

## Longitudinal Analysis of Lymphocyte Function and Numbers in the First Year of Life in Chromosome 22q11.2 Deletion Syndrome (DiGeorge Syndrome/Velocardiofacial Syndrome)†

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**Chromosome 22q11.2 deletion syndrome is a common syndrome typically consisting of variable cardiac defects, hypoparathyroidism, developmental delay, and immunodeficiency. The hemizygous deletion has variable effects on the immune system even within the same kindred, and the extent of the immunodeficiency is difficult to predict. Some patients have shown improvement over time; however, this is the first prospective longitudinal study of the dynamic nature of the immunodeficiency. Nineteen patients were studied prospectively between 1994 and 1997. The results of the newborn immunologic studies in the chromosome 22q11.2 deletion group were significantly different from those of a group of newborns with cardiac disease due to other causes. Peripheral blood T-cell numbers were decreased in the chromosome 22q11.2 deletion group, although T-cell function was largely preserved. The group as a whole demonstrated few changes in the first year of life, but a subset of patients with markedly diminished T-cell numbers did demonstrate improvement. Therefore, improvement in peripheral blood T-cell counts is variable in chromosome 22q11.2 deletion syndrome. The patients with the lowest T-cell counts improved the most in the first year of life.**

Chromosome 22q11.2 deletion syndrome is one of the most common primary immunodeficiencies, with an estimated incidence of 1 in 3,000 live births. In spite of this frequency, little is known about the natural history because of the difficulty in establishing the diagnosis until recently. Hemizygous deletions of chromosome 22 in association with this syndrome were originally described in 1981 (11, 20, 24, 29). Now it is estimated that 10 to 30% of patients with DiGeorge syndrome have a cytogenetically visible deletion and 95% have some deletion that encompasses the critical region (6, 14, 15, 40, 49). Furthermore, the same deletion has been described in the majority of patients with velocardiofacial syndrome and conotruncal anomaly face syndrome (5, 7, 30). In the past, patients were diagnosed on the basis of syndromic characteristics and were categorized as having DiGeorge syndrome if they had hypocalcemia, a hypoplastic thymus, and a conotruncal cardiac anomaly (9, 26). Patients were categorized as having velocardiofacial syndrome if they had dysmorphic facies and a conotruncal cardiac anomaly (33), and many patients were probably not diagnosed with a specific syndrome. The phenotypic diversity appears not to be determined by the deletion endpoints because over 90% of patients have the same deletion breakpoints (7). Furthermore, even within a single family, there can be various expressions of the syndrome (39). Because of the phenotypic diversity in this syndrome, it is more appropriate to use the chromosome deletion rather than syndromic characteristics as the defining feature. Several groups have proposed the nomenclature be changed to CATCH 22 or chromosome 22q11.2 deletion syndrome to reflect this (48, 50). Adding to

the confusion, there are patients with a clinical phenotype consistent with a diagnosis of DiGeorge syndrome or velocardiofacial syndrome who do not have the characteristic chromosome deletion. Some of these patients have different chromosomal abnormalities or fetal exposure to alcohol or isotretinoin (17, 20, 32). Therefore, to delineate our study population, we elected to use the chromosome deletion as our defining feature.

The fluorescence in situ hybridization analysis for chromosome 22q11.2 deletion syndrome was first used in 1992 and now has become widely available. Since the advent of widespread testing for chromosome 22q11.2 deletion in target populations, it has become clear that the chromosome 22q11.2 deletion and the immunodeficiency classically associated with DiGeorge syndrome may be seen in a variety of clinical settings (15, 19, 41, 47). The deletion is consistent in the majority of patients, regardless of the phenotypic manifestations, suggesting that it is more appropriate to consider this population as having a chromosome 22q11.2 deletion rather than distinct syndromic populations. As with the other phenotypic features, there is a broad range of immunologic defects in patients with chromosome 22q11.2 deletion syndrome (3, 4, 34, 35, 43, 44, 47). Past longitudinal studies of small numbers of patients with clinically defined DiGeorge syndrome suggested that the immunologic defects could improve throughout childhood (3, 4). Additional cross-sectional studies of patients with DiGeorge syndrome also suggested that the immunodeficiency improves with age (43), although certain other studies have failed to demonstrate any improvement (23).

The characteristic immunodeficiency is a mild to moderate defect in T-cell production as a consequence of thymic hypoplasia (9, 26). These patients typically do not suffer from opportunistic infections characteristic of severe T-cell immunodeficiencies. A small fraction of patients have a more profound immunodeficiency with markedly impaired T-cell production

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† Dedicated to the memory of Justina Finkle Foley.

and T-cell function (sometimes called complete DiGeorge syndrome), and some patients have normal immunologic function as determined by standard laboratory assays (3, 4, 27, 34). There can be variable secondary humoral defects (16, 31, 42, 45). We wished to analyze a cohort of patients with chromosome 22q11.2 deletion syndrome over the first year of life to define the frequency of significant immunodeficiency and to characterize the dynamic nature of the immunodeficiency.

#### MATERIALS AND METHODS

**Patients.** Nineteen patients (17 Caucasian, 1 Hispanic, and 1 African-American) who were diagnosed between 1994 and 1997 with chromosome 22q11.2 deletion syndrome in the first few days of life were evaluated. All patients were full-term infants and were hemodynamically stable at the time of analysis. The Oncor N25 probe was used to detect the hemizygous deletion (14, 15). All patients had a cardiac anomaly which led to their early diagnosis. Immunologic evaluations were performed prior to cardiac surgery and transfusion in 8 patients and 2 weeks after cardiac repair and any transfusion with irradiated blood in 11 patients. Seven patients had tetralogy of Fallot, six patients had interrupted aortic arch, two patients had simple ventricular septal defects, one patient had truncus arteriosus, and three patients had other cardiac defects. Eleven patients had sustained hypocalcemia, while eight patients had either hypocalcemia lasting less than 48 h after cardiac repair or no hypocalcemia. At the 1 year time point, immunologic evaluations were not performed if the child was felt to have an intercurrent illness or if the child had weight loss in the previous month. All immunologic evaluations were performed in the Clinical Immunology Laboratory at The Children's Hospital of Philadelphia. The institutional review board at The Children's Hospital of Philadelphia approved these studies.

Management of these patients was consistent. Because none of the patients had severe immunodeficiency, they were not placed in isolation. Prophylactic antimicrobials were not generally used. Reasonable precautions against infectious exposures were recommended. Blood products were irradiated. Prophylaxis for varicella exposure was given to two patients. Two patients transiently required trimethoprim-sulfamethoxazole prophylaxis for pneumocystis because they had markedly diminished T-cell numbers. Live viral vaccines were not administered in the first year of life. After the 1-year evaluation, live viral vaccines were allowed for those patients whose immunologic evaluations had normalized.

**Immunologic evaluations.** At the time of diagnosis, two- or three-color flow cytometry was performed on a Coulter EPICS XL to define the following lymphocyte populations: CD3<sup>+</sup>, CD3/CD4<sup>+</sup>, CD3/CD8<sup>+</sup>, CD3<sup>-</sup>/CD16/56<sup>+</sup>, CD19<sup>+</sup>, CD5/19<sup>+</sup>, and TCR $\gamma\delta$ <sup>+</sup>. CD14 and CD45 were used to confirm the purity of the lymphocyte population. Proliferative responses to phytohemagglutinin (PHA), pokeweed mitogen (PWM), and concanavalin A (ConA) were measured in triplicate cultures of two dilutions of stimulus harvested 72 h after stimulation. A total of 10<sup>5</sup> peripheral blood mononuclear cells purified by Ficoll-Paque (Pharmacia, Uppsala, Sweden) were used per well. PWM was used at final concentrations of 3 and 2.5 ng/ml. PHA was used at final concentrations of 12.5 and 10 ng/ml. ConA was used at final concentrations of 50 and 25 ng/ml. Incorporation of [<sup>3</sup>H]thymidine was determined for each well, and the average of each triplicate set was used for reporting the counts per minute (cpm). The stimulation index (SI) was determined by dividing the average cpm from the stimulated cells by the average cpm from the unstimulated cells. At 1 year of age, the same studies were repeated. Although we did not recruit age-matched healthy subjects as controls for this study, samples from adult controls were run on each day as controls for staining and flow cytometry. In addition, a few immunologic evaluations were obtained from patients with conotruncal cardiac defects who were thought to be likely to have the chromosome deletion but who later turned out to not have the deletion. These results for these patients are reported as cardiac control results. These samples also validate our use of published normative data for comparison (8).

**Statistical analyses.** A paired Student *t* test was used to compare changes over time in the study population. The Student *t* test was used to compare the mean values between different groups. A correction for multiple comparisons was not performed.

#### RESULTS

**Newborns with chromosome 22q11.2 deletion syndrome have significantly fewer cells of thymic lineage than newborns without the chromosome 22q11.2 deletion.** Nineteen infants who were diagnosed with chromosome 22q11.2 deletion syndrome in the first few days of life constituted our study population. Eleven newborns with suspected chromosome 22q11.2 deletion who later turned out not to have the deletion were evaluated for the immunodeficiency associated with chromosome 22q11.2 deletion syndrome. These children had cardiac

lesions comparable to those of the study group (tetralogy of Fallot, three children; truncus arteriosus, two; other, three; minor cardiac lesions, three), and both groups had a median age of 17 days. To determine whether a cardiac lesion could be responsible for the immunodeficiency, we compared the mean values for lymphocyte subsets between the cardiac control group and the chromosome 22q11.2 deletion group. The lymphocyte subsets in the cardiac control group were comparable to the published normative data from a group of Dutch infants (8). The CD8 counts from the cardiac patients were slightly higher than those of the Dutch controls; however, CD8 counts have been reported to be in the same range (median, 1,420 cells/mm<sup>3</sup>; 95 to 5% range, 650 to 2,450 cells/mm<sup>3</sup>) in a study of American children of diverse ethnicities (12). The results for newborns with chromosome 22q11.2 deletion syndrome were different from those for cardiac controls and the published normative data in that all of the thymic lineage cell types were decreased (Table 1). Specifically, the absolute lymphocyte count and the CD3, CD4, and CD8 counts were significantly lower in the chromosome 22q11.2 deletion syndrome group than in the cardiac controls. Similarly, the fraction of the peripheral blood lymphocyte pool comprised of thymus-dependent lineages was lower in the patients with chromosome 22q11.2 deletions than in the cardiac controls. The percentage and absolute count of CD8 cells were the most abnormal findings. In contrast, lineages which do not require the thymus for maturation such as B cells (CD19), natural killer cells (CD16/56), and T cells bearing the  $\gamma\delta$  receptor were not significantly different between the two groups. CD5/19 B cells are a subgroup of B cells important in autoimmunity that have been found in thymic tissue, although it is not clear whether they require the thymus for maturation or whether they are passive residents (22, 36). This population was no different between the two groups, although for both groups it was slightly lower than that for published age-matched controls. Finally, proliferative responses as measured by responses to PHA were no different between the two groups, i.e., normal. These results suggest that the immunodeficiency associated with chromosome 22q11.2 deletion syndrome is a specific result of the hemizygous chromosome 22q11.2 deletion and resulting thymic hypoplasia and not simply a result of the stress associated with significant cardiac defects.

**Longitudinal analysis of lymphocyte subsets and lymphocyte function in infants with chromosome 22q11.2 deletion syndrome.** To define the dynamic nature of the immunodeficiency, we monitored 19 patients with chromosome 22q11.2 deletion syndrome over the first year of life. Previous studies had suggested that there could be significant improvement in immunologic function in the first year of life (3, 4, 35). This is the first longitudinal analysis in which the ages of the patients were controlled. Table 2 demonstrates that the population as a whole did not demonstrate significant improvement in peripheral blood T-cell numbers or in the lymphocyte fraction corresponding to thymus-dependent lineages over the first year of life. The patients' lymphocyte subset values are closer to the published normative data at 1 year of age because T-cell counts in normal infants typically decrease in the first year of life (8). For example, 3 of 19 patients in the newborn period had normal numbers of lymphocytes, while 18 of 19 had normal numbers at 1 year of age. Similarly, 3 of 19 patients had normal numbers of CD3 T cells in the newborn period compared to 12 of 19 at 1 year of age. Three of 19 patients (the same three patients as before) had normal numbers of CD4 T cells in the newborn period compared to 12 of 19 at 1 year of age. Eight of nineteen patients had CD8 T cells in the normal range in the newborn period compared to 11 of 19 at 1 year of age.

TABLE 1. Analyses of lymphocyte subsets in infants with cardiac anomalies with and without chromosome 22q11.2 deletion syndrome

Determination	Results for:				P value	Values for healthy controls	
	Patients with chromosome 22q11.2 deletion ( <i>n</i> = 19)		Cardiac controls ( <i>n</i> = 11)			Mean	5–95% range
	Mean	5–95% range	Mean	5–95% range			
Absolute lymphocyte count (cells/mm <sup>3</sup> )	3,164	2,183–4,142	5,128	3,472–6,784	0.0254	6,700	3,500–13,100
CD3							
Cells/mm <sup>3</sup>	1,625	1,058–2,192	3,907	2,652–5,163	0.0003	4,600	2,300–7,000
%	50.5	42–59	77.1	70–84	<0.0001	72	60–85
CD4							
Cells/mm <sup>3</sup>	1,117	753–1,482	2,749	1,865–3,633	0.0002	3,500	1,700–5,300
%	35.4	29–41	55.1	48–62	0.0001	55	41–68
CD8							
Cells/mm <sup>3</sup>	480	290–670	1,412	894–1,930	0.0001	1,000	400–1,700
%	14.4	12–17	20.6	17–24	0.0083	16	9–23
TCR-γδ							
Cells/mm <sup>3</sup>	110	57–162	134	38–230	0.6084		
%	2.3	1–4	2.2	1–3	0.8818		
CD5/19							
Cells/mm <sup>3</sup>	74	13–134	127	76–179	0.1642	600	300–1,100
%	2.1	1–3	2.8	1–4	0.4021		
CD19							
Cells/mm <sup>3</sup>	484	329–638	589	314–863	0.4402	1,000	600–1,900
%	21.5	16–27	12.1	6–18	0.0208	15	4–26
CD16/56							
Cells/mm <sup>3</sup>	835	364–1,305	463	119–807	0.2269	500	200–1,400
%	21.0	14–28	7.8	4–12	0.0112	5	1–38
PHA <sup>a</sup>							
SI	102	55–149	173	52–346	0.1984	587 <sup>b</sup>	416–758
cpm	52,867	31,826–73,908	53,055	35,509–70,601	0.9902	88,179 <sup>b</sup>	54,064–122,294

<sup>a</sup> *n* = 13 for the chromosome 22q11.2 deletion group; *n* = 6 for the cardiac control group.

<sup>b</sup> These represent results for samples from adult controls run simultaneously with the patient samples.

Four immunologic evaluations changed significantly in the first year of life. The mean absolute lymphocyte count rose from 3,164 cells/mm<sup>3</sup> in the newborn group to 4,631 cells/mm<sup>3</sup> in the 1-year-old group. The CD19 B-cell count rose from 484 to 1,832 cells/mm<sup>3</sup> in the 1-year-old group, while the B-cell fraction rose from 21.5 to 39.4%. The CD5/19 B-cell count rose from 74 to 278 cells/mm<sup>3</sup>, while the CD5/19 fraction rose from 2.1 to 7.2%. Mitogen proliferation, as measured by cpm, in response to PHA improved significantly, although responses to ConA and PWM were stable over time. Interestingly, the SIs corresponding to all three mitogens improved over the first year of life, but this was due in large part to decreasing spontaneous uptake of [<sup>3</sup>H]thymidine. The percentages of CD4 and CD8 cells both decreased slightly in the first year of life.

We hypothesized that patients with worse peripheral blood T-cell counts might have greater improvement in the first year of life than those less impaired. To test this, we selected 10 patients whose initial CD3 count was less than the median for the population, 1,344 cells/mm<sup>3</sup>. We reanalyzed the longitudinal data on these 10 patients with the paired Student *t* test (Table 3). These 10 patients demonstrated significant improvement in peripheral blood T-cell counts in the first year of life, as well as a significant rise in circulating B-cell numbers. Natural killer cell numbers and T cells bearing the TCR-γδ receptor did not change significantly over the first year of life, sug-

gesting that the findings do not represent global changes in lymphocyte production. Therefore, there is a subgroup of patients with chromosome 22q11.2 deletion syndrome in which significant improvement in T-cell production occurs in the first year of life.

## DISCUSSION

Two previous longitudinal studies of patients with DiGeorge syndrome (as clinically defined) revealed diverse outcomes. In one study, eight patients had CD4 counts measured in the first month of life and then repeated at various follow-up intervals ranging from 12 to 38 months. Four of the eight patients demonstrated improvement in their CD4 count, and four patients had fewer CD4 T cells on follow-up (4). A second longitudinal study evaluated five patients clinically defined as having DiGeorge syndrome. In this study, initial evaluations of total T-cell numbers were performed in the first 4 months of life and follow-up ranged from 3 months to 2 years. Four of the five patients demonstrated consistent improvement over time in total T-cell numbers. One patient had declining T-cell numbers (3). Several cross-sectional studies have addressed this question with conflicting results. The mean CD3, CD4, CD8, and CD19 cell counts progressively decreased for the 0- to 3-month, 2- to 6-year, and 6- to 18-year-old groups in one study

TABLE 2. Longitudinal analysis of lymphocyte subsets and function in patients with chromosome 22q11.2 deletion syndrome in the first year of life

Determination	Results for patients with chromosome 22q11.2 deletion				P value <sup>a</sup>	Values for 1-yr-old healthy controls	
	Newborns (n = 19)		1-yr-olds (n = 19)			Mean	5-95% range
	Mean	5-95% range	Mean	5-95% range			
Absolute lymphocyte count (cells/mm <sup>3</sup> )	3,164	2,183-4,142	4,631	3,563-5,700	<b>0.041</b>	5,500	2,600-10,400
CD3							
Cells/mm <sup>3</sup>	1,625	1,058-2,192	1,854	1,475-2,235	0.497	3,400	1,600-6,700
%	50.5	42-59	42.6	37-48	<b>0.028</b>	65	54-76
CD4							
Cells/mm <sup>3</sup>	1,117	753-482	1,233	1,000-1,465	0.601	2,300	1,000-4,600
%	35.4	29-41	28.2	25-31	<b>0.006</b>	44	31-54
CD8							
Cells/mm <sup>3</sup>	480	290-670	502	362-643	0.846	1,100	400-2,100
%	14.4	12-17	11.5	9-14	0.068	18	12-28
TCR-γδ							
Cells/mm <sup>3</sup>	110	49-171	227	24-429	0.199		
%	2.3	1-4	3.4	3-4	0.091		
CD5/19							
Cells/mm <sup>3</sup>	74	13-134	278	154-402	<b>0.011</b>		
%	2.1	1-3	7.2	4-10	<b>0.003</b>		
CD19							
Cells/mm <sup>3</sup>	484	329-638	1,832	1,260-2,403	<b>&lt;0.001</b>	1,400	600-2,700
%	21.5	16-27	39.4	34-45	<b>&lt;0.001</b>	25	15-39
CD16/56							
Cells/mm <sup>3</sup>	835	364-1,305	785	407-1,163	0.781	400	200-1,200
%	21.0	14-28	28.8	1-58	0.510	7	3-17
PHA (n = 13)							
cpm	52,867	31,826-73,908	82,594	67,579-97,609	<b>0.002</b>		
SI	107	55-160	373	277-468	<b>&lt;0.001</b>		
ConA (n = 13)							
cpm	54,005	31,724-76,286	62,084	44,550-79,617	0.541		
SI	98	60-136	319	197-441	<b>0.004</b>		
PWM (n = 13)							
cpm	32,603	20,955-44,252	30,843	22,856-38,831	0.788		
SI	59	37-82	154	91-218	<b>0.010</b>		

<sup>a</sup> P values < 0.05 are boldfaced.

(23). In a second study, the percentage of CD4 cells in a group of children less than 1 year of age (43%) was no different than the percentage of CD4 cells in the children over 1 year of age (42%) (34). Because of the uncertainty surrounding the natural history of the immunodeficiency in this syndrome, we undertook the current study.

This study demonstrates that the immunodeficiency is related to the chromosome deletion and is not simply due to the stress of the cardiac anomaly. The differences between the chromosome 22q11.2 deletion syndrome group and the cardiac control group were primarily in the thymus-derived lineages, which is consistent with the known pathophysiology of the immunodeficiency. A hemizygous deletion of chromosome 22q11.2 affects the immune system through its effects on thymic development. Although the thymus may be macroscopically absent, in most cases there are microscopic rests of thymic tissue in the neck, suggesting that migration is aberrant in this syndrome (2). The limitation of thymic tissue to support T-cell

maturation underlies the immunodeficiency seen in this syndrome, and replacement of thymic tissue constitutes an important therapeutic intervention (10, 28). The T-cell immunodeficiency ranges from severe to nonexistent, with most patients exhibiting a mild to moderate defect in T-cell production (47). Significant defects in T-cell function are less common (3, 4, 27, 34), and there may be variable humoral dysfunction in a small subset of patients (16, 18, 23, 31, 42, 45). The prevalence of infection and autoimmune disease is higher in this population, suggesting that the immunodeficiency is clinically relevant (13, 16, 21, 23, 25, 31, 37, 38, 42, 45, 46). Although the immunodeficiency is clinically relevant, most patients do not suffer from opportunistic infections and they do not require isolation or other precautions used with patients with severe T-cell immunodeficiencies. It is believed that only 1% of patients with clinical DiGeorge syndrome or with the chromosome deletion have the serious immunodeficiency.

The paired newborn and 1-year immunologic evaluations

TABLE 3. Longitudinal analysis of lymphocyte subsets and function in 10 patients with initial CD3 counts of <1,344 cell/mm<sup>3</sup>

Determination	Results for patients with chromosome 22q11.2 deletion				P value <sup>a</sup>
	Newborns (n = 10)		1-yr-olds (n = 10)		
	Mean	5-95% range	Mean	5-95% range	
Absolute lymphocyte count (cells/mm <sup>3</sup> )	2,159	1,548-2,771	4,953	2,962-6,945	<b>0.017</b>
CD3					
Cells/mm <sup>3</sup>	808	530-1,086	1,862	1,119-2,605	<b>0.019</b>
%	33.2	16-50	40.7	32-50	0.343
CD4					
Cells/mm <sup>3</sup>	590	380-800	1,271	808-1,734	<b>0.021</b>
%	29.1	20-39	27.3	21-33	0.625
CD8					
Cells/mm <sup>3</sup>	218	131-305	489	229-748	0.058
%	11.1	6-16	13.2	6-21	0.363
TCR-γδ					
Cells/mm <sup>3</sup>	92	10-174	297	122-717	0.221
%	1.6	0.4-3	2.8	1-4	<b>0.046</b>
CD5/19					
Cells/mm <sup>3</sup>	37	9-65	174	69-279	<b>0.026</b>
%	2.2	0.3-5	5.9	2-10	0.062
CD19					
Cells/mm <sup>3</sup>	369	152-586	2,166	1,098-3,235	<b>0.007</b>
%	19.5	9-29	42.8	37-49	<b>&lt;0.001</b>
CD16/56					
Cells/mm <sup>3</sup>	591	125-1,058	845	140-1,550	0.281
%	25.1	8-42	14.4	8-20	0.112
PHA					
cpm (n = 13)	59,035	25,345-92,725	32,494	60,260-104,730	0.053
SI (n = 13)	123	39-206	357	262-451	<b>0.009</b>

<sup>a</sup> P values < 0.05 are boldfaced.

allowed us to define the early natural history of the immunodeficiency in this syndrome. Within the whole group, there were few consistent changes over time. Notably, the absolute lymphocyte count and the B-cell count improved significantly over the first year of life. When we evaluated a subpopulation which presented with CD3 counts lower than 1,344 cells/mm<sup>3</sup>, it was clear that there could be significant improvement in thymus-derived cell lineages over the first year of life. All of the thymus-derived lineages improved in the first year of life in this subpopulation, and B-cell numbers improved as well. The consistent improvement in B-cell numbers may be due to improved T-cell help being available or to persisting defects in T cells which control B-cell proliferation. One study of patients with DiGeorge syndrome found that increased B-cell numbers correlated with a worse immunologic outcome (34).

Another notable finding from this study is that the CD8 T-cell subset appears to be more significantly affected than the CD4 T-cell compartment. The size of the CD4 and CD8 T-cell compartments is, at least in part, genetically controlled (1). The size of each compartment is determined by both positive and negative selection within the thymus as well as a commitment to either a CD4 or CD8 lineage. One potential explanation for the more marked effect on CD8 lineage T cells would be that the limited thymus epithelium has fewer developmental niches and thus restricts the commitment of CD8 T cells. Until the genetic control of T-cell homeostasis is better understood,

it will be difficult to identify the mechanism underlying the decreased CD8 cell compartment in patients with this syndrome.

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