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_001306179.2:c.781G>A

Version: 1.1

CA386966092

1327600 (ClinVar)

Gene: HNF1A (HGNC:6927)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Autosomal dominant inheritance
UUID: 0e58f20e-3d68-4996-ae8d-cb99d8653f95
Approved on: 2025/8/5
Published on: 2025/8/5

HGVS expressions

NM_001306179.2:c.781G>A
NC_000012.12:g.120994231G>A
CM000674.2:g.120994231G>A
NC_000012.11:g.121432034G>A
CM000674.1:g.121432034G>A
NC_000012.10:g.119916417G>A
NG_011731.2:g.20486G>A
ENST00000560968.6:c.750+31G>A
ENST00000257555.11:c.781G>A
ENST00000257555.10:c.781G>A
ENST00000400024.6:c.781G>A
ENST00000402929.5:n.916G>A
ENST00000535955.5:n.43-3260G>A
ENST00000538626.2:n.191-3260G>A
ENST00000538646.5:c.594G>A
ENST00000540108.1:c.*221G>A
ENST00000541395.5:c.781G>A
ENST00000541924.5:c.713+525G>A
ENST00000543427.5:c.633+605G>A
ENST00000544413.2:c.781G>A
ENST00000544574.5:c.73-2386G>A
ENST00000560968.5:c.893+31G>A
ENST00000615446.4:c.-257-2031G>A
ENST00000617366.4:c.586+652G>A
NM_000545.5:c.781G>A
NM_000545.6:c.781G>A
NM_001306179.1:c.781G>A
NM_000545.8:c.781G>A

Likely Pathogenic

Met criteria codes 5

PM2_Supporting PP3 PP4 PM1_Supporting PP1_Moderate

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 HNF1A Version 3.0.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.781G>A variant in the HNF1 homeobox A gene, HNF1A, causes an amino acid change of glutamic acid to lysine at codon 261 (p.(Glu261Lys)) of NM_000545.8. This variant is located within the DNA binding domain (codons 201-280) of HNF1A, which is defined as critical for the protein's function by the ClinGen MDEP (PM1_Supporting). Additionally, this variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.943, which is greater than the MDEP threshold of 0.70 (PP3). This variant has a gnomAD v4.1.0 Grpmax filtering allele frequency of 2.80e-7, which is below the ClinGen MDEP threshold of 0.000003 (PM2_Supporting). This variant was identified in an individual with a clinical history highly specific for HNF1A-MODY (MODY probability calculator result >50%, negative genetic testing for HNF4A) (PP4; PMID:16917892, internal lab contributor). This variant segregated with diabetes, with four informative meioses in this individual's family (PP1_Moderate; internal lab contributor). Taken together, this evidence supports the classification of c.781G>A as likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 3.0.0, approved 6/30/2025): PP1_Moderate, PP3, PP4, PM1_Supporting, PM2_Supporting.

Met criteria codes

PM2_Supporting	✔	This variant has a gnomAD v4.1.0 Grpmax filtering allele frequency of 2.80e-7, which is below the ClinGen MDEP threshold of 0.000003 (PM2_Supporting).
PP3	✔	This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.943, which is greater than the MDEP threshold of 0.70 (PP3).
PP4	✔	This variant was identified in an inidividual with a clinical history highly specific for HNF1A-MODY (MODY probability calculator result >50%, negative genetic testing for HNF4A) (PP4; PMID:16917892, internal lab contributor).
PM1_Supporting	✔	This variant is located within the DNA binding domain (codons 201-280) of HNF1A, which is defined as critical for the protein's function by the ClinGen MDEP (PM1_Supporting).
PP1_Moderate	✔	This variant segregated with diabetes, with four informative meioses in one family with MODY (PP1_Moderate; internal lab contributor).

Curation History

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