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Variant Translocation of the *BCL6* Gene to Immunoglobulin κ Light Chain Gene in B-Cell Lymphoma

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A lymphoma cell line with a variant type of translocation, t(2;3)(p11;q27), was established from a patient who had received liver transplantation. To elucidate the molecular mechanism of the t(2;3)(p11;q27) chromosomal translocation, we compared the structures of both derivative (der) chromosomal breakpoints with those of their germline predecessors. We noted that the *BCL6* gene on chromosome 3 was juxtaposed with the immunoglobulin κ light chain (Igκ) gene on chromosome 2 in a head-to-head configuration. The breakpoint of the *BCL6* gene was within a previously reported breakpoint cluster region. The breakpoint on chromosome 2 was within the intron between the leader (L) and variable (V) sequences of one of the Vκ genes, which was fused to the Jκ3 (J=joining) segment. At chromosomal junctures, a direct repeat duplication of chromosome 3 sequences and a deletion of chromosome 2 sequences were discovered. These results are consistent with a translocation model with illegitimate pairing of staggered double-stranded DNA breaks at 3q27 and 2p11, repair, and ligation to generate der(3) and der(2) chromosomes.

Key words: *BCL6* — 3q27 breakpoint — 3q27 translocation

Chromosomal abnormalities are present in most hematopoietic malignancies.[1] Involvement of the immunoglobulin genes in chromosomal translocations is observed in various types of B-cell malignancies.[2] The most frequent in non-Hodgkin's lymphomas (NHL) are t(14;18)(q32;q21), associated with follicular lymphoma,[3–5] and t(8;14)(q24;q32) and its variants, associated with Burkitt's lymphoma.[6,7]

A new nonrandom chromosomal translocation between 3q27 and one of three loci of the immunoglobulin genes, has been found in up to 6.3% of B-cell NHL cases by cytogenic analysis, particularly in diffuse large-cell type NHL.[8,9] This translocation seems to be the third most common recurring translocation in NHL.[8,9] Recently, we have cloned a 3q27 breakpoint from a cell line, MD901, carrying t(3;22)[10] and identified a novel zinc-finger encoding gene, termed *BCL5*.[11] Other groups have also characterized 3q27 breakpoints from cases carrying t(3;14),[12–14] and identified the same gene, named LAZ3[15] or *BCL-6*.[16] We have changed the name of the gene to *BCL6*.

In the present study, we report the cloning of breakpoints from a B-cell lymphoma carrying t(2;3)(p11;q27),[17] representing a variant translocation involving *BCL6* gene, and characterize the sites of chromosomal junctures on both derivative (der) chromosomes 2 and 3.

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MATERIALS AND METHODS

DNA DNA was derived from a lymphoma cell line, designated SUBL.[17] This cell line was established from a patient with Epstein-Barr virus (EBV)-associated lymphoma, which developed during immunosuppressive therapy with FK 506 after liver transplantation. Chromosomal analysis of the SUBL cells revealed the karyotype 46,XY,t(2;3)(p11;q27), as the sole abnormality. The cultured cells were positive for CD19, CD20, CD22, CD23, and HLA-DR, and negative for CD10 and surface immunoglobulins. Cytoplasmic immunoglobulin γ heavy chain and κ light chain were detected. These data indicate that this cell line represents the B-cell lineage at a pre-B cell stage. The SUBL cells were positive for Epstein-Barr virus nuclear antigen (EBNA).

DNA extraction and Southern blot analysis DNA was extracted by the sarcosyl-proteinase K-phenol/chloroform method. After digestion with appropriate restriction endonucleases, DNA fragments were electrophoresed on a 0.8% agarose gel and transferred onto a nylon membrane as described.[18] Southern blot hybridization analysis was performed in 50% formamide, 3×standard saline-citrate, 10×dextran sulfate-5×Denhardt's solution-0.5% sodium dodecyl sulfate at 37°C for 16 h. Filters were washed in 0.2×standard saline-citrate-0.5% sodium dodecyl sulfate at 65°C for 2 h. A probe used for Southern blot analysis of *BCL6* gene rearrangement was

a 1.2-kb *Xho*I-*Hin*dIII fragment from the human *BCL6* gene locus,[10] ^{32}P-labeled by the random priming method.

DNA cloning and sequencing DNA from SUBL was partially digested with the restriction enzyme *Mbo*I and fractionated by sucrose gradient centrifugation. Then, 15- to 20-kb DNA fragments were pooled and ligated with λ FIX II phage vector as recommended by the suppliers (Stratagene, La Jolla, CA). The resulting library was screened with a 1.2-kb *Xho*I-*Hin*dIII fragment of chromosome 3 and/or a 0.6-kb *Hin*dIII-*Eco*RI fragment of chromosome 3, as indicated in the text. Both probes were ^{32}P-labeled by the random priming method. Genomic DNA fragments encompassing the breakpoint junctions of the t(2;3) from the presumptive der(2) and der(3) chromosomes were digested with *Hin*dIII [der(2) chromosome] or *Bam*HI [der(3) chromosome] and then subcloned into the plasmid pUC19 or pUC18 (Takara, Kyoto). Nucleotide sequences were determined by the dideoxy chain termination method, using an Applied Biosystems 373A automatic DNA sequencer and a *Taq* dye primer cycle sequencing kit (Applied Biosystems, Foster City, CA).

RESULTS

Southern blot analysis of DNA from the cell line SUBL, hybridized with a 1.2 kb *Xho*I-*Hin*dIII fragment, revealed rearranged bands as shown in Fig. 1. From this result and a previously reported restriction map[10] of chromosome 3 shown in Fig. 2, we mapped a 3q27 breakpoint of SUBL within a 3.2 kb *Eco*RI-*Hin*dIII fragment as illustrated in Fig. 2. This was compatible with our previously reported finding of a breakpoint cluster region of the *BCL6* gene on 3q27.[10] Furthermore, using a 0.6 kb *Hin*dIII-*Eco*RI fragment (indicated in Fig. 2) as a probe on Southern blot analysis, one rearranged 2.7 kb *Hin*dIII fragment was detected (data not shown).

To clone a breakpoint at 3q27 of SUBL, a λ FIX II library prepared after partial digestion with *Mbo*I of SUBL DNA was screened with the probes used for Southern blot analysis. To distinguish clones containing a breakpoint from germline clones of chromosome 3, clones hybridizing only with one of two probes were selected for DNA extraction and mapping. The maps of these clones are illustrated in Fig. 2 and compared with those reported for germline chromosomes 2 and 3.[10, 19] The possibility of a cloning artifact was ruled out, since restriction mapping of both clones was consistent with the sizes of rearranged fragments detected on Southern blot analysis of SUBL DNA (Fig. 1).

To determine the origin of the sequences adjacent to the breakpoints of the der(2) and der(3) chromosomes, the 3.9 kb and 7.3 kb *Bam*HI fragments on the der(3) chromosome and the 2.7 kb *Hin*dIII fragment on the der(2) chromosome were subcloned into the plasmids pUC19 and pUC18, respectively, and sequence analysis of these subclones was performed.

The sequences adjacent to chromosome 3 sequences in the der(3) chromosome matched the intron sequences betweeen the leader (L) and variable (V) segments of a member of the VκII family registered in GenBank (locus in GenBank: HSIKLVA17). Restriction mapping and sequences of this VκII gene region in the der(2) and der(3) chromosomes in Fig. 2 were consistent with the reported ones.[20, 21] These results indicate that in this human B-cell lymphoma cell line, SUBL, the reciprocal chromosomal translocation involving band 3q27 and 2p11 resulted in illegitimate joining of the *BCL6* and immunoglobulin κ light chain (Igκ) genes in a head-to-head configuration.

This VκII gene fused to Jκ3 (J=joining segment) sequences, as shown in Fig. 3. At the VJ junction, dinucleotides CC might be due to imprecise VJ recombination and derived from the intervening sequences 3′ to the V coding sequences.[22-24] In addition, the first four potential coding nucleotides of germline Jκ3 segment, TTCA,

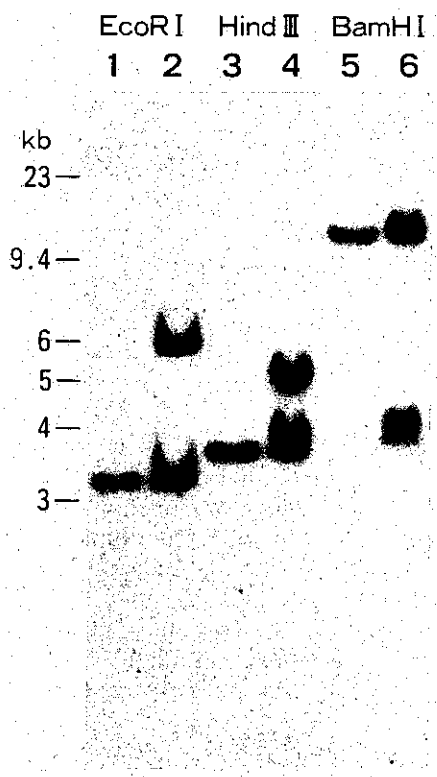

Fig. 1. Southern blot analysis of SUBL DNA. DNA was digested with the indicated restriction enzymes and electrophoresed on a 0.8% gel. The probe used was a 3q27 specific probe, a 1.2-kb *Xho*I-*Hin*dIII fragment.[10] Lanes 1, 3, and 5, MOLT-4 used as the control; 2, 4, and 6, SUBL. Fragment sizes are given in kb.

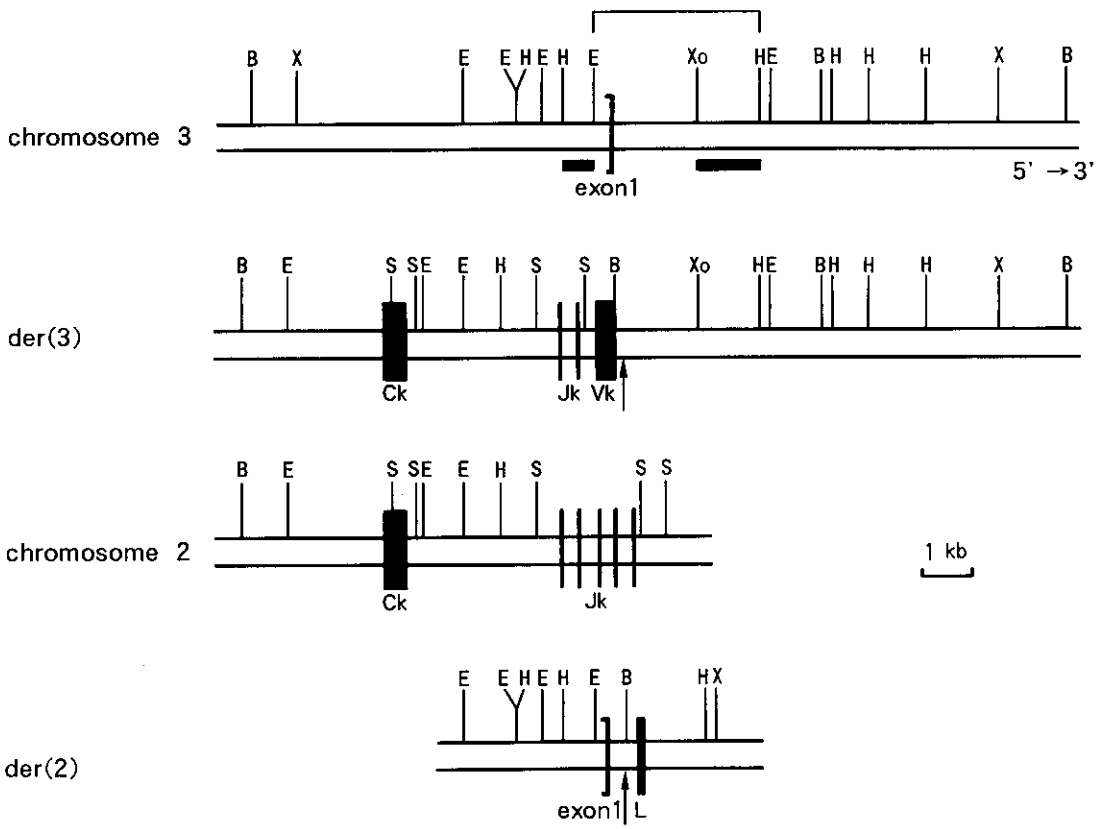

Fig. 2. Comparative restriction maps of the cloned breakpoint regions of SUBL cells and germline counterparts of chromosomes 2 and 3. Breakpoints are shown by arrows. The bracketed region is a 3q27 breakpoint cluster region previously reported by us.[10] The leader (L), variable (V), joining (J), and constant (C) regions on chromosome 2 are represented by filled boxes. The Vκ-Jκ fusion could have occurred before or after the translocation. The locations of probes are indicated by thick bars. Restriction endonuclease sites are abbreviated as follows: B, *Bam*HI; E, *Eco*RI; H, *Hin*dIII; S, *Sac*I; X, *Xba*I; and Xo, *Xho*I. (*Hin*dIII sites on chromosome 3 are not complete.)

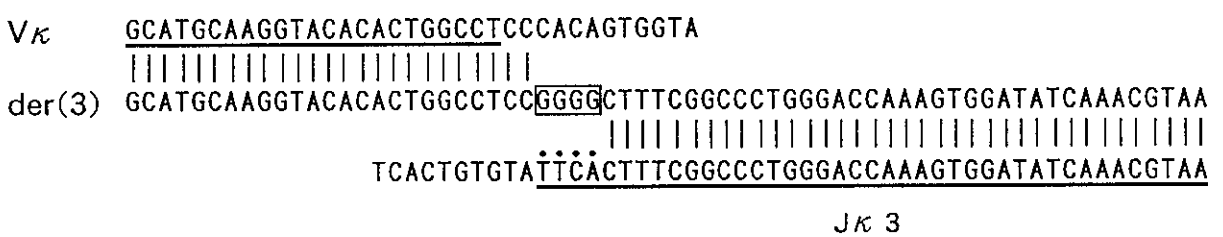

Fig. 3. Nucleotide sequence comparison of the germline Vκ and Jκ3 segments on chromosome 2 and the der(3) at VJ junction. The four N-region nucleotides at the VJ junction of the der(3) are boxed. An initial 4 bp deletion of Jκ3 segment is marked by dots. Potential coding bases of the variable (V) and joining (J) segments on germline chromosome 2 are underlined. Sequence identity is shown by vertical lines.

were deleted and extraneous nucleotides (N region), GGGG, were inserted instead.

The nucleotide sequences at the site of chromosomal juncture on both the der(3) and der(2) chromosomes were compared with those of the germline *BCL6* locus of chromosome 3 and the germline VκII region (HSIKLVA17 in GenBank) of chromosome 2 (Fig. 4). Every base pair of germline *BCL6* information could be found within either the der(3) or der(2) chromosome, including an octanucleotide (ATGTGTAT) duplication found at the juncture site of both the der(3) or der(2) chromosomes. In contrast, a deletion of eleven nucleo-

Fig. 4. Nucleotide sequences encompassing the joining region of chromosomes 2 and 3. Arrowheads indicate the sites of breakage. Sequence identity is shown by vertical lines. The 8 nucleotides present in the germline 3q27 region and at both der(2) and der(3) junctions are boxed. A deletion of 11 nucleotides in the germline 2p11 region is underlined.

tides (or ten nucleotides in an alternative interpretation) of the VκII region was noted. Note also that no extra nucleotide was found at the joining sites of the *BCL6* and Vκ loci. In contrast to the junctions observed in *bcl-2*[25] and c-*myc*,[26] sequences similar to the heptamer-nonamer recombination signals could not be recognized in the vicinity of the breakpoint sites on either chromosome 2 or chromosome 3. No sequence homology to the immunoglobulin switch region sequences (a pseudo-switch region) or Chi sequences (GCTGGTGG) that have been noted in immunoglobulin and *myc* loci[27, 28] could be detected in the vicinity of breakpoint sites on either of the chromosomes. Although structural associations between inter-chromosomal *Alu* sequences may be implicated in some Philadelphia chromosome rearrangements,[29–31] the chromosome 2 and 3 sequences at or adjacent to the breakpoints did not show any homology to the consensus *Alu* sequences. It was also clear that no extensive sequence homology around the breakpoint sites existed between the *BCL6* gene and the involved variable region gene of Igκ, from the absence of hybridization between molecular clones containing these regions and from comparisons of sequences of these regions. This suggests that a non-homologous recombination must have taken place between these two chromosomes.

The nucleotide sequence data reported in this paper will appear in the GSDB, DDBJ, EMBLE, and NCBI nucleotide sequence databases with the accession numbers D28522, D28523, D28524, and D28525.

DISCUSSION

We have cloned the breakpoint junctions of the t(2;3) in a B-cell lymphoma line, SUBL. The t(2;3) is a variant of three different translocations involving band 3q27-t(3;14), t(3;22), and t(2;3). These translocations are observed mainly in diffuse large cell type of non-Hodgkin's lymphoma.[8, 9] Recently we and others reported 3q27 breakpoints and found a novel zinc-finger encoding gene.[11, 15, 16]

It has been shown that the *BCL6* gene can rearrange with immunoglobulin λ light chain (Igλ) gene on chromosome 22,[10] as illustrated in Fig. 5. The same gene has been reported to rearrange with immunoglobulin heavy chain (IgH) gene on chromosome 14.[12, 13] In this paper, we have described a B-cell lymphoma in which *BCL6* gene rearranged with Igκ gene in a head-to-head configuration (Fig. 5).

The breakpoint in SUBL is located within a breakpoint cluster region of *BCL6* gene, which was previously reported by us[10] and others,[12, 13] as shown in Figs. 2 and 5. This cluster region is located upstream to coding exons of this gene.[15, 16, 32] Thus, the *BCL6* gene can rearrange at the 5′ untranslated region of the gene with both IgH and IgL genes.[10, 12, 13] This is in contrast with the c-*myc* and *bcl-2* gene rearrangements.[33] The c-*myc* gene can rearrange at the 5′ and 3′ regions of the gene with IgH and IgL genes, respectively. The *bcl-2* gene can also rearrange at the 5′ and 3′ regions with IgL and IgH genes, respectively. The interesting feature of these translocated *bcl-2* and c-*myc* genes is that these genes are always located 5′ to immunoglobulin constant loci. This configuration might be crucial for activation of these genes. But this is not the case in the translocated *BCL6* gene, in which disruption of the 5′ untranslated region of the gene is the sole constant feature, and its effect may be more important than the effect of the conventional enhancer element in immunoglobulin constant loci.

At the VJ junction of der(3) chromosome, there were extraneous nucleotides (N region). These inserted sequences, GGGG, are consistent with the GC-rich character of N regions, and are supposed to be added by the lymphoid-specific enzyme terminal deoxynucleotidyltransferase (TdT).[34, 35] Generally heavy chain variable region genes are assembled before light chain variable region genes and, where examined, TdT has been found to be expressed primarily at the earlier (heavy chain rearranging) stages of B cell differentiation.[36] Thus the major difference between reported immunoglobulin heavy and light chain coding joins is the frequent appear-

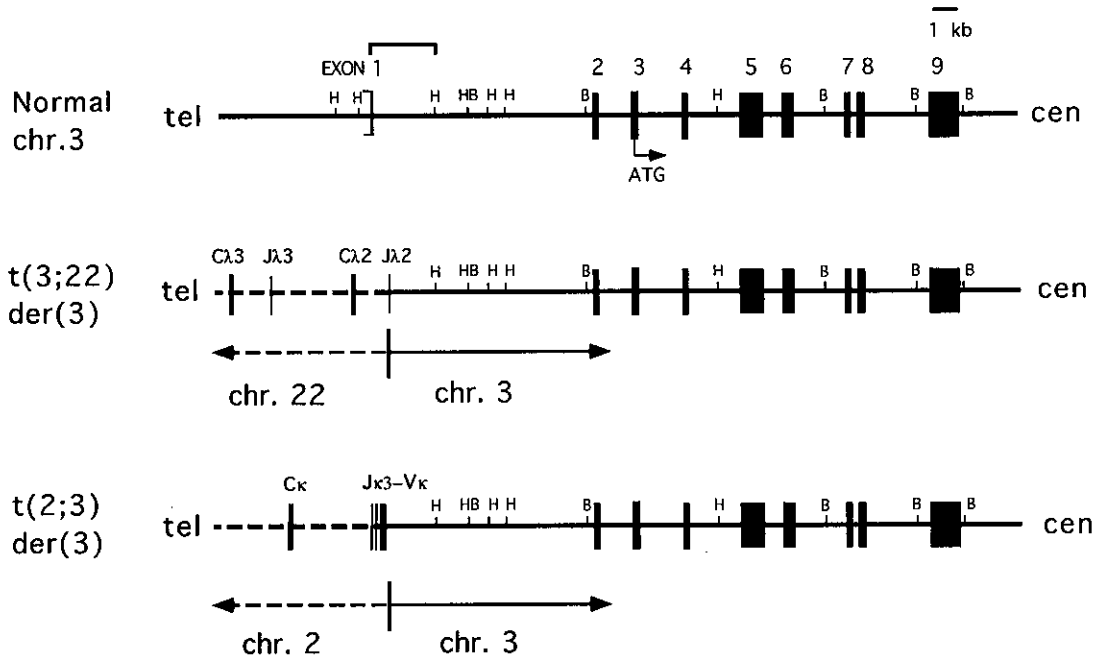

Fig. 5. The *BCL6* gene fused to both Igλ and Igκ genes in a head-to-head configuration. The bracketed region is a breakpoint cluster region of the *BCL6* gene. The exons of each gene are represented by filled boxes. The translation initiation site of the *BCL6* gene is shown by an arrow. Restriction endonuclease sites on chromosome 3 are abbreviated as follows: B, *Bam*HI; H, *Hin*dIII. (*Hin*dIII sites on chromosome 3 are not complete.)

ance of N regions in the former but not the latter.[33, 34, 36] This suggests that the presumed recombinase-mediated fusion of Vκ and Jκ elements shown in Fig. 3 occurred before physiological rearrangement of IgL genes.

In the structural analysis of the chromosomal junctions, the presence of duplicated sequences from chromosome 3, was our most unexpected observation. Since these sequences occur precisely at the breakpoint, we assume that the duplication was generated during translocation. This suggests the occurrence of staggered double-strand DNA breaks followed by filling-in of the protruding strand and interchromosomal ligation. A similar staggered break, along with exonuclease-mediated removal of the single strands, can account for the deletion of sequences from chromosome 2. Deletions and duplications are frequently found at the chromosomal junctions, and these events are typical of the repair of randomly occurring staggered double-strand DNA breaks.[28, 37–39]

Since staggered double-strand DNA breaks may occur randomly in genomic DNA, there should be additional reasons for the clustering of breakpoints within the *BCL6* gene. Homologous recombination is unlikely, since there are no significant similarities in sequence between the chromosomes 2 and 3 germline DNA in the region of the breaks. One possibility is that DNA fragility over this region may be involved in translocations.

The chromosomal translocation within a breakpoint cluster region of the *BCL6* gene interrupts the 5′ untranslated region of this gene without affecting coding exons, perhaps resulting in deregulation, which may offer a proliferative advantage to tumor cell clones. Actually the *BCL6* gene encodes a 79 kDa protein containing six zinc-finger motifs and sharing amino-terminal homology with several transcription factors including the *Drosophila* tramtrack and broad-complex genes, both of which are developmental transcription regulators.[11, 15, 16] In hematologic malignancies specific chromosomal translocations that involve transcription factor genes often lead to the oncogenic conversion of proto-oncogenes encoding transcription regulators.[40–42]

The breakpoints described here demonstrate that the Igκ and *BCL6* genes may participate in illegitimate chromosome translocations of B cells without obvious involvement of the VJ recombinase systems.

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