

Letter to the Editor

Elevated IgE and atopy in patients treated for early-onset ADA-SCID

To the Editor:

Adenosine deaminase (ADA) mutations can lead to severe combined immunodeficiency (SCID), profound T-cell, B-cell, and natural killer-cell lymphopenia, and the impairment of cellular and humoral immunity. Without intervention, patients with early-onset ADA-SCID can die of infection and failure to thrive within the first 2 years of life. Treatment options include bone marrow transplant (BMT), enzyme replacement therapy with pegylated ADA (PEG-ADA), and gene therapy (GT).¹

Elevated IgE level has been well described in delayed-onset ADA-SCID, but literature on similar phenotypes in early-onset ADA-SCID is limited, with little description of clinical allergy.² We therefore decided to characterize the clinical and cellular allergic phenotypes in a cross-sectional cohort of 18 patients treated for early-onset ADA-SCID with BMT, GT, and/or PEG-ADA (Table I; also see Table E1 in this article's Online Repository at www.jacionline.org).

Allergic histories, allergen skin prick test (SPT), total and allergen-specific IgE (sIgE) serum level, and peripheral absolute eosinophil count were measured in a subset of patients consenting to participation and where clinically feasible (Table E1; please see the Methods section in this article's Online Repository at www.jacionline.org). Atopy was defined as the presence of (1) clinical allergy (history of allergic rhinitis, food allergy, asthma, atopic

dermatitis, or urticaria) and (2) elevated total serum IgE level or evidence of allergic sensitization (positive allergen sIgE or positive SPT result). Overall, atopy was present in 56% of the patients (Table I). Not all laboratory measurements of allergic sensitization were completed in 9 of the 18 patients, 2 of whom had clinical symptoms consistent with allergy; thus, this may represent an underestimate of the atopic prevalence in this population. The most common atopic manifestations were allergic rhinitis (50%) and asthma (22.2%), followed by food allergy (11.1%), mild atopic dermatitis (11.1%), and urticaria (11.1%); interestingly, severe atopic dermatitis was not a common feature. For further information regarding SPT and sIgE results, see Table E1.

Median serum IgE level was 879 IU/mL in the atopic patients and 28 IU/mL in the nonatopic patients (normal 0-90 IU/mL) (Table I), while the median absolute eosinophil count was within the normal range in both groups. The degree of lymphopenia did not differ between the groups. Patients had a marked increase in CD3⁺HLA-DR⁺ T cells, which was even greater in atopic patients (47% vs 34%), suggesting a high degree of immune activation. Patients with atopy were significantly older (median 13 years) than those without atopy (median 6 years) (Table I).

The T_H2 cytokines IL-4, IL-5, and IL-13 are critical for the development of IgE-mediated hypersensitivity and eosinophilic inflammation.³ By intracellular cytokine staining, significantly higher percentages of *ex vivo* central memory and effector memory CD4⁺ cells produced IL-4 and IL-13 in patients with ADA-SCID than in healthy donors (Fig 1, A, and Fig E1, A), with no difference seen in the percentage of IFN- γ cells

TABLE I. Patient characteristics of atopic and nonatopic groups

	Overall	Atopic	Nonatopic	Normal range	P value (significance)
No.	18	10	8		
Age (y)	8 (2-31)	13 (6-31)	6 (2-13)		.03 (*)
Age at diagnosis of ADA-SCID (mo)	5 (0-60)	6 (2-60)	2 (0-18)		.07 (NS)
CD3 (cells/ μ L)	305 (23-2455)	261 (23-2455)	368 (116-1047)	714-2266	.46 (NS)
% CD4 ⁺	55.5 (6-83)	56 (10-83)	52 (6-64)	27-59	.93 (NS)
% CD8 ⁺	34 (4-86)	28 (4-86)	38 (22-86)	13-33	.51 (NS)
% CD4 ⁺ CD8 ⁻	6.5 (1-29)	5 (1-21)	9 (3-29)	1.3-9.2	.31 (NS)
CD4:CD8 ratio	1.77 (0.07-5.29)	2.08 (0.12-5.29)	1.29 (0.07-2.88)	1.11-5.17	.57 (NS)
% HLA-DR ⁺	42 (10-81)	47 (22-81)	34 (10-67)	0-19.6	.13 (NS)
IgE (IU/mL)	230 (0-2808)	879 (42-2808)	28 (0-612)	0-90	.0009 (†)
Absolute eosinophil count (cells/ μ L)	202 (10-1840)	160 (60-1840)	265 (10-1030)	30-470	.56 (NS)
Clinical allergy (%)					
Allergic rhinitis	50.0	80.0	25.0		
Asthma	22.2	40.0	0.0		
Atopic dermatitis	11.1	10.0	12.5		
Food allergy	11.1	20.0	0.0		
Urticaria	11.1	20.0	0.0		
No. (%) with ≥ 1 positive allergen SPT result	6 of 9 (66.7)	6 of 7 (85.7)	0 of 2 (0)		
No. (%) with ≥ 1 positive allergen sIgE	7 of 13 (53.8)	7 of 8 (87.5)	0 of 5 (0)		
Current PEG-ADA use	12	9	3		
PEG-ADA alone (no prior BMT or GT)	2	1	1		
Post-BMT, on PEG-ADA	5	3	2		
Post-GT, on PEG-ADA	5	5	0		
No current PEG-ADA use	6	1	5		
Post-BMT, off PEG-ADA	1	0	1		
Post-GT, off PEG-ADA	5	1	4		

Age, lymphocyte subsets, IgE, and eosinophil count represent median (range) values. P values < .05 are considered significant.

NS, Nonsignificant. *P < .05 and †P < .001.

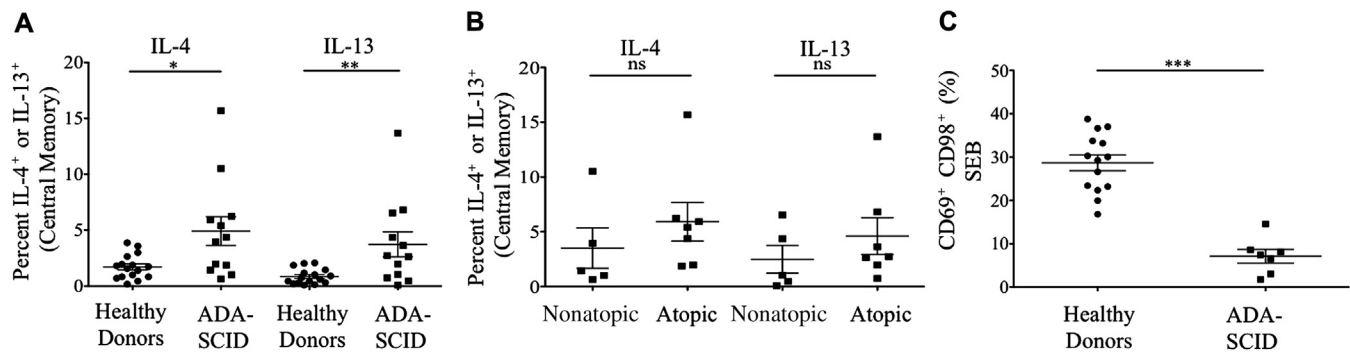


FIG 1. Percentage of IL-4⁺ or IL-13⁺ central memory CD4⁺ cells from healthy donors (n = 16) versus donors with ADA-SCID (n = 12) (**A**) and atopic (n = 7) versus nonatopic (n = 5) patients with ADA-SCID (**B**). **C**, Percentage of CD69⁺CD98⁺CD4⁺ cells following stimulation with staphylococcal enterotoxin B (SEB) in healthy donors (n = 14) versus donors with ADA-SCID (n = 7). ns, Nonsignificant. *P < .05, **P < .01, and ***P < .001.

(Fig E1, C). No statistically significant differences were found in T_H2-cytokine-producing cells between the atopic and nonatopic groups (Fig 1, B, and Fig E1, B).

One previous study attributed the T_H2 phenotype in a patient with ADA-SCID who had undergone GT to T_H2 cytokines produced by transduced CD8⁺ cells.⁴ Only 3 of 12 patients in our cohort had an increased percentage of IL-4⁺ or IL-13⁺ CD8⁺ cells compared with healthy donors (Fig E1, D), only 1 of whom had undergone GT, making it unlikely that the observed T_H2 cytokine production by CD8⁺ T cells is a direct effect of transduction.

Eight of the 9 patients with atopy in our cohort were currently being treated with PEG-ADA. However, patients treated with PEG-ADA were also older and most had undergone prior BMT or GT, making it difficult to establish a direct link between PEG-ADA and atopy (Table I).

While defects in regulatory T (Treg) cell number and function are associated with a variety of allergic and autoimmune diseases, we found a similar percentage of CD4⁺CD45RO⁺FoxP3⁺ Treg cells in our cohort as a whole compared with healthy controls (Fig E2, A). Patients who were atopic paradoxically had a higher percentage of Treg cells compared with nonatopic patients (Fig E2, B). Aberrant cytokine production by Treg cells, a hallmark of Treg-cell dysfunction, was not seen in atopic or nonatopic patients with ADA-SCID (Fig E2, C); however, it is still possible that functional suppression is impaired.

Weak T-cell receptor (TCR) signaling is associated with T_H2 differentiation and atopy,⁵ and evidence exists for abnormal TCR signaling in untreated ADA-SCID in cell lines and in murine models.^{6,7} Short-term PBMC activation was markedly impaired in patients treated for ADA-SCID (Fig 1, C, and Fig E3, A) but did not correlate with atopic status. There was a trend toward an inverse correlation between activation to staphylococcal enterotoxin B and T_H2 cytokine production (Fig E3, B and C). This dysfunction could be due to intrinsic signaling defects but also could reflect *in vitro* anergy due to chronic *in vivo* T-cell activation.

Patients treated for early-onset ADA-SCID have a high incidence of atopy. They have elevated IgE level, manifest clinical symptoms, particularly allergic rhinitis and asthma, and have increased CD4⁺ T_H2 cytokine production even in the absence of clinical allergy. Because nonatopic patients were much younger in our cohort, it is quite likely that many of them will go on to

develop allergic disease as well. Clinicians caring for patients with both early- and delayed-onset ADA-SCID should be attuned to this allergic predisposition and consider referral for allergic evaluation and appropriate pharmacologic treatment in addition to managing the infectious phenotypes.

While complete abrogation of T-cell function usually leads to immunodeficiency, hypomorphic T-cell function can lead to autoimmune disease or allergy, with Omenn syndrome as an extreme example.^{2,8,9} We propose that patients with early-onset ADA-SCID shift from a virtually complete lack of T-cell-mediated immune response prior to treatment to an intermediate level of T-cell function following treatment with BMT, PEG-ADA, or GT, which allows for the development of allergy with a phenotype less severe than Omenn syndrome.

This study represents a description of the cellular and clinical allergic phenotypes of patients treated for ADA-SCID. However, longitudinal assessments of T-cell differentiation, cytokine production, and clinical atopy of patients with ADA-SCID at diagnosis, and during treatment, are necessary to explain the correlation between T-cell function, development of a T_H2 milieu, and the manifestation of allergic disease.

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METHODS

Human subjects and clinical studies

All studies involving human subjects were performed in accordance with National Institute of Allergy and Infectious Diseases Institutional Review Board–approved protocol 10-I-0148 and National Human Genome Research Institute Institutional Review Board–approved protocol 01-HG-0189, as well as the guidelines in the Declaration of Helsinki. The study population included 18 consecutive patients with ADA-SCID currently enrolled in a research protocol of the National Human Genome Research Institute, with length of follow-up ranging from 0 to 23 years. The median age at diagnosis was 5 months, and all patients were classified as early-onset ADA-SCID. All but 2 patients had erythrocyte deoxyadenosine nucleotides (dAXP) levels of 10% or less for patients postcytotoxic therapy, or 1% or less for patients maintained on PEG-ADA.

Allergic histories, allergen SPT, total and allergen sIgE serum level, and peripheral absolute eosinophil count were measured in a subset of patients who agreed to and were available for testing (SPT, $n = 9$; blood draw, $n = 13$; interview, $n = 17$). For those subjects who refused or were unavailable for SPT, blood draw, or interview but who consented to participation in the study, the patient's medical chart was reviewed and relevant information included when available.

Subjects were interviewed by an allergist/immunologist to assess the presence of allergic rhinitis, asthma, atopic dermatitis, urticaria, and IgE-mediated food allergy. Diagnoses were based on published consensus guidelines.^{E1-E4} If the etiology of rhinitis or wheezing could not be clearly established by history alone as allergic rather than infectious, available supporting laboratory data (total IgE level, allergen sIgE level, absolute eosinophil count, allergen SPT) were used to establish a diagnosis. A childhood history of atopic disease that was subsequently outgrown was recorded as a positive response. Family histories were obtained from first-degree relatives of patients.

Atopy was defined as the presence of (1) clinical allergy (history of allergic rhinitis, food allergy, asthma, atopic dermatitis, or urticaria) and (2) elevated total serum IgE level or evidence of allergic sensitization (positive allergen sIgE or positive SPT result). Ten of 18 patients were classified as atopic on the basis of these criteria (Table 1 and Table E1). Two patients, ADA10 and ADA7, were not characterized as atopic for the purposes of the study despite the presence of symptoms consistent with clinical allergy. One of these patients, ADA10, had a normal serum IgE level, negative allergen SPT result, and negative allergen sIgE testing despite reporting symptoms consistent with seasonal allergic rhinitis. The other patient, ADA7, reported symptoms consistent with perennial allergic rhinitis but did not have elevated total IgE level. The patient was not available for SPT or allergen sIgE testing, however, and so it is possible that further testing would demonstrate evidence of allergic sensitization and he would be categorized as atopic.

Skin prick test

SPT to a panel of 7 food and 13 aeroallergen extracts (United States Army Centralized Allergen Extract Laboratory, Bethesda, Md) was performed on the forearm with a Greer Pick (Greer Laboratories, Lenoir, NC). Positive histamine and negative diluent controls were used. Reactions were recorded at 15 minutes as the length equating to the widest point on the wheal and the width measuring perpendicular to the widest point. A wheal of 3 mm or greater than the negative control was considered positive.

ImmunoCAP assay

Sera were analyzed for allergen-specific IgE antibodies by a commercial laboratory (Mayo Medical Laboratories, Rochester, Minn) or by using the Phadia ImmunoCAP System (Phadia AB, Uppsala, Sweden) as detailed by the manufacturer. Sera/plasma were analyzed for some/all of the following food and inhalant allergens: egg white, soy, milk, peanut, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, *Alternaria alternata*, cat dander, cockroach, and rabbit. Values of 0.35 kU/L or more were considered positive.

Flow cytometry

PBMCs were isolated by using Ficoll-Hypaque density centrifugation and resuspended in RPMI 1640 medium supplemented with 100 U/mL of penicillin, 100 μ g/mL of streptomycin, 29.2 μ g/mL of L-glutamine (all GIBCO, Carlsbad, Calif) and 10% heat-inactivated FCS (Gemini Bio-Products, Sacramento, Calif).

For Treg-cell phenotyping, PBMCs were surface stained with Live/Dead Fixable Aqua viability dye, CD3 Qdot 605 (both Invitrogen, Carlsbad, Calif), CD4 phycoerythrin (PE)-Cy7, CD8 allophycocyanin-H7 (BD Biosciences, San Jose, Calif), CD27 PE-Cy5, and CD45RO Texas Red PE (Beckman Coulter, Brea, Calif), fixed and permeabilized with the Foxp3 staining kit, and stained intracellularly for FoxP3 effluor 450 (eBioscience, San Diego, Calif).

For cytokine analysis, PBMCs were examined after stimulation with 20 ng/mL of phorbol 12-myristate 13-acetate and 1 μ mol/L of ionomycin (CalBioChem, Billerica, Mass) for 16 hours with 10 μ g/mL of Brefeldin A (Sigma-Aldrich, St Louis, Mo). Cells were surface stained, fixed with 4% paraformaldehyde, permeabilized with a saponin-based buffer, and stained intracellularly for IL-4 PE, IFN- γ v450 (BD Biosciences), and IL-13 allophycocyanin (Biolegend, San Diego, Calif).

For activation assays, PBMCs were resuspended at 1 million cells/mL R10 and 5 U/mL recombinant human IL-2 (Peprotech, Rocky Hill, NJ) and stimulated in 96-well plates with staphylococcal enterotoxin B (1 μ g/mL, Sigma-Aldrich), or anti-CD3 (OKT3) (1 μ g/mL, eBioscience) and anti-CD28 (1 μ g/mL, BD Biosciences). After 40 hours, cells were stained for CD69-fluorescein isothiocyanate, CD98-PE (BD Biosciences).

Events were collected on an LSRFortessa (BD Biosciences) and analyzed with FlowJo (Treestar, Ashland, Ore). All plots are gated on live, singlet lymphocytes.

Statistical analysis

The Mann-Whitney (Wilcoxon) 2-sample nonparametric test was used to compare the observed distributions of variables between groups.

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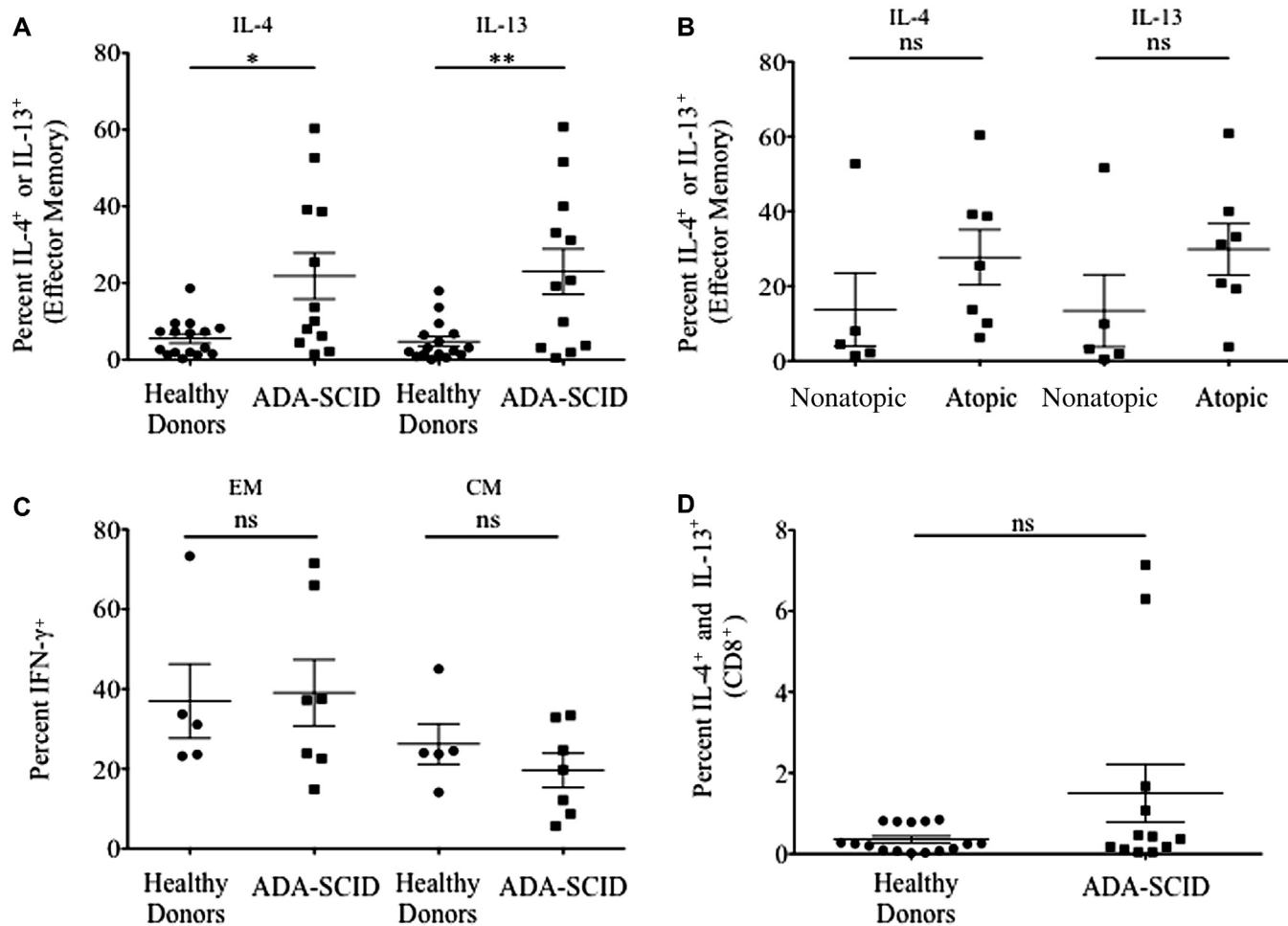


FIG E1. Percentage of IL-4⁺ or IL-13⁺ effector memory (EM) CD4⁺ cells from healthy donors (n = 16) versus donors with ADA-SCID (n = 12) (**A**) and atopic (n = 7) versus nonatopic (n = 5) patients with ADA-SCID (**B**). **C**, Percentage of IFN-γ⁺ EM and central memory (CM) CD4⁺ cells from healthy donors (n = 5) versus donors with ADA-SCID (n = 17). **D**, Percentage of IL-4⁺ and IL-13⁺ CD8⁺ cells from healthy donors (n = 16) versus donors with ADA-SCID (n = 12). ns, Nonsignificant. **P* < .05 and ***P* < .01.

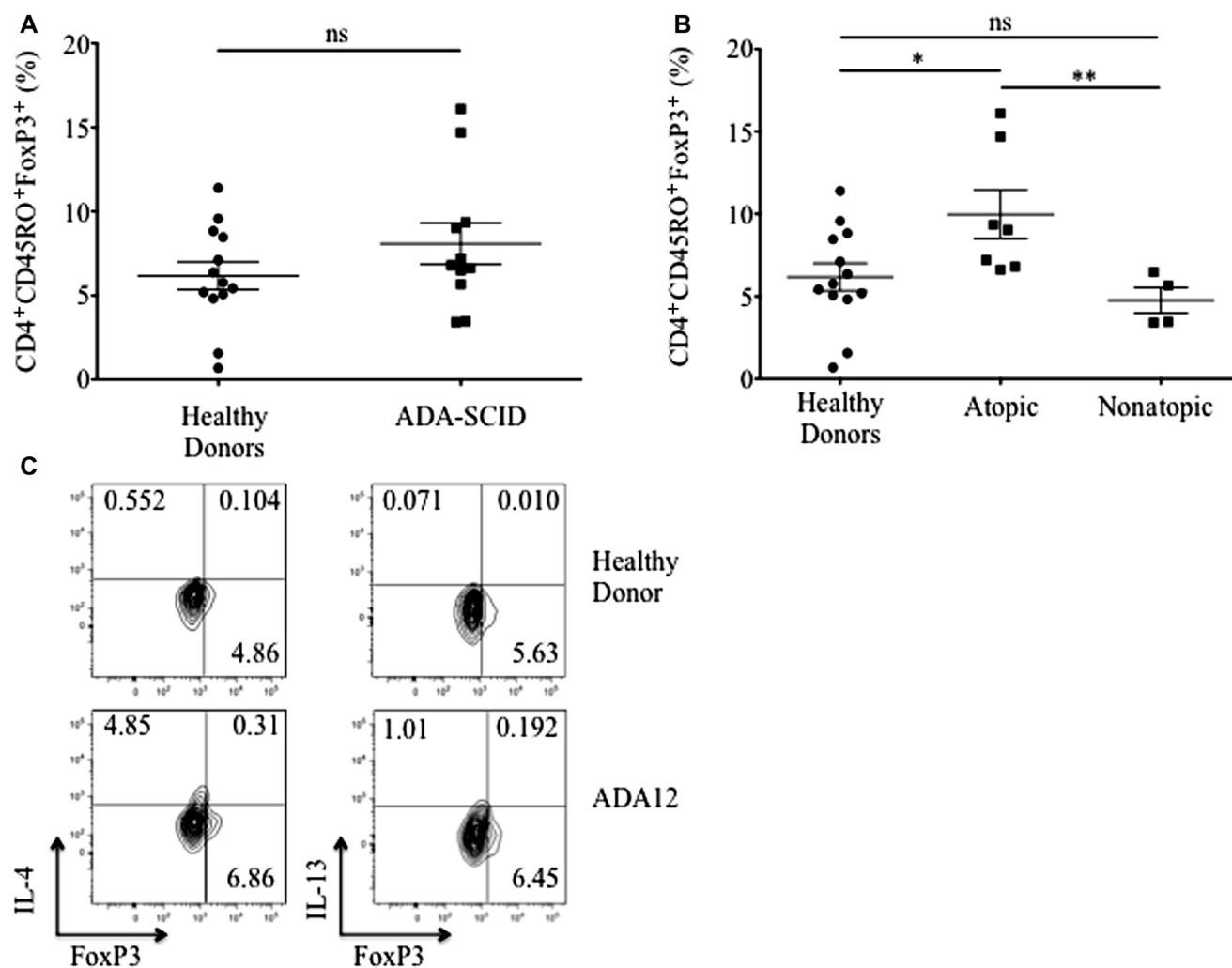


FIG E2. **A**, Percentage of CD4⁺CD45RO⁺FoxP3⁺ cells in healthy donors ($n = 13$) versus donors with ADA-SCID ($n = 11$). **B**, Percentage of CD4⁺CD45RO⁺FoxP3⁺ cells in healthy donors ($n = 13$) versus atopic ($n = 7$) and nonatopic ($n = 4$) patients with ADA-SCID. **C**, Representative FACS plot demonstrating lack of abnormal T_H2 cytokine production by CD4⁺CD45RO⁺FoxP3⁺ cells in a healthy donor (*top*) versus patient ADA12 (*bottom*). A similar lack of cytokine production was noted in all patients and controls tested. FACS, Fluorescence-activated cell sorting; ns, nonsignificant.

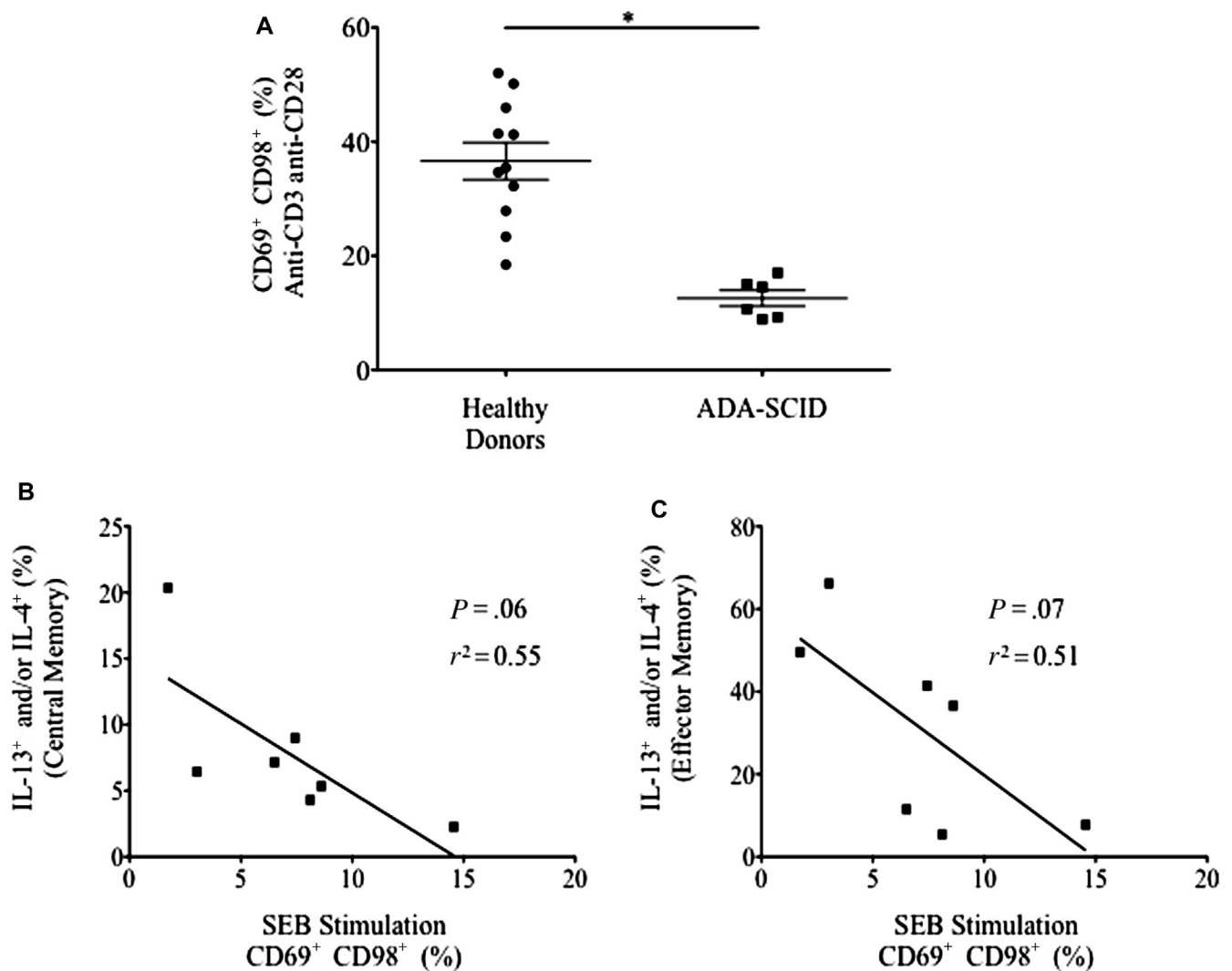


FIG E3. A, Percentage of CD69⁺CD98⁺CD4⁺ cells following stimulation with anti-CD3 and anti-CD28 in healthy donors (n = 11) versus donors with ADA-SCID (n = 6). **B** and **C**, Level of activation (CD69⁺CD98⁺) in response to stimulation with staphylococcal enterotoxin B (SEB) versus percentage of T_H2 cytokine (IL-4 and/or IL-13) positive (Fig E3, **B**) central memory CD4⁺ cells and (Fig E3, **C**) effector memory CD4⁺ cells. * $P < .05$.

TABLE E1. Age, treatment history, and atopic characteristics of each patient in the study group

Patient	Age (y)	Age at diagnosis of ADA-SCID (mo)	Treatment	Atopic disease (age in years at initial manifestation, when available)	Allergic sensitization (positive SPT result or allergen sIgE)	Family history of atopy
Prior T-cell or BM CD34 ⁺ GT						
ADA1	26	24	T-cell gene therapy, remains on PEG-ADA	Perennial allergic rhinitis, asthma	<i>Dermatophagoides farinae</i> , <i>Dermatophagoides pteronyssinus</i> , cat hair	None
ADA12	16	4	BM CD34 ⁺ gene therapy, remains on PEG-ADA	Perennial allergic rhinitis (14), egg allergy (2)	Egg white, wheat, peanut, milk	None
ADA13	31	60	T-cell and BM CD34 ⁺ gene therapy, remains on PEG-ADA	Exercise-induced asthma (4)	Egg white, cockroach mix, <i>D farinae</i>	Father—shellfish allergy
ADA14	6	9	BM CD34 ⁺ gene therapy, remains on PEG-ADA	Chronic idiopathic urticaria (6)	Peanut	Mother—allergic rhinitis, atopic dermatitis, asthma
ADA17	14	5	BM CD34 ⁺ gene therapy, remains on PEG-ADA	Perennial allergic rhinitis, asthma, atopic dermatitis, shellfish allergy	<i>D farinae</i> , <i>D pteronyssinus</i> , <i>Alternaria alternata</i> , cockroach mix	Mother—allergic rhinitis
ADA16	8	5	BM CD34 ⁺ gene therapy, off PEG-ADA	None	None; SPT not done (patient refused)	None
ADA5	11	7	BM CD34 ⁺ gene therapy, off PEG-ADA	Perennial allergic rhinitis (9)	<i>D farinae</i> , <i>D pteronyssinus</i>	NA—patient adopted
ADA10	5	2	BM CD34 ⁺ gene therapy, off PEG-ADA	Seasonal allergic rhinitis (3)	None	Father—allergic rhinitis
ADA26	3	1	BM CD34 ⁺ gene therapy, off PEG-ADA	None	None; SPT not done (patient refused)	Brother—asthma
ADA28	2	0	BM CD34 ⁺ gene therapy, off PEG-ADA	None	None; SPT not done (patient refused)	Father—allergic rhinitis
Prior BMT						
ADA3	15	5	BMT, remains on PEG-ADA	Perennial allergic rhinitis (13), asthma (13)	Peanut; SPT not done (patient refused)	Half brother—allergic rhinitis
ADA6	6	10	BMT, remained on PEG-ADA until death	Allergic rhinoconjunctivitis	Not evaluated (patient lost to follow-up)	Mother—childhood asthma
ADA7	8	0	BMT, remains on PEG-ADA	Perennial allergic rhinitis (8)	Not evaluated (patient unavailable)	Father—allergic rhinitis
ADA15	6	2	BMT, remains on PEG-ADA (lost to follow-up)	Allergic rhinoconjunctivitis, chronic idiopathic urticaria	Not evaluated (patient lost to follow-up)	NA (patient lost to follow-up)
ADA25	3	1	BMT, remains on PEG-ADA	None	Not evaluated (patient unavailable)	None
ADA4	13	4	BMT, off PEG-ADA	None	None	Father—allergic rhinitis
PEG-ADA alone						
ADA9	6	18	PEG-ADA (no prior GT or BMT)	Atopic dermatitis (1)	Not evaluated (patient unavailable)	Father—allergic rhinitis
ADA18	7	2	PEG-ADA (no prior GT or BMT)	Perennial allergic rhinitis (4)	<i>D farinae</i> , <i>D pteronyssinus</i> , cockroach mix, cat hair, egg white, peanut, milk	Mother—allergic rhinitis

Treatment reflects status as of most recent evaluation at the NIH.

BM, Bone marrow; NA, data not available; NIH, National Institutes of Health.