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.224G>A (p.Arg75Lys)

Version: 2.0

CA409104032

430844 (ClinVar)

Gene: HNF4A (HGNC:3172)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Autosomal dominant inheritance
UUID: 2585227f-6c9e-4b91-9cb1-ae2e68195fb1
Approved on: 2025-10-28
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HGVS expressions

NM_175914.5:c.224G>A
NM_175914.5(HNF4A):c.224G>A (p.Arg75Lys)
NC_000020.11:g.44406232G>A
CM000682.2:g.44406232G>A
NC_000020.10:g.43034872G>A
CM000682.1:g.43034872G>A
NC_000020.9:g.42468286G>A
NG_009818.1:g.55432G>A
ENST00000316673.9:c.224G>A
ENST00000316099.10:c.290G>A
ENST00000619550.5:c.264G>A
ENST00000681977.1:c.266G>A
ENST00000682169.1:c.243G>A
ENST00000683148.1:n.266G>A
ENST00000683657.1:n.266G>A
ENST00000684046.1:c.266G>A
ENST00000684136.1:c.266G>A
ENST00000684476.1:c.247G>A
ENST00000316099.9:c.290G>A
ENST00000316099.8:c.290G>A
ENST00000316673.8:c.224G>A
ENST00000372920.1:c.*57G>A
ENST00000415691.2:c.290G>A
ENST00000443598.6:c.290G>A
ENST00000457232.5:c.224G>A
ENST00000609262.5:c.215G>A
ENST00000609795.5:c.224G>A
ENST00000619550.4:c.215G>A
NM_000457.4:c.290G>A
NM_001030003.2:c.224G>A
NM_001030004.2:c.224G>A
NM_001258355.1:c.269G>A
NM_001287182.1:c.215G>A
NM_001287183.1:c.215G>A
NM_001287184.1:c.215G>A
NM_175914.4:c.224G>A
NM_178849.2:c.290G>A

NM_178850.2:c.290G>A
NM_001030003.3:c.224G>A
NM_001030004.3:c.224G>A
NM_001258355.2:c.269G>A
NM_001287182.2:c.215G>A
NM_001287184.2:c.215G>A
NM_178849.3:c.290G>A
NM_178850.3:c.290G>A
NM_000457.5:c.290G>A
NM_000457.6:c.290G>A
NM_001287183.2:c.215G>A

Likely Pathogenic

Met criteria codes 4

PP3 PM1 PP4_Moderate PM2_Supporting

Not Met criteria codes 1

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 4.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.224G>A variant in the hepatocyte nuclear factor 4-alpha gene, HNF4A, causes an amino acid change of arginine to lysine at codon 75 (p.Arg75Lys)) of NM_175914.5. This variant resides in an amino acid within the HNF4α DNA binding domain that are necessary for homodimer formation, which is defined as critical for the protein's function by the ClinGen MDEP (PM1). This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.777, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent in gnomAD v2.1.1 (PM2_Supporting). This variant was identified in two unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (ClinVar: 430844, internal lab contributors). One of these individuals did have a clinical history highly specific for HNF4A-monogenic diabetes (MODY probability calculator result >50%, negative genetic testing for HNF1A, and negative antibodies) (PP4_Moderate; internal lab contributors). In summary, c.224G>A meets the criteria to be classified as likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 4.0.0, approved 10/10/2025): PM1, PP4_Moderate, PP3, PM2_Supporting.

Met criteria codes

PP3	✔	This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.777, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PM1	✔	This variant resides in an amino acid within the HNF4α DNA binding domain that are necessary for homodimer formation, which is defined as critical for the protein's function by the ClinGen MDEP (PM1).

PP4_Moderate	ℹ	✔	This variant was identified in an individual with a clinical history highly specific for HNF4A-monogenic diabetes (MODY probability calculator result >50%, negative genetic testing for HNF1A, and negative antibodies) (PP4_Moderate; internal lab contributors).
PM2_Supporting	ℹ	✔	This variant is absent in gnomAD v4.1.0 (PM2_Supporting).

Not Met criteria codes

PS4	ℹ	✖	This variant was identified in two unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (ClinVar: 430844, internal lab contributors).

Curation History

Showing 1 to 3 of 3 rows