The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_001306179.2:c.715G>A

Version: 1.0

CA386965729

Gene: HNF1A (HGNC:6927)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Autosomal dominant inheritance
UUID: 378bc88c-c66e-4734-98d5-1489c4c6146e
Approved on: 2024/10/13
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HGVS expressions

NM_001306179.2:c.715G>A
NC_000012.12:g.120994165G>A
CM000674.2:g.120994165G>A
NC_000012.11:g.121431968G>A
CM000674.1:g.121431968G>A
NC_000012.10:g.119916351G>A
NG_011731.2:g.20420G>A
ENST00000560968.6:c.715G>A
ENST00000257555.11:c.715G>A
ENST00000257555.10:c.715G>A
ENST00000400024.6:c.715G>A
ENST00000402929.5:n.850G>A
ENST00000535955.5:n.43-3326G>A
ENST00000538626.2:n.191-3326G>A
ENST00000538646.5:c.528G>A
ENST00000540108.1:c.*155G>A
ENST00000541395.5:c.715G>A
ENST00000541924.5:c.713+459G>A
ENST00000543427.5:c.633+539G>A
ENST00000544413.2:c.715G>A
ENST00000544574.5:c.73-2452G>A
ENST00000560968.5:c.858G>A
ENST00000615446.4:c.-257-2097G>A
ENST00000617366.4:c.586+586G>A
NM_000545.5:c.715G>A
NM_000545.6:c.715G>A
NM_001306179.1:c.715G>A
NM_000545.8:c.715G>A

Likely Pathogenic

Met criteria codes 5

PP1_Strong PM1_Supporting PS4_Moderate PM2_Supporting PP3

Evidence Links 0

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

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.715G>A variant in the HNF1 homeobox A gene, HNF1A, causes an amino acid change of alanine to threonine at codon 239 (p.(Ala239Thr)) 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). Additionally, this variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.902, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent from gnomAD v2.1.1 and v4.1 (PM2_Supporting). This variant was identified in 5 unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4_Moderate; internal lab contributors). Furthermore, this variant segregated with diabetes with at least 4 informative meioses in four families (PP1_Strong; internal lab contributors). In summary, c.707G>A meets the criteria to be classified as likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 2.1.1, approved 8/11/2023): PM1_Supporting, PM2_Supporting, PP3, PS4_Moderate, PP1_Strong.

Met criteria codes

PP1_Strong	✔	This variant segregated with diabetes with at least 4 informative meioses in four families (PP1_Strong; 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_Moderate	✔	This variant was identified in 5 unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4_Moderate; internal lab contributors).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 and v4.1 (PM2_Supporting).
PP3	✔	REVEL 0.902

Curation History

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