1:g.5007G>A
ENST00000316673.9:c.3G>A
ENST00000316673.8:c.3G>A
ENST00000457232.5:c.3G>A
ENST00000609262.5:c.-229G>A
ENST00000609795.5:c.3G>A
ENST00000619550.4:c.-229G>A
NM_001030003.2:c.3G>A
NM_001030004.2:c.3G>A
NM_001287182.1:c.-229G>A
NM_001287183.1:c.-229G>A
NM_001287184.1:c.-229G>A
NM_175914.4:c.3G>A
NM_001030003.3:c.3G>A
NM_001030004.3:c.3G>A
NM_001287182.2:c.-229G>A
NM_001287184.2:c.-229G>A
NM_001287183.2:c.-229G>A

Likely Pathogenic

Met criteria codes 3

PVS1_Strong PP4_Moderate PM2_Supporting

Not Met criteria codes 2

PS4 PP1

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.3G>A variant in the hepatocyte nuclear factor -4 alpha gene, HNF4A, results in a start loss at the initiation codon in NM_175914.4. By altering the start codon of the coding sequence, this variant may cause a truncated or absent protein in a gene in which loss-of-function is an established disease mechanism (PVS1_Strong; PMID: 23348805). In addition, this variant is absent from gnomAD v2.1.1 (PM2_Supporting). This variant was identified in an individual with a clinical history highly specific for HNF4A-MODY (MODY probability calculator result >50%, negative genetic testing for HNF1A, and negative diabetes autoantibodies (PP4_Moderate; PMID: 30977832, internal lab contributors). In summary, c.3G>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_Strong, PM2_Supporting, PP4_Moderate.

Met criteria codes

PVS1_Strong	✓	By altering the start codon of the coding sequence, this variant may cause a truncated or absent protein in a gene in which loss-of-function is an established disease mechanism (PMID: 23348805).
PP4_Moderate	✓	This variant was identified in an individual with a clinical history highly specific for HNF4A-MODY (MODY probability calculator result >50%, negative genetic testing for HNF1A, and negative diabetes autoantibodies (PP4_Moderate; PMID: 30977832, internal lab contributors).
PM2_Supporting	✓	This variant is absent from 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 (PMID: 30977832, 21683639, internal lab contributors).
PP1	✗	This variant segregated with diabetes with two informative meioses in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (PMID: 27236918, internal lab contributors).

Curation History

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