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Defective human interleukin 2 receptor γ chain in an atypical X chromosome-linked severe combined immunodeficiency with peripheral T cells

(cytokine receptors/immune deficiency)

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ABSTRACT **X chromosome-linked severe combined immunodeficiency disease (SCIDX1) is characterized by the absence of T-cell and natural killer cell development and results from molecular mutations of the interleukin 2 receptor (IL-2R) γ chain. The IL-2Rγ chain is a common component of the IL-2, IL-4, and IL-7 receptor systems, which may explain the severe immunophenotype in SCIDX1. We have previously described an atypical SCIDX1 syndrome demonstrating poorly functioning peripheral T cells, which we hypothesized to represent a variant allele at the *SCIDX1* locus. We now demonstrate that a splice site mutation in the IL-2Rγ gene is responsible for this atypical SCIDX1. Aberrant RNA splicing resulted in the generation of two IL-2Rγ transcripts: an abundant, nonfunctional isoform containing a small intronic insertion and a second functional isoform with a single amino acid substitution present in limited amounts. Radiolabeled IL-2 binding studies revealed a 5-fold decreased level of expression of functional high-affinity IL-2Rs, which correlated with the quantity of full-length IL-2Rγ transcripts. Further analysis of the T-cell antigen receptor β-chain repertoire of the patient's T cells demonstrated oligoclonality in multiple V_β families, thus strongly suggesting that the defect in the IL-2Rγ chain generated a limited number of peripheral T-cell clones. This atypical SCIDX1 patient demonstrates that certain IL-2Rγ chain abnormalities can also result in partial immunodeficiency phenotypes, potentially through differential effects on the IL-2, IL-4, or IL-7 receptor systems.**

X chromosome-linked severe combined immunodeficiency disease (SCIDX1) is a recessive hereditary disorder characterized by a complete absence of immature and mature T cells and natural killer (NK) cells, whereas B cells are present in normal or elevated numbers (reviewed in ref. 1). SCIDX1 infants present with severe and persistent infections, resulting in failure to thrive and early death without curative bone marrow transplantation. Obligatory carrier females of SCIDX1 are immunologically normal but display a nonrandom pattern of X inactivation in their T-, B-, and NK-cell populations (2, 3), suggesting a role for the *SCIDX1* gene product in the development of these lymphoid lineages.

The gene defective in SCIDX1 has been identified as the interleukin 2 receptor (IL-2R) γ chain (4). The IL-2R is composed of three chains (IL-2Rα, -β and -γ), which noncovalently associate in combination to form high-(αβγ), intermediate- (βγ or αβ), and low-affinity (α) IL-2Rs (5, 6). Although the IL-2/IL-2R system has been extensively studied in the context of proliferating mature T cells, the role of the IL-2/IL-2R pair in early T-cell development remains controversial (7–10). Additionally, there exists evidence that the IL-2Rγ chain functions outside of the IL-2 system. Normal T-cell differentiation occurs in patients with a failure to produce IL-2 (11, 12), as well as in mice rendered IL-2-deficient by gene targeting (13). Recently, IL-2Rγ has been shown to participate in the IL-4 and IL-7 receptor systems (14–17). Thus, perturbations in IL-2, IL-4, and/or IL-7 receptors may explain the severe defects seen in SCIDX1.

We have previously analyzed a family that presented an immunodeficiency disease characterized by poorly functioning mature T cells (18). The gene responsible for this disease mapped to the *SCIDX1* region (19), and we hypothesized that this family manifested an atypical form of SCIDX1 with an attenuated phenotype. We now report the molecular characterization of the IL-2Rγ chain defect responsible for this atypical SCIDX1.

MATERIALS AND METHODS

Description of the Atypical SCIDX1 Phenotype. The clinical presentation of the patient and the atypical SCIDX1 disease have been described (18). The patient presented with protracted diarrhea and failure to thrive at 9 months. B-lymphoblastoid cell lines (B-LCLs) were established from the patient by standard Epstein–Barr virus infection protocols.

Analysis of IL-2Rγ cDNA and Genomic Sequences. Full-length IL-2Rγ chain transcripts were PCR amplified from peripheral T-cell cDNA for direct sequence analysis using reverse transcription–PCR as described (20). Genomic sequences were PCR amplified using primers corresponding to the first two exons (forward exon I primer: 5′-AAGCCATCATTACCATTCACA-3′ and reverse exon II primer: 5′-GTGGAAACGCTGAGGGAGTC-3′), which amplified the intervening first intron. Genomic PCR conditions were 30 cycles of 94°C for 1 min, 54°C for 1 min, and 73°C for 1 min. Amplification products were purified by agarose gel electrophoresis and binding to glass powder (Geneclean; Bio 101).

Immunofluorescence and Characterization of High-Affinity IL-2Rs. Immunofluorescence was performed as described (20) using monoclonal antibodies directed against the IL-2Rα (TAC; ref. 21) and IL-2Rβ (561; gift of R. J. Robb, DuPont) chains. Scatchard analysis and endocytosis studies using ^{125}I-labeled IL-2 were performed as described (22–24). Analyses of five different control B-LCLs and the patient B-LCLs were performed twice each with similar results.

Analysis of the T-Cell Antigen Receptor (TCR) β-Chain Repertoire. The anchor-PCR method for generation of the V_β

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Abbreviations: SCIDX1, X chromosome-linked severe combined immunodeficiency disease; B-LCL, B-lymphoblastoid cell line; TCR, T-cell antigen receptor; IL, interleukin; IL-2R, IL-2 receptor; NK, natural killer.

"minilibraries" was performed as described (25) using total RNA from the patient's peripheral T cells. Analysis of V_β and J_β segments was performed on >600 C_β^+ clones. Sequences of oligonucleotides used for the J_β analysis are available from the authors. TCRβ transcripts were sequenced using a T7 polymerase kit (Sequenase) with either vector-specific or V_β-specific primers.

RESULTS

Characteristics of the Atypical SCIDX1 Phenotype. The patient studied belonged to a family with a history of an atypical immune deficiency with an X chromosome-linked recessive mode of inheritance. The clinical characteristics of this immune deficiency have been described (18) and included increased susceptibility to infections, severe diarrhea, and failure to thrive. Immunological findings included normal numbers of T, B, and NK cells with normal immunoglobulin levels; however, there was a severe and progressive functional immune deficit characterized by defective antigen-specific responses (20). Linkage analysis localized the disease gene to the same region as *SCIDX1*. Based on the clinical, immunological, and genetic analyses, we hypothesized that the disease presenting in this family represented an attenuated form of SCIDX1 with an abnormality in the IL-2Rγ chain.

Analysis of the IL-2Rγ Gene in the Atypical SCIDX1 Patient. Full-length IL-2Rγ transcripts were amplified from peripheral T cells of the patient by reverse transcription–nested PCR. No deviations from the IL-2Rγ sequence (26) were noted except in the 5′ region of the transcript, where direct sequence analysis was not possible because of superimposition of two different sequences. PCR using primers flanking this region resulted in the generation of two amplification products, differing in ≈30 bp (Fig. 1*A*). The lower molecular weight PCR species comigrated with the single product obtained from normal control samples. The two products from the patient were isolated and sequenced. The smaller molecular weight product accounted for ≈20% of the cDNA obtained and was identical to the wild-type IL-2Rγ sequence with the exception of a single base change (G to A) at bp 115 (A in the initiator Met = 1). This substitution resulted in an amino acid change at position 17 of the mature protein (D17N). The larger product, which accounted for ≈80% of the cDNA obtained, also contained this base pair change; however, it was followed by a 27-bp insertion, which truncated the predicted protein by introducing a stop codon at amino acid position 25 (Fig. 1*B*). Thus, two IL-2Rγ transcripts can be detected in the T cells of this atypical SCIDX1 patient: a less abundant, normal-sized species containing a single amino acid substitution and a more abundant, nonfunctional transcript containing an insertion of 27 bp.

Because this nucleotide change was present at the first exon–intron boundary of the IL-2Rγ gene (27), we hypothesized that a splicing defect might account for the two transcripts observed. Genomic DNA from the atypical SCIDX1 patient and from a normal control was subjected to PCR using primers flanking the abnormal region (Fig. 1*C*). Sequence from the normal control DNA verified the end of the first exon of the IL-2Rγ gene and the subsequent splice donor site. This splice donor (TG/*gt*ggg) conformed well to the consensus donor motif (AG/*gt*rag; r = a or g; canonical *gt* is italicized) compiled from data base sequences (28). The sequence from the patient showed only a G to A substitution at the last base of the first exon (TA/*gt*ggg). Mutations at the penultimate base of the exon adjacent to a splice donor site can reduce the usage of these sites in RNA splicing (29). In addition, the 27-bp insertion found in the larger cDNA (Fig. 1*B*) was identical to the intronic sequence directly following the first exon (Fig. 1*C*, and data not shown), and a cryptic

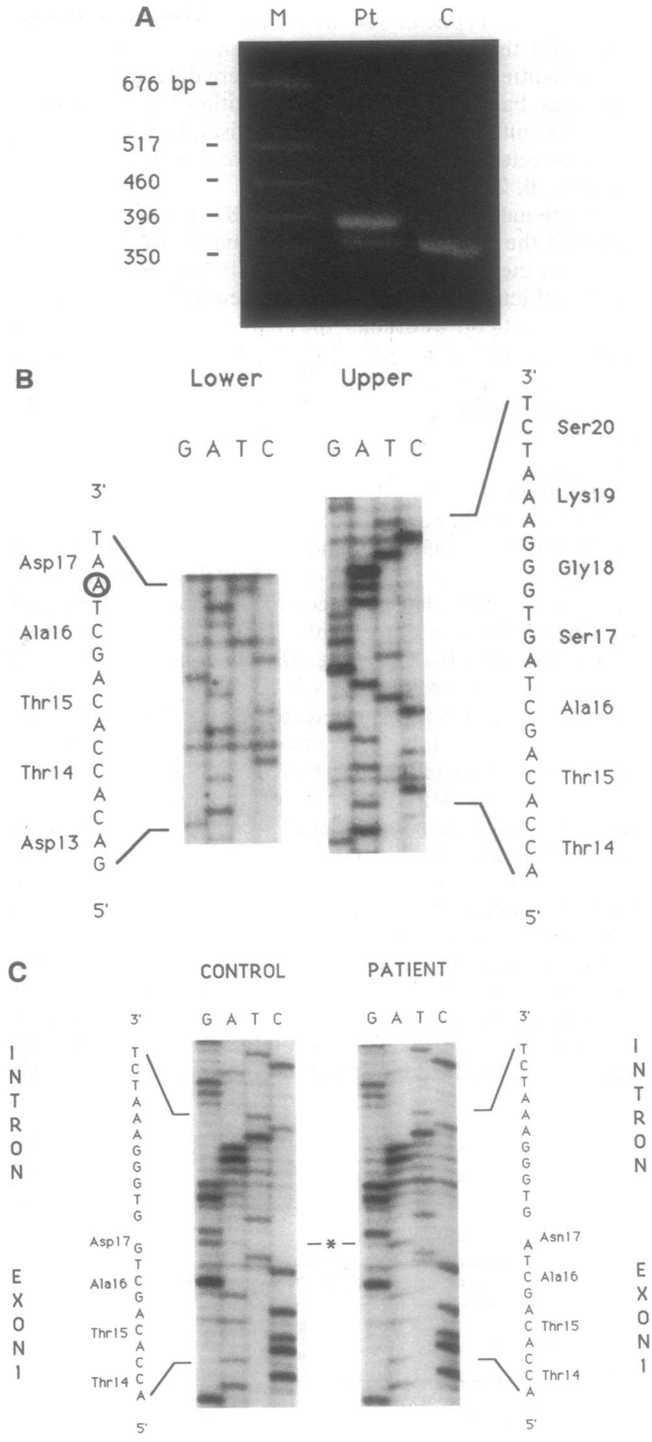

FIG. 1. (*A*) PCR amplification around the suspected abnormal region of the IL-2Rγ transcript. PCR products from the atypical SCIDX1 patient (Pt) and from a normal control (C) were electrophoresed on a 4% Nu-Sieve agarose gel and stained with ethidium bromide. M, molecular size standards. (*B*) Sequence analysis of IL-2Rγ cDNAs from the patient's T cells. Only the relevant portion of the sequencing gel is shown of the lower and upper PCR products in *A*. The upper product contains a 27-bp insertion (beginning at the G residue of codon S17), which generates an in-frame stop codon. The lower product contains a G to A point mutation (circled). (*C*) Genomic sequence of the first exon–intron junction of the IL-2Rγ gene. Control DNA contained a G residue just before the splice donor site (*gt*ggg), whereas the patient DNA demonstrated an A at this position (indicated by an asterisk).

splice donor site can be found after this sequence in the intron (tg/*gt*aga). Thus, splicing in this patient is presumably fa-

vored at the cryptic donor site rather than the normal donor site, with the resultant insertion event (Fig. 2). No other abnormalities of IL-2Rγ transcripts were detected other than the single base change (G to A) at position 115. It is unlikely that this mutation represented an allelism, because it has not been detected in IL-2Rγ sequences from numerous individuals (4, 20, 26).

Functional Analysis of Cell Surface IL-2Rs. We next determined if the defect in the IL-2Rγ chain transcripts had any effect on the expression of the high-affinity IL-2R. Because of the difficulty in establishing mitogen-induced T-cell lines from this patient, we studied the characteristics of the IL-2Rs expressed on the patient's Epstein–Barr virus-transformed B-LCLs. Three different affinity IL-2Rs are formed by association of the IL-2R chain subunits. Low-affinity receptors (K_d = 10 nM) contain the IL-2Rα chain, whereas intermediate- (K_d = 1 nM) and high-affinity (K_d = 10–100 pM) receptors contain IL-2Rβγ or IL-2Rαβ and IL-2Rαβγ, respectively. Surface expression of the IL-2Rα (p55; CD25) and IL-2Rβ (p75) chains was found at a level comparable to that of control B-LCLs and about 10-fold lower than normal activated T cells (data not shown). By Scatchard analysis, ≈24 high-affinity receptors with a $K_d \approx 75$ pM were detected on the patient's B-LCLs (Fig. 3*B*), as compared to 90–125 receptors on control B-LCLs (Fig. 3*A*). An intermediate-affinity receptor was also detected ($K_d \approx 700$ pM), which probably corresponds to receptors formed of IL-2Rαβ or IL-2Rβγ or both (30). The level of high-affinity receptors correlated well with the level of the full-length IL-2Rγ transcript detected in the patient's T cells (Fig. 1*A*). Previous studies have reported the requirement of the IL-2Rγ chain for endocytosis of the high-affinity IL-2R (26). IL-2 is internalized after high-affinity binding to the patient's B-LCLs, with kinetics similar to control B-LCLs (Fig. 4) and in T cells. Thus, this patient's B-LCLs express a decreased level of high-affinity IL-2Rs (about 4- to 5-fold less abundant compared to control B-LCLs), which are competent for receptor-mediated endocytosis. The point mutation (D17N) does not appear to affect IL-2 binding or its subsequent endocytosis.

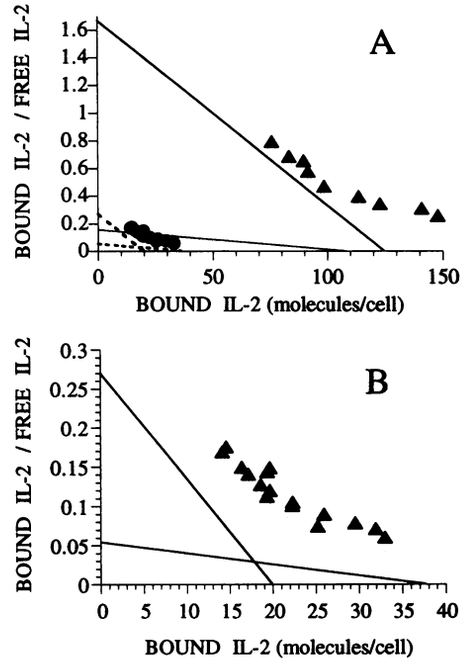

FIG. 3. Binding of ^{125}I-labeled IL-2 to control or patient B-LCLs. B-LCLs were incubated with ^{125}I-labeled IL-2 for 20 min at 37°C and washed at 4°C, and cell-associated radioactivity was determined. Nonspecific binding was determined at each concentration of IL-2 by the addition of a 100-fold excess of unlabeled IL-2 and was subtracted. A representative control is shown (similar results were obtained in five normal control B-LCLs). (*A*) Scatchard plot of the data is presented using similar scales for comparison. ●, Patient's B-LCLs; ▲, control B-LCLs. (*B*) Enlarged scale of Scatchard binding to patient's B-LCLs (▲).

Analysis of TCRβ Repertoire. We have characterized the extent of T-cell development in this SCIDX1 patient through an analysis of the TCR V_β and J_β repertoires. Since few V_β monoclonal antibodies are available, TCRβ-chain transcripts were amplified from the patient's T cells by anchor PCR,

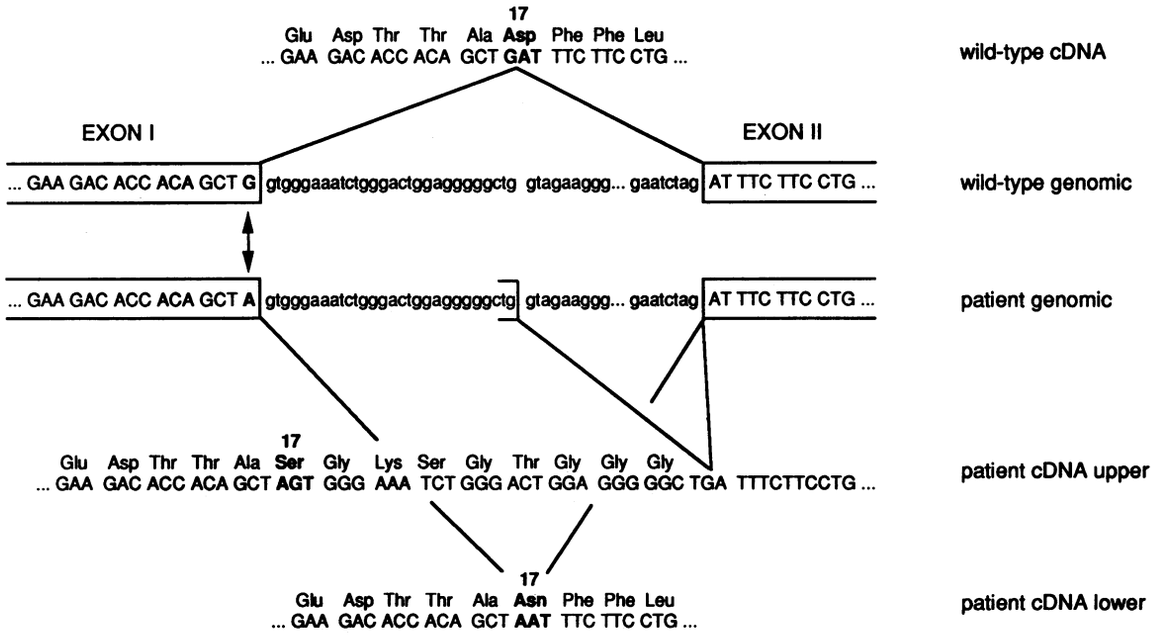

FIG. 2. Summary of the splicing events in the atypical SCIDX1 patient. Splicing of exons I and II normally generates the codon GAT (D17). In the SCIDX1 patient, this residue is changed to A (arrows). "Patient cDNA upper" (upper product in Fig. 1*A*) results from usage of a cryptic splice donor 27 bp downstream of the normal donor site and terminates prematurely at amino acid 25. "Patient cDNA lower" (lower product in Fig. 1*A*) results from usage of the normal splice donor site, but with the base change, the resultant codon becomes AAT (N17).

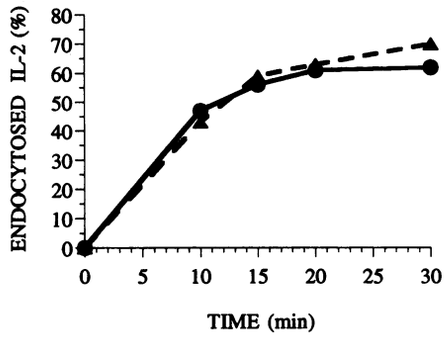

FIG. 4. Endocytosis of IL-2. Normal control (▲) or atypical SCIDX1 (●) B-LCLs were incubated with 150 pM ^{125}I-labeled IL-2 for the indicated times at 37°C and then washed at 4°C to remove unbound ligand. Cells were acid-treated to remove cell surface-associated ligand. Percent internalization is the ratio of intracellular counts to total cellular counts (×100%). Similar results were obtained in five normal control B-LCLs.

cloned, and analyzed by hybridization with V_β- and J_β-specific oligonucleotides (25). The patient's V_β profile appeared similar to normal control samples (Fig. 5) in that ≈70% of the V_β segments are derived from V_β2–6 and V_β13, as has been demonstrated in normal adults (25, 31) and neonates (32). However, some variation in the V_β usage can be seen in this patient; for example, V_β2 and V_β19 appeared slightly overexpressed depending on the control, whereas V_β13 was considerably overexpressed. In contrast, V_β9, V_β11, V_β14–18, and V_β20–24 were relatively underexpressed in the patient.

The usage of J_β segments was determined in parallel. Comparison of the J_β repertoire of the SCIDX1 patient with control samples demonstrated an overexpression of J_β2.7, whereas usage of other J_β segments was similar to controls (data not shown). Alignment of the J_β2.7 filters with the V_β panel demonstrated that 75% of the V_β13$^+$ clones were J_β2.7$^+$. Subsequent sequencing of individual V_β13–J_β2.7 clones revealed the same complimentarity determining region sequence in six out of nine isolates (Table 1). Redundant clones from a single V_β family are not found in minilibraries from normal control T cells (25) but have been identified in some autoimmune situations (33, 34). In these cases, it is assumed that antigen-specific T-cell expansion is responsible for the oligoclonality of the particular V_β segment. Additional V_β families (V_β2-, V_β4-, and V_β6-specific clones) were then sequenced from the SCIDX1 patient's T cells. Surprisingly, these V_β families also revealed substantial oligoclonality (Table 1). Sequencing of TCRβ isolates from control T cells (both adult and neonatal) as well as other primary immunodeficiency disease patients (age-matched) failed to demonstrate any TCRβ oligoclonality. As antigen-specific responses are not usually associated with oligoclonality of multiple V_β families, these results strongly suggest that the peripheral T cells of this patient manifested a restricted TCRβ repertoire. Thus, although all known V_β families were utilized by this patient, the defect in the IL-2Rγ chain resulted in the selection of a reduced number of circulating, peripheral T-cell clones for each V_β segment analyzed.

Table 1. Oligoclonality of TCRβ sequences in T cells from atypical SCIDX1 patients

V_β family	Type	Isolate*	Complimentarity determining region 3	J_β-C_β usage
		Patient TCRβ sequences		
V_β2	Clone A	5/10	CSAR PTSGSYNEQ FFGPG	J_β2.1–C_β2
	Unique	5/10		
V_β4	Clone A	6/10	CSVD GGQLEQ YFGPG	J_β2.7–C_β2
	Clone B	2/10	CSVG TSGQTNEQ FFGPG	J_β2.1–C_β2
	Unique	2/10		
V_β6	Clone A	2/10	CASS SSWSSYEQ YFGPG	J_β2.7–C_β2
	Clone B	2/10	CASS SGQGAYEQ YFGPG	J_β2.7–C_β2
	Clone C	2/10	CASS FLVFYTYEQ YFGPG	J_β2.7–C_β2
	Clone D	2/10	CASS PNGPRGY TFGSG	J_β1.2–C_β1
	Unique	2/10		
V_β13	Clone A	6/9	CASS LPNNRVYEQ YFGPG	J_β2.7–C_β2
	Clone B	3/9	CASG RTSPSTDTQ YFGPG	J_β2.3–C_β2
		Control TCRβ sequences		
V_β2	Unique	53/53		
V_β4	Unique	20/20		
V_β6	Unique	30/30		
V_β13	Unique	8/8		

Control sequences were derived from normal adult (n = 2), age-matched neonates (n = 1), and age-matched primary immunodeficiency disease patients (n = 4) TCRβ minilibraries.
*Number of isolates with given complimentarity determining region 3 sequence/total number of isolates.

DISCUSSION

The gene encoding the IL-2Rγ chain has been demonstrated to be defective in SCIDX1. Point mutations and deletions (4, 20) have been found in the IL-2Rγ chain gene in patients with the typical phenotype of SCIDX1 (including the absence of T-cell and NK-cell development, elevated numbers of B cells, and pan hypogammaglobulinemia). In contrast to typical SCIDX1 infants, this patient belonged to a family where four male children in two generations presented with phenotypically normal T cells and normal immunoglobulin levels but with abnormal cellular and antibody responses to specific antigens (18). However, like typical SCIDX1 patients, all of the affected male children in this family suffered multiple infectious episodes during the early years of life.

A genetic analysis performed in this family led us to hypothesize that this disease might correspond to an attenuated form of SCIDX1 (18). The identification of a point mutation in a splicing signal of the IL-2Rγ gene confirms the

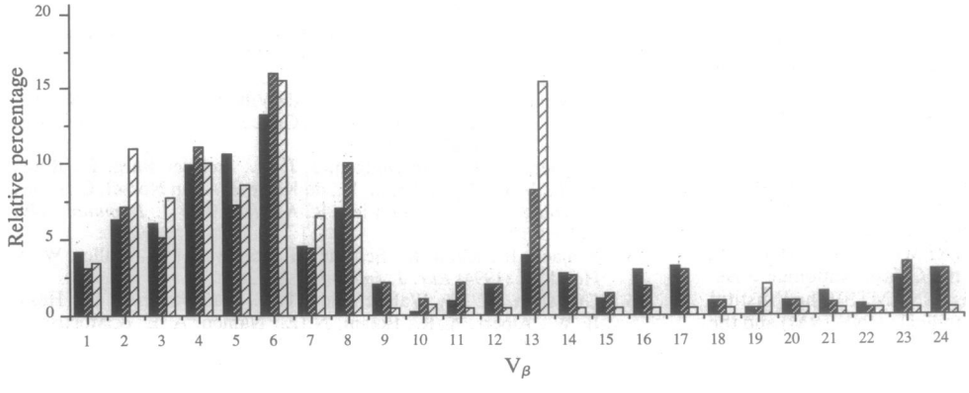

FIG. 5. Relative TCR V_β levels in peripheral T cells as assayed by anchor PCR. Two normal controls (solid bars and dark hatched bars) are compared with the atypical SCIDX1 patient (light hatched bars; i.e., third bar in each set). Results are expressed as a percentage of detectable C_β^+ clones.

initial hypothesis. This exonic mutation apparently diminished the ability to splice a correct sized transcript, while promoting the production of a nonfunctional transcript containing a segment of the adjacent intron. The residual amount of normal-length IL-2Rγ transcripts can account for the limited number of functional high-affinity IL-2R complexes detectable at the cell surface. Thus, in this atypical SCIDX1 patient, the molecular defect resides in the IL-2Rγ gene with one consequence of a decrease in the number of high-affinity IL-2Rs. Despite this defect, mature T cells, although functionally abnormal in antigen-specific responses, were present in the circulation (18). We now demonstrate that these T cells also utilize a limited V_β pool. Thus, the abnormal IL-2Rγ expression can also be correlated with defective T-cell differentiation (limited TCRβ heterogeneity and diminished functional activity).

Comparisons of the immunological defects seen in IL-2-deficient conditions (11–13) that show mature T-cells and IL-2Rγ mutations in SCIDX1 patients that lack T cells suggested a role for the IL-2Rγ chain in additional cytokine receptors. Recently, IL-2Rγ has been demonstrated to participate in the formation and function of the IL-4 and IL-7 receptors (14–17). Although mice deficient in both IL-2 and IL-4 develop normally functioning T cells (35), blockade of the IL-7/IL-7 receptor system impairs both T- and B-cell development (36). Thus, the immunological defects seen in SCIDX1 may result from a combination of disturbances in the IL-2, IL-4, and IL-7 receptors, although a role for the IL-2Rγ chain in additional cytokine receptors critical for lymphoid development remains possible.

The immunological defect in this atypical SCIDX1 patient may result from the diminished IL-2Rγ expression or from the amino acid substitution (D17N). Although the point mutation appears not to affect IL-2 function, it may potentially impact on IL-4 or IL-7 binding and/or signaling. The abnormal IL-2Rγ expression may affect T-cell development during intrathymic passage or after primary immune responses in the peripheral lymphoid organs. Defective IL-2Rγ chain function may limit the number of developing early thymocytes, and therefore this atypical X-linked SCID patient would represent a truly attenuated SCIDX1 phenotype. Alternatively, the abnormality in thymic differentiation may reside at a later stage in T-cell development where thymocytes expand through cytokine-dependent mechanisms. Decreased numbers of high-affinity IL-2Rs might also limit peripheral T-cell responses, in analogy to the defects seen in IL-2-deficient conditions (11–13).

If reduced IL-2Rγ chain levels are responsible for this atypical SCIDX1 phenotype, there will be important implications for possible genetic therapy of SCIDX1. Limited levels of IL-2Rγ chain might allow for thymic passage and production of some peripheral T cells; however, in this patient, these phenotypically mature T cells were functionally abnormal. There may exist a threshold level of IL-2Rγ expression necessary for complete T-cell development. These considerations may be of interest for the design of gene therapy strategies for SCIDX1. Expression systems using the endogenous human IL-2Rγ promoter may provide adequate levels of transcription. Constitutive high-level expression of the IL-2Rγ chain, which is normally achieved in lymphoid cells, may be critical for therapeutic success.

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