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Variant: NM_000545.8(HNF1A):c.827C>A (p.Ala276Asp)

Version: 1.0

CA124481

14945 (ClinVar)

Gene: HNF1A (HGNC:6927)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Autosomal dominant inheritance
UUID: b1ec8b81-961e-47de-94da-be293288ac39
Approved on: 2022/4/18
Published on: 2022/4/18

HGVS expressions

NM_000545.8:c.827C>A
NM_000545.8(HNF1A):c.827C>A (p.Ala276Asp)
NC_000012.12:g.120994277C>A
CM000674.2:g.120994277C>A
NC_000012.11:g.121432080C>A
CM000674.1:g.121432080C>A
NC_000012.10:g.119916463C>A
NG_011731.2:g.20532C>A
ENST00000560968.6:c.750+77C>A
ENST00000257555.11:c.827C>A
ENST00000257555.10:c.827C>A
ENST00000400024.6:c.827C>A
ENST00000402929.5:n.962C>A
ENST00000535955.5:n.43-3214C>A
ENST00000538626.2:n.191-3214C>A
ENST00000538646.5:c.640C>A
ENST00000540108.1:c.*267C>A
ENST00000541395.5:c.827C>A
ENST00000541924.5:c.713+571C>A
ENST00000543427.5:c.633+651C>A
ENST00000544413.2:c.827C>A
ENST00000544574.5:c.73-2340C>A
ENST00000560968.5:c.893+77C>A
ENST00000615446.4:c.-257-1985C>A
ENST00000617366.4:c.586+698C>A
NM_000545.5:c.827C>A
NM_000545.6:c.827C>A
NM_001306179.1:c.827C>A
NM_001306179.2:c.827C>A

Pathogenic

Met criteria codes 6

PS3_Supporting PM1_Supporting PP4_Moderate PP1_Strong PM5_Supporting PP3

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

Not Met criteria codes 2

PS4 PM2

Evidence Links 0

Criteria Specification: *ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1.1*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.827C>A variant in the HNF1 homeobox A gene, HNF1A, causes an amino acid change of alanine to aspartic acid at codon 276 (p.(Ala276Asp)) of NM_000545.8. This variant is located within a conserved region of the DNA binding domain (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 0.956, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant was identified in two individuals with a clinical history highly specific for HNF1A-MODY (MODY probability calculator result >50%, negative genetic testing for HNF4A, antibody-negative, and response to low-dose sulfonylurea (PP4_Moderate, internal lab contributors). Another missense variant, c.827C>G (p.Ala276Gly), has been classified as likely pathogenic by the ClinGen MDEP (PM5_Supporting). Also, the variant segregated with diabetes, with four informative meioses in two families with MODY (PP1_Strong; internal lab contributors). Functional studies demonstrated abnormal nuclear localization, DNA binding less than 40% of wildtype, and normal transactivation (PS3_Supporting; PMID:12574234). This variant is absent from the gnomAD European non-Finnish population, but two copies are present in the African population; therefore PM2_Supporting cannot be applied. This variant was identified in at least 12 unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes; however, PS4 cannot be applied because the variant MAF in gnomAD is above the ClinGen MDEP PM2_Supporting cutoff (PMID: 12574234, internal lab contributors). In summary, c.827C>A meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.1, approved 9/30/2021): PP1_Strong, PP4_Moderate, PP3, PM1_Supporting, PM5_Supporting, PS3_Supporting.

Met criteria codes

PS3_Supporting	✔	Functional studies demonstrated abnormal nuclear localization, DNA binding 30% of WT, and normal transactivational activity (no correlation between DNA binding and transactivation activity).
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.
PP4_Moderate	✔	This variant was identified in two individuals with a clinical history highly specific for HNF1A-MODY (MODY probability calculator result of greater than 50%, negative genetic testing for HNF4A, antibody negative, and sulfonylurea-sensitive).
PP1_Strong	✔	This variant segregated with diabetes, with four informative meioses in two families with MODY (internal lab contributors).
PM5_Supporting	✔	The p.Ala276Gly variant has been interpreted as likely pathogenic by the MDEP.
PP3	✔	REVEL 0.956 + GERP, FATHMM, LRT, MetaLR, MetaSVM, MutationAssessor, MutationTaster, PROVEAN and SIFT all predict deleterious

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Not Met criteria codes

PS4	✖	This variant was identified in at least 12 unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes; however, PS4 cannot be applied because the variant MAF in gnomAD is above the ClinGen MDEP PM2_Supporting cutoff (PMID: 12574234, internal lab contributors).
PM2	✖	This variant is absent from the gnomAD European non-Finnish population, but two copies are present in the African population.

Curation History

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