The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_175914.5(HNF4A):c.787G>C (p.Glu263Gln)

Version: 1.0

CA409107565

1700660 (ClinVar)

Gene: HNF4A (HGNC:3172)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Autosomal dominant inheritance
UUID: 916d59d1-a541-4381-acd4-90405f706697
Approved on: 2023/5/27
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HGVS expressions

NM_175914.5:c.787G>C
NM_175914.5(HNF4A):c.787G>C (p.Glu263Gln)
NC_000020.11:g.44419837G>C
CM000682.2:g.44419837G>C
NC_000020.10:g.43048477G>C
CM000682.1:g.43048477G>C
NC_000020.9:g.42481891G>C
NG_009818.1:g.69037G>C
ENST00000316673.9:c.787G>C
ENST00000316099.10:c.853G>C
ENST00000619550.5:c.827G>C
ENST00000683148.1:n.829G>C
ENST00000683657.1:n.1977G>C
ENST00000316099.9:c.853G>C
ENST00000316099.8:c.853G>C
ENST00000316673.8:c.787G>C
ENST00000372920.1:c.*620G>C
ENST00000415691.2:c.853G>C
ENST00000443598.6:c.853G>C
ENST00000457232.5:c.787G>C
ENST00000609795.5:c.787G>C
ENST00000619550.4:c.778G>C
NM_000457.4:c.853G>C
NM_001030003.2:c.787G>C
NM_001030004.2:c.787G>C
NM_001258355.1:c.832G>C
NM_001287182.1:c.778G>C
NM_001287183.1:c.778G>C
NM_001287184.1:c.778G>C
NM_175914.4:c.787G>C
NM_178849.2:c.853G>C
NM_178850.2:c.853G>C
NM_001030003.3:c.787G>C
NM_001030004.3:c.787G>C
NM_001258355.2:c.832G>C
NM_001287182.2:c.778G>C
NM_001287184.2:c.778G>C

NM_178849.3:c.853G>C
NM_178850.3:c.853G>C
NM_000457.5:c.853G>C
NM_000457.6:c.853G>C
NM_001287183.2:c.778G>C

Likely Pathogenic

Met criteria codes 5

PP1_Strong PS3_Supporting PM2_Supporting PP3 PP4_Moderate

Not Met criteria codes 3

PM1 PM5 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 1.0.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.787G>C variant in the HNF4A gene causes an amino acid change of glutamic acid to glutamine at codon 263 (p.Glu263Gln) of NM_175914.5. Functional studies demonstrated the p.Glu276Gln protein has transactivation below 60% of wildtype, indicating that this variant impacts protein function (PS3_Supporting; PMIDs: 30325586, 30191603). This variant is outside of the region defined as critical for the protein's function by the ClinGen MDEP (codons 37-113, 180-220 and 300-350). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). Another missense variant, c.789G>C p.Glu263Asp has been classified as a VUS by the ClinGen MDEP; therefore, PM5 will not be applied. This variant segregated with diabetes, with at least 5 informative meioses in 1 family with MODY (PP1_Strong). This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.952, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant was identified in an individual with a clinical history highly specific for HNF4A-MODY (MODY probability calculator result >50% and a family history of neonatal hyperglycemia and response to sulphonylurea) (PP4_Moderate; internal lab collaborator). In summary, c.787G>C meets the criteria to be classified as likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.0.0, approved 11/16/2022): PS3_Supporting PM2_Supporting, PP1_Strong, PP3_Supporting, PP4_Moderate.

Met criteria codes

PP1_Strong	✔	This variant segregated with diabetes, with at least 5 informative meioses in 1 family with MODY (PP1_Strong).
PS3_Supporting	✔	Functional studies demonstrated the p.Glu276Gln protein has transactivation below 60% of wildtype, indicating that this variant impacts protein function (PS3_Supporting; PMIDs: 30325586, 30191603).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PP3	✔	This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.952, which is greater than the MDEP VCEP threshold of 0.70 (PP3).

PP4_Moderate		✔	This variant was identified in an individual with a clinical history highly specific for HNF4A-MODY (MODY probability calculator result >50% and a family history of neonatal hyperglycemia and response to sulphonylurea) (PP4_Moderate; internal lab collaborator).

Not Met criteria codes

PM1		✖	This variant is outside of the region defined as critical for the protein's function by the ClinGen MDEP (codons 37-113, 180-220 and 300-350)
PM5		✖	Another missense variant, c.789G>C p.Glu263Asp has been classified as a VUS by the ClinGen MDEP; therefore, PM5 will not be applied.
PS4		✖	One case

Curation History

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