

FOXI3 Variant Associated with Persistent T Cell Lymphopenia

Abstract

FOXI3 is a transcription factor essential for pharyngeal arch development, with certain variants linked to autosomal dominant craniofacial microsomia. Emerging evidence implicates specific FOXI3 mutations in thymic hypoplasia and lymphopenia, akin to 2p11.2 deletions involving the FOXI3 locus. We describe a full-term female infant identified through newborn screening with low TREC levels, subsequently referred for immunologic evaluation. She demonstrated a low absolute number of TREC copies, moderately decreased CD4 (~600 cells/ μ L) and CD8 (~200 cells/ μ L) T cell counts with preserved functional responses. Additional findings included mild hypogammaglobulinemia and mild B cell lymphopenia age-appropriate class-switched memory B cells. Genetic analysis revealed a missense variant of uncertain significance in FOXI3 (c.512T>C, p.Ile171Thr) within the DNA-binding domain, alongside variants in DNAAF4 (heterozygous frameshift) and G6PD (pathogenic). Cytogenomic studies were unremarkable. We propose FOXI3 haploinsufficiency as a potential mechanism underlying her T cell lymphopenia. At 20 months of age, she remains clinically stable on trimethoprim-sulfamethoxazole prophylaxis, without significant infections, and live viral vaccines have been withheld. This case highlights the potential role of FOXI3 in thymic function and T cell development. The long-term prognosis remains uncertain, underscoring the need for further biochemical and functional studies to clarify the pathogenicity of FOXI3 variants and optimize clinical management strategies.

Background

- The newborn born screening (NBS) program evaluates for many heritable disorders including severe combined immunodeficiency (SCID). The screen has been able to identify non-SCID immune deficiencies (e.g., 22q11 deletion).
- Several chromosomal disorders such as 22q11.2 and 2p11.2 deletions are associated with variable thymic aplasia and T cell lymphopenia.
- The FOXI3 (forkhead box transcription factor) protein is a critical transcription factor for the development of ectodermal structures and the pharyngeal arch.
- Loss of the FOXI3 locus is likely responsible for the phenotype seen with 2p11.2 deletions.
- Pathogenic heterozygous nonsense and frameshift variants in FOXI3 contribute to thymic hypoplasia and T cell lymphopenia (TCL) without dysmorphic features (Gosh et al).
- We present the case of a newborn baby girl with an abnormal NBS for SCID and was found to have non-SCID T cell lymphopenia secondary to a FOXI3 missense variant.

Patient

- African-American female evaluated at 4 weeks old in the setting of abnormal newborn concerning for HIGH RISK SCID.
- Born at 35 weeks to non-consanguineous parents.
- C-section; BW <25000g; APGAR 8 and 9 (1 & 5 min).
- No family history of immunodeficiency or immune dysregulation.
- Infection history: COVID, parainfluenza, AOM

Laboratory Evaluation

CBC ($\times 10^3/\mu$ L)	Normal Range	Patient	Antibody	Normal Range	Patient
WBC	6.48-13	3.04	IgM	19-146	45
RBC ($\times 10^6/\mu$ L)	3.9-5.01	4.61	IgG	453-916	517
Platelet Count	214-459	344	IgA	20-100	35
Absolute Neutrophils	1.27-7.18	0.86	Tetanus	>0.1	1.8
Absolute Lymphocytes	1.52-8.09	1.72	Diphtheria	>0.1	0.5
			S.pneum	>1.3	10 of 23

T/NK Subsets	1mo		20mo	
	Normal Range	Patient	Normal Range	Patient
TREC (per 10^6 CD3 cells)	>6794	7534		
CD3+ T cells	2500-5500	1,111	2100-6200	988
CD3+ HLA-DR+ T activated	0-250	56	0-250	40
CD3+CD4+ Th cells	1600-4000	807	1300-3400	690
CD3+CD8+ Tc cells	560-1700	268	620-2000	230
CD4:CD8	0.7-2.6	3	0.7-2.6	3
CD3+ CD4+ CD45RA+ Th naïve	1200-3700	775	1000-2900	483
CD3+ CD4+ CD45RO+ Th memory	60-900	32	210-850	207
CD3+ CD8+ CD45RA+ Tc naïve		Not reported	490-1700	216
CD3+ CD8+ CD45RO+ Tc memory		Not reported	60-570	14
CD3- CD56+ CD16+ NK	170-1100	614	180-920	256
CD3- CD19+ (Total B cells)	720-2600			651
CD3- CD19+ CD21+ Mature	238-860			534
CD3- CD19+ CD27- IgM+ IgD+ Naive	120-430			462
CD3- CD19+ CD27+ IgM- IgD- CSM	30-110			111



Thymus present

Normal proliferation with candida antigen stimulation.

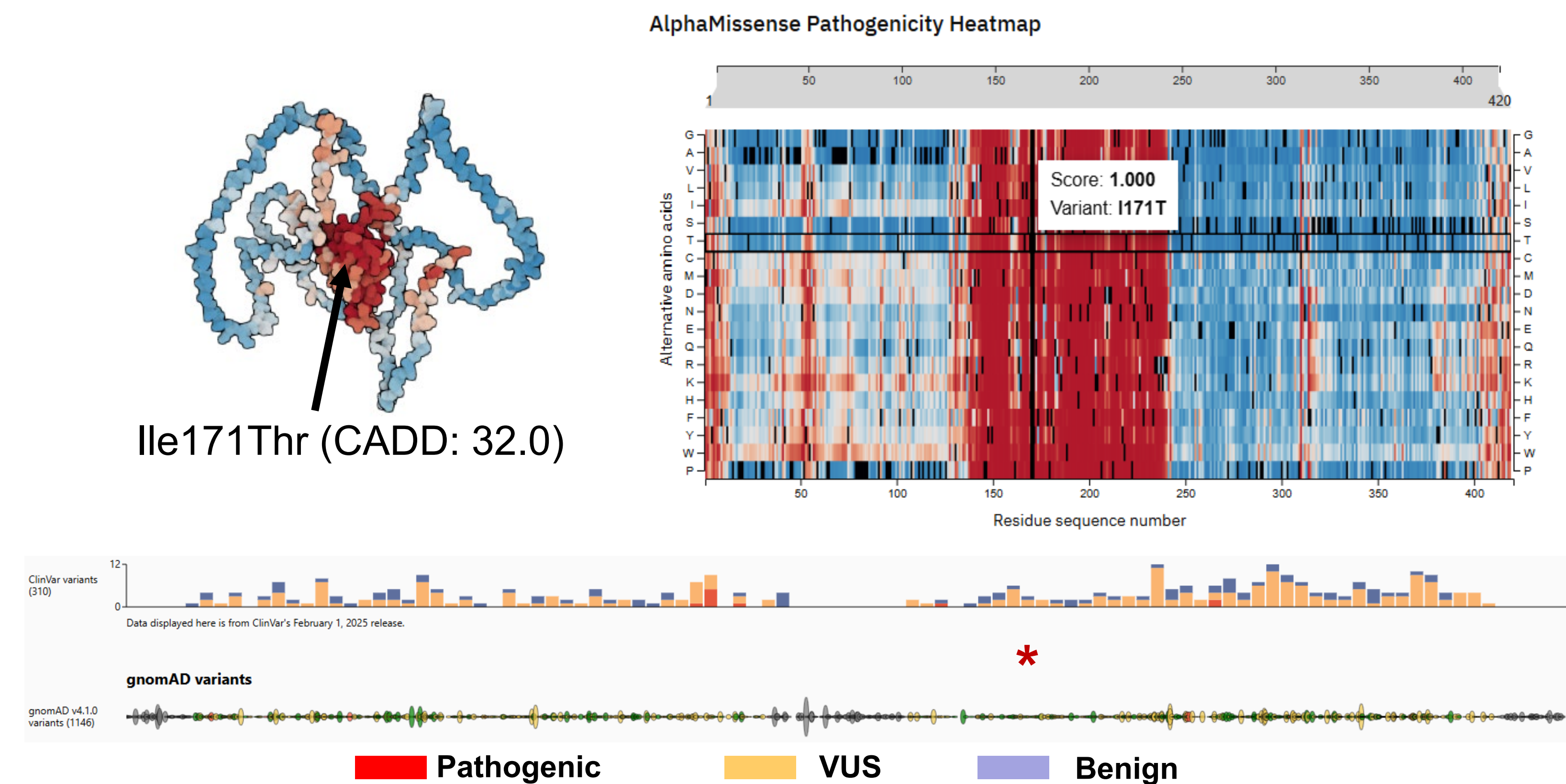
Normal response to tetanus antigen and mitogens (ConA/PWM/PHA).

Red = abnormal * = baseline

Laboratory Evaluation

Genetic Testing

Chromosomal microarray (CMA): normal
FOXI3: c.512T>C (p.Ile171Thr): VUS
DNAAF4: c.496dup (p.Gln166Profs*5): Pathogenic
KMT2D2a: c.11217_11222del (p.Gln3744_Gln3745del): VUS
G6PD: c.202G>A (p.Val68Met): Pathogenic
G6PD: c.376A>G (p.Asn126Asp): VUS



Discussion

- Patient was started on TMP/SMX prophylaxis and has done well from an infection standpoint.
- Live viral vaccines withheld based on HIV CD8 <250 criteria and CD4 partial DiGeorge anomaly criteria (CD4 >1300 for 1-2 yo).
- Neutropenia is believed to be due to Duffy-null associated neutrophil count (DANC).
- Current case suggests that missense variants in FOXI3 may contribute to the TCL and expands on the varying spectrum of immunodeficiency in patients with IEI involving FOXI3.

Next steps:

- Administered PPV23 challenge after 24mo of age.
- In vitro testing of FOXI3 binding vs activity.
- Develop artificial thymic organoid (ATO) model to study differentiation of patient CD34+ into T cells.

References

- Ghosh R, Bosticardo M, Singh S, Similuk M, Delmonte OM, Pala F, Peng C, Jodarski C, Keller MD, Chinn IK, Groves AK, Notarangelo LD, Walkiewicz MA, Chinen J, Bundy V. FOXI3 haploinsufficiency contributes to low T-cell receptor excision circles and T-cell lymphopenia. J Allergy Clin Immunol. 2022 Dec;150(6):1556-1562. doi: 10.1016/j.jaci.2022.08.005. Epub 2022 Aug 18. PMID: 35987349; PMCID: PMC9742176.
- Bernstock JD, Totten AH, Elkahlon AG, Johnson KR, Hurst AC, Goldman F, Groves AK, Mikhail FM, Atkinson TP. Recurrent microdeletions at chromosome 2p11.2 are associated with thymic hypoplasia and features resembling DiGeorge syndrome. J Allergy Clin Immunol. 2020 Jan;145(1):358-367.e2. doi: 10.1016/j.jaci.2019.09.020. Epub 2019 Oct 7. PMID: 31600545; PMCID: PMC6949372.