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Clinical and genetic heterogeneity in Omenn syndrome and severe combined immune deficiency

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Abstract: OS has been described as a clinical phenotype in infants characterized by SCID, diffuse erythroderma, and other distinct features. The pathogenesis is secondary to autologous, auto-reactive T cells produced as rare escapees from the SCID blockade. Mutations in either the *RAG1* or *RAG2* gene that lead to partial recombinase activity are responsible for many of the patients with these clinical features. We report on two patients, one with an atypical phenotype of OS (absence of rash but presence of other typical features) who harbored a previously undescribed mutation in *RAG1*, and a second who had many of the classic features of OS but was found to have a mutation in the common gamma chain (γ_c) cytokine receptor gene. These cases highlight the clinical and genetic heterogeneity of OS.

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OS is an inherited disorder characterized by immunodeficiency, diffuse erythroderma, hepatosplenomegaly, lymphadenopathy, protracted diarrhea, and failure to thrive. It was first described by Gilbert S. Omenn in 1965 (1). The report centered on an inbred Irish Catholic family whose family history was significant for 12 infants that died with similar clinical features. The propositus of the report presented at 33 days of age with a generalized erythematous papular and vesicular skin eruption, chronic diarrhea, hepatomegaly, conjunctivitis, and mild fevers, with laboratory findings significant for eosinophilia. During the course of the infant's hospital stay, he developed multiple infections and eventually died of respiratory and cardiac failure. Autopsy demonstrated pneumonitis secondary to *Pneumocystis carinii*, bilateral otitis media and inflammatory infiltrates in the lymph nodes, skin, liver, and spleen. Pedigree analysis of the family demonstrated the syndrome to be inherited in an autosomal recessive manner.

Since that initial report, inherited mutations in either of the recombination activating genes *RAG1* or *RAG2*, resulting in partial V(D)J recombinase activity, have been shown to be responsible for many cases of OS, although there is significant clinical and genetic heterogeneity

Abbreviations: DTaP, diphtheria tetanus and pertussis; GVH, graft vs. host; HLA, human leukocyte antigen; IPV, inactivated polio vaccine; NK, natural killer; OS, Omenn syndrome; PBMC, peripheral blood mononuclear cells; PCP, Pneumocystic carinii; rATG, rabbit anti-thymocyte globulin; RT-PCR, reverse transcription-polymerase chain reaction; SCID, severe combined immune deficiency; TCRBV, T cell receptor β chain variable; V(D)J, variable region; WBC, white blood cell.

(2). We report two patients who recently received hematopoietic stem cell transplantation for SCID, the first with an atypical clinical presentation of OS who was found to have a mutation in the *RAG1* gene not previously described. The second patient had many of the classical features of OS but was found to have a defect in the common gamma chain (γ_c) gene, which has not yet been reported.

Case reports

Patient 1

A previously healthy four-month-old female presented with a chief complaint of wheezing and wet cough. A chest x-ray demonstrated presumptive pneumonia with extensive bilateral perihilar infiltrates. This episode was treated with oral and intravenous antibiotics; however, the patient continued to have periodic wheezing following treatment so a chest CT was obtained. The study was significant for ground glass changes bilaterally throughout the upper lobes of the lungs and to a lesser extent in the lower lobes. A bronchoscopy and bronchoalveolar lavage were performed, which showed pulmonary macrophages and mild acute inflammation. Stains of the specimens were negative for bacteria, PCP, pathogenic fungi, and acid fast bacilli.

At seven months of age, she developed chronic diarrhea with 5–8 episodes of loose green watery stools each day. *Clostridium difficile* toxin, ova, and parasites were not found in the stool at that time. At eight months of age she began having daily low grade temperatures and was hospitalized for dehydration secondary to the continuing diarrhea. A colonoscopy demonstrated atrophic villi and some chronic inflammation including lymphocytes and eosinophils. The patient was neutropenic at that time as well and so bone marrow aspirates and biopsies were performed which were unremarkable with the exception of decreased numbers of lymphocytes.

Prior to the onset of her symptoms, the infant received both her two and four month immunizations with DTaP, IPV, Hepatitis B, and Prevnar. There was no family history of immunodeficiency, cystic fibrosis, consanguinity, or death in early infancy.

On physical exam the patient was noted to have a height and weight less than the third percentile for age (61.5 cm and 5.76 kg, respectively). The infant was thin and in no acute distress. There was no evidence of oral candidiasis, lymphadenopathy, or visible tonsils. The liver was approximately 2 cm below the costal margin and the spleen was not enlarged. There were no rashes on the infant's body with the exception of mild erythema in the vaginal folds and perianal region, attributed to her chronic diarrhea. Exam was otherwise unremarkable.

Hematological and immunological evaluations are shown in Table 1. The patient was found to have an absolute lymphocyte count of 433 (normal range 5400–7200 at six months of age). Lymphocyte subset analysis showed low levels of CD3-positive T cells and CD19-positive B cells as well as normal levels of CD56-positive CD3-negative NK cells. Antibodies to diphtheria and tetanus antitoxin were negative. Quantitative immunoglobulins were low including IgE (Table 1). Analysis of T lymphocytes was significant for the presence of oligoclonal T cells based

Table 1. Hematologic and immunologic evaluation at diagnosis

	Patient 1*	Patient 2†	Normal values‡
Total WBC	2280 cells/mm^3	20 290 cells/mm^3	6000–17 500 cells/mm^3
% Eosinophil/absolute eosinophil count	18%/410 cells/mm^3	23%/4667 cells/mm^3	300 cells/mm^3
Absolute neutrophil count	880 cells/mm^3	9130 cells/mm^3	1000–8500 cells/mm^3
Absolute lymphocyte count	433 cells/mm^3	5681 cells/mm^3	5400–7200 cells/mm^3
Absolute CD3 count	199 cells/mm^3	1935 cells/mm3	2400–6900 cells/mm^3
Absolute CD19 count	218 cells/mm^3	4715 cells/mm3	700–2500 cells/mm^3
Absolute CD3−/CD56+ Cells	410 cells/mm^3	105 cells/mm3	100–1000 cells/mm^3
IgG	177 mg/dL	41 mg/dL	480–1152 mg/dL
IgM	33 mg/dL	58 mg/dL	41–227 mg/dL
IgA	30 mg/dL	10 mg/dL	14–107 mg/dL
IgE	<2 mg/dL	36 mg/dL	1–17 mg/dL

*At 8 months of age.

†At 4 months of age.

‡Normal values for WBC count, absolute eosinophil count, and absolute neutrophil count obtained from Nathan and Oski's Hematology of Infancy and Childhood. Values listed are for children 6 months of age, ranges listed include 95% confidence interval, mean value listed for absolute eosinophil count. Normal values for absolute CD3, CD19, and CD3−/CD56+ cells obtained from Comans-Bitter WM et al. ``Immunophenotyping of blood lymphocytes in childhood'' *J Pediatrics* 1997: 130: 388–393. Values listed are for children 5–9 months of age, ranges listed include 95% confidence interval.

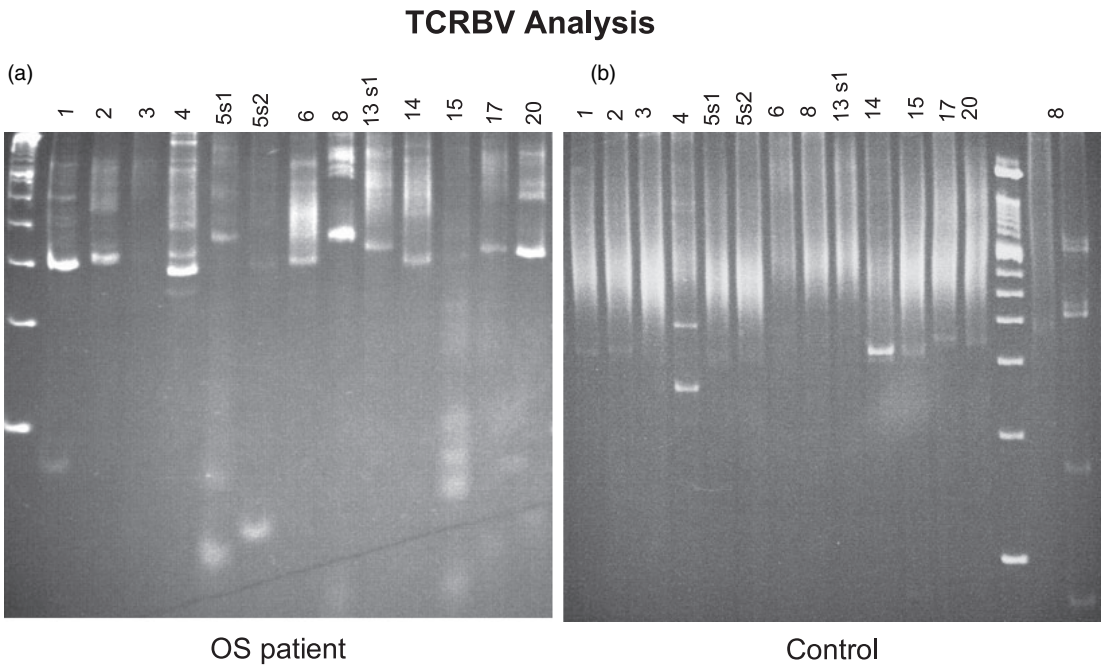

Fig. 1. Oligoclonal T lymphocyte analysis in patient 1. V(D)J rearrangement analysis showed restricted heterogeneity within all TCRBV segments analyzed. Heteroduplex analysis of the indicated TCRBV genes' RT-PCR products of PBMC from patient 1 (Panel: a) and a healthy control (Panel: b). TCRBV amplified products, prepared from polyclonal (CD3 activated lymphocyte) and monoclonal cell (J77) preparations, were used as polyclonal and monoclonal controls on the right two lanes of gel B. TCRBV products obtained from the patient migrated as single, double or several homoduplex bands in the context of a background of heteroduplex bands in the polyacrylamide gel, suggesting the existence of mono/oligoclonal T-cell subset within the TCRBV segment analyzed. TCRBV products obtained from healthy donor migrated as smears in the polyacrylamide gel, indicating the presence of heterogeneous molecular species.

upon RT-PCR of TCR β chain variable region (Fig. 1). There was no evidence of maternal fetal engraftment in the patient's peripheral blood by HLA typing (data not shown). Sequencing of *IL2R*γ, JAK3, RAG1, RAG2, ADA, IL7R, CD3δ, and *CD3*ϵ genes performed commercially (Correlagen Diagnostics, Inc.®, Cambridge, MA, USA) revealed two mutations in the *RAG1* gene at amino acids 474 and 624 (Arg474His and Arg624Cys). Analysis of parental DNA confirmed that the patient was a compound heterozygote for two different mutations.

Following the diagnosis of OS, the patient was given a course of rATG (1.25 mg/kg/dose daily on four subsequent days) in addition to the monoclonal antibody Rituxan (20 mg/kg/dose × two doses one wk apart), which led to near resolution of her diarrhea and respiratory symptoms. The patient received an unrelated cord blood transplant following conditioning with Busulfan, Fludarabine, Cyclophosphamide, and rATG. The patient now has immunological reconstitution (Table 2).

Patient 2

A three-wk-old male presented with a rash that was diagnosed as neonatal acne. He was seen several times thereafter for an erythematous scaly rash with icthyosis of his scalp and was treated for atopic dermatitis. He had one episode of otitis media at age two months that was treated with antibiotics and resolved on follow-up exam. At four months of age he developed a fever and was admitted to the hospital for evaluation of fever of unknown origin. At that time he did not have any history of diarrhea, and was eating and thriving well.

There was a family history of a maternal cousin having had three previous miscarriages. There was no history of any immunodeficiencies, deaths in early infancy, or consanguinity. The patient had received his first set of immunizations with DTaP and IPV.

On physical examination the patient's height and weight were at the 50th percentile for age (63 cm and 6.86 kg, respectively). Notable findings included a severe erythematous macular-papular rash throughout his body with lichenified and weeping lesions of the scalp (Fig. 2). He had oral candidiasis, which upon further questioning had been present for weeks prior to his presentation. He had no lymphadenopathy, the liver was palpable 8 cm below the right costal

Table 2. Hematologic and immunologic function post-transplant

	Patient 1*	Patient 2†	Normal values‡
Total white blood cell count	6270 cells/mm^3	8090 cells/mm^3	6000–17 500 cells/mm^3
Hemoglobin	12.4 g/dL	11.2 g/dL	10.5–14 g/dL
Platelet count	169 K/μL	207 K/μL	150–450 K/μL
Absolute CD3 count	632 cells/mm^3	1934 cells/mm3	1400–8000 cells/mm^3
Absolute CD19 count	521 cells/mm^3	1370 cells/mm3	600–3100 cells/mm^3
Tetanus antibody titer	Not done	2.25 IU/mL	0.1–2.9 IU/mL
Blastogenesis§ to PHA mitogen	44 SI	338 SI	NA
Blastogenesis§ to tetanus antigen	1 SI	2 SI	NA
Blastogenesis§ to *Candida* antigen	1 SI	2 SI	NA
Blastogenesis§ to CMV antigen	2 SI	3 SI	NA
Blastogenesis§ to HSV antigen	1 SI	1 SI	NA
Blastogenesis§ to VZV antigen	1 SI	2 SI	NA
Blastogenesis§ to ADV antigen	1 SI	2 SI	NA

*At 24 months of age.
†At 15 months of age.
‡Normal values for WBC, hemoglobin, and platelet count obtained from Nathan and Oski's Hematology of Infancy and Childhood. Normal values for absolute CD3, CD19, and CD3−/CD56+ cells obtained from Comans-Bitter WM et al. ``Immunophenotyping of blood lymphocytes in childhood'' *J Pediatrics* 1997: 130: 388–393. Values listed are for children 15–24 months of age, ranges listed include 95% confidence interval.
§In assays of mitogen-induced blastogenesis, leukocytes were incubated with phytohemagglutinin (PHA) or indicated specific antigen. Control wells with no mitogen were included. Tritiated thymidine was subsequently added to measure radioactivity as an indicator of proliferation. The stimulation index (SI) for response to each mitogen was calculated as follows: SI = (cpm with mitogen − cpm without mitogen)/cpm without mitogen.

margin across the midline, and the splenic tip was 7 cm below the left costal margin.

Hematological and immunological evaluations are shown in Table 1. He was found to have an elevated total WBC count of 26 000 with an absolute eosinophil count of 4667. The T cell repertoire was restricted, with oligoclonal T cells present upon analysis of the TCR β variable region by RT-PCR and flow cytometry (Fig. 3). B lymphocytes were elevated, quantitative immunoglobulins revealed low IgG and elevated IgE, while responses to antigen and mitogen stimulation were diminished (data not shown). There was no evidence of maternal engraftment by either FISH analysis of peripheral blood CD3 positive T lymphocytes or by HLA typing (data not shown). Flow cytometry analysis showed the presence of the IL2 receptor gamma chain; however, genetic testing was significant for a Tyr125Cys missense mutation in the common gamma chain. This specific mutation has been reported previously in patients with X-SCID (3), but has not been identified as being associated with OS. *RAG1* and *RAG2* sequencing did not demonstrate the presence of any mutations.

The patient underwent a matched unrelated bone marrow transplant with a conditioning regimen consisting of Busulfan, Fludarabine, Cytoxan, and rATG. His erythematous rash improved within one wk of conditioning and completely resolved by two wk. The patient now has immunological reconstitution and is doing well at home (Table 2).

Discussion

Classically OS has the typical features of SCID plus the complications from autoreactive T lymphocytes that invade the skin and intestine. It was first etiologically associated with either *RAG1* or *RAG2* mutations; however, since that time multiple additional genetic causes have been identified. These include *AIRE*, *IL7Rα*, ARTEMIS, and *RMRP RNA* gene mutations (4–8). In some patients no genetic mutation has been identified. To our knowledge, case two is the first report of a patient with a mutation in the γ_c that presented with many of the classical symptoms of OS including oligoclonal autoreactive T lymphocytes.

The clinical phenotype referred to as OS is characterized by early onset erythroderma, hepatomegaly, failure to thrive, protracted diarrhea, hypereosinophilia, high IgE levels, low to absent

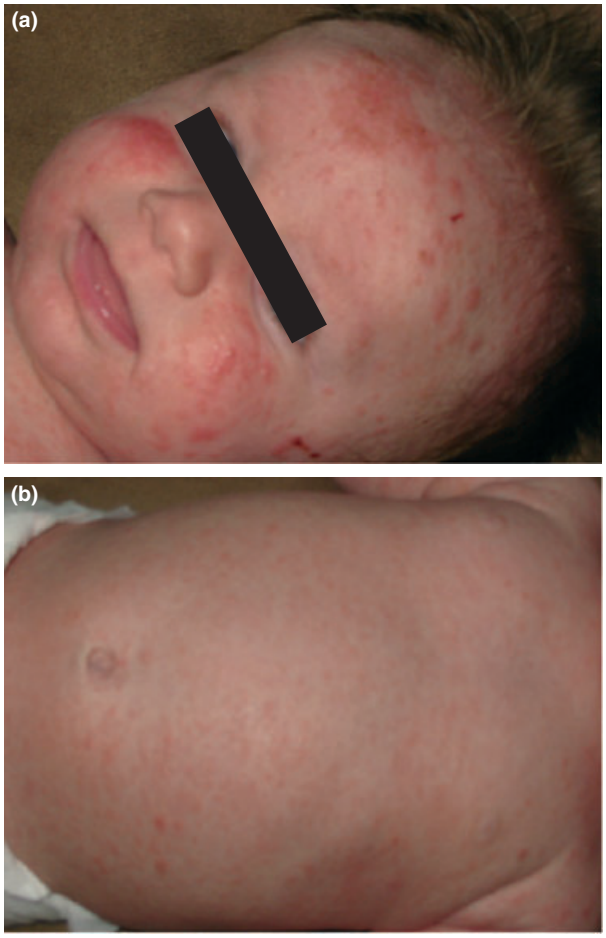

Fig. 2. Maculopapular rash in patient 2 at 3 months of age. (a) Scalp region. Areas of the scalp were lichenified and weeping. Patient was treated with antibiotics for superinfection, and the rash resolved following conditioning of the patient in preparation for an unrelated bone marrow transplant. (b) Abdominal rash in patient 2.

B cell numbers, and normal to low T cell numbers. These T lymphocytes are activated, anergic, and oligoclonal. Typically they invade the skin, liver, spleen, and intestine causing a GVH-like disease in patients. The activated T lymphocytes are host derived (autologous), however, and not of maternal origin. They produce Th_2 type cytokines and have a restricted T cell receptor heterogeneity.

RAG1 and *RAG2* are genes that encode lymphoid specific proteins that form a complex that is required for V(D)J recombination in T and B cells to produce the broad array of immunoglobulin and T cell antigen receptors. Functional T and B cell antigen receptors are required for survival of these cell types. Missense or non-sense mutations within either *RAG1* or *RAG2* that lead to a complete lack of functional recombinase activity result in an absence of these receptors and as a consequence lead to an absence of mature T and B cells. This phenotypically results in SCID (T-B-SCID). Less severe *RAG1* or *RAG2* mutations result in a partially active product which can allow some degree of V(D)J recombination to occur.

While *RAG1* and *RAG2* mutations were initially described in patients with a classical phenotypical presentation of OS, more recently it has been shown that *RAG* dependent immunodeficiency covers a broader clinical spectrum that is partially dependent on the specific mutation in the *RAG* genes. "Atypical" SCID/OS patients have been described with *RAG* mutations that have a lack of skin findings and have heterozygous missense mutations (9). Patient 1 was phenotypically atypical as well in that there were low numbers of activated CD45RO T lymphocytes that were oligoclonal; however, there were no skin findings. Rather the T lymphocytes were infiltrating the intestine, lungs, and liver. The two mutations seen in patient 1 (Arg624His and Arg474Cys) both occurred in amino acids within the active core of the protein and have been reported separately in other patients with OS (Fig. 4). Furthermore, *RAG1* mutations in either of these amino acids have been shown previously to have decreased V(D)J recombination activity *in vitro* (9). One of the mutations found in patient 1 is unique in that previously reported mutations at amino acid 474 resulted in an arginine to histine substitution whereas our patient had an arginine to cysteine substitution. A summary of reported mutations found in *RAG1* and *RAG2* are listed as a supplemental Table (Table S1).

The different clinical picture seen in patients with defects in the same gene can be caused by the specific mutations, other genetic factors, or epigenetic mechanisms. Previous mutational analysis of the *RAG* loci have failed to indicate a specific association of the clinical phenotype with the presence of mutations in either the *RAG1* or *RAG2* gene (10). In contrast, the type of mutation (e.g. missense, non-sense, or frameshift) has emerged as a major determinant of the clinical and immunologic phenotype. The majority of patients with T-B-SCID phenotype that have a mutation in *RAG* have null mutations, whereas in OS the patients predominantly have missense mutations that are permissive for *RAG* protein expression and some minimal recombinase function (10, 11). Interestingly, there are siblings reported who had the same homozygous missense mutations of *RAG1* but who had two clinically distinct phenotypes: that

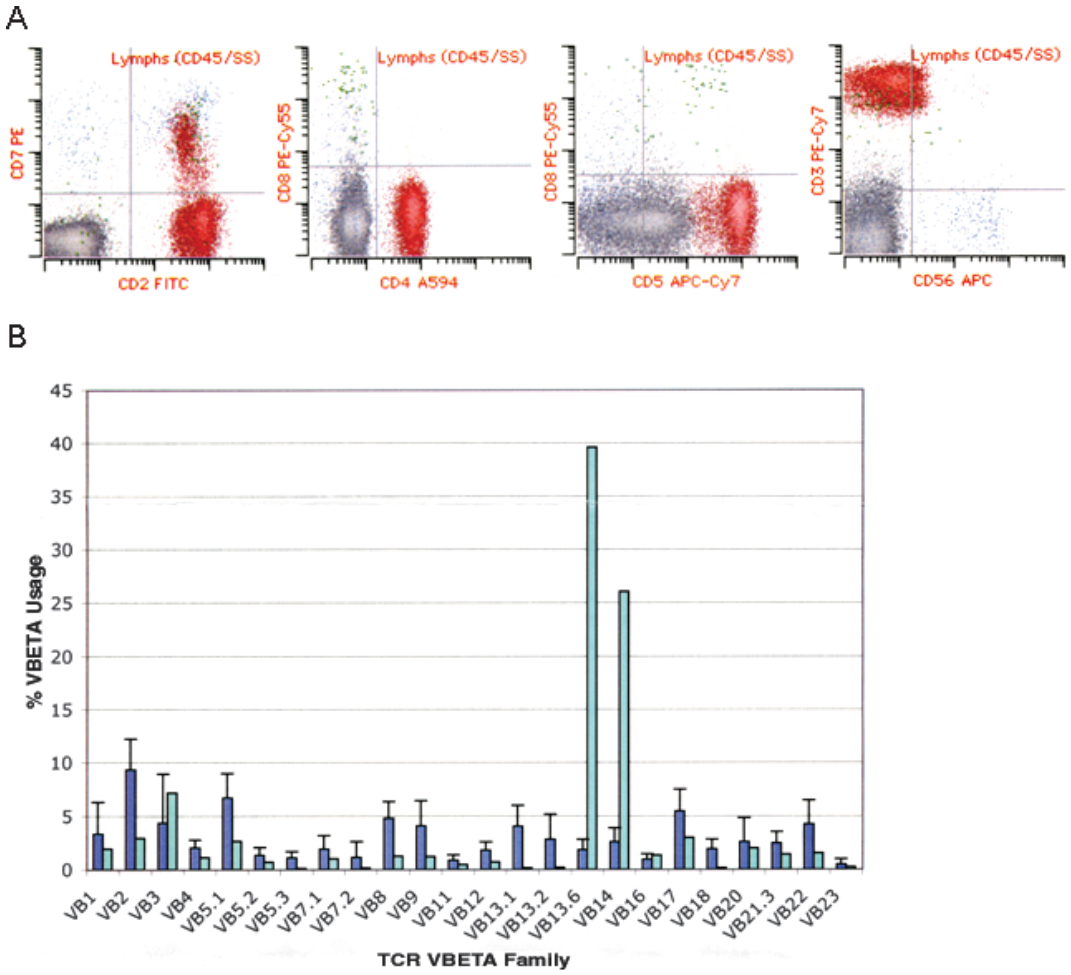

Fig. 3. Oligoclonal T lymphocyte analysis in patient 2 by flow cytometry. (a) Flow cytometry reveals a marked relative expansion of CD4-positive T cells as compared with CD8 positive T cells. (b) Evaluation of T-cell receptor beta-chain usage shows two prominent clonal populations having expression of VB13.6 and VB14 that exceed the reference range for these isoforms.

of classical OS in one sibling and an atypical clinical presentation that lacked skin involvement in the other (9). Thus, an additional factor is likely to play a role. This additional factor has been hypothesized to be unknown antigen(s) that are present in OS patients triggering a few T cell clones that expand in these patients and become constantly activated *in vivo* (9). In the absence of the specific antigen the clones would otherwise undergo apoptosis. Although this hypothesized antigen is unknown, others have postulated that the antigen is present on the organs which are involved. In the case of patient 1 this would implicate antigen(s) are present in the intestines, lungs, and liver while in patients with a rash as is typical, the antigen would be present in the skin. A lack of antigen in the intestines of patient 2 would explain the absence of diarrhea and failure to thrive in this patient.

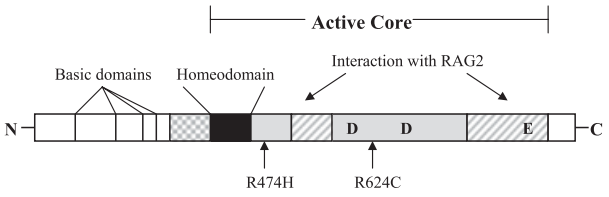

Fig. 4. Structure of the human RAG1 protein and localization of missense mutations. Both mutations are within the active core (amino acids 384–1009) of the protein. Three acidic residues (D, D, E) define the catalytic site of RAG1.

The γ_c mutation found in patient 2 is a known mutation located in the extracellular domain within exon 3 near one of the conserved cysteine residues that is important for protein configuration. Missense mutations in this region are presumed to disrupt the γ_c configuration. Patients with a Tyr125Asn missense mutation have trace γ_c on the cell surface by flow, and B

lymphocytes, similar to our patient, indicating that the protein is sufficiently stable to be expressed on the cell surface but not functionally normal (12). Mutations in the γ_c have not been previously reported with an OS presentation. Patient 2 had oligoclonal T lymphocytes infiltrating the skin and a Th_2 skewed repertoire as suggested by the peripheral blood eosinophilia. Defects in the common gamma chain lead to absent signaling in IL2, IL4, IL7, IL9, IL15, and IL21 that collectively lead to an essential absence of T lymphocytes. However, the presence of activated T lymphocytes in patient 2 indicated a leakiness of the γ_c defect allowing a few autoreactive T lymphocytes to be produced that may recognize an antigen in the skin. Unlike typical SCID, patient 2 did not have lymphopenia. The high level of T cells is likely due to the oligoclonal expansion of autoreactive T cells, while the presence of B cells is not uncommon in X linked SCID due to γ_c mutations. Thus, a cardinal sign of SCID, severe lymphopenia was not present in this patient.

Conclusions

These two cases demonstrate the clinical and genetic heterogeneity of OS. Partial recombinase activity or residual T lymphocyte cytokine signaling that leads to the presence of oligoclonal T lymphocytes is one of the key aspects of OS. However, the classic description of erythroderma or lymphopenia may be lacking in some patients which may delay recognition.

Acknowledgments

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Summary of mutations in RAG-deficient patients.

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Supplemental Table 1s. Summary of mutations in RAG-deficient patients

Patient	Gene	Nucleotide mutation	Effect	Diagnosis	Status
1	RAG1	C1879G	Y589X	T-B- SCID	Homoz
2	RAG1	G2276A, G2432T	E722K, E774X	T-B- SCID	Heteroz
3	RAG1	T2727A	L872X	T-B- SCID	Homoz
4	RAG1	del 2182-2189	Frameshift	T-B- SCID	Homoz
5	RAG1	del T1173, T2727A	Frameshift, L872X	T-B- SCID	Heteroz
6	RAG1	del 1521-1522	Frameshift	T-B- SCID	Homoz
7	RAG1	del 2114	Framshift	T-B- SCID*	Homoz
8	RAG1	C579T, del	A156V, Framshift	T-B- SCID*	Heteroz
9	RAG1	A2676T	N855I	SCID with MFT	Homoz
10	RAG1	C2801T, G1983A	R897X, R624H	SCID with MFT	Heteroz
11	RAG1	G2988A	W959X	SCID with MFT	Homoz
12	RAG1	T2926G	Y938X	SCID with MFT	Homoz
13	RAG1	del 1258	Frameshift	SCID with MFT	Homoz
14	RAG1	C1298T	R396C	Atypical SCID/OS	Homoz
15	RAG1	G1533A, A2370T	R474H, H753L	Atypical SCID/OS	Heteroz
16	RAG1	G1409A, C1443T	V433M, A444V	Atypical SCID/OS	Heteroz
17	RAG1	C1631T, C1793T	R507W, R561C	Atypical SCID/OS	Heteroz
18	RAG1	A1398G, del 368-369	D429G, Frameshift	Atypical SCID/OS	Heteroz
19	RAG1	C2633T, G1341A	R841W, R410Q	Atypical SCID/OS	Heteroz
20	RAG1	C1443T	A444V	Atypical SCID/OS	Homoz
21	RAG1	G1678T, G2276A	W522C, E722K	Atypical SCID/OS	Heteroz
22	**RAG1**	**G1871A, C1420T**	**R624H, R474C**	**Atypical SCID/OS**	**Heteroz**
23	RAG1	A3054C	Q981P	Atypical SCID/OS	Homoz
24	RAG1	C2633T	R841W	Atypical SCID/OS	Homoz
25	RAG1	T1313C	S401P	Omenn	Homoz
26	RAG1	G1095	C328Y	Omenn	Homoz
27	RAG1	G1299A, del 1723-1735	R396H, Frameshift	Omenn	Heteroz
28	RAG1	A2118G, C2812A	E669G, C900X	Omenn	Heteroz
29	RAG1	C1298T, A2847G	R396C, Y912C	Omenn	Heteroz
30-33	RAG1	G1794A	R561H	Atypical SCID/OS	Homoz
34	RAG1	G1299T, G3036A	R396L, R975Q	Omenn	Heteroz
35	RAG1	C1298T	R396C	Omenn	Homoz
36	RAG1	C1793T, G2322A	R561C, R737H	Omenn	Heteroz
37	RAG1	del 368-369, G2276A	Frameshift, E722K	Omenn	Heteroz
38	RAG1	del 368-369, C1982T	Frameshift, R624C	Omenn	Heteroz
39	RAG1	G1789T, A1415G	R559S, M435V	Omenn	Heteroz
40	RAG1	C1443T	A444V	Omenn	Homoz
41	RAG1	del 368-369	Frameshift	Omenn	Homoz
42	RAG1	del 368-369, G2599T, A2600T	Frameshift, R829X	Omenn	Heteroz
43	RAG1	del 368-369, 19nt dupl 2020- 2038	Frameshift	Omenn	Heteroz
44	RAG1	del 887	Frameshift	Omenn	Homoz
45	RAG1	C2306 T	L732F	Omenn	Homoz
46	RAG1	G3030A	R973H	Omenn	Homoz
47- 49	RAG1	del 631	Frameshift	Omenn	Homoz
50	RAG1	C1322T, del 2735	R404W, Frameshift	Omenn	Heteroz
51	RAG1	G1533A, G2301T	R474H, G730F	Omenn	Heteroz
52	RAG1	G1983A, A3086G	R624H, K992E	Omenn	Heteroz
53	RAG1	del 368, T1111A	Frameshift, Y333X	Omenn	Heteroz
54	RAG2	G2122A	W307X	T-B- SCID	Homoz
55	RAG2	Ins 1665 TGTTC	Frameshift	T-B- SCID	Homoz
56	RAG2	G2634A	C478Y	T-B- SCID	Homoz
57-59	RAG2	G1350T	G35V	T-B- SCID	Homoz
60	RAG2	A2622G	N474S	SCID with MFT	Homoz
61	RAG2	G2634A	C478Y	SCID with MFT	Homoz
62	RAG2	G1887A, locus deletion	R229Q, no protein	Atypical SCID/OS	Heteroz
63-65	RAG2	C1886T	R229W	Atypical SCID/OS	Homoz
66	RAG2	G1887A	R229Q	Atypical SCID/OS	Homoz
67	RAG2	A1316G, G1887A	R39G, R229Q	Omenn	Heteroz
68	RAG2	T1818G, C1643T	F206C, R148X	Omenn	Heteroz
69	RAG2	C1324G, T2055G	C41W, M285R	Omenn	Heteroz

Abbreviations: Omenn Syndrome (OS), Maternal Fetal Engraftment (MFT), Homozygous (Homoz), Heterozygous (Heteroz)
Information compiled from references 2, 9-11, 13-18.
Patient described in this case report in bold
*Patients clinical phenotype changed to OS following somatic revertant T cell mosaicism (16).