Variant: NM_000545.6(HNF1A):c.526+2dup

Version: 2.1

CA658658176

447494 (ClinVar)

Gene: HNF1A (HGNC:6927)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Autosomal dominant inheritance
UUID: 02476433-cb6b-488a-8d31-1acbb44e90ce
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HGVS expressions

NM_000545.6:c.526+2dup
NM_000545.6(HNF1A):c.526+2dup
NC_000012.12:g.120989034dup
CM000674.2:g.120989034dup
NC_000012.11:g.121426837dup
CM000674.1:g.121426837dup
NC_000012.10:g.119911220dup
NG_011731.2:g.15289dup
ENST00000560968.6:c.526+2dup
ENST00000257555.11:c.526+2dup
ENST00000257555.10:c.526+2dup
ENST00000400024.6:c.526+2dup
ENST00000402929.5:n.661+2dup
ENST00000535955.5:n.43-8457dup
ENST00000538626.2:n.191-8457dup
ENST00000538646.5:c.526+2dup
ENST00000540108.1:c.327-4486dup
ENST00000541395.5:c.526+2dup
ENST00000541924.5:c.526+2dup
ENST00000543427.5:c.526+2dup
ENST00000544413.2:c.526+2dup
ENST00000544574.5:c.73-7583dup
ENST00000560968.5:c.669+2dup
ENST00000615446.4:c.-257-7228dup
ENST00000617366.4:c.526+2dup
NM_000545.5:c.526+2dup
NM_001306179.1:c.526+2dup
NM_000545.8:c.526+2dup
NM_001306179.2:c.526+2dup

Likely Pathogenic

Met criteria codes 4

PM2_Supporting PP3 PP4_Moderate PS1_Moderate

Not Met criteria codes 1

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

PS4

Evidence Links 0

Criteria Specification: *ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for HNF1A Version 3.1.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.526+2dup 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 absent from gnomAD v2.1.1 (PM2_Supporting). This variant was also identified in an individual 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). The computational splicing predictor SpliceAI gives a score of 0.48 for donor loss, predicting that the variant disrupts the donor site of intron 2 of HNF1A (PP3). Other variants at this splice donor site, c.526+1G>C, c.526+1G>T, c.526+1G>A, and c.526+2del, have all been classified as pathogenic by the ClinGen Monogenic Diabetes VCEP (PS1_Moderate). This variant was identified in three unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (internal lab contributors). In summary, c.526+2dup meets the criteria to be classified as likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 3.1.0, approved 10/10/2025): PS1_Moderate, PM2_Supporting, PP4_Moderate, PP3.

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v4.1.
PP3	✔	The computational splicing predictor SpliceAI gives a score of 0.48 for donor loss, predicting that the variant disrupts the donor site of intron 2 of HNF1A.
PP4_Moderate	✔	This variant was identified in one individual with a clinical history highly specific for HNF1A-MODY (MODY probability calculator result >50%, negative genetic testing for HNF4A, and sulfonylurea-responsive) (internal lab contributor).
PS1_Moderate	✔	Other variants at this splice donor site, c.526+1G>C, c.526+1G>T, c.526+1G>A, and c.526+2del, have all been classified as pathogenic by the ClinGen Monogenic Diabetes VCEP (PS1_Moderate)

Not Met criteria codes

PS4	✖	This variant was identified in three unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes; however, PS4_Moderate cannot be applied because this number is below the ClinGen MDEP threshold (internal lab contributors).

Curation History

ng 1 to 3 of 3 rows