

## Variant: NM\_000545.8(HNF1A):c.1859C>T (p.Thr620Ile)

Version: 1.1

CA124466 [↗](#)

14935 (ClinVar) [↗](#)

**Gene:** HNF1A ([HGNC:6927](#))

**Condition:** monogenic diabetes ([MONDO:0015967](#))

**Inheritance Mode:** Autosomal dominant inheritance

**UID:** 5468a875-818b-44a1-b8cd-4e08577c4d5b

**Approved on:** 2025-09-02

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### HGVS expressions

#### NM\_000545.8:c.1859C>T

NM\_000545.8(HNF1A):c.1859C>T (p.Thr620Ile)

NC\_000012.12:g.121001155C>T

CM000674.2:g.121001155C>T

NC\_000012.11:g.121438958C>T

CM000674.1:g.121438958C>T

NC\_000012.10:g.119923341C>T

NG\_011731.2:g.27410C>T

ENST00000560968.6:c.\*606C>T

ENST00000257555.11:c.1859C>T

ENST00000257555.10:c.1859C>T

ENST00000288757.7:c.\*2998G>A

ENST00000540108.1:c.\*1299C>T

ENST00000541395.5:c.1952C>T

ENST00000543427.5:c.1322C>T

ENST00000544413.2:c.1880C>T

ENST00000560968.5:c.1676C>T

ENST00000615446.4:c.647C>T

ENST00000617366.4:c.\*268C>T

NM\_000545.5:c.1859C>T

NM\_000545.6:c.1859C>T

NM\_001306179.1:c.1880C>T

NM\_001286191.2:c.\*2998G>A

NM\_001286196.2:c.\*2998G>A

NM\_001306179.2:c.1880C>T

NM\_022895.3:c.\*2998G>A

Uncertain Significance

#### Met criteria codes **5**

PP4 BS3\_Supporting

PM2\_Supporting PP1\_Strong BS2

#### 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 HNF1A Version 3.0.0

Evidence submitted by expert panel



**Monogenic Diabetes VCEP**

The c.1859C>T variant in the HNF1 homeobox A gene, HNF1A, causes an amino acid change of threonine to isoleucine at codon 620 (p.Thr620Ile) of NM\_000545.8. This variant is absent from gnomAD v4.1.0 (PM2\_Supporting). This variant was identified in three 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 (PMID: 9075818, 25414397, 10482964, internal lab contributors). One of these individuals did have a clinical history highly specific for HNF1A-MODY (MODY probability calculator result >50%, negative genetic testing for HNF4A) (PP4; internal lab contributors). Furthermore, this variant segregated with diabetes, with 7 informative meioses in a single family (PP1\_Strong; PMID: 10482964). Functional studies demonstrated the p.Thr620Ile protein has transactivation above 75% of wildtype, indicating that this variant does not impact protein function (PMID: 12530534) (BS3\_Supporting). This variant was also identified in a normoglycemic individual >70 years old, and the expected penetrance for HNF1A-MODY is 95% by age 70 (PMID: 10482964) (BS2). In summary, c.1859C>T meets the criteria to be classified as a variant of uncertain significance for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 3.0.0 approved 6/30/2025): PM2\_Supporting, PP1\_Strong, BS3\_Supporting, BS2, PP4.

**Met criteria codes**

<b>PP4</b>	 	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) (internal lab contributors).
<b>BS3_Supporting</b>	 	Thomas 2002 (PMID: 12530534) reported transactivation activity equal to WT on HP1 construct (HNF1 binding site) and increased transactivation activity using HNF4A promoter construct. Authors suggested a possible a gain-of-function mutation. DNA binding was present (no quantification).
<b>PM2_Supporting</b>	 	Absent from gnomAD v4.1.0 (PM2_Supporting).
<b>PP1_Strong</b>	 	This variant segregated with diabetes, with seven informative meioses in one family with MODY (internal lab contributors).
<b>BS2</b>	 	This variant was identified in a normoglycemic individual >70 years old, and the expected penetrance for HNF1A-MODY is 95% by age 70 (PMID: 10482964).

**Not Met criteria codes**

<b>PS4</b>	 	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 (PMID: 9075818, 25414397, 10482964, internal lab contributors).
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Showing 1 to 2 of 2 rows

See Report	Preferred Variant Title	Classification ⓘ	Condition	Published Date	Version ⓘ	Criteria Specification	Gene
<a href="#">View</a>	NM_000545.8(HNF1A):c.1859C>T (p.T...	Uncertain Significance	Monogenic Diabetes <a href="#">↗</a>	2025-09-02	1.1	ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for HNF1A Version 3.0.0 <a href="#">↗</a>	HNF1A <a href="#">↗</a>
<a href="#">View</a>	NM_000545.8(HNF1A):c.1859C>T (p.T...	Uncertain Significance	Monogenic Diabetes <a href="#">↗</a>	2022-04-24	1.0	ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1.1 <a href="#">↗</a>	HNF1A <a href="#">↗</a>

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