Variant: NM_000545.6(HNF1A):c.872dup (p.Gly292fs)

Version: 1.1

CA124453

14927 (ClinVar)

Gene: HNF1A (HGNC:6927)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Autosomal dominant inheritance
UUID: cde6fb52-5469-4017-b30d-60b5d552ef1f
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HGVS expressions

NM_000545.6:c.872dup
NM_000545.6(HNF1A):c.872dup (p.Gly292fs)
NC_000012.12:g.120994322dup
CM000674.2:g.120994322dup
NC_000012.11:g.121432125dup
CM000674.1:g.121432125dup
NC_000012.10:g.119916508dup
NG_011731.2:g.20577dup
ENST00000560968.6:c.750+122dup
ENST00000257555.11:c.872dup
ENST00000257555.10:c.872dup
ENST00000400024.6:c.872dup
ENST00000402929.5:n.1007dup
ENST00000535955.5:n.43-3169dup
ENST00000538626.2:n.191-3169dup
ENST00000538646.5:c.685dup
ENST00000540108.1:c.*312dup
ENST00000541395.5:c.872dup
ENST00000541924.5:c.713+616dup
ENST00000543427.5:c.633+696dup
ENST00000544413.2:c.872dup
ENST00000544574.5:c.73-2295dup
ENST00000560968.5:c.893+122dup
ENST00000615446.4:c.-257-1940dup
ENST00000617366.4:c.586+743dup
NM_000545.5:c.872dup
NM_001306179.1:c.872dup
NM_000545.8:c.872dup
NM_001306179.2:c.872dup

Pathogenic

Met criteria codes 3

PP1_Strong | PS2_Moderate | PVS1

Not Met criteria codes 2

PS4 | PM2

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

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.872dupC variant in the HNF1 homeobox A gene, HNF1A, causes a frameshift in the protein at codon 292 (NM_000545.8), adding 25 novel amino acids before encountering a stop codon (p.(Gly292ArgfsTer25)). This variant, located in biologically-relevant exon 4 of 10, is predicted to lead to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1; PMID: 23348805). Additionally, this variant segregated with diabetes, with at least 100 informative meioses in multiple families with MODY (PP1_Strong; internal lab contributors). This variant was identified as a de novo occurrence with confirmed parental relationships in one individual and unconfirmed parental relationships in another individual with diabetes, but whose clinical picture is suggestive but not highly specific for HNF1A-MODY (MODY probability calculator result >50% but HNF4A not tested) (PS2_Moderate; PMID:9166684, internal lab contributors). The variant is located in a poly-C tract and failed QC in gnomAD v2.1.1 in a manner typical of single base deletions in poly-C tracts in NGS; therefore, PM2_Supporting could not be applied. This variant was identified in at least 200 unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes; however, PS4_Moderate cannot be applied because PM2_Supporting cannot be applied (internal lab contributors). In summary, c.872dupC 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 9/30/21): PVS1, PS2_Moderate, PP1_Strong.

Met criteria codes

PP1_Strong	✔	This variant segregated with disease with at least 100 informative meioses observed in multiple families with MODY (internal laboratory contributors).
PS2_Moderate	✔	This variant was found in two individuals with diabetes (MPC >50% but HNF4A not tested), one confirmed de novo and one assumed de novo (PMID: 9166684, internal lab contributor).
PVS1	✔	This variant is predicted to cause loss of function by resulting in nonsense mediated decay of a biologically relevant transcript.

Not Met criteria codes

PS4	✖	This variant was identified in at least 200 unrelated individuals with non- autoimmune and non-absolute/near-absolute insulin-deficient diabetes; however, PS4_Moderate cannot be applied because the variant failed QC in gnomAD and it cannot be determined if PM2_Supporting applies (internal lab contributors). PS4 cannot be used if PM2_supporting does not apply.
PM2	✖	Failed gnomAD QC.

Curation History

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