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Variant: NM_175914.5:c.320C>A

Version: 1.0

CA409105356

3068530 (ClinVar)

Gene: HNF4A (HGNC:3172)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Autosomal dominant inheritance
UUID: d4af0091-13af-4c9f-ab4f-a6c94b719c72
Approved on: 2024/4/6
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HGVS expressions

NM_175914.5:c.320C>A
NC_000020.11:g.44413694C>A
CM000682.2:g.44413694C>A
NC_000020.10:g.43042334C>A
CM000682.1:g.43042334C>A
NC_000020.9:g.42475748C>A
NG_009818.1:g.62894C>A
ENST00000316673.9:c.320C>A
ENST00000316099.10:c.386C>A
ENST00000619550.5:c.360C>A
ENST00000683148.1:n.362C>A
ENST00000683657.1:n.1510C>A
ENST00000316099.9:c.386C>A
ENST00000316099.8:c.386C>A
ENST00000316673.8:c.320C>A
ENST00000372920.1:c.*153C>A
ENST00000415691.2:c.386C>A
ENST00000443598.6:c.386C>A
ENST00000457232.5:c.320C>A
ENST00000609795.5:c.320C>A
ENST00000619550.4:c.311C>A
NM_000457.4:c.386C>A
NM_001030003.2:c.320C>A
NM_001030004.2:c.320C>A
NM_001258355.1:c.365C>A
NM_001287182.1:c.311C>A
NM_001287183.1:c.311C>A
NM_001287184.1:c.311C>A
NM_175914.4:c.320C>A
NM_178849.2:c.386C>A
NM_178850.2:c.386C>A
NM_001030003.3:c.320C>A
NM_001030004.3:c.320C>A
NM_001258355.2:c.365C>A
NM_001287182.2:c.311C>A
NM_001287184.2:c.311C>A
NM_178849.3:c.386C>A

NM_178850.3:c.386C>A
NM_000457.5:c.386C>A
NM_000457.6:c.386C>A
NM_001287183.2:c.311C>A

Pathogenic

Met criteria codes 6

PP4_Moderate | PM1_Supporting | PP1_Strong | PM2_Supporting | PS4_Moderate | PP3

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.320C>A variant in the hepatocyte nuclear factor 4-alpha gene, HNF4A, causes an amino acid change of alanine to aspartic acid at codon 107 (p.(Ala107Asp)) of NM_175914.5. This variant failed quality control metrics in gnomAD v2.1.1; however, it was absent in gnomAD genomes v3.1 and additional population databases and therefore PM2_Supporting will be applied per guidance of the ClinGen MDEP (PM2_Supporting). This variant was identified in four unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4_Moderate; internal lab contributors). The variant segregated with diabetes, with at least 7 informative meioses in 3 families (PP1_Strong; internal lab contributors). One of these individuals has a clinical history highly specific for HNF4A-MODY (MODY probability calculator result >50%, negative genetic testing for HNF1A, and negative antibodies) (PP4_Moderate; internal lab contributor). This variant is located within the DNA binding domain (codons 37-113) of HNF4A, which is defined as critical for the protein's function by the ClinGen MDEP (PM1_Supporting). It is also predicted to be deleterious by computational evidence, with a REVEL score of 0.938, which is greater than the MDEP VCEP threshold of 0.70 (PP3). In summary, c.320C>A meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 2.0.0, approved 10/11/23): PP1_Strong, PP4_Moderate, PS4_Moderate, PP3, PM1_Supporting, PM2_Supporting.

Met criteria codes

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 antibodies) (PP4_Moderate; internal lab contributor).
PM1_Supporting	✔	This variant is located within the DNA binding domain (codons 37-113) of HNF4A, which is defined as critical for the protein's function by the ClinGen MDEP (PM1_Supporting).
PP1_Strong	✔	This variant segregated with diabetes, with at least 7 informative meioses in 3 families (PP1_Strong; internal lab contributors).
PM2_Supporting	✔	This variant failed quality control metrics in gnomAD v2.1.1, however it was absent in gnomAD genomes v3.1 and additional population databases and therefore PM2_Supporting will be applied per guidance of the ClinGen MDEP

(PM2_Supporting).

PS4_Moderate		✔	This variant was identified in four 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 0.938, which is greater than the MDEP VCEP threshold of 0.70 (PP3).

Curation History

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