Variant: NM_000545.8(HNF1A):c.335C>T (p.Pro112Leu)

Version: 1.1

CA124475

14942 (ClinVar)

Gene: HNF1A (HGNC:6927)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Autosomal dominant inheritance
UUID: 53a9fce0-d78f-477d-9a67-dfcbda28884c
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HGVS expressions

NM_000545.8:c.335C>T
NM_000545.8(HNF1A):c.335C>T (p.Pro112Leu)
NC_000012.12:g.120988841C>T
CM000674.2:g.120988841C>T
NC_000012.11:g.121426644C>T
CM000674.1:g.121426644C>T
NC_000012.10:g.119911027C>T
NG_011731.2:g.15096C>T
ENST00000560968.6:c.335C>T
ENST00000257555.11:c.335C>T
ENST00000257555.10:c.335C>T
ENST00000400024.6:c.335C>T
ENST00000402929.5:n.470C>T
ENST00000535955.5:n.43-8650C>T
ENST00000538626.2:n.191-8650C>T
ENST00000538646.5:c.335C>T
ENST00000540108.1:c.327-4679C>T
ENST00000541395.5:c.335C>T
ENST00000541924.5:c.335C>T
ENST00000543427.5:c.335C>T
ENST00000544413.2:c.335C>T
ENST00000544574.5:c.73-7776C>T
ENST00000560968.5:c.478C>T
ENST00000615446.4:c.-257-7421C>T
ENST00000617366.4:c.335C>T
NM_000545.5:c.335C>T
NM_000545.6:c.335C>T
NM_001306179.1:c.335C>T
NM_001306179.2:c.335C>T

Pathogenic

Met criteria codes 7

PM2_Supporting PP3 PS4_Moderate PM1 PP4_Moderate PP1_Strong PS3

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 Version 1.1*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.335C>T variant in the HNF1 homeobox A gene, HNF1A, causes an amino acid change of proline to leucine at codon 112 (p.(Pro112Leu)) of NM_000545.8. This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.966, which is greater than the MDEP VCEP threshold of 0.70 (PP3) and is absent from gnomAD v2.1.1 (PM2_Supporting). Additionally, this variant is located within a conserved region of the DNA binding domain (codons 107-174 and 201-280) of HNF1A, which is defined as critical for the protein's function by the ClinGen MDEP (PM1_Supporting). This variant was identified in six unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4_Moderate; internal lab contributors). This variant was identified in two individuals with a clinical history highly specific for HNF1A-MODY (MODY probability calculator result >50%, negative genetic testing for HNF4A, and response to low dose sulfonylureas) (PP4_Moderate; internal lab contributors). A luciferase assay meeting the ClinGen MDEP quality control specifications demonstrated that the p.Pro112Leu protein has transactivation activity below 40% of wildtype, indicating that this variant impacts protein function (PS3_Moderate, PMID: 32910913). Lastly, this variant segregated with diabetes, with 11 informative meioses in six families with MODY (PP1_Strong; internal lab contributors). In summary, c.335C>T meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.1, approved 9/30/21): PP3, PM1_Supporting, PM2_Supporting, PP4_Moderate, PS4_Moderate,PS3_Moderate, PP1_Strong.

Met criteria codes

PM2_Supporting	✔	This variant has a minor allele frequency in gnomAD of less than 0.00002 in the European non-Finnish sub-population (actual value = 0.000008803) and is absent from other gnomAD sub-populations.
PP3	✔	REVEL 0.966+ FATHMM, LRT, MetaLR, MetaSVM, MutationTaster, PROVEAN and SIFT all predict deleterious; MutationAssessor said Medium, GERP score 5.08
PS4_Moderate	✔	This variant was identified in six unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4_Moderate; internal lab contributors).
PM1	✔	This variant is located within a conserved region of the DNA binding domain (codons 107-174 and 201-280 of HNF1A), which is defined as critical for the protein's function by the ClinGen MDEP/
PP4_Moderate	✔	This variant was identified in two individuals with a clinical history highly significant HNF1A-MODY (MODY probability calculator result >50% and negative genetic testing for HNF4A), who also responded to low dose sulfonylureas.
PP1_Strong	✔	This variant segregated with disease in 11 informative meioses in six families with MODY (internal lab contributors).
PS3	✔	Two functional in vitro studies demonstrated that cells with this variant display decreased transactivation and DNA binding (both <40% compared to wild type), but do retain normal cellular localization (PMIDs: 27899486 and 12574234).

Curation History

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