Variant: NM_001306179.2:c.865C>T

Version: 1.2

CA386966635

1315612 (ClinVar)

Gene: HNF1A (HGNC:6927)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Autosomal dominant inheritance
UUID: 8e113349-d440-4f07-8182-c050d43a54bf
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HGVS expressions

NM_001306179.2:c.865C>T
NC_000012.12:g.120994315C>T
CM000674.2:g.120994315C>T
NC_000012.11:g.121432118C>T
CM000674.1:g.121432118C>T
NC_000012.10:g.119916501C>T
NG_011731.2:g.20570C>T
ENST00000560968.6:c.750+115C>T
ENST00000257555.11:c.865C>T
ENST00000257555.10:c.865C>T
ENST00000400024.6:c.865C>T
ENST00000402929.5:n.1000C>T
ENST00000535955.5:n.43-3176C>T
ENST00000538626.2:n.191-3176C>T
ENST00000538646.5:c.678C>T
ENST00000540108.1:c.*305C>T
ENST00000541395.5:c.865C>T
ENST00000541924.5:c.713+609C>T
ENST00000543427.5:c.633+689C>T
ENST00000544413.2:c.865C>T
ENST00000544574.5:c.73-2302C>T
ENST00000560968.5:c.893+115C>T
ENST00000615446.4:c.-257-1947C>T
ENST00000617366.4:c.586+736C>T
NM_000545.5:c.865C>T
NM_000545.6:c.865C>T
NM_001306179.1:c.865C>T
NM_000545.8:c.865C>T

Uncertain Significance

Met criteria codes 1

PM2_Supporting

Not Met criteria codes 6

PM5 PS4 PP1 PP3 PP4 BP4

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

Evidence Links 0

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.865C>T variant in the e.g. HNF1 homeobox A gene, HNF1A, causes an amino acid change of proline to serine at codon 289 (p.(Pro289Ser)) of NM_000545.8. This variant has a gnomAD v4.1.0 Grpmax filtering allele frequency of 6.9e-7, which is below the ClinGen MDEP threshold of 0.000003 (PM2_Supporting). This variant has a REVEL score of 0.604, which is between the ClinGen MDEP thresholds for BP4 and PP3, predicting neither a damaging nor benign impact on HNF1A function. 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 (internal lab contributors). In one of these individuals the MODY probability is unable to be calculated due to age of diagnosis over 35 and the other has a MODY probability less than 50%, so PP4 cannot be applied for either case. This variant segregated with diabetes with one informative meioses in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (PMID: 27236918; internal lab contributors). Two other missense variants at the same residue, c.866C>A (p.Pro289His) and c.866C>G (p.Pro289Arg), have been classified as VUS by the ClinGen MDEP; therefore PM5 will not be applied. In summary, c.865C>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.

Met criteria codes

PM2_Supporting	✔	This variant has a gnomAD v4.1.0 Grpmax filtering allele frequency of 6.9e-7, which is below the ClinGen MDEP threshold of 0.000003 (PM2_Supporting).

Not Met criteria codes

PM5	✖	Two other missense variants, c.866C>A (p.Pro289His) and c.866C>G (p.Pro289Arg), have been classified as VUS by the ClinGen MDEP; therefore, PM5 will not be applied.
PS4	✖	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 (internal lab contributors).
PP1	✖	This variant segregated with diabetes with one informative meioses in a single family; however, this does not meet the thresholds for PP1 set by the ClinGen MDEP (PMID: 27236918; internal lab contributors).
PP3	✖	This variant has a REVEL score of 0.604, which is between the ClinGen MDEP thresholds for BP4 and PP3, predicting neither a damaging nor benign impact on HNF1A function.
PP4	✖	This variant was identified in an individual with diabetes; however, the calculated MODY probability is less than 50%, so PP4 does not apply (internal lab contributors).

BP4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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