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Variant: NM_001306179.2:c.425C>T

Version: 1.0

CA386959900

1327620 (ClinVar)

Gene: HNF1A (HGNC:6927)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Autosomal dominant inheritance
UUID: 206d446e-d869-4d21-bb61-58eb7bb57dd0
Approved on: 2021/8/24
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HGVS expressions

NM_001306179.2:c.425C>T
NC_000012.12:g.120988931C>T
CM000674.2:g.120988931C>T
NC_000012.11:g.121426734C>T
CM000674.1:g.121426734C>T
NC_000012.10:g.119911117C>T
NG_011731.2:g.15186C>T
ENST00000560968.6:c.425C>T
ENST00000257555.11:c.425C>T
ENST00000257555.10:c.425C>T
ENST00000400024.6:c.425C>T
ENST00000402929.5:n.560C>T
ENST00000535955.5:n.43-8560C>T
ENST00000538626.2:n.191-8560C>T
ENST00000538646.5:c.425C>T
ENST00000540108.1:c.327-4589C>T
ENST00000541395.5:c.425C>T
ENST00000541924.5:c.425C>T
ENST00000543427.5:c.425C>T
ENST00000544413.2:c.425C>T
ENST00000544574.5:c.73-7686C>T
ENST00000560968.5:c.568C>T
ENST00000615446.4:c.-257-7331C>T
ENST00000617366.4:c.425C>T
NM_000545.5:c.425C>T
NM_000545.6:c.425C>T
NM_001306179.1:c.425C>T
NM_000545.8:c.425C>T

Pathogenic

Met criteria codes 7

PM2_Supporting PP3 PP4 PS3_Supporting PM1_Supporting PS4 PP1_Strong

Evidence Links 0

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.425C>T variant in the HNF1 homeobox A gene, HNF1A, causes an amino acid change of serine to phenylalanine at codon 142 (p.(Ser142Phe)) of NM_000545.8. This variant is located within the DNA binding domain (codons 107-174) of HNF1A, which is defined as critical for the protein's function by the ClinGen MDEP (PM1_Supporting). This is supported by functional studies that demonstrated the p.Ser142Phe protein has DNA binding below 40% of wild type, indicating that this variant impacts protein function (PS3_Supporting, PMID: 10585442). This variant is also predicted to be deleterious by computational evidence, with a REVEL score of 0.977, which is greater than the MDEP threshold of 0.70 (PP3). This variant is absent in gnomAD v2.1.1 (PM2_Supporting), and was identified in at least 9 unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4; PMID 31968686, PMID 9097962, PMID: 23610083, PMID: 21224407, internal lab contributors). This variant segregated with diabetes, with 14 informative meioses in 5 families with MODY (PP1_Strong; PMID 31968686, PMID 9097962, internal lab contributors). This variant was identified in an individual with diabetes with a calculated MODY probability of <50%, however the presence of a moderate level of criteria (persistent C-peptide) allows the application of this criteria at a supporting level per the ClinGen MDEP's approval (PP4; PMID 31968686). Taken together, this evidence supports the classification of this variant as pathogenic for monogenic diabetes. ACMG/AMP criteria applied (specification version 1.0, approved 8/24/21): PP1_Strong, PS4, PP3, PP4, PM1_Supporting, PM2_Supporting, PS3_Supporting.

Met criteria codes

PM2_Supporting	✔	This variant is absent in gnomAD v2.1.1 (PM2_Supporting).
PP3	✔	This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.977, which is greater than the MDEP threshold of 0.70 (PP3).
PP4	✔	This variant was identified in an individual with diabetes with a calculated MODY probability of <50%, however the presence of a moderate level of criteria (persistent C-peptide) allows the application of this criteria at a supporting level per the ClinGen MDEP's approval (PP4; PMID 31968686).
PS3_Supporting	✔	Functional studies demonstrated the p.Ser142Phe protein has DNA binding below 40% of wild type, indicating that this variant impacts protein function (PS3_Supporting, PMID: 10585442).
PM1_Supporting	✔	This variant is located within the DNA binding domain (codons 107-174) 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 9 unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4; PMID 31968686, PMID 9097962, PMID: 23610083, PMID: 21224407, internal lab contributors).
PP1_Strong	✔	This variant segregated with diabetes, with 14 informative meioses in 5 families with MODY (PP1_Strong; PMID 31968686, PMID 9097962, internal lab contributors).

Curation History

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