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Variant: NM_000545.8(HNF1A):c.347C>T (p.Ala116Val)

Version: 1.0

CA6831743

1700671 (ClinVar)

Gene: HNF1A (HGNC:6927)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Autosomal dominant inheritance
UUID: bc1083d2-3f14-43b0-8cfd-5b12006c6b59
Approved on: 2024/6/9
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HGVS expressions

NM_000545.8(HNF1A):c.347C>T (p.Ala116Val)
NM_000545.8:c.347C>T
NC_000012.12:g.120988853C>T
CM000674.2:g.120988853C>T
NC_000012.11:g.121426656C>T
CM000674.1:g.121426656C>T
NC_000012.10:g.119911039C>T
NG_011731.2:g.15108C>T
ENST00000560968.6:c.347C>T
ENST00000257555.11:c.347C>T
ENST00000257555.10:c.347C>T
ENST00000400024.6:c.347C>T
ENST00000402929.5:n.482C>T
ENST00000535955.5:n.43-8638C>T
ENST00000538626.2:n.191-8638C>T
ENST00000538646.5:c.347C>T
ENST00000540108.1:c.327-4667C>T
ENST00000541395.5:c.347C>T
ENST00000541924.5:c.347C>T
ENST00000543427.5:c.347C>T
ENST00000544413.2:c.347C>T
ENST00000544574.5:c.73-7764C>T
ENST00000560968.5:c.490C>T
ENST00000615446.4:c.-257-7409C>T
ENST00000617366.4:c.347C>T
NM_000545.5:c.347C>T
NM_000545.6:c.347C>T
NM_001306179.1:c.347C>T
NM_001306179.2:c.347C>T

Pathogenic

Met criteria codes 6

PP1_Strong | PM1_Supporting | PS4 | PM2_Supporting | PP3 | PP4_Moderate

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

Not Met criteria codes 1

PS3

Evidence Links 1

Criteria Specification: *ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for HNF1A Version 2.1.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.347C>T variant in the HNF1 homeobox A gene, HNF1A, causes an amino acid change of alanine to valine at codon 116 (p.(Ala116Val)) of NM_000545.8. 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 is predicted to be deleterious by computational evidence, with a REVEL score of 0.951, which is greater than the MDEP VCEP threshold of 0.70 (PP3). While studies exploring the effect of this variant on protein function have been performed, these studies do not meet the criteria set forth by the MDEP for the application of PS3 or BS3 as the transactivation values were not consistently within or outside the cutoffs for PS3_Moderate or BS3_Supporting (PMID: 32910913). This variant has an incomputable gnomAD v2.1.1 Popmax filtering allele frequency due to 0 copies in the European non-Finnish subpopulation and 1 copy in the East Asian subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting (ENF Popmax FAF <= 0.000003 and <= 2 copies in ENF and <=1 copy in any other subpopulation) (PM2_Supporting). This variant was identified in at least 20 unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4; PMID: 36257325, 31658956, 12453976, internal lab contributors). At least 4 of these individuals had a clinical history highly specific for HNF1A-monogenic diabetes (MODY probability calculator result >50%, negative genetic testing for HNF4A, and negative antibodies or SU-sensitivity) (PP4_Moderate; internal lab contributors). This variant segregated with diabetes, with 24 informative meioses in multiple families (PP1_Strong; PMID: 12453976, internal lab contributors). In summary, c.347C>T meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 2.1.1, approved 8/11/2023): PP1_Strong, PS4, PP4_Moderate, PP3, PM1_Supporting, PM2_Supporting.

Met criteria codes

PP1_Strong	✔	This variant segregated with diabetes, with 24 informative meioses in multiple families (PP1_Strong; PMID: 12453976, internal lab contributors).
PM1_Supporting	✔	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).
PS4	✔	This variant was identified in at least 20 unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4; PMID: 36257325, 31658956, 12453976, internal lab contributors).
PM2_Supporting	✔	This variant has an incomputable gnomAD v2.1.1 Popmax filtering allele frequency due to 0 copies in the European non-Finnish subpopulation and 1 copy in the East Asian subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting (ENF Popmax FAF <= 0.000003 and <= 2 copies in ENF and <=1 copy in any other subpopulation) (PM2_Supporting).
PP3	✔	This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.951, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PP4_Moderate	✔	This variant was identified in at least 4 individuals with a clinical history highly specific for HNF1A-monogenic diabetes (MODY probability calculator result >50%, negative genetic testing for HNF4A, and negative antibodies or

SU-sensitivity) (PP4_Moderate; internal lab contributors).

Not Met criteria codes

PS3

While studies exploring the effect of this variant on protein function have been performed, these studies do not meet the criteria set forth by the MDEP for the application of PS3 or BS3 as the transactitivation values were not consistently within or outside the cutoffs for PS3_Moderate or BS3_Supporting (PMID: 32910913).

yielded transactivation values of 40% and ~60% in HeLa and ~50 and ~100% in INS-1 assays, respectively
PubMed:32910913

Curation History

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