Variant: NM_175914.5(HNF4A):c.763C>T (p.Gln255Ter)

Version: 1.0

CA120182

9210 (ClinVar)

Gene: HNF4A (HGNC:3172)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Autosomal dominant inheritance
UUID: c3388a6a-bb70-404d-9071-818cc4259294
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HGVS expressions

NM_175914.5:c.763C>T
NM_175914.5(HNF4A):c.763C>T (p.Gln255Ter)
NC_000020.11:g.44419813C>T
CM000682.2:g.44419813C>T
NC_000020.10:g.43048453C>T
CM000682.1:g.43048453C>T
NC_000020.9:g.42481867C>T
NG_009818.1:g.69013C>T
ENST00000316673.9:c.763C>T
ENST00000316099.10:c.829C>T
ENST00000619550.5:c.803C>T
ENST00000683148.1:n.805C>T
ENST00000683657.1:n.1953C>T
ENST00000316099.9:c.829C>T
ENST00000316099.8:c.829C>T
ENST00000316673.8:c.763C>T
ENST00000372920.1:c.*596C>T
ENST00000415691.2:c.829C>T
ENST00000443598.6:c.829C>T
ENST00000457232.5:c.763C>T
ENST00000609795.5:c.763C>T
ENST00000619550.4:c.754C>T
NM_000457.4:c.829C>T
NM_001030003.2:c.763C>T
NM_001030004.2:c.763C>T
NM_001258355.1:c.808C>T
NM_001287182.1:c.754C>T
NM_001287183.1:c.754C>T
NM_001287184.1:c.754C>T
NM_175914.4:c.763C>T
NM_178849.2:c.829C>T
NM_178850.2:c.829C>T
NM_001030003.3:c.763C>T
NM_001030004.3:c.763C>T
NM_001258355.2:c.808C>T
NM_001287182.2:c.754C>T
NM_001287184.2:c.754C>T

NM_178849.3:c.829C>T
NM_178850.3:c.829C>T
NM_000457.5:c.829C>T
NM_000457.6:c.829C>T
NM_001287183.2:c.754C>T

Pathogenic

Met criteria codes 5

PP1_Strong PVS1 PS4_Moderate PM2_Supporting PP4

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.763C>T variant in the hepatocyte nuclear factor 4-alpha gene, HNF4A, results in a premature termination at codon 255 (p.(Gln255Ter)) of NM_175914.5. This variant is absent in gnomAD v2.1.1 (PM2_Supporting) and located in biologically relevant exon 7 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 was identified in five unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4_Moderate; PMID: 8945471, 22060211, internal lab contributors). This variant was segregated with diabetes, with at least 33 informative meioses in three families (PP1_Strong; PMID: 8945471, internal lab contributors). This variant was identified in an individual with a clinical history highly specific for HNF4A-MODY (MODY probability calculator result >50% and, negative genetic testing for HNF1A) (PP4; internal lab contributors). In summary, c.763C>T 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 10/11/2023): PVS1, PS4_moderate, PP1_strong, PP4, PM2_Supporting.

Met criteria codes

PP1_Strong	✔	This variant was segregated with diabetes, with at least 33 informative meioses in three families (PP1_Strong; PMID: 8945471, internal lab contributors).
PVS1	✔	This variant, located in biologically-relevant exon 7 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).
PS4_Moderate	✔	This variant was identified in five unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4_Moderate; PMID: 8945471, 22060211, internal lab contributors).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting). gnomAD v4.1.0, absent
PP4	✔	

This variant was identified in an individual with a clinical history highly specific for HNF4A-MODY (MODY probability calculator result >50% and, negative genetic testing for HNF1A) (PP4; internal lab contributors).

Curation History

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