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Variant: NM_001369369.1(FOXN1):c.1049C>T (p.Pro350Leu)

Version: 1.0

CA8459424

1966519 (ClinVar)

Gene: FOXN1 (HGNC:8456)
Condition: T-cell immunodeficiency, congenital alopecia, and nail dystrophy (MONDO:0011132)
Inheritance Mode: Semidominant inheritance
UUID: 2d1eb815-6c23-4456-b617-5f09db470564
Approved on: 2024/9/27
Published on: 2024/9/27

HGVS expressions

NM_001369369.1:c.1049C>T
NM_001369369.1(FOXN1):c.1049C>T (p.Pro350Leu)
NC_000017.11:g.28534452C>T
CM000679.2:g.28534452C>T
NC_000017.10:g.26861470C>T
CM000679.1:g.26861470C>T
NC_000017.9:g.23885597C>T
NG_007260.1:g.15512C>T
ENST00000577936.2:c.1049C>T
ENST00000579795.6:c.1049C>T
ENST00000226247.2:c.1049C>T
ENST00000481916.6:c.*1195+69599G>A
ENST00000579795.5:c.1049C>T
NM_003593.2:c.1049C>T
NM_003593.3:c.1049C>T

Likely Pathogenic

Met criteria codes 5

PM2_Supporting PP3 PP4 PM1 PM3_Supporting

Not Met criteria codes 1

PS3

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

NM_001369369.1(FOXN1):c.1049C>T (p.Pro350Leu) is a missense variant predicted to cause a proline to leucine substitution at amino acid residue 350. The variant has been found, by whole exome sequencing, in at least one compound heterozygous patient with FOXN1

deficiency (P9, PMID: 33464451). The patient displayed alopecia and low t-cell numbers (less than 1,000,000 cells/L) (PP4). They also had poor proliferative response to phytohemagglutinin on total cells, though normal when evaluated on separated T cells, flow cytometric analysis showed near complete absence of CD45RA+ CD4 T cells, and they had very low TRECs. They received a thymus transplant but T cell levels were not reported post transplant. Interestingly the patients alopecia spontaneously reversed at age 3. The patient (P9 of PMID: 33464451) is compound heterozygous with pathogenic variant NM_001369369.1(FOXN1):c.246C>A (p.Cys82Ter), confirmation of trans phase not reported (PM3_supporting). The variant has a gnomADv4.1 Grpmax filtering allele frequency of 0.000003590, which is based upon the European (non-Finnish) population (9/1180006 alleles), which is lower than the ClinGen SCID VCEP threshold (≤0.00002412) for PM2_Supporting. The computational predictor REVEL gives a score of 0.893, which is above the threshold of ≥0.644, evidence that correlates with impact to FOXN1 function (PP3). Additionally, this variant is found within the DNA binding forkhead domain, a well established functional domain (PM1). In vitro assays demonstrated conflicting results, the p.Pro350Leu variant showed significantly reduced activity in a luciferase assay (<50%) from PMID: 33464451, though the variant showed only partial loss of function (88%) in another luciferase assay as part of a validated assay with pathogenic and benign controls (PMID: 37419334, PS3 not met). This may be a mild hypomorphic variant, contributing to the patients phenotype in the context of a second pathogenic variant. 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: PP4, PP3, PM2_supporting, PM3_supporting, PM1 as specified by the ClinGen SCID VCEP FOXN1 subgroup (Pilot, date of approval 03/01/2024).

Met criteria codes

PM2_Supporting	✔	The variant has a gnomADv4.1 Grpmax filtering allele frequency of 0.000003590, which is based upon the European (non-Finnish) population (9/1180006 alleles), which is lower than the ClinGen SCID VCEP threshold (≤0.00002412) for PM2_Supporting,
PP3	✔	The computational predictor REVEL gives a score of 0.893, which is above the threshold of ≥0.644, evidence that correlates with impact to FOXN1 function (PP3)
PP4	✔	At least one patient (P9 of PMID: 33464451) with this variant displayed alopecia (0.25 pts) and low t-cell numbers (less than 1,000,000 cells/L; 0.5pts). The patient had whole exome sequencing (0.5pt) Total 1.25pt (PP4). The patient also had poor proliferative response to phytohemagglutinin on total cells, while it was normal when evaluated on separated T cells, flow cytometric analysis showed near complete absence of CD45RA+ CD4 T cells, and they had very low TRECs. They received a thymus transplant but T cell levels were not reported post transplant. Interestingly the patients alopecia spontaneously reversed at age 3.
PM1	✔	This variant is found in the DNA binding forkhead domain (amino acids 270-367), which is a well-established functional domain (Newman et al., 2020; PMID: 31914405) of FOXN1, which has low tolerance for benign variation (PM1).
PM3_Supporting	✔	The patient (P9 of PMID: 33464451) is compound heterozygous with pathogenic variant NM_001369369.1(FOXN1):c.246C>A (p.Cys82Ter), confirmation of trans phase not reported (0.5pt; PM3_supporting)

Not Met criteria codes

PS3	✖	The p.Pro350Leu variant showed significantly reduced activity in a luciferase assay (<50%) from PMID: 33464451, though the variant showed only partial loss of function (88%) in another luciferase assay as part of a validated assay with pathogenic and benign controls (PMID: 37419334).

Curation History

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