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Variant: NM_003593.3:c.880G>A

Version: 1.0

CA398323709

Gene: FOXN1 (HGNC:8456)
Condition: T-cell immunodeficiency, congenital alopecia, and nail dystrophy (MONDO:0011132)
Inheritance Mode: Semidominant inheritance
UUID: eab22ed7-b1c5-444f-ba9f-0de25bfa14bd
Approved on: 2024/7/29
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HGVS expressions

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

Pathogenic

Met criteria codes 8

PM3_Supporting PS3_Moderate PM2_Supporting PM1 PM5_Supporting PP1 PP3 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 1.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Severe Combined Immunodeficiency Disease VCEP

The missense variant NM_001369369.1(FOXN1):c.880G>A (p.Val294Ile) is located within the DNA binding forkhead domain (amino acids 270-367) at amino acid position 294, and thus meets PM1. This variant occurs at the same codon as Val294Leu which has been classified as Likely Pathogenic by the SCID VCEP (PM5_supporting). The variant has a REVEL score of 0.731 which is above the SCID VCEP specified

threshold of ≥0.644 to support a deleterious effect of the variant (PP3). A luciferase reporter construct was cotransfected into heterologous cells together with an expression vector containing FOXN1. The Val294Ile variant had 18% luciferase activity compared to WT which is below the <50% threshold for PS3_moderate(PMID: 37419334). The highest MAF in gnomAD v2.1.1 is 0.000008790 (1/113770 alleles) in the European (non-Finnish) population. This is below the SCID VCEP specified threshold of <0.00002412 (PM2_supporting). Patient P2 (PMID: 30903456) is homozygous for this variant (PM3_supporting), and was diagnosed with T-B+NK+ SCID with absent CD3+ cells and absent TRECs, a poor proliferative response to PHA, athymia, alopecia totalis, and nail dystrophy. The patient was sequenced using a NGS panel of 18 common SCID-related genes and Sanger sequencing for FOXN1. Together this is a highly specific phenotype for FOXN1-related T-cell immunodeficiency, congenital alopecia, and nail dystrophy (PP4). Siblings P1 and P2 (PMID: 30903456) are both affected with T-B+NK+ SCID and homozygous for this variant (PP1), the parents are both heterozygous and do not have any immunodeficiency but have decreased T cell counts and reduced TREC levels compared to age-matched controls. 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, PM5_supporting, PP3, PS3_moderate, PM2_supporting, PM3_supporting, PP1, and PP4, as specified by the ClinGen SCID VCEP FOXN1 subgroup.

Met criteria codes

PM3_Supporting	✔	Patient P2 (PMID: 30903456) is homozygous for this variant (1pt; PM3_supporting).
PS3_Moderate	✔	A luciferase reporter construct was cotransfected into heterologous cells together with an expression vector containing FOXN1. The Val294Ile variant had 18% luciferase activity compared to WT which is below the <50% threshold for PS3_moderate (PMID: 37419334).
PM2_Supporting	✔	The highest MAF in gnomADv4.0 is 0.000002705 (3/1108866 alleles) in the European (non-Finnish) population. This is below the SCID VCEP specified threshold of <0.00002412 (PM2_supporting).
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.
PM5_Supporting	✔	This variant occurs at the same codon as Val294Leu which has been classified as Likely Pathogenic by the SCID VCEP (PM5_supporting).
PP1	✔	Siblings P1 and P2 (PMID: 30903456) are both affected with T-B+NK+ SCID and homozygous for this variant, the parents are both heterozygous and do not have any immunodeficiency but have decreased T cell counts and reduced TREC levels compared to age-matched controls.
PP3	✔	The variant has a REVEL score of 0.731 which is above the SCID VCEP specified threshold of ≥0.644 to support a deleterious effect of the variant (PP3).
PP4	✔	Patient P2 (PMID: 30903456) homozygous for this variant, was diagnosed with T-B+NK+ SCID with absent CD3+ cells (0.5pt). There were also absent TRECs and a poor proliferative response to PHA, athymia, alopecia totalis (0.25pt), and nail dystrophy (0.25pt). The patient was sequenced using a NGS panel of 18 common SCID-related genes and Sanger sequencing for FOXN1 (0.5pt). Total 1.5pt (PP4)

Curation History

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