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Smith-Magenis syndrome patients often display antibody deficiency but not other immune pathologies

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Abstract

Background—Smith-Magenis syndrome (SMS) is a complex neurobehavioral disorder associated with recurrent otitis. Most SMS cases result from heterozygous interstitial chromosome 17p11.2 deletions that encompass not only the intellectual disability gene *RAI1* but also other genes associated with immunodeficiency, autoimmunity and/or malignancy.

Objectives—The goals of this study were to describe the immunological consequence of 17p11.2 deletions by determining the prevalence of immunological diseases in SMS subjects and by assessing their immune systems via laboratory methods.

Methods—We assessed clinical histories of 76 SMS subjects with heterozygous 17p11.2 deletions and performed in-depth immunological testing on 25 representative cohort members. Laboratory testing included determination of serum antibody concentrations, vaccine titers and

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lymphocyte subset frequencies. Detailed reactivity profiles of SMS serum antibodies were performed using custom-made antigen microarrays.

Results—74 of 76 SMS subjects reported recurrent infections including otitis (88%), pneumonia (47%), sinusitis (42%), and gastroenteritis (34%). Infections were associated with worsening SMS-related neurobehavioral symptoms. The prevalence of autoimmune and atopic diseases was not increased. Malignancy was not reported. Laboratory evaluation revealed most SMS subjects to be deficient of isotype-switched memory B cells and many to lack protective antipneumococcal antibodies. SMS antibodies were not more reactive than control antibodies to self-antigens.

Conclusions—SMS patients with heterozygous 17p.11.2 deletions display an increased susceptibility to sinopulmonary infections, but not to autoimmune, allergic or malignant diseases. SMS sera display an antibody reactivity profile favoring neither recognition of pathogen-associated or self-antigens. Prophylactic strategies to prevent infections may also provide neurobehavioral benefits to selected SMS patients.

Keywords

Smith-Magenis syndrome; chromosome 17p11.2 deletion; immune deficiency; autoantibody; *TNFRSF13B*; *FLCN* and *TOM1L2*; B-cell tolerance

INTRODUCTION

Smith–Magenis syndrome (SMS; OMIM #182290, *607642) is a complex genetic disorder, estimated prevalence 1: 15,000–25,000. SMS is characterized by intellectual disability, sleep disturbances, self-injurious behaviors and skeletal abnormalities.[1–3] Although ear infections are commonly described in SMS patients,[4] it is unclear if the predisposition is due to an anatomic or immunologic abnormality. Diminished anti-pneumococcal antibodies have been described in SMS sera[5] but neither a comprehensive clinical evaluation of the SMS immune system nor a detailed account of the full spectrum of infections experienced by SMS patients have been reported Similarly, it is unknown is if the SMS immune system is prone to the development of autoimmune, malignant, and/or atopic diseases as is the case in many primary immunodeficiencies.[6–9]

Approximately 90% of SMS cases are caused by the heterozygous 3.7 Mb interstitial deletion of 17p11.2, a region encompassing the retinoic acid-induced 1 (*RAI1*) gene locus.[3] In rare cases, SMS may be caused by deleterious *RAI1* point mutations, without deletion of 17p11.2, suggesting that *RAI1* is the gene primarily responsible for the neuro-developmental features of SMS.[10] *RAI1* serves no known immunologic function,[11] but proximate genes also lost to 17p11.2 deletion, including *TNFRSF13B, FLCN* and *TOM1L2*, do. *TNFRSF13B* encodes TACI, which controls T-independent humoral responses and B cell tolerance.[12–15] Heterozygous missense *TNFRSF13B* mutations are associated with Common Variable Immune Deficiency (CVID),[16,17] an antibody deficiency disorder often complicated by autoantibody production and hematologic malignancy.[18] Autoimmune disease occurs in 41% of CVID patients with heterozygous *TNFRSF13B* missense mutations.[19] *FLCN* is a tumor suppressor gene mutated in Birt-Hogg-Dubé syndrome (BHDS).[20] BHDS patients accumulate both benign and malignant tumors.[20] *TOM1L2* is not

implicated in a human disease, but *Tom1l2*-deficient mice are susceptible to infections and tumors.[21]

Since many SMS patients are hemizygous for multiple genes associated with immunodeficiency, autoimmunity and/or malignancy, we hypothesized they may also be susceptible to these diseases. To test this hypothesis, we surveyed medical histories, spanning 970 person-years, from a large cohort of 76 SMS subjects ages 6 months to 37 years (mean 13.8 years) with 17p11.2 deletions. We obtained peripheral blood samples on 25 representative subjects from our cohort, all with deletions encompassing *RAI1, TNFRSF13B, FLCN* and *TOM1L2*, to create in-depth immunologic profiles via laboratory assessments that included serum immunoglobulin quantification, vaccine titers, lymphocyte flow-cytometry and custom-made antigen microarrays. Our results indicate that SMS patients are antibody deficient and frequently experience sinopulmonary infections, including severe bacterial illnesses like pneumonia. Unlike many primary immunodeficiency patients, SMS subjects were not more susceptible to autoimmune, allergic or malignant diseases, nor did they frequently display increased serum autoantibodies or elevated IgE.

METHODS

Study subjects and clinical history evaluations

We enrolled 76 SMS subjects with heterozygous chromosome 17p11.2 deletions. Subjects ranged from 6 months to 37 years in age (mean 13.8 years); 52% were female (Table 1). Informed consent was obtained for all individuals before study enrollment. TThe study protocol was approved by the Human Subjects Committee of Yale University, the Institutional Review Board of the Children's Hospital of Philadelphia and the professional advisory board of Parents and Researchers Interested in Smith-Magenis Syndrome (PRISMS). An immunological diseases questionnaire was distributed to families of SMS subjects at the international PRISMS family meeting, on the PRISMS web-site or in the course of the authors' clinical practice. When subjects were identifiable (n=12), survey responses were secondarily confirmed for accuracy using electronic medical records (EMR). Overall good concordance between survey and EMR data was observed. For survey responses, a recurrent infection was defined as at least 4 infections per year. Peripheral blood samples, paired to survey data, were obtained either at the 2014 International PRISMS Conference and family meeting (n=18), at Yale New Haven Hospital (n=5), or the Children's Hospital of Philadelphia (n=2). Blood based screening evaluations were performed on 25 SMS subjects; all possessed a chromosome 17p11.2 deletion spanning *TNFRSF13B, RAI1, FLCN* and *TOM2L1* as determined by florescence in situ hybridization or chromosomal microarray (see Table E1 in the Online Repository); all had completed a primary vaccination series; none were receiving antibody replacement or immunosuppressive therapies. Healthy control adult serum samples were obtained from 3 first-degree relatives of SMS subjects and 6 unrelated adult donors after obtaining informed consent. Serum samples from 8 healthy unrelated children were purchased as comparators (Biodesign International Inc., Saco, Maine).

Quantitative and qualitative antibody testing

Measurement of IgM, IgA, IgE, IgG, IgG subclass 1–4 concentrations and antibody responses to tetanus toxoid, *Haemophilus influenza* type B and 14 serotypes of *Streptococcus pneumonia* (1, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 12F, 14, 18C, 19F, 23F) were performed on 20 serum samples by the Yale New Haven Hospital clinical laboratory. Results from 5 additional SMS patients, performed by other clinical reference laboratories were also included. Age specific normal value ranges were used to assess if a subject's laboratory assessments were abnormal.[22] Anti-*Haemophilus influenza* type B and anti-tetanus toxoid antibody concentrations were considered protective at concentrations of ≥0.15 μg/ml and ≥0.15 IU/ml respecitively.[23] Anti-pneumococcal antibodies were considered protective at concentrations >0.35 μg/ml.[24] For the subset of 6 patients challenged with the 23-valent pneumococcal vaccine, an adequate vaccine response was defined as anti-pneumococcal antibody concentrations of 1.3 μg/ml to >50% serotypes assessed.[25]

Flow cytometry

Flow cytometry sample acquisition was performed on a LSR Fortessa (BD Biosciences, Mountain View, Calif). The following antibodies were used for flow cytometric stainings: anti-TACI PE (clone 1A1), anti-CD19 APC-Cy7, anti-CD27 AF700, anti-CD4 APC-Cy7, anti-CD8 BV711, anti-CD25 Pe/Dazzle 594, anti-CD127 PerCPCy5.5 (all from BioLegend, San Diego, Calif), anti-IgM PerCPCy5.5 and anti-CD3 eFluor 605NC (BD). Intracellular staining for FOXP3 Alexa Fluor 488 (clone 150D; Biolegend) was performed using the FOXP3/Transcription Factor Staining Buffer Set (eBioscience, San Diego, Calif) in accordance with the manufacturer's instructions. Subset analysis was performed with FlowJo software (Tree Star, Ashland, Ore).

Antigen microarrays

Antigen microarrays were generated using a VersArray ChipWriter™ Pro microarrayer (Bio-Rad, Hercules, Calif) and using customized printheads from Silicon Microarray Spotting Pins (Parallel Synthesis Technologies, Santa Clara, Calif) as previously described.[26] Briefly, 337 purified biomolecules including autoantigens, cytokines, and chemokines were purchased from multiple vendors and printed in triplicate at dilutions of 200μg/ml onto Nexterion E epoxysilane-coated glass slides (Schott, Duryea, Pa). A complete list of molecules printed can be found in Figure E1. Arrays were blocked, then washed in 7% fetal bovine serum in PBS plus 0.1% Tween (PBST). Arrays were probed for one hour with sera, diluted 1:150 in 30% FBS 1% PBS, from 18 SMS subjects with heterozygous 17p11.2 deletions, 3 of their healthy first-degree relatives and 14 healthy unrelated pediatric controls. After washing in PBST, serum reactivity was detected using an Alexafluor 647-conjugated goat anti-human IgG (Fc-specific) secondary antibody (Jackson, West Grove, Pa). After washing, arrays were dried under negative pressure and scanned using an Agilent microarray scanner. Data were bioinformatically processed using GenePix 6 software. Mean fluorescence intensity (MFI) values for each antigen were calculated by taking the mean of median fluorescence intensity for each feature. From this value was subtracted the value of MFI reactivity by probing with secondary antibody alone.

Statistical Methods

Linear regression modeling was conducted using PRISM software (GraphPad, San Diego, CA). Significance Analysis of Microarrays (SAM), a permutation-based algorithm for determining statistically significant differences in large datasets, was used to determine differences in antibody reactivities between SMS and control serum samples.[27] For SAM analyses, a false discovery rate (FDR) of <0.001 was accepted and an adjusted *P* value of <0.05 was considered statistically significant. Antigen microarray analyses were powered (>0.8) to detect at least 1.5-fold reactivity differences between subject and control sera.

RESULTS

SMS subjects are susceptible to sinopulmonary infections

A history of recurrent and/or severe infections was reported in 72 of 76 (95%) SMS subjects (Table 2). Sinopulmonary infections were most commonly described and included recurrent otitis media (88% of subjects), recurrent upper respiratory tract infections (61%), pneumonia (47%) and recurrent sinusitis (42%). Recurrent gastroenteritis was described by 34% of respondents. Skin infections were also reported, including bacterial cellulitis (17%) and warts (16%) primarily affecting the hands and feet (Figure E2). A history of bacteremia was reported in 2 subjects; hematogenously seeded osteomyelitis in another. No cases of abscesses, deep tissue infections or joint infections were identified. Excluding warts, other opportunistic infections like mucocutaneous *Candidiasis*, *Pneumocystis* pneumonia, *Cryptococcosis*, *Cryptosporidiosis*, molluscum and cytomegalovirus infections were not identified.

25 (33%) SMS subjects surveyed had previously received an immunological evaluation. Of those evaluations, 68% were performed by allergists/clinical immunologists, 21% by clinical geneticists and 8% by infectious disease physicians. 67 (87%) SMS subjects had received a complete primary vaccine series. 6 (9%) SMS subjects were currently receiving, or had at one time received, antibody replacement therapy. Altogether, these results show that SMS patients display an increased susceptibility to sinopulmonary infections.

Infections negatively impact SMS-associated sleep disturbances, maladaptive behaviors and seizures

SMS-associated sleep disturbances and maladaptive behaviors, which included self-injury by onychotillomania or polyembolokoilamania, temper tantrums and attention deficit/hyperactivity, were described by all respondents. During acute infections, 72% of SMS caregivers perceived a worsening of sleep disturbances and 79% perceived a worsening of behavioral issues (Figure 1). Of those reporting a negative impact, the majority described the effect of infections to be “significant.” Seizures were reported in 10 SMS subjects; infections increased seizure frequency and severity in 8 of these (Figure 1).

Autoimmune, atopic and malignant diseases do not occur frequently in SMS subjects

Autoimmune diseases, which included autoimmune thyroiditis (n=2), autoimmune neutropenia (n=1) and pernicious anemia (n=1), were reported in 5% of SMS subjects (Table E2). This frequency was identical to that reported in subjects’ siblings suggesting

autoimmunity was not increased in our young SMS cohort. Atopy was reported in 27% of subjects with a prevalence and variety (Table E3) similar to large national health surveys.[28,29] A modestly elevated serum IgE concentration was identified in 1 subject (Table 1). Malignant diseases were not reported in our cohort.

Antibody responses are impaired in SMS

We assessed SMS serum for immunoglobulin isotypes and IgG subclass concentrations and identified at least 1 abnormal result in the majority of subjects (60%) (Table 1). IgM, IgA, and IgG concentrations were beneath age-adjusted institutional normal ranges in 22%, 16%, and 28% of serum samples respectively. 2 subjects were selectively IgG2 deficient. All subjects possessed protective anti-*Haemophilus influenza* type B (HiB) antibody concentrations and most possessed protective concentrations to tetanus toxoid (92%). In contrast, 32% lacked protective antibody concentrations (>0.35 μg/ml) to the majority of the 14 *Streptococcus pneumonia* serotypes tested. Vaccine challenges with the 23-valent pneumococcal vaccine were performed on 6 SMS subjects, 4 of these were unable to generate appropriate anti-pneumococcal antibody responses. 2 vaccine non-responders met CVID diagnostic criteria (Table 1). Although there was a trend of improving pneumococcal vaccine titers with advancing age, we conclude that many SMS subjects suffer from decreased antibody production and impaired pneumococcal responses.

Many primary antibody deficiency diseases are associated with diminished class-switched memory B cells.[30,31] In our SMS cohort, total B-cell and total memory B-cell frequencies were not diminished compared to age-matched institutional normal ranges whereas isotype-switched memory B cells were diminished in 17 of 19 SMS subjects. This is consistent with our previous study analyzing fewer subjects.[32] Enumeration of T cell subsets including CD4 T cells, CD8 T cells and T regulatory cells in our cohort revealed no consistent abnormal trends (Table E4). Significant T cell lymphopenia was identified in only one SMS subject (SMS2), a boy with a history of partial thymectomy secondary to surgical correction of a congenital heart defect. He did not experience opportunistic infections. Natural killer cell deficiency was not identified in our SMS cohort.

SMS antibody reactivities to pathogens and to self-antigens are limited

To create an unbiased and in-depth reactivity profile of SMS protective IgG antibodies and autoantibodies, we designed and fabricated antigen microarrays and probed them with sera from 18 SMS subjects and 17 healthy controls. Antigen microarrays contained a total of 337 antigens including 19 pathogen-specific antigens and autoantigens, including cytokines, chemokines, and growth factors.[33] Serum reactivities measured by microarray and by conventional laboratory testing linearly correlated (R^2=0.54, $p<0.0005$) and were generally concordant (Figure E3). For instance, 10 of 10 of the most reactive SMS serum samples to veterinary tetanus vaccine also demonstrated protective tetanus specific IgG levels (≥0.15μg/ml) by conventional clinical laboratory testing.

To measure differences in the levels of antibodies between SMS patients and age-matched, related and unrelated controls, we performed Significance Analysis of Microarrays (SAM), a permutation-based algorithm for determining statistically significant differences in large

datasets.[27] SAM analysis of the 19 pathogen-associated antigens on the array demonstrated that antibodies against 4 pathogens were decreased in SMS patient sera compared to healthy controls. These antigens were the HiB-conjugate vaccine, Hepatitis B surface antigen, bacterial flagellin, and horse tetanus vaccine (Figure 2). No anti-pathogen antibodies tested were significantly elevated in SMS sera compared to controls.

Antigen microarrays have previously identified diverse and numerous autoantibodies in the sera from patients with autoimmune diseases including systemic lupus erythematosus, juvenile dermatomyositis and RAG deficiency compared to healthy controls.[34–36] We therefore assessed autoantibody profiles between SMS and healthy control sera by performing SAM a second time using array values for autoantibody reactivity against classical self-antigens. Of the 94 self-antigens tested, no autoantibody was significantly increased in the SMS population. There were 3 autoantibodies found at lower levels in SMS sera than healthy sera, among these was anti-thyroid peroxidase (Figure 2). Given the newly recognized importance of anti-cytokine autoantibodies in primary immunodeficiencies,[33,36,37] we also performed SAM for sera reactivities to cytokines, chemokines and growth factors. No statistically significant differences were identified. Taken together, these data demonstrate a deficiency of pathogen protective antibodies in SMS subjects without an increased presence of autoantibodies.

DISCUSSION

Herein, we report that SMS patients display an increased susceptibility to sinopulmonary infections including otitis but also invasive bacterial infections. During our study, a 35-year-old female subject succumbed to pneumonia, an infection affecting nearly half our cohort, underscoring the potential infectious acuity of SMS. Our results are consistent with the limited number of previously published reports on the immunologic phenotype of SMS patients that were either more limited in scope[38] or were mechanistic and not clinical.[5,32] Here, we provide a unique and detailed analysis of SMS antibody reactivities to pathogen-associated antigens and self-antigens by traditional clinical laboratory testing and by in-depth antigen microarray We have demonstrated decreased pathogen-specific antibodies, impaired pneumococcal responses and fewer isotype-switched memory B cells to be general features of SMS. Such immune defects mirror those of CVID patients and reinforce the essential role TACI in mediating T-independent humoral responses and regulating late-stage B cell differentiation.[15,32] Yet, despite such dysfunction, SMS B cells do not preferentially produce serum autoantibodies as CVID B cells do.[14] Why are SMS patients and *TNFRSF13B* mutated CVID patients similarly susceptible to infections but not to autoimmune diseases? One possible explanation is that the single unmutated *TNFRSF13B* allele possessed by most SMS patients is sufficient to establish B-cell tolerance whereas a CVID-associated *TNFRSF13B* mutant allele, likely encoding a dominant-negative product, interferes with it.[14,32] Unlike tolerance formation, optimal antibody production requires B cells with two functional *TNFRSF13B* alleles. Hence, SMS and CVID patients with *TNFRSF13B* mutations are both susceptible to antibody deficiency-associated sinopulmonary infections.

Several SMS subjects reported warts, an uncharacteristic finding for pure antibody deficiency diseases, but one that may be explained by “skin picking,” a compulsive SMS behavior. Warts may also be related to fibrofolliculomas, benign hair follicle tumors pathognomonic for BHDS. However, since 30% of BHDS patients also develop renal cancer, and cancer was not reported in our cohort, it appears heterozygous BHDS-associated *FLCN* mutations and SMS-associated *FLCN* hemizygosity are not equivalent.[20] Longitudinal study of our relatively young cohort may provide further confirmation of this hopeful finding.

Despite a significant infectious burden, family members of SMS subjects consistently rate behavioral issues and sleep disturbances to be the most challenging aspects of the disease.[39] Such prioritization is understandable and may partially explain why only 35% of our cohort received a prior immunological evaluation. Yet, we report here that SMS caregivers also perceive infections to significantly aggravate SMS-associated neurobehavioral problems. As many laboratory abnormalities we identified in SMS subjects, including hypogammaglobulinemia, IgG subclass deficiency and specific antibody deficiency, are indications for prophylactic antibody replacement, a trial of this therapy in selected SMS patients may improve both infectious and non-infectious outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BHDS	Birt-Hogg-Dubé syndrome
CVID	Common variable immune deficiency
FCLN	Folliculin
MFI	Mean fluorescence intensity
RAI1	Retinoic acid-induced 1
SAM	Significance Analysis of Microarrays
SMS	Smith-Magenis syndrome
TNFRSF13B	Tumor necrosis factor receptor superfamily member 13b
TOM1L2	Target of myb1 like 2 membrane trafficking protein

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Highlights box

What's is already known on this topic?

Smith-Magenis syndrome (SMS) is a complex neurobehavioral disorder associated with otitis. Most SMS cases result from chromosome 17p11.2 deletions that encompass the intellectual disability gene *RAI1* and also genes associated with immunodeficiency, autoimmunity and/or malignancy.

What does this article add to our knowledge?

Description of the immunopathologies and laboratory immunological features of a large cohort of 76 SMS patients reveals a consistent susceptibly to sinopulmonary infections, including pneumonia, but not to autoimmune, allergic or malignant diseases.

How does this study impact current management guidelines

As with other genetic syndromes associated with antibody deficiency listed in the AAAI practice parameters for diagnosis and management of primary immunodeficiency, all SMS patients should receive an immunologic evaluation. Infectious prophylaxis should be considered in selected SMS patients.

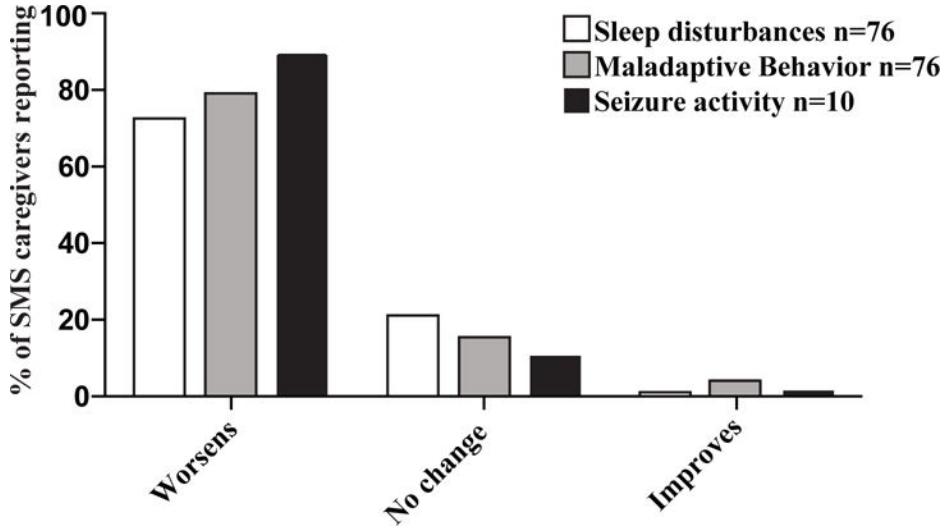

Figure 1.

Most SMS caregivers perceive acute infections to worsen SMS-associated sleep disturbances, maladaptive behaviors and seizures.

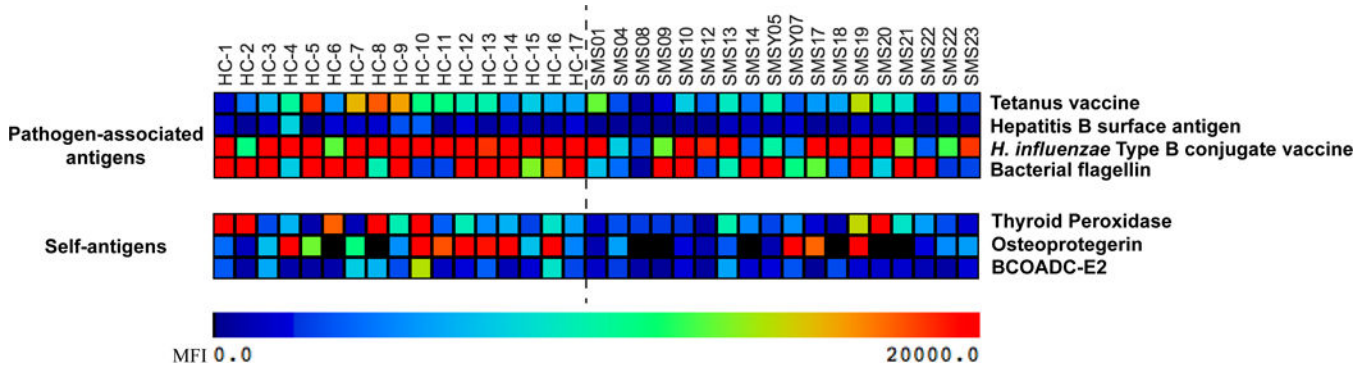

Figure 2.

SMS sera are less reactive than control sera to pathogen-associated and self-antigens. The heat map displays sera reactivities to 4 pathogen-associated antigens (upper panel) and 3 self-antigens (lower panel) lower in 18 SMS serum samples than 17 healthy-related and unrelated control samples. Colorimetric differences corresponding to array MFIs are indicated.

Table 1

Clinical serum antibody testing and infectious histories of 25 SMS subjects not receiving antibody replacement therapy

	Age[a]	Sex	IgM (mg/dL)	IgA (mg/dL)	IgG (mg/dL)	IgG2 (mg/dL)	Tetanus Ab (IU/ml)	Hib Ab (μg/ml)	Pneumococca Ab (μg/ml), 14 serotypes	IgE (ng/mL)	Infections
Reference			**__[b]**	**__[b]**	**__[b]**	**__[b]**	**≥0.15**	**≥0.15**	**≥0.35**	**__[b]**	
SMS1	4	M	41 **(L)**	76	863	114	>7	0.4	6/14 **(L)**	158 **(H)**	O, P, S, G, U
SMS2	6	M	82	106	1040	122	>7	1.5	11/14	<4	P, U
SMSY2	6	F	113	124	891	117	<0.1 **(L)**	6.25	11/14	<2	O
SMS4[d]	7	M	44 **(L)**	38 **(L)**	508 **(L)**	95	0.7	0.8	3/14[c] **(L)**	3	O
SMS5	7	F	51	12 **(L)**	650	42 **(L)**	3.2	1.1	3/14[c] **(L)**	<2	W, O
SMSY6	9	M	134	303	490 **(L)**	194	0.37	0.5	9/14	43	O
SMS7	10	M	113	91	928	93	0.23	0.6	7/14	3	O, S, P, G, U
SMS8	10	F	83	67 **(L)**	675	119	0.26	0.4	11/14	<2	P, U
SMS9	11	M	72	73	879	190	0.75	0.5	11/14	14	O
SMSY3	12	F	51	12 **(L)**	680	121	>7	1.1	6/14 **(L)**	ND	O, W, U
SMS10	13	F	118	54 **(L)**	642 **(L)**	114	1.76	1.4	12/14	32	O, S, G, W,
SMS11[d]	15	F	53 **(L)**	97	585 **(L)**	176	2.02	0.7	4/14[c] **(L)**	38	O, S, P
SMS12	16	F	99	32 **(L)**	718	112	1.06	4.3	6/14 **(L)**	5	O, S, P, G
SMS13	16	M	77	126	1470	304	1	3.6	14/14	15	O
SMS14	20	F	62	217	1210	404	0.1 **(L)**	0.7	8/14	5	C, O, S, G, W
SMSY5	20	F	72	114	1400	377	0.53	0.9	14/14	<2	O, G
SMSY7	20	M	18 **(L)**	<7 **(L)**	1050	ND	0.23	19.5	13/14	45	O, S, P, B
SMS17	20	F	59 **(L)**	83	720	257	0.4	1.1	13/14	5	O, S, P
SMS18	21	F	26 **(L)**	195	925	178	2.55	1.4	11/14	5	O, S, P
SMS19	22	M	48	181	1150	214	3.7	1.5	5/14 **(L)**	7	O, OE
SMS20	22	F	71	90	1280	351	2.05	4.1	11/14	42	O, U, G
SMS21	23	M	119	71	1250	148	1.64	4.4	14/14	22	O, P, O, U
SMS22	23	F	174	140	1500	190	1.24	2.1	11/14	5	O, S,
SMSY4	26	F	83	278	1360	67 **(L)**	5.36	4.3	4/14[c] **(L)**	5	O, C, W
SMS23	27	M	68	82	904	170	1	4.8	13/14	8	O, U

Ab, antibody; B, bacteremia; C, cellulitis; F, female; G, gastroenteritis; H, higher than normal range; Hib, Haemophilus influenza type B; L, below normal/protective range; M, male; ND, not determined; O, otitis; OE, osteomyelitis; P, pneumonia; S, sinusitis; U, upper respiratory tract infection;

[a] Age (years) at time of testing

[b] Reference range varies with age[20]

[c] Patient failed a challenge with the 23-valent pneumococcal vaccine. The number of protective serotypes displayed reflect pre-challenge values.

[d] Patient meets diagnostic criteria for Common Variable Immune Deficiency including vaccine challenge failure.

Table 2

Infections reported in 76 SMS subjects (ages 6 months-37 years)

	Percentage (n)
Recurrent ear infections	88.2 (67)
Recurrent viral respiratory	60.5 (46)
Pneumonia	47.4 (36)
Recurrent sinus infections	42.1 (32)
Recurrent gastroenteritis	34.2 (26)
Bacterial cellulitis	17.1 (13)
Warts	15.8 (12)
Bacteremia	2.6 (2)
Osteomyelitis	1.3 (1)