Heterozygous TACI Mutation (TNFRSF13B: A181E) Causing Decreased TACI Cell Surface Expression,Significant Infections in a Patient with Normal Immunoglobulins and Antibody Response

Shan Shan Wu DO, Jenny Lee MD, Michelle Sergi, David P. McGarry DO, Robert Hostoffer DO

Allergy & Immunology Fellowship Program, University Hospitals, Cleveland Medical Center, Cleveland, Ohio ; Internal Medicine/Pediatrics Program, University Hospitals, Cleveland Medical Center/Rainbow Babies and Children's Hospital, Cleveland, Ohio; Ohio University Heritage College of Osteopathic Medicine, Warrensville Heights, Ohio; Allergy & Immunology Associates Inc, Mayfield Heights, Ohio

INTRODUCTION

Common variable immunodeficiency (CVID) is a primary immune deficiency associated with loss of B-cell functions. Genetics of CVID are multifactorial, although both monogenic and polygenic forms have been described in the literature. Mutations (heterozygote and homozygote) in TNFRSF13B, the gene that encodes the transmembrane receptor, or TACI, are associated with 8-10% of CVID patients.

TACI mutation with reduced TACI expression on marginal zone and CD27+ memory B-cells can impair B-cell differentiation, proliferation, and isotype switching, contributing to the pathogenicity of CVID. Asymptomatic individuals with normal immunoglobulin levels who have TACI mutation are also reported in the current literature. We aim to describe the significance of the heterozygous TNFRSF13B variant in a patient with recurrent sinopulmonary and skin infections without apparent B-cell dysfunction.

CASE REPORT

A 27-year-old male presented with a history of multiple infections since four months old, including recurrent sinopulmonary infections, viral meningitis, mastoiditis, and cellulitis with abscesses of the axilla, thigh, and perianal region. Genetic testing revealed the patient to have the TNFRSF13B, Exon 4.c.542C>A (p.Ala181Glu) heterozygous TACI variant associated with CVID. Serum immunoglobulins, antibody response to both protein and polysaccharide antigens, as well as bacteriophage Φx174 were normal. Due to clinical manifestations and the finding of a pathologic variant associated with CVID, immunoglobulin therapy was initiated, resulting in a decrease in the frequency of skin and sinopulmonary infections. A decrease in TACI expression was identified.

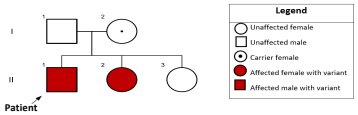

Figure 1. Family pedigree displaying individuals affected with the TACI variant, c.542C>A (p.Ala181Glu).

RESULTS

Immunologic studies for the patient included serum immunoglobulins (IgG, IgA, IgM) and IgG subclasses, B-cell phenotyping, lymphocyte subset markers, mannose-binding lectin, mitogen and antigen stimulation, NK function, bacteriophage study, *Streptococcus pneumoniae* titers to 23 serotypes after administration of *Pneumovax-23* , BAFF-R and TACI receptor expressions and genetic sequence testing of 207 genes associated with primary immunodeficiencies. Genetic testing was also performed on the patient's mother, father, and two sisters.

B Cell Phenotyping	Result, Patient	Result, Mother	Reference Range	Units
CD19 %	17	11	6-19	%
CD19 Absolute	0.223	0.186	0.070-0.910	X 10E9/L
CD19+CD27-IgD+ %	85.5 (H)	59.8	58.0-72.1	%
CD19+CD27+IgD+ %	3.6% (L)	26.1 (H)	13.4-21.4	%
CD19+CD27+IgD- %	6.0 (L)	11.7	9.2-18.9	%
CD19+CD24++CD38++ %	6.1% (H)	4.7% (H)	1.0-3.6	%
CD19+CD24-CD38++ %	2.7% (H)	0.5% (L)	0.6-1.6	%
Serum Immunoglobulins				
IgG	1140	939	700-1600	mg/dL
IgA	167	266	70-400	mg/dL
IgM	98	77	40-230	mg/dL
Antibodies	Response after pneumococcal polysaccharide, Patient	Response after pneumococcal polysaccharide, Mother		
Pneumococcal	11/14	14/14	Protective serotype >1.3	µg/mL
Tetanus	3.88	1.73	<0.10	IU/mL

Table 1. B-cell phenotyping profile, serum immunoglobulins, and pneumococcal and tetanus titers between patient and patient's mother.

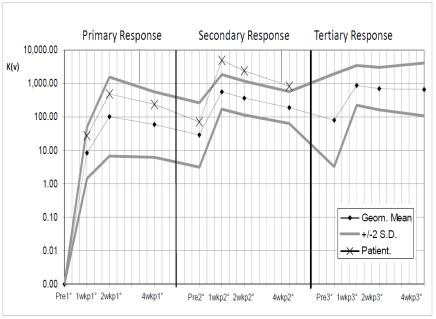

Figure 2. Patient's immune response to bacteriophage

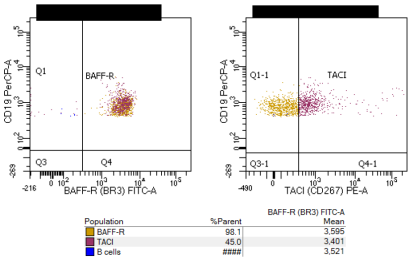

Figure 3a. These four-quadrant scattered plot show normal expression of TACI (control).

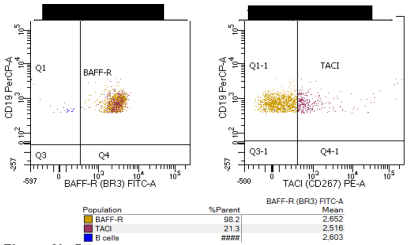

Figure 3b. These four-quadrant scattered plot show decrease expression of TACI (patient).

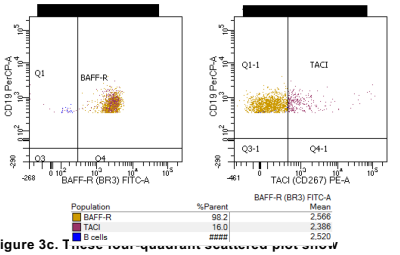

Figure 3c. These four-quadrant scattered plot show decrease expression of TACI (mother).

DISCUSSION

The gene for TACI, TNFRSF13B, is found on the short arm of chromosome 17 at position 11.2. One of the most common TACI variant in CVID is A181E, located within the transmembrane (TM) domain on Exon 4.

Our patient exhibited similar clinical presentations as those diagnosed with CVID and has the same pathologic variant associated with CVID. The patient's mother is the asymptomatic carrier with the same TACI variant. The patient's sister who has a history of multiple though less severe sinopulmonary infections also has the same TACI variant. His father and one other sister who are both asymptomatic do not have the TACI mutation.

The patient's clinical phenotype and improvement with Ig therapy indicate a dysregulation in B-cell differentiation and proliferation into memory B-cells and impairment in isotype class-switching commonly found in individuals with CVID harboring TACI mutations. Yet the immunoglobulin levels and vaccine response were appropriate, excluding a diagnosis of CVID. The level of TACI expressions on B cells was reduced for both the patient and the patient's mother to around half that of the control.

We hypothesize that other unmeasurable antibody mechanisms might play a role in the phenotype of this kindred. Other individuals with TACI variants presenting with similar infectious patterns and lab findings as our patient may also benefit from Ig treatment.

CONCLUSION

- CVID is a heterogeneous disease that may be associated with genetic defects.
- TACI mutations found in a small percentage of individuals with CVID result in B-cell dysfunction and hypogammaglobinemia.
- We describe a patient with a heterozygous TNFRSF13B variant with decreased cell surface expression of TACI and with the clinical manifestations of those with CVID despite normal immunologic findings inconsistent with CVID.