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

Version: 1.0

CA386960865

846588 (ClinVar)

Gene: HNF1A (HGNC:6927)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Autosomal dominant inheritance
UUID: ebcb920b-da8b-40fa-b495-eb37a9491ba9
Approved on: 2023-12-02
Published on: 2023-12-02

HGVS expressions

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

Pathogenic

Met criteria codes 5

PP1_Strong PS4 PVS1 PP4_Moderate PM2_Supporting

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.526+1G>A 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. This variant was identified in 12 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%, negative genetic testing for HNF4A, and negative autoantibodies) (PP4_Moderate, internal lab contributor). This variant segregated with diabetes, with six informative meioses in five families with MODY (PP1_Strong, internal lab collaborators). In summary, c.526+1G>A 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, PP1_Strong, PS4, PP4_Moderate, PM2_Supporting.

Met criteria codes

PP1_Strong	✔	This variant segregated with diabetes, with six informative meioses in five families with MODY (internal lab collaborators).
PS4	✔	This variant was identified in 12 unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4; PMIDs: 21242637, internal lab contributors).
PVS1	✔	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.
PP4_Moderate	✔	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, and negative autoantibodies) (PP4_Moderate, internal lab contributor).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1.

Curation History

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