Variant: NM_000545.8(HNF1A):c.526+1G>C

Version: 1.1

CA386960848

1338446 (ClinVar)

Gene: HNF1A (HGNC:6927)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Autosomal dominant inheritance
UUID: 702b812f-014e-492b-88c7-b2b4632cd24c
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HGVS expressions

NM_000545.8:c.526+1G>C
NM_000545.8(HNF1A):c.526+1G>C
NC_000012.12:g.120989033G>C
CM000674.2:g.120989033G>C
NC_000012.11:g.121426836G>C
CM000674.1:g.121426836G>C
NC_000012.10:g.119911219G>C
NG_011731.2:g.15288G>C
ENST00000560968.6:c.526+1G>C
ENST00000257555.11:c.526+1G>C
ENST00000257555.10:c.526+1G>C
ENST00000400024.6:c.526+1G>C
ENST00000402929.5:n.661+1G>C
ENST00000535955.5:n.43-8458G>C
ENST00000538626.2:n.191-8458G>C
ENST00000538646.5:c.526+1G>C
ENST00000540108.1:c.327-4487G>C
ENST00000541395.5:c.526+1G>C
ENST00000541924.5:c.526+1G>C
ENST00000543427.5:c.526+1G>C
ENST00000544413.2:c.526+1G>C
ENST00000544574.5:c.73-7584G>C
ENST00000560968.5:c.669+1G>C
ENST00000615446.4:c.-257-7229G>C
ENST00000617366.4:c.526+1G>C
NM_000545.5:c.526+1G>C
NM_000545.6:c.526+1G>C
NM_001306179.1:c.526+1G>C
NM_001306179.2:c.526+1G>C

Pathogenic

Met criteria codes 6

PVS1 PP1_Moderate PS4 PS1_Supporting PP4 PM2_Supporting

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

Evidence Links 0

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.526+1G>C variant in the HNF1 homeobox A gene, HNF1A, is predicted to remove a canonical splice donor site in intron 2 of NM_000545.8. This variant is predicted to cause loss of part of exon 2, leading to nonsense-mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1, PMID: 23348805). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). This variant was identified in nine unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4; PMIDs: 21242637, internal lab contributors), including an individual with a clinical history highly specific for HNF1A-MODY (MODY probability calculator result >50% and negative genetic testing for HNF4A) (PP4, internal lab contributor). This variant segregated with diabetes, with three informative meioses in three families (PP1_Moderate, internal lab collaborators). The HNF1A(NM_000545.8):c.526+1G>A variant at the same canonical nucleotide has been classified as pathogenic for monogenic diabetes by the ClinGen MDEP, and c.526+1G>C has a similar predicted impact by Splice AI (donor loss 100% and donor gain at -33 bp 64% vs. 65%). In summary, c.526+1G>C 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): PVS1, PS4, PP1_Moderate, PS1_Supporting, PP4, PM2_Supporting.

Met criteria codes

PVS1	✔	This variant is predicted to cause loss of part exon 2, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1).
PP1_Moderate	✔	This variant segregated with diabetes, with three informative meioses in three families (PP1_Moderate; internal lab contributors).
PS4	✔	This variant was identified in 9 unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4).
PS1_Supporting	✔	The HNF1A(NM_000545.8):c.526+1G>A variant at the same canonical nucleotide has been classified as pathogenic for monogenic diabetes by the ClinGen MDEP, and c.526+1G>C has a similar predicted impact by Splice AI (donor loss 100% and donor gain at -33 bp 64% vs. 65%) (PS1_Supporting).
PP4	✔	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) (PP4).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1

Curation History

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