Case Report

Heterozygous Frameshift Genetic Variant in *TNFRSF13C* Gene Associated with Specific Antibody Deficiency Memory Phenotype

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Abstract: Specific antibody deficiency (SAD) is a primary immunodeficiency disease (PID) in which patients present with recurrent sinopulmonary bacterial infections and decreased antibody responses to polysaccharide antigens following vaccination. SAD memory phenotype refers to an initial serologic and clinical response to the 23-valent polysaccharide vaccine followed by the loss of protective antibodies within six months. Various PID can present with diminished specific antibody responses, and it is known that patients with SAD can develop Common Variable Immunodeficiency (CVID) later in life. We present the case of a 7-year-old male with significant history of recurrent sinopulmonary infections since the age of two, who was diagnosed with SAD memory phenotype. A PID genetic panel revealed a *TNFRSF13C* genetic variant of unknown significance in Exon 3: c.534_543delinsAATAGCAGG (p.Ala179Ilefs*46). This variant results in a frameshift in the B cell-activating factor receptor (BAFFR) encoding gene. BAFFR is essential for the survival and maturation of transitional B cells into mature follicular and marginal zone B cells and has an important role in the development of T-independent antibody responses. BAFFR deficiency is known to be a genetic etiology for CVID and heterozygous missense polymorphisms have been implicated as risk factors for the development of CVID. The patient's phenotype, which demonstrates inadequate T-independent antibody responses, correlates with the previously described phenotype of patients with *TNFRSF13C* variants. Here, we present a patient with SAD memory phenotype harboring a frameshift heterozygous variant in BAFFR. This case highlights the need to consider rare genetic causes in patients with PID.

Keywords: Specific Antibody Deficiency; BAFFR; *TNFRSF13C*

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1. Introduction

Specific antibody deficiency (SAD) is a primary immunodeficiency disease (PID) in which patients present with recurrent sinopulmonary bacterial infections and decreased antibody responses to polysaccharide antigens following vaccination. Patients with SAD have normal responses to protein or conjugate vaccines and immunoglobulin levels, including IgA, IgM, IgG and IgG subclasses [1-3]. SAD is estimated to affect up to 6-10% of individuals referred for evaluation of primary immunodeficiency, although it is likely underdiagnosed. SAD is clinically classified in mild, moderate, severe, and memory phenotype based on the persistence and degree of vaccine response. The memory phenotype refers to an initial serologic and clinical response to the 23-valent polysaccharide vaccine followed by the loss of protective antibodies within six months [4]. Various inborn errors of immunity (IEI) can present with diminished specific antibody responses, including some combined immunodeficiencies such as *MALT1* and *RELB* deficiency, Hyper IgE Syndromes including STAT3 LOF, IL-6 receptor deficiency and CARD11 deficiency, and defects with predominantly antibody deficiencies such as common variable immunodeficiency (CVID), CD21, TWEAK deficiency (*TNFSF12* genetic variants), among others [5]. Although the prevalence of

SAD in Puerto Rico is currently unknown, it is likely underreported, as seen in other underrepresented populations.

B cell-activating factor receptor (BAFFR) deficiency was first described in two related patients that presented with late-onset CVID. These first patients carried a homozygous deletion within the BAFFR encoding *TNFRSF13C* gene [6]. BAFFR, which is highly expressed in mature naive follicular or marginal zone B cells but not in plasma cells, is part of the large tumor necrosis factor (TNF)-receptor superfamily (TNFRSF) that includes other receptors such as TACI, CD40, and Fas [7]. TACI (*TNFRSF13B* gene) genetic variants have been reported as the most common genetic defects in patients with CVID [8]. Both homozygous and heterozygous variants in TACI have been described in patients with CVID [9-10]. CVID is the most prevalent clinically significant primary immunodeficiency in humans and is characterized by hypogammaglobulinemia in association with an increased susceptibility to infections and other clinical manifestations of immune dysregulation [11-12]. It has been reported that patients with SAD can develop CVID later in life, and even though cases of CVID have been associated with *TNFRSF13C* homozygous variants and one missense heterozygous variant, frameshift mutations in *TNFRSF13C* have not been reported to be associated with predominantly antibody deficiencies [6, 13-14]. In Puerto Rico, the prevalence of CVID, SAD and genetic variants associated with humoral immunodeficiencies remains unknown. This report aims to present the first documented case of a BAFFR genetic defect in a Puerto Rican pediatric patient, contributing to the understanding of SAD and its genetic underpinnings in this population.

2. Case Presentation

We present the case of a 7-year-old male with history of allergic rhinitis, moderate persistent asthma, and eosinophilic esophagitis (EoE) recently diagnosed with Specific Antibody Deficiency (SAD) at the age of seven. The patient presented with remarkable history of recurrent sinopulmonary infections since the age of two, leading to more than 20 hospitalizations over the last five years. Family history was only remarkable for asthma in paternal grandmother; parents denied consanguinity or family history of inborn errors of immunity. He is followed in the pediatric pulmonary clinic and was given a diagnosis of moderate persistent asthma for which he was started on high dose inhaled corticosteroid (ICS) treatment and leukotriene inhibitors.

Given the patient's unusual medical history, including recurrent bronchitis, acute bacterial sinusitis, and multiple episodes of *Mycoplasma* pneumonia, which often required hospitalization for intravenous antibiotics, genetic testing was ordered by the pulmonary service. The genetic panel for primary immunodeficiencies, primary ciliary dyskinesia, and cystic fibrosis included 471 genes. The genetic testing results were significant for six heterozygous variants of unknown significance (VUS) in genes: *ATM, C6, C9, CIITA, FCHO1, TNFRSF13C*. Besides the *TNFRSF13C* variant in Exon 3 c.534_543delinsAATAGCAGG (p.Ala179Ilefs*46), the other VUS did not correlate with his clinical phenotype.

Following the genetic testing results, further immune evaluation was ordered including immunoglobulin levels, lymphocyte subset panel, and tetanus and diphteria antibody levels that were within normal limits for age (Table 1, 2). However, 23 *Streptococcus pneumonia* titers were only protective for three serotypes (8, 17F, 19F) even though he had received his childhood vaccinations, including four doses of Pneumococcal 13-valent conjugate vaccine. Based on these results, the patient was instructed to get vaccinated with pneumococcal vaccine polyvalent for 23 serotypes (PPV23). Post-vaccination titers showed seroprotective levels (>1.3 μg/mL) for nineteen titers (83%) six weeks after vaccination (Table 3).

Table 1. Lymphocyte subset panel

Lymphocyte subset	**Results**	**Normal Range**
% CD3 T Cells	79	60-76%
Absolute CD3+ Cells	2884	1200-2600 cells/uL
% Cd4	37	31-47%
Absolute CD4+ Cells	1296	650-1500 cells/uL
%CD8	36	18-35%
Absolute CD8+ Cells	1257	370-1100 cells/uL
CD4/CD8 Ratio	1.03	1-3
% CD16+CD56 (NK Cells)	3	4-17%
Absolute NK Cells	95	100-480 cells/uL
%Cd19 (B Cells)	18	13-27%
Absolute CD19+ Cells	669	270-860 cells/uL
Absolute Lymphocytes	3656	1500-6800 cells/uL

Table 1. *Results showing normal B cell count, mildly increased total T cell count, and mildly decreased NK cell count.*

Table 2. Immunoglobulin levels

Immunoglobulin	**Results (mg/DL)**	**Normal Range (mg/DL)**
IgA	74.04	70.00-400.00
IgG	1009.58	700.00-1600.00
IgM	105.74	40.0-230.00

Table 2. *Normal immunoglobulin levels for age.*

Even after vaccination with PPV23 with an adequate protective response and being on antibiotic prophylaxis with macrolides, the patient continued to have recurrent sinopulmonary infections. Given a high suspicion for a humoral immunity defect, 23 pneumococcal serotype titers were repeated six months after vaccination by the Immunology service with results showing seroprotective levels (>1.3 μg/mL) in only 10 out of 23 serotypes (43%) (Table 3, Figure 1). Due to the recurrent *Mycoplasma*

pneumonia diagnoses, an antibody level to *Mycoplasma* was ordered which showed undetected levels of specific IgG.

Table 3. 23 pneumococcal serotype titers

IgG	Pre-vaccination (mcg/mL)	Six weeks Post-vaccination (mcg/mL)	Six months Post-vaccination (mcg/mL)
Serotype 1	0.4	51.9	2.8
Serotype 2	<0.3	9.1	1.7
Serotype 3	<0.3	>44.0	0.4
Serotype 4	<0.3	15.5	0.7
Serotype 5	0.7	61.7	2.5
Serotype 8	3.5	>86.0	11
Serotype 9 (9N)	<0.3	9.8	0.8
Serotype 12 (12F)	<0.3	<0.3	<0.1
Serotype 14 (14)	<0.3	56	6.5
Serotype 17 (17F)	<0.3	40.1	4.8
Serotype 19 (19F)	1.3	35.5	3.3
Serotype 20 (20)	3.3	>54.0	15.6
Serotype 22 (22F)	<0.3	2.4	0.6
Serotype 23 (23F)	0.4	23.1	1
Serotype 26 (6F)	0.6	24.5	0.8
Serotype 34 (10A)	<0.3	1.1	0.3
Serotype 43 (11A)	<0.3	0.7	0.2

Serotype 51 (7F)	0.4	46	1.5
Serotype 54 (15B)	<0.3	1.2	0.9
Serotype 56 (18C)	<0.3	17.2	0.6
Serotype 57 (19A)	<0.3	9	1.3
Serotype 68 (9V)	<0.3	7.9	0.5
Serotype 70 (33F)	<0.3	1.8	0.8

Table 3. *23 Streptococcus pneumoniae IgG levels showing inadequate protective levels pre-PPV23 vaccination, adequate response six weeks post-vaccination, and loss of protective levels six months after PPV23 vaccination.*

Figure 1. 23 pneumococcal serotype titers pre- and post-PPV23 vaccination

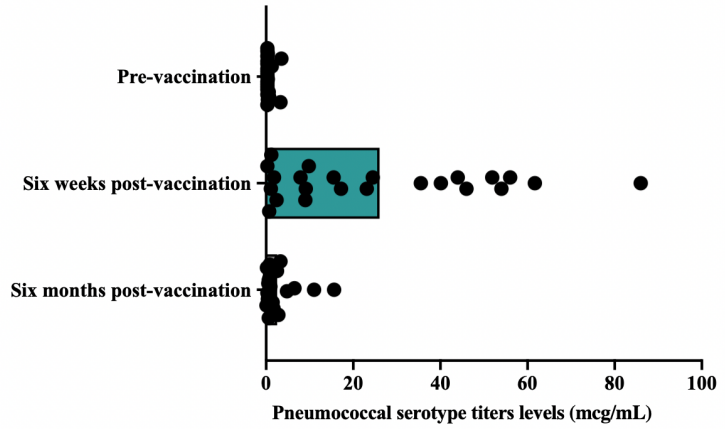

Figure 1. *Visual representation of 23 Streptococcus pneumoniae IgG levels pre- and post-vaccination (six weeks and six months after PPV23 vaccination).*

According to the working group report of the Basic and Clinical Immunology Interest Section of the American Academy of Allergy, Asthma & Immunology, a serotype-specific level of 1.3 mg/mL or greater is considered protective against invasive disease following polysaccharide immunization [4]. Based on the clinical findings and laboratory results, the patient was diagnosed with SAD memory phenotype. The SAD memory phenotype criteria include an adequate initial response to PPV23 (>50% protective for children 2-5 years of age and >70% protective for those 6-65 years of age) with loss of this response within 6 months. At this time the patient was started on immunoglobulin replacement therapy and continues treatment for EoE, Asthma, and Allergic Rhinitis.

3. Discussion

This case describes a pediatric patient with SAD memory phenotype and genetic testing results showing a VUS in the exon 3 of the *TNFRSF13C* gene (p.Ala179Ilefs*46). This genetic variant results in a frameshift in the gene that encodes for BAFFR. BAFFR is essential for the survival and maturation of transitional B cells into mature follicular and marginal zone B cells. BAFFR is also thought to enhance the survival and expansion of germinal center B cells by promoting the selection of high affinity switched memory B cells and plasma cells. BAFFR is also expressed in central and effector memory T cells, providing a costimulatory signal [15].

BAFFR deficient mice are known to have impaired antibody responses to T cell-dependent and T cell-independent antigens, but this is less likely in human, as BAFFR expression is absent in resting and activated $CD4^+$ T cells [6,16]. These mice also have severely reduced follicular and marginal zone B cells, but have normal IgA secreting plasma cells [17]. Deficiency of BAFFR in humans has only been described once in two siblings. The patients carried a homozygous 24-bp in-frame deletion (del89–96) located in exon 2. The described patients had B cell lymphopenia, low IgG levels with normal IgA, and decreased IgM^+ $CD27^+$ marginal zone B cells, which are thought to be the precursor cell of T-independent antibody responses against encapsulated bacteria. The most clinically severely affected patient had absent T-independent and T-dependent antibody responses, but the second sibling only had impairment of T-independent humoral responses and did not meet criteria for CVID diagnosis. These findings demonstrated variable expressivity of BAFFR deficiency [6].

SAD is a subtype of primary immunodeficiency characterized by the inability to mount an adequate T-independent antibody response to specific antigens despite having normal immunoglobulin levels. While SAD is often distinguished from other primary immunodeficiencies by its isolated antibody response impairment, a specific genetic mutation has not been associated with isolated SAD. Rather, emerging evidence suggests potential intersections of SAD in multiple inborn errors of immunity, such as *NEMO, TACI*, *MALT1, RelB, STAT3* deficiencies, among others [5,7].

Our patient's heterozygous variant is expected to disrupt the last six amino acids of the BAFFR protein and extend the protein by 39 additional amino acid residues. BAFFR is a homotrimeric receptor, and its C-terminal domain, located on the cytoplasmic side, is crucial for downstream signaling through the NF-κB pathway. Alterations in this region could impair signal transduction even in the heterozygous state, potentially explaining the patient's impaired antibody maintenance. Even though the patient presented with a heterozygous variant, previous studies have shown that a single-nucleotide polymorphism in *TNFRSF13C* gene, Pro21>Arg (P21R) (c.62C>G; rs77874543), present in homo- or heterozygous forms may contribute to the development of CVID [14]. This is a phenomenon also recognized in the *TNFRSF13B* (TACI) gene, in which homozygous and heterozygous mutations have been described as risk factors for the development of CVID [9-10].

The clinical presentation of our patient, including recurrent sinopulmonary infections and a decline in pneumococcal serotype-specific antibody titers within six months post-immunization, aligns with the memory phenotype of SAD. Although, no other functional studies have been done in this case to prove abnormalities in the BAFFR protein, the patient's SAD memory phenotype, which demonstrates inadequate T-independent antibody responses, correlates with the previously described clinical phenotypes of patients with *TNFRSF13C* genetic variants [6,14].

Management of SAD primarily focuses on preventing infections and optimizing the patient's quality of life. This includes immunization with conjugate vaccines, prophylactic antibiotics, and, in severe or refractory cases, immunoglobulin replacement therapy. While this patient achieved protective titers for most pneumococcal serotypes shortly after vaccination, the subsequent decline highlights the limitations of polysaccharide vaccine responses in individuals with SAD. The progressive decline in pneumococcal serotype-specific antibody titers highlights the importance of regularly monitoring specific antibody responses in patients with recurrent infections, even when their immunoglobulin levels are within normal limits. The patient's history of eosinophilic

esophagitis, asthma, and allergic rhinitis highlights the interplay between immune dysregulation and atopic conditions, which may contribute to an increased susceptibility to infections.

This case contributes to the understanding of SAD as a potentially heterogeneous disorder, where underlying genetic variants, such as those involving BAFFR, may play a contributory role. Highlighting genetic contributors, such as this novel frameshift variant, not only advances our understanding of SAD but also underscores the importance of equitable diagnostic access for both local and diaspora Puerto Rican populations. Notably, there is a lack of information about genetic variants associated to inborn errors of immunity in populations from Puerto Rico, highlighting the need for localized research and awareness. In Puerto Rico, the diagnosis of SAD remains challenging due to limited awareness and access to immunologic and genetic testing. These barriers can delay appropriate care and increase the risk of complications such as bronchiectasis and chronic lung disease. Early diagnosis is essential, as effective interventions - including conjugate vaccine boosting, prophylactic antibiotics, and immunoglobulin replacement - can significantly reduce infections and improve long-term outcomes. Also, further research is needed to explore the genetic and molecular mechanisms linking specific antibody deficiencies to broader immune dysregulation and to explore the potential progression of SAD to CVID. Pediatricians, immunologists, pulmonologists, infectious disease specialists, and other health care providers must collaborate to recognize and manage cases promptly. Physicians practicing in our region may need to maintain a high index of suspicion to accurately diagnose both SAD and CVID, given their potential for under-recognition.

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References

1. Perez, E., Bonilla, F. A., Orange, J. S., & Ballow, M. Specific Antibody Deficiency: Controversies in Diagnosis and Management. *Frontiers in immunology* 2017, *8*, 586. https://doi.org/10.3389/fimmu.2017.00586
2. Perez, E. E., & Ballow, M. Diagnosis and management of Specific Antibody Deficiency. *Immunology and allergy clinics of North America* 2020, *40*(3), 499–510. https://doi.org/10.1016/j.iac.2020.03.005
3. Bonilla, F. A., Khan, D. A., Ballas, Z. K., Chinen, J., Frank, M. M., Hsu, J. T., Keller, M., Kobrynski, L. J., Komarow, H. D., Mazer, B., Nelson, R. P., Jr, Orange, J. S., Routes, J. M., Shearer, W. T., Sorensen, R. U., Verbsky, J. W., Bernstein, D. I., Blessing-Moore, J., Lang, D., Nicklas, R. A., … Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma & Immunology; the American College of Allergy, Asthma & Immunology; and the Joint Council of Allergy, Asthma & Immunology. Practice parameter for the diagnosis and management of primary immunodeficiency. *The Journal of allergy and clinical immunology* 2015, *136*(5), 1186–205.e2078. https://doi.org/10.1016/j.jaci.2015.04.049
4. Orange, J. S., Ballow, M., Stiehm, E. R., Ballas, Z. K., Chinen, J., De La Morena, M., Kumararatne, D., Harville, T. O., Hesterberg, P., Koleilat, M., McGhee, S., Perez, E. E., Raasch, J., Scherzer, R., Schroeder, H., Seroogy, C., Huissoon, A., Sorensen, R. U., & Katial, R. Use and interpretation of diagnostic vaccination in primary immunodeficiency: a working group report of the Basic and Clinical Immunology Interest Section of the American Academy of Allergy, Asthma & Immunology. *The Journal of allergy and clinical immunology* 2012, *130*(3 Suppl), S1–S24. https://doi.org/10.1016/j.jaci.2012.07.002
5. Tangye, S. G., Al-Herz, W., Bousfiha, A., Cunningham-Rundles, C., Franco, J. L., Holland, S. M., Klein, C., Morio, T., Oksenhendler, E., Picard, C., Puel, A., Puck, J., Seppänen, M. R. J., Somech, R., Su, H. C., Sullivan, K. E., Torgerson, T. R., & Meyts, I. Human Inborn Errors of Immunity: 2022 Update on the Classification from the International Union of Immunological Societies Expert Committee. *Journal of clinical immunology* 2022, *42*(7), 1473–1507. https://doi.org/10.1007/s10875-022-01289-3

6. Warnatz, K., Salzer, U., Rizzi, M., Fischer, B., Gutenberger, S., Böhm, J., Kienzler, A. K., Pan-Hammarström, Q., Hammarström, L., Rakhmanov, M., Schlesier, M., Grimbacher, B., Peter, H. H., & Eibel, H. B-cell activating factor receptor deficiency is associated with an adult-onset antibody deficiency syndrome in humans. *Proceedings of the National Academy of Sciences of the United States of America* 2009, *106*(33), 13945–13950. https://doi.org/10.1073/pnas.0903543106
7. Sevdali, E., Block Saldana, V., Speletas, M., & Eibel, H. BAFF receptor polymorphisms and deficiency in humans. *Current opinion in immunology* 2021, *71*, 103–110. https://doi.org/10.1016/j.coi.2021.06.008
8. Kakkas, I., Tsinti, G., Kalala, F., Farmaki, E., Kourakli, A., Kapousouzi, A., Dimou, M., Kalaitzidou, V., Sevdali, E., Peristeri, A. M., Tsiouma, G., Patiou, P., Papadimitriou, E., Vassilakopoulos, T. P., Panayiotidis, P., Kioumi, A., Symeonidis, A., & Speletas, M. TACI Mutations in Primary Antibody Deficiencies: A Nationwide Study in Greece. *Medicina* 2021, *57*(8), 827. https://doi.org/10.3390/medicina57080827
9. Salzer, U., Chapel, H. M., Webster, A. D., Pan-Hammarström, Q., Schmitt-Graeff, A., Schlesier, M., Peter, H. H., Rockstroh, J. K., Schneider, P., Schäffer, A. A., Hammarström, L., & Grimbacher, B. Mutations in TNFRSF13B encoding TACI are associated with common variable immunodeficiency in humans. *Nature genetics* 2005, *37*(8), 820–828. https://doi.org/10.1038/ng1600
10. Martinez-Gallo, M., Radigan, L., Almejún, M. B., Martínez-Pomar, N., Matamoros, N., & Cunningham-Rundles, C. TACI mutations and impaired B-cell function in subjects with CVID and healthy heterozygotes. *The Journal of allergy and clinical immunology* 2013, *131*(2), 468–476. https://doi.org/10.1016/j.jaci.2012.10.029
11. Remiker, A., Bolling, K., & Verbsky, J. Common Variable Immunodeficiency. *The Medical clinics of North America* 2024, *108*(1), 107–121. https://doi.org/10.1016/j.mcna.2023.06.012
12. Bonilla, F. A., Barlan, I., Chapel, H., Costa-Carvalho, B. T., Cunningham-Rundles, C., de la Morena, M. T., Espinosa-Rosales, F. J., Hammarström, L., Nonoyama, S., Quinti, I., Routes, J. M., Tang, M. L., & Warnatz, K. International Consensus Document (ICON): Common Variable Immunodeficiency Disorders. *The journal of allergy and clinical immunology. In practice* 2016, *4*(1), 38–59. https://doi.org/10.1016/j.jaip.2015.07.025
13. Wilson, S. P., & Ballas, Z. K. Progression of specific antibody deficiency to common variable immunodeficiency. *Journal of Allergy and Clinical Immunology* 2010, 125*(6), 1393-1396. https://doi.org/10.1016/j.jaci.2009.12.989
14. Pieper, K., Rizzi, M., Speletas, M., Smulski, C. R., Sic, H., Kraus, H., Salzer, U., Fiala, G. J., Schamel, W. W., Lougaris, V., Plebani, A., Hammarstrom, L., Recher, M., Germenis, A. E., Grimbacher, B., Warnatz, K., Rolink, A. G., Schneider, P., Notarangelo, L. D., & Eibel, H. A common single nucleotide polymorphism impairs B-cell activating factor receptor's multimerization, contributing to common variable immunodeficiency. *The Journal of allergy and clinical immunology* 2014, *133*(4), 1222–1225. https://doi.org/10.1016/j.jaci.2013.11.021
15. Ng, L. G., Sutherland, A. P., Newton, R., Qian, F., Cachero, T. G., Scott, M. L., Thompson, J. S., Wheway, J., Chtanova, T., Groom, J., Sutton, I. J., Xin, C., Tangye, S. G., Kalled, S. L., Mackay, F., & Mackay, C. R. B cell-activating factor belonging to the TNF family (BAFF)-R is the principal BAFF receptor facilitating BAFF costimulation of circulating T and B cells. *Journal of immunology* 2004, *173*(2), 807–817. https://doi.org/10.4049/jimmunol.173.2.807
16. Sakai, J., & Akkoyunlu, M. The Role of BAFF System Molecules in Host Response to Pathogens. *Clinical microbiology reviews* 2017, *30*(4), 991–1014. https://doi.org/10.1128/CMR.00046-17
17. Sasaki, Y., Casola, S., Kutok, J. L., Rajewsky, K., & Schmidt-Supprian, M. TNF family member B cell-activating factor (BAFF) receptor-dependent and -independent roles for BAFF in B cell physiology. *Journal of immunology* 2004, *173*(4), 2245–2252. https://doi.org/10.4049/jimmunol.173.4.2245