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Variant: NM_175914.5(HNF4A):c.745G>T (p.Glu249Ter)

Version: 1.0

CA409107472

447522 (ClinVar)

Gene: HNF4A (HGNC:3172)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Autosomal dominant inheritance
UUID: 69254db0-97b7-4d3a-a8f3-a3fca6fb3495
Approved on: 2024/8/30
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HGVS expressions

NM_175914.5(HNF4A):c.745G>T (p.Glu249Ter)
NM_175914.5:c.745G>T
NC_000020.11:g.44419795G>T
CM000682.2:g.44419795G>T
NC_000020.10:g.43048435G>T
CM000682.1:g.43048435G>T
NC_000020.9:g.42481849G>T
NG_009818.1:g.68995G>T
ENST00000316673.9:c.745G>T
ENST00000316099.10:c.811G>T
ENST00000619550.5:c.785G>T
ENST00000683148.1:n.787G>T
ENST00000683657.1:n.1935G>T
ENST00000316099.9:c.811G>T
ENST00000316099.8:c.811G>T
ENST00000316673.8:c.745G>T
ENST00000372920.1:c.*578G>T
ENST00000415691.2:c.811G>T
ENST00000443598.6:c.811G>T
ENST00000457232.5:c.745G>T
ENST00000609795.5:c.745G>T
ENST00000619550.4:c.736G>T
NM_000457.4:c.811G>T
NM_001030003.2:c.745G>T
NM_001030004.2:c.745G>T
NM_001258355.1:c.790G>T
NM_001287182.1:c.736G>T
NM_001287183.1:c.736G>T
NM_001287184.1:c.736G>T
NM_175914.4:c.745G>T
NM_178849.2:c.811G>T
NM_178850.2:c.811G>T
NM_001030003.3:c.745G>T
NM_001030004.3:c.745G>T
NM_001258355.2:c.790G>T
NM_001287182.2:c.736G>T
NM_001287184.2:c.736G>T

NM_178849.3:c.811G>T
NM_178850.3:c.811G>T
NM_000457.5:c.811G>T
NM_000457.6:c.811G>T
NM_001287183.2:c.736G>T

Pathogenic

Met criteria codes 3

PM2_Supporting | PP4 | PVS1

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.745G>T variant in the hepatocyte nuclear factor 4-alpha gene, HNF4A, results in a premature termination at codon 249 (p.(Glu249Ter)) 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 an individual with a clinical history suggestive of HNF4A-MODY (neonatal hypoglycemia that is responsive to diazoxide and negative genetic testing for ABCC8 and KCNJ11)(PP4; internal lab contributors). In summary, c.745G>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, PP4, PM2_Supporting.

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting). gnomAD v4.1.0, absent
PP4	✔	HNF4A: This variant was identified in an individual with a clinical history suggestive of HNF4A-MODY (neonatal hypoglycemia that is responsive to diazoxide and negative genetic testing for ABCC8 and KCNJ11)(PP4; 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).

Curation History

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