Variant: NM_001369369.1(FOXN1):c.965A>G (p.Asn322Ser)

Version: 1.0

CA398324499

573130 (ClinVar)

Gene: FOXN1 (HGNC:8456)
Condition: T-cell immunodeficiency, congenital alopecia, and nail dystrophy (MONDO:0011132)
Inheritance Mode: Semidominant inheritance
UUID: 478b8236-0260-49a4-b20f-6bd7fa6b29de
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HGVS expressions

NM_001369369.1:c.965A>G
NM_001369369.1(FOXN1):c.965A>G (p.Asn322Ser)
NC_000017.11:g.28534368A>G
CM000679.2:g.28534368A>G
NC_000017.10:g.26861386A>G
CM000679.1:g.26861386A>G
NC_000017.9:g.23885513A>G
NG_007260.1:g.15428A>G
ENST00000577936.2:c.965A>G
ENST00000579795.6:c.965A>G
ENST00000226247.2:c.965A>G
ENST00000481916.6:c.*1195+69683T>C
ENST00000579795.5:c.965A>G
NM_003593.2:c.965A>G
NM_003593.3:c.965A>G

Likely Pathogenic

Met criteria codes 4

PM2_Supporting PS3 PM1 PP3_Moderate

Not Met criteria codes 1

PP4

Evidence Links 0

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 2.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Severe Combined Immunodeficiency Disease VCEP

The variant NM_001369369.1(FOXN1):c.965A>G is predicted to cause a asparagine to serine substitution at amino acid position 322. The variant is absent from gnomAD 4.0 (PM2_supporting). The meta predictor REVEL predicts a potential disrupting effect on protein function

with a score of 0.947, above the ≥0.932 threshold for PP3_moderate. The missense variant is located within the DNA binding forkhead domain (amino acids 270-367) at amino acid position 322, and thus meets PM1. The variant was found in the heterozygous state in patient 5 from PMID:30809743 who had lymphopenia CD3 1007, CD4 782, reduced NBS TRECs 12 copies/uL. The patient was gene panel sequenced for SCID related genes. Additionally, in an unpublished mouse model, the variant when expressed in mice in the heterozygous state recapitulated features of FOXN1 immunodeficiency including T cell lymphopenia, decreased thymocytes, and a decreased thymic epithelial component. Heterozygous mice had normal FOXN1 protein expression and did not display hair loss (PS3). In summary this variant meets criteria to be classified as Likely Pathogenic for semidominant cell immunodeficiency, congenital alopecia, and nail dystrophy due to FOXN1 deficiency based on the ACMG/AMP criteria applied: PM1, PP3_moderate, PS3, and PM2_supporting as specified by the ClinGen SCID VCEP FOXN1 subgroup.

Met criteria codes

PM2_Supporting	✔	Variant is absent from gnomADv4.1.
PS3	✔	From unpublished data, the variant when expressed in mice in the heterozygous state recapitulated features of FOXN1 immunodeficiency including T cell lymphopenia, decreased thymocytes, and a decreased thymic epithelial component. Heterozygous mice had normal FOXN1 protein expression and did not display hair loss.
PM1	✔	The missense variant is located within the DNA binding forkhead domain (amino acids 270-367) at amino acid position 322, and thus meets PM1.
PP3_Moderate	✔	A deleterious effect is predicted by REVEL with a score of 0.947, above the ≥0.932 threshold for PP3_moderate.

Not Met criteria codes

PP4	✖	Found in the heterozygous state in one patient (patient 5) from PMID:30809743 who had CD3 1007 and CD4 782 cell counts, reduced NBS TRECs 12 copies/uL (0.25pt), The patient was gene panel sequenced for SCID related genes (0.5pt) (Total 0.75pt, PP4_NotMet).

Curation History

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