

# A Boy Aged 5 Years 10 Months with IgM Deficiency and Antibody Deficiency to *Streptococcus pneumoniae* Associated with *TNFRSF13B* C104R Heterozygous Mutation

Carrie Caruthers, MD, and Alan P. Knutsen, MD

The case is presented of a boy aged 5 years and 10 months with recurrent infections and intermittent thrombocytopenia who had immunoglobulin M (IgM) deficiency and specific antibody deficiency to *Streptococcus pneumoniae*. Whole exome sequencing was performed and revealed a transmembrane activator and calcium modulator and cyclophilin ligand interactor gene mutation, which has been seen in common variable immunodeficiency. He was treated with IgG antibody replacement therapy and has been free of infection with resolution of his thrombocytopenia.

## Introduction

PRIMARY IMMUNODEFICIENCY DISEASES (PIDs) include a vast array of immune defects with the commonality of recurrent infections. With our advancing knowledge, we continue to recognize and define these diseases. Overlap between different primary immunodeficiency diseases may exist, making a definitive diagnosis sometimes a challenge. Our ability to evaluate the human genome further may provide clues to categorize and identify PIDs further. Specific antibody deficiency (SAD) is a B-cell immunodeficiency disorder characterized by normal serum immunoglobulin G (IgG), IgA, and IgM levels, normal antibody responses to protein antigens, but decreased protective antibody responses to *Streptococcus pneumoniae* (Spn).<sup>1,2</sup> SAD is manifested by susceptibility to recurrent sinopulmonary infections. Studies have shown that patients with SAD have decreased memory B-cells compared to patients without SAD.<sup>1</sup> SAD is commonly diagnosed in children and may resolve as the child matures.<sup>3</sup> Common variable immunodeficiency (CVID) is a more severe B-cell immunodeficiency characterized by a decrease in two or more of the serum immunoglobulins, typically IgG or IgA ± IgM, associated with severe antibody deficiency.<sup>4</sup> CVID may be associated with mutations such as *TNFRSF13B*, whereas SAD has not been identified as being associated with gene mutations.<sup>5–8</sup> Recently, Lewis and Gupta<sup>9</sup> reviewed selective IgM deficiency. They reported that a subset of children with selective IgM deficiency may have impaired antibody responses to *S. pneumoniae*. Selective IgM deficiency may resolve spontaneously, and the pathogenesis of selective IgM deficiency is unknown. Here, the case is presented of a boy with IgM deficiency and antibody deficiency to Spn.

## Case Report

A 5-year-old boy with a history of recurrent infections beginning in infancy manifested by frequent otitis media; sinusitis; bronchitis; streptococcal pharyngitis; hand, foot, and mouth disease; and roseola. He also had a history of intermittent thrombocytopenia with a normal to decreased mean platelet volume (MPV) ranging from 5.5 to 9.0 fL. He was evaluated by the hematology department for Wiskott–Aldrich syndrome (WAS) and had normal WAS protein (WASP) gene analysis and protein expression by flow cytometry.

He was referred for further immunologic evaluation at the age of 5 years and 10 months. As seen in Table 1, his serum IgM (<5 mg/dL) was decreased with normal serum IgG (802 mg/dL) and IgA (102 mg/dL) levels, normal IgG antibodies to diphtheria toxoid, tetanus toxoid, and *Hemophilus influenzae* type B (HiB) immunizations. Repeat serum IgM levels were persistently decreased (<5, 12, 18, and 8 mg/dL; Table 1). Anti-Spn antibody titers were decreased (<1.3 µg/mL) to 19 of 23 serotypes (17.4% protective), and 8 weeks after receiving Spn 23-seotype polysaccharide vaccination (Pneumovax<sup>®</sup>), repeat anti-Spn antibody titers were still decreased to 21 of 23 serotypes (8.7% protective). There were decreased CD3<sup>+</sup> T-cells, 1,076 cells/mm<sup>3</sup>, CD4<sup>+</sup> T-cells, 520 cells/mm<sup>3</sup>, and CD8<sup>+</sup> T-cells, 269 cells/mm<sup>3</sup>, and CD19<sup>+</sup> B-cells, 179 cells/mm<sup>3</sup>. Naïve CD4<sup>+</sup>CD45 RA<sup>+</sup> T-cells were decreased (38%) and memory CD4<sup>+</sup>CD45 RO<sup>+</sup> T-cells were increased (72%). Repeat studies at the age of 7 years 8 months revealed a similar pattern (Table 1). Lymphoproliferative responses to mitogen and antigen stimulations were normal. A diagnosis of IgM deficiency and antibody deficiency to Spn was made. The patient was started initially with intravenous immunoglobulin (IVIG) at 6 years

TABLE 1. IMMUNOLOGIC FINDINGS IN A BOY AGED 5 YEARS 10 MONTHS WITH IgM DEFICIENCY AND ANTIBODY DEFICIENCY TO *STREPTOCOCCUS PNEUMONIAE* ASSOCIATED WITH *TNFRSF13B* C104R HETEROZYGOUS MUTATION

|                                                          | Patient      |            | Normal      |
|----------------------------------------------------------|--------------|------------|-------------|
| Age, years                                               | 5 10/12      | 7 8/12*    |             |
| IgG, mg/dL                                               | 802          | 1,095      | 508–1,359   |
| IgA, mg/dL                                               | 102          | 103        | 23–144      |
| IgM, mg/dL                                               | <b>&lt;5</b> | <b>8</b>   | 40–163      |
| IgE, IU/mL                                               | 17           |            | 9–69        |
| IgG-1, mg/dL                                             | 473          |            | 300–850     |
| IgG-2, mg/dL                                             | 138          |            | 60–400      |
| IgG-3, mg/dL                                             | 53           |            | 10–80       |
| IgG-4, mg/dL                                             | 64           |            | 3–80        |
| Anti-diphtheria, µg/mL                                   | 0.4          |            | ≥0.15       |
| Anti-tetanus, µg/mL                                      | 1.8          |            | ≥0.15       |
| Anti-HiB, ng/mL                                          | 10.3         |            | ≥1.0        |
| Anti-Spn, % protective                                   | <b>8.7</b>   |            | ≥50         |
| ALC, cells/mm <sup>3</sup>                               | 1794         |            | 2,300–5,400 |
| CD3 <sup>+</sup> cells/mm <sup>3</sup>                   | <b>1076</b>  | <b>870</b> | 1,400–3,700 |
| CD4 <sup>+</sup> cells/mm <sup>3</sup>                   | <b>520</b>   | <b>534</b> | 700–2,200   |
| CD8 <sup>+</sup> cells/mm <sup>3</sup>                   | <b>269</b>   | <b>224</b> | 490–1,300   |
| CD19 <sup>+</sup> cells/mm <sup>3</sup>                  | <b>179</b>   | <b>140</b> | 390–1,400   |
| CD56 <sup>+</sup> cells/mm <sup>3</sup>                  | 301          | 322        | 130–720     |
| CD4 <sup>+</sup> CD45RA <sup>+</sup> , %                 | <b>38</b>    | <b>39</b>  | 69–97       |
| CD4 <sup>+</sup> CD45RO <sup>+</sup> , %                 | <b>72</b>    | <b>79</b>  | 3–12        |
| CD27 <sup>+</sup> CD19 <sup>+</sup> , %                  | <b>10</b>    | <b>17</b>  | 25–40       |
| IgD <sup>+</sup> CD27 <sup>+</sup> CD19 <sup>+</sup> , % | 9            | 14         | ≥6          |

\*Patient being treated with subcutaneous gammaglobulin (SCGG).

#Normal reference range.<sup>13</sup>

Bold indicates abnormal laboratory study.

ALC, absolute lymphocyte count; HiB, *Hemophilus influenzae* type B; Spn, *Streptococcus pneumoniae*.

old and subsequently switched to subcutaneous gammaglobulin (SCGG). Since starting IVIG/SCGG treatment, the patient has remained free of infections, and his platelets are >100,000 cells/mm<sup>3</sup> with a normal MPV of >9 fL.

Whole exome sequencing (WES, GeneDx) was subsequently performed and identified a heterozygous mutation of the *TNFRSF13B* c. 310T>C (p. C104R). The *TNFRSF13B* gene encodes for transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI), and the heterozygous C104R mutation has been previously identified in patients with CVID. However, it has not been reported in association with IgM deficiency and specific antibody deficiency to Spn.

## Discussion

CVID has been associated with mutations of the *TNFRSF13B* gene encoding the protein TACI.<sup>5–8</sup> TACI is a tumor necrosis factor (TNF) receptor superfamily member, and plays a vital role in the development of humoral immunity. It interacts with B-cell activating factor (BAFF) or proliferation-inducing ligand (APRIL), which causes activation of several transcription factors and initiates isotype switching in B-cells. Mutations of TACI may be homozygous, compound heterozygous, or heterozygous inherited as autosomal recessive or autosomal dominant. Zhang *et al.*<sup>6</sup> reported that there is B-cell dysfunction in those subjects with heterozygous TACI mutations. Haploinsufficiency and dominant-negative effect have been proposed by which

heterozygous human C104R and the corresponding murine C76R TACI mutations lead to antibody deficiency. In a murine C76R heterozygous mutant model, Lee *et al.*<sup>10</sup> reported that antibody responses to type II T-independent trinitrophenylated-Ficoll immunizations were severely impaired. They proposed that the human TACI C104R heterozygous mutation also impaired TACI function due to haploinsufficiency. Subsequently, Garibyan *et al.*<sup>11</sup> reported using an *in vitro* transfection assay that the human heterozygous C104R mutation did not interfere with ligand binding but did dominantly interfere with TACI signaling. C104R mutation is a common mutation of TACI, and 82% of symptomatic patients with recurrent infections with heterozygous C104R mutation had antibody deficiencies, most commonly CVID or selective IgA deficiency (SIGAD).<sup>7</sup> Salzer *et al.*<sup>7</sup> found that 76% of the patients had reduced switched memory B-cells, and 76% patients with heterozygous C104R mutations had switched memory B-cells <2% of their total B-cells. The patient in the present study had a heterozygous mutation with normal serum IgG and IgA levels, but decreased IgM level, antibody deficiency to Spn, and slightly decreased memory B-cells but normal switched B-cells. Heterozygous mutation for C104R increases the risk of developing hypogammaglobulinemia but does not necessarily lead to development of CVID. However, there is evidence of B-cell dysfunction in those subjects with normal serum IgG levels and heterozygous TACI mutations.<sup>6</sup> Patients with heterozygous C104R mutation are also at increased risk compared to patients without any mutations on the *TNFRSF13B* gene for developing autoimmune disorders, especially autoimmune thrombocytopenia, and lymphoproliferation, including malignancies. The present patient had a past medical history of thrombocytopenia, though the etiology was never determined.

WES can be a very useful tool to help identify the genes involved with primary immunodeficiency.<sup>12</sup> With the use of WES, a genetic mutation could be identified in this patient. Despite the many advances that have been made in identifying mutations such as the *TNFRSF13B* gene, further understanding of the clinical application of these mutations will provide insight in future evaluation and treatment options for these patients. The patient in this study presents an unusual presentation of the *TNFRSF13B* gene mutation that differs from previously documented cases. It reinforces the need to explore further other possible gene mutations playing a role in primary immunodeficiency.

## Author Disclosure Statement

No competing financial interests exist.

## References

1. Leiva LE, Monjure H, Sorensen RU. Recurrent respiratory infections, specific antibody deficiencies, and memory B cells. *J Clin Immunol* 2013;33:S57–61.
2. Boyle RJ, Le C, Balloch A, Tang ML-K. The clinical syndrome of specific antibody deficiency in children. *Clin Exp Immunol* 2006;146:486–492.
3. Wolpert J, Knutsen AP. Natural history of selective antibody deficiency to bacterial polysaccharide antigens in children. *Pediatr Asthma Allergy Immunol* 1998;12:183–191.
4. Resnick ES, Moshier EL, Godbold JH, Cunningham-Rundles C. Morbidity and mortality in common variable immune deficiency over 4 decades. *Blood* 2012;119:1650–1657.

5. Salzer U, Chapel H, Webster A, et al. Mutations in TNFRSF13B encoding TACI are associated with common variable immunodeficiency in humans. *Nature Genetics* 2005;37:820–828.
6. Martínez-Gallo, Radigan L, Almejún MB, Martínez-Pomar N, Matamoros N, Cunningham-Rundles C. TACI mutations and impaired B-cell function in subjects with CVID and healthy heterozygotes. *J Allergy Clin Immunol* 2013;131:468–476.
7. Salzer U, Bacchelli C, Buckridge S, et al. Relevance of biallelic versus monoallelic TNFRSF13B mutations in distinguishing disease-causing from risk-increasing TNFRSF13B variants in antibody deficiency syndromes. *Blood* 2009;113:1967–1976.
8. Freiburger T, Ravčukova B, Grodecka L, et al. Sequence variants of the TNFRSF13B gene in Czech CVID and IgAD patients in the context of other populations. *Human Immunol* 2012;73:1147–1154.
9. Louis AG, Gupta S. Primary selective IgM deficiency: an ignored immunodeficiency. *Clin Rev Allergy Immunol* 2014;46:104–111.
10. Lee JJ, Jabara HH, Garibyan L, et al. The C104R mutant impairs the function of transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) through haploinsufficiency. *J Allergy Clin Immunol* 2010;126:1234–1241.
11. Garibyan L, Lobito AA, Siegel RM, Call ME, Wucherpennig KW, Geha RS. Dominant-negative effect of the heterozygous C104R TACI mutation in common variable immunodeficiency (CVID). *J Clin Immunol* 2007;117:1550–1557.
12. Chou J, Ohsumi T, Geha R. Use of whole exome and genome sequencing in the identification of genetic causes of primary immunodeficiencies. *Curr Opin Allergy Clin Immunol* 2012;12:623–628.
13. Shearer WT, Rosenblatt HM, Gelman RS, et al. Lymphocyte subsets in healthy children from birth through 18 years of age: the Pediatric AIDS Clinical Trials Group P1009 study. *J Allergy Clin Immunol* 2003;112:973–980.

Address correspondence to:

Alan P. Knutsen, MD  
*Pediatric Allergy and Immunology*  
*Saint Louis University*  
*1465 S. Grand Boulevard*  
*St. Louis, MO 63104-1095*

E-mail: knutsenm@slu.edu

Received for publication November 17, 2014; accepted after revision December 4, 2014.

**This article has been cited by:**

1. Sorensen Ricardo U.. 2015. Respiratory Infections, Antibody Deficiency, and Gene Mutations. *Pediatric Allergy, Immunology, and Pulmonology* **28**:2, 135-137. [[Citation](#)] [[Full Text HTML](#)] [[Full Text PDF](#)] [[Full Text PDF with Links](#)]