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_001369369.1(FOXN1):c.880G>C (p.Val294Leu)

Version: 1.0

CA398323707

644342 (ClinVar)

Gene: FOXN1 (HGNC:8456)
Condition: T-cell immunodeficiency, congenital alopecia, and nail dystrophy (MONDO:0011132)
Inheritance Mode: Semidominant inheritance
UUID: 1a17ad23-4a69-49ba-94f0-ea6d369b6360
Approved on: 2024/7/29
Published on: 2024/7/29

HGVS expressions

NM_001369369.1(FOXN1):c.880G>C (p.Val294Leu)
NM_001369369.1:c.880G>C
NC_000017.11:g.28530798G>C
CM000679.2:g.28530798G>C
NC_000017.10:g.26857816G>C
CM000679.1:g.26857816G>C
NC_000017.9:g.23881943G>C
NG_007260.1:g.11858G>C
ENST00000577936.2:c.880G>C
ENST00000579795.6:c.880G>C
ENST00000226247.2:c.880G>C
ENST00000481916.6:c.*1195+73253C>G
ENST00000579795.5:c.880G>C
NM_003593.2:c.880G>C
NM_003593.3:c.880G>C

Likely Pathogenic

Met criteria codes 4

PM1 PS3_Moderate PP3 PM2_Supporting

Not Met criteria codes 3

PM5 PS4 PP4

Evidence Links 1

Expert Panel

Severe Combined Immunodeficiency Disease VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Severe Combined Immunodeficiency Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for FOXN1 Version 1.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Severe Combined Immunodeficiency Disease VCEP

The NM_001369369.1(FOXN1):c.880G>C (p.Val294Leu) missense variant is located within the DNA binding forkhead domain (amino acids 270-367) at amino acid position 294, and thus meets PM1. The variant has a REVEL score of 0.68 which is above the SCID VCEP specified

threshold of ≥0.644 to support a deleterious effect of the variant (PP3). The variant is absent from gonmADv2.1.1 (PM2_supporting). A comprehensive literature search, did not identify the variant in any individuals with T-cell immunodeficiency, congenital alopecia, and nail dystrophy, however personal communication with Invitae confirmed the variant has been observed in one neonate with low TRECs. A luciferase reporter construct was cotransfected into heterologous cells together with an expression vector containing FOXN1. This variant had 13.5% luciferase activity compared to WT, which is below the <50% threshold for PS3_moderate (PMID: 37419334). In summary this variant meets criteria to be classified as likely pathogenic for semidominant T-cell immunodeficiency, congenital alopecia, and nail dystrophy due to FOXN1 deficiency based on the ACMG/AMP criteria applied: PM1, PM2_supporting, PS3_Moderate, and PP3, as specified by the ClinGen SCID VCEP FOXN1 subgroup.

Met criteria codes

PM1	✔	The missense variant is located within the DNA binding forkhead domain (amino acids 270-367) at amino acid position 294, and thus meets PM1.
PS3_Moderate	✔	A luciferase reporter construct was cotransfected into heterologous cells together with an expression vector containing FOXN1. This variant had 13.5% luciferase activity compared to WT, which is below the <50% threshold for PS3_moderate (PMID: 37419334). A luciferase reporter construct was cotransfected into heterologous cells together with an expression vector containing FOXN1. This variant had 13.5% luciferase activity compared to WT, which is below the <50% threshold for PS3_moderate **PubMed:37419334**
PP3	✔	The variant has a REVEL score of 0.68 which is above the SCID VCEP specified threshold of ≥0.644 to support a deleterious effect of the variant (PP3).
PM2_Supporting	✔	The variant is absent from gonmADv4.0 (PM2_supporting).

Not Met criteria codes

PM5	✖	This variant occurs at the same codon as a previously identified variant, NM_001369369.1(FOXN1):c.880G>A (p.Val294Ile), which has been classified Pathogenic by the SCID VCEP. It is not considered here to avoid circularity.
PS4	✖	The variant has been seen in one patient, by Invitae, with low TRECs (0.25pt; insufficient for PS4)
PP4	✖	Invitae patient with low TRECs (insufficient to apply PP4).

Curation History

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