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Variant: NM_175914.5:c.278G>C

Version: 1.1

CA409104280

3068527 (ClinVar)

Gene: HNF4A (HGNC:3172)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Autosomal dominant inheritance
UUID: 0941223d-5840-418a-9380-0202df7633ef
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HGVS expressions

NM_175914.5:c.278G>C
NC_000020.11:g.44407434G>C
CM000682.2:g.44407434G>C
NC_000020.10:g.43036074G>C
CM000682.1:g.43036074G>C
NC_000020.9:g.42469488G>C
NG_009818.1:g.56634G>C
ENST00000316673.9:c.278G>C
ENST00000316099.10:c.344G>C
ENST00000619550.5:c.318G>C
ENST00000681977.1:c.320G>C
ENST00000682169.1:c.297G>C
ENST00000683148.1:n.320G>C
ENST00000683657.1:n.1468G>C
ENST00000684046.1:c.320G>C
ENST00000684136.1:c.330G>C
ENST00000684476.1:c.301G>C
ENST00000316099.9:c.344G>C
ENST00000316099.8:c.344G>C
ENST00000316673.8:c.278G>C
ENST00000372920.1:c.*111G>C
ENST00000415691.2:c.344G>C
ENST00000443598.6:c.344G>C
ENST00000457232.5:c.278G>C
ENST00000609262.5:c.269G>C
ENST00000609795.5:c.278G>C
ENST00000619550.4:c.269G>C
NM_000457.4:c.344G>C
NM_001030003.2:c.278G>C
NM_001030004.2:c.278G>C
NM_001258355.1:c.323G>C
NM_001287182.1:c.269G>C
NM_001287183.1:c.269G>C
NM_001287184.1:c.269G>C
NM_175914.4:c.278G>C
NM_178849.2:c.344G>C
NM_178850.2:c.344G>C

NM_001030003.3:c.278G>C
NM_001030004.3:c.278G>C
NM_001258355.2:c.323G>C
NM_001287182.2:c.269G>C
NM_001287184.2:c.269G>C
NM_178849.3:c.344G>C
NM_178850.3:c.344G>C
NM_000457.5:c.344G>C
NM_000457.6:c.344G>C
NM_001287183.2:c.269G>C

Pathogenic

Met criteria codes 5

PP4_Moderate PM2_Supporting PM1 PS2 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.278G>C variant in the hepatocyte nuclear factor 4-alpha gene, HNF4A, causes an amino acid change of cysteine to serine at codon 93 (p.(Cys93Ser)) of NM_175914.5. This variant is absent in gnomAD v2.1.1 (PM2_Supporting). It was identified in an individual with a clinical history highly specific for HNF4A-MODY neonatal hypoglycemia that is responsive to diazoxide, negative genetic testing for ABCC8 and KCNJ11, and history of macrosomia in the absence of sufficient maternal hyperglycemia)(PP4_Moderate; PMID: 20164212). This variant was identified as a de novo occurrence with confirmed parental relationships in this individual (PS2; PMID: 20164212). This variant resides in an amino acid within the HNF4A DNA binding domain that directly binds DNA and is necessary for zinc finger formation which is defined as critical for the protein's function by the ClinGen MDEP (PM1). It is also predicted to be deleterious by computational evidence, with a REVEL score of 0.986, which is greater than the MDEP VCEP threshold of 0.70 (PP3). In summary, c.278G>C 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): PS2, PP4_Moderate, PM1, PP3, PM2_Supporting.

Met criteria codes

PP4_Moderate	✔	This variant was identified in an individual with a clinical history highly specific for HNF4A-MODY neonatal hypoglycemia that is responsive to diazoxide, negative genetic testing for ABCC8 and KCNJ11, and history of macrosomia in the absence of sufficient maternal hyperglycemia)(PP4_Moderate; internal lab contributor).
PM2_Supporting	✔	This variant is absent in gnomAD v2.1.1 (PM2_Supporting).
PM1	✔	This variant resides in an amino acid within the HNF4A DNA binding domain that directly binds DNA and is necessary for zinc finger formation which is defined as critical for the protein's function by the ClinGen MDEP (PM1).

PS2		✔	This variant was identified as a de novo occurrence with confirmed parental relationships in an individual with a clinical picture consistent with HNF4A-MODY (neonatal hypoglycemia that is responsive to diazoxide, hyperinsulinemic hypoglycemia, and negative genetic testing for ABCC8 and KCNJ11)(PS2; PMID: 20164212).
PP3		✔	This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.986, which is greater than the MDEP VCEP threshold of 0.70 (PP3).

Curation History

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