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The t(2;3)(q21;q27) translocation in non-Hodgkin's lymphoma displays *BCL6* mutations in the 5′ regulatory region and chromosomal breakpoints distant from the gene

Weiyi Chen[1], Marion Butler[2], Pulivarthi H Rao[1], Seeta R Chaganti[1], Diane C Louie[1], Riccardo Dalla-Favera[2] and RSK Chaganti[1]

[1]*Cell Biology Program and the Departments of Human Genetics and Pathology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA; and* [2]*Division of Oncology, Department of Pathology, College of Physicians and Surgeons, Columbia University, 630 West 168th Street, New York, NY 10032, USA*

The *BCL6* gene, mapped at the chromosomal band 3q27, encodes a POZ/Zinc finger transcription repressor protein. It is frequently activated in Non-Hodgkin's lymphomas (NHL) by translocations with breakpoints clustering in the 5′ major breakpoint region (MBR) as well as by mutations in the same region. The translocations lead to *BCL6* activation by substitution of promoters of rearranging genes derived from the reciprocal chromosomal partners such as *IG*. We report the molecular genetic analysis of a novel t(2;3)(q21;q27) translocation subset in NHL comprising three cases without apparent *BCL6* involvement in the translocation. Southern blot analysis of tumor DNAs utilizing *BCL6* MBR probes revealed no rearrangement in two cases. Two rearranged bands in the third case resulted from a deletion in one allele and a mutation in the other allele. Southern blot analysis of DNA from one of the two tumors without *BCL6* rearrangement, using a probe derived from the recently identified alternative breakpoint region (ABR), showed a rearrangement. The ABR is located 200–270 kb telomeric to MBR. Mutations were identified in the previously reported hypermutable region of *BCL6* in all three tumors. In one, the mutant allele alone was found to be expressed by RT–PCR analysis of RNA. These results demonstrate the presence of 3q27 translocation breakpoints at a distance from *BCL6* suggesting distant breaks that deregulate the gene or involvement of other genes that may be subject to rearrangement.

Keywords: *BCL6* mutation; 3q27 translocation; NHL

Introduction

Chromosomal translocations affecting band 3q27 have been noted to occur frequently in diffuse large cell lymphoma (DLCL) and other subsets of non-Hodgkin's lymphoma (NHL) (Offit *et al*., 1989; Bastard *et al*., 1992). By molecular genetic analysis of t(3;14) (q27;q32) translocations, the *BCL6* gene was isolated and mapped to 3q27 adjacent to the chromosomal breakpoint (Baron *et al*., 1993; Kerckaert *et al*., 1993; Ye *et al*., 1993a; Miki *et al*., 1994). The *BCL6* gene encodes a POZ/Zinc finger transcription factor which functions as a sequence specific transcription repressor (Deweindt *et al*., 1995; Chang *et al*., 1996; Seyfert 1996; Baron *et al*., 1997). The primary function of *BCL6* appears to be regulation of germinal center (GC) development and T-cell directed immune response (Dent *et al*., 1997; Ye *et al*., 1997). Activating *BCL6* rearrangements have been shown to result from chromosomal translocations with *IG* or other loci that alter *BCL6* expression by promoter substitution, or from point mutations in the 5′ regulatory region (Migliazza *et al*., 1995; Ye *et al*., 1995; Chen *et al*., 1998). The rearrangements cluster in a major breakpoint region (MBR) mapped to the first non-coding exon and 5′ of the first intron (Ye *et al*., 1993b). More recently, an alternative breakpoint region (ABR) to the MBR was identified in B-cell NHL at 3q27 and shown to be located 200–270 kb in the telomeric direction of BCL6 (Butler *et al*., 1997). *BCL6* mutations, which have been noted in 73% of DLCLs and 47% of follicular lymphomas (FL), cluster in a ~730 bp noncoding region which spans the first exon-intron boundary (Migliazza *et al*., 1995). Recent studies also identified recurrent deletions in the MBR region, independent of chromosomal rearrangements (Nakamura *et al*., 1996; Bernardin *et al*., 1997).

We and others have shown that 3q27 promiscuous translocations involve multiple partner chromosomal sites such as 1q21, 2q21, 4q21, 5q13, 11q13, 12q24 and 15q21 (Ye *et al* 1993a; Wlodarska *et al*., 1995). Recently, three genes, *TTF*, *BOB1* and *H4*, have been identified by cloning the *BCL6* breakpoints in tumors with t(3;4)(q27;p11), t(3;11)(q27;q23) and t(3;6)(q27;p21) translocations, respectively (Dallery *et al*., 1995; Galiegue-Zouitina *et al*., 1995; Akasaka *et al*., 1997). We report here the results of molecular genetic analysis of a novel t(2;3)(q21;q27) subset in NHL, in which the *BCL6* gene exhibits deletions and point mutations in the 5′ regulatory region; however, the translocation breakpoint is at a distance upstream of the locus.

Results

Southern blot analysis of rearrangements

In an attempt to detect *BCL6* rearrangements in the three tumors, Southern blot analysis was performed on

Correspondence: RSK Chaganti
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available genomic DNA digested with the restriction enzymes *Bam*HI, *Xba*I, and *Hind*III using genomic probes spanning the MBR and ABR. No rearrangement was detected with the MBR probes in tumors 1187 and 1562. In the case of tumor 1254, one rearranged *Bam*HI fragment and two rearranged *Xba*I fragments were detected upon hybridization with the probe pGS4.0 (Figures 1 and 2a). A genomic library constructed from this tumor was screened with the same probe, which yielded six *BCL6* positive clones. Mapping analysis of these clones identified two rearrangement fragments. In one, the rearrangement resulted from a 2.3 kb deletion within a 3.4 kb *Eco*RI fragment spanning the first exon and the 5′ region of the first intron, while the other resulted from a point mutation that generated a new *Xba*I site in the first exon (Figure 2b). Both alterations were located in the previously identified hypermutable region (Migliazza *et al*., 1995). Further subcloning and sequencing of the rearranged fragments identified additional subtle mutations (Figures 2b and 3).

In tumor 1562, the ABR probe (XN 1.3) detected rearrangement with two restriction enzymes (Figure 4). Thus, the t(2;3)(q21;q27) translocation in this case is most likely associated with a chromosomal break occurring within the ABR at 3q27 200–270 kb telomeric to *BCL6*. No rearrangement was noted in tumor 1187, while DNA for similar analysis was unavailable for tumor 1254.

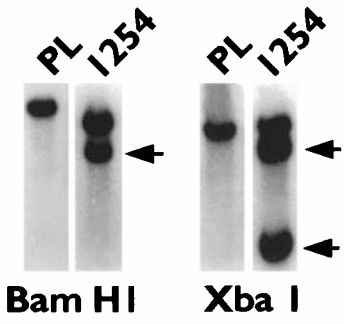

Figure 1 Southern blot analysis of DNA from tumor 1254 showing DNA rearrangements in *BCL6* with the probe pGS4.0. Arrows point to rearranged bands. PL = placental DNA (normal control)

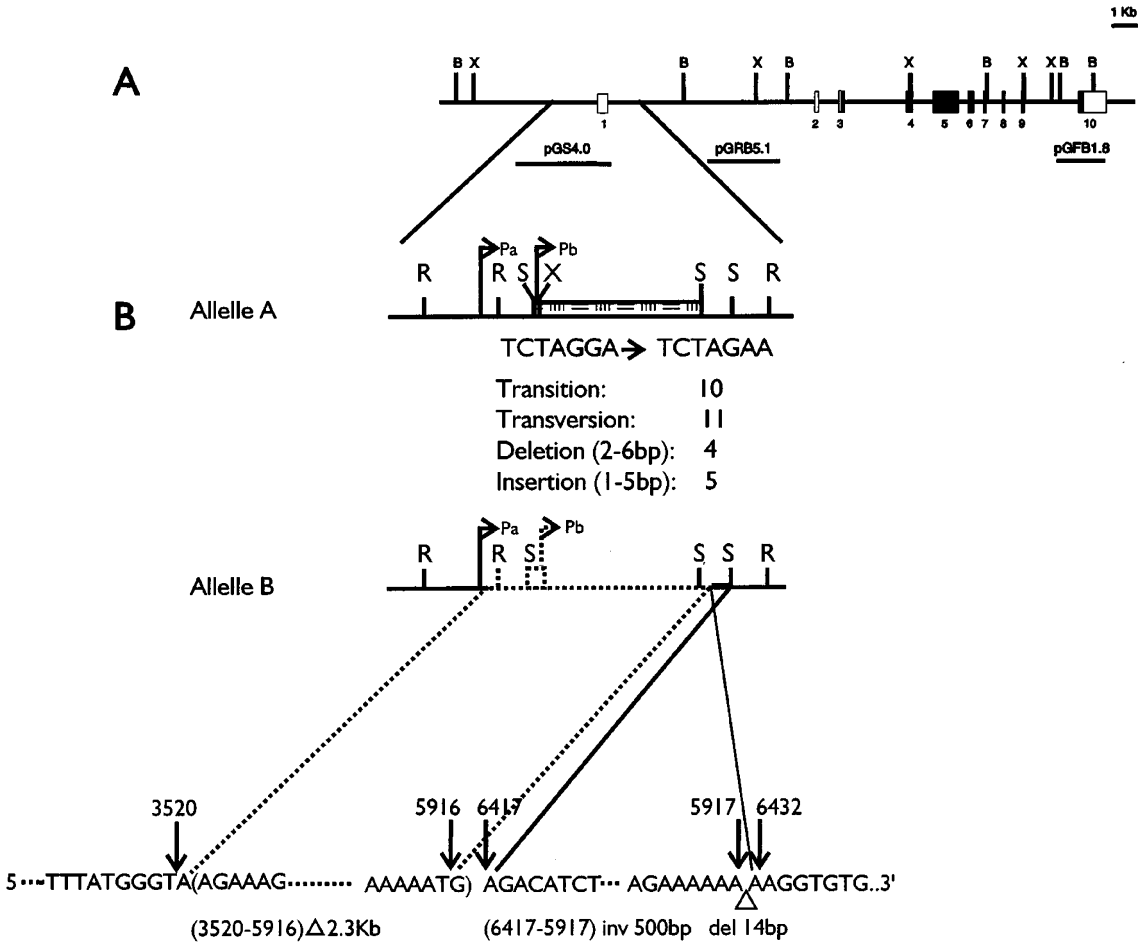

Figure 2 (**a**) Restriction map of *BCL6* showing the probes used in Southern blotting analysis (pGS4.0, pGRB 5.1 and pGFB1.8), B, *Bam*HI; X *Xba*I. Open boxes represent non-coding exon regions and filled boxes represent coding exon regions. (**b**) Schematic representation of the *BCL6* mutations found in tumor 1254 in the region surrounding the first exon. In allele A, a point mutation of G to A generated a new *Xba*I restriction site (TCTAGA) in exon 1. The hatched box covers the region with all the mutations detected, the frequency of each type of mutation is also shown. In allele B, the dotted line identifies the deletion. An inversion and another deletion also were noted 3′ of this deletion. Pa and Pb denote *BCL6* promoters. R, S, and X indicate the restriction enzymes *Eco*RI, *Sac*I, and *Xba*I, respectively

FISH analysis

FISH analysis was also performed on interphase nuclei from tumors 1254 and 1562 using the PAC-133-MI9 and P1-371-08 and YAC 19G10 (Figure 4). No split signal was detected in 100 interphase nuclei from each tumor following hybridization with the PAC and P1 probes, while the YAC hybridization results were uninformative due to high repeat sequence content. Lymphoma cells suitable for FISH analysis were not available from tumor 1187.

PCR–SSCP analysis of mutations

Mutation analysis was performed on tumors 1187 and 1562 by PCR–SSCP of *BCL6* sequences flanking the hypermutable region using previously described primers (Mgliazza *et al*., 1995). SSCP variants were observed in the PCR fragments El.11 and El.14, representing the first exon and exon-intron boundary in both tumors (Figure 5).

Identification of the expressed allele in tumor 1254 by RT–PCR

The biallelic nature of the mutations observed in tumor 1254 prompted us to analyse the expression of the two alleles. For this, RT–PCR was performed using RNA isolated from a snap-frozen biopsy of the tumor. Since the deletions occurred almost at the beginning of the *BCL6* transcript, the 5′ anchor primer was adapted for amplification of the CDNA. The final PCR product amplified by the 5′ anchor primer and primer 567 at exon 4 yielded ~ 400 bp fragment on the agarose gel, corresponding to the *BCL6* germline fragment (Figure 6). No variant transcript corresponding to allele B with the deletion was detected. The 400 bp PCR fragment was subloned into pGEM-T vector (Promega) and sequenced. The point mutation in allele A that generated a new *Xba*I site (Figure 2b) was found in all of the 10 selected cDNA clones. These results suggest that the only expressed *BCL6* allele in this tumor was the mutated allele.

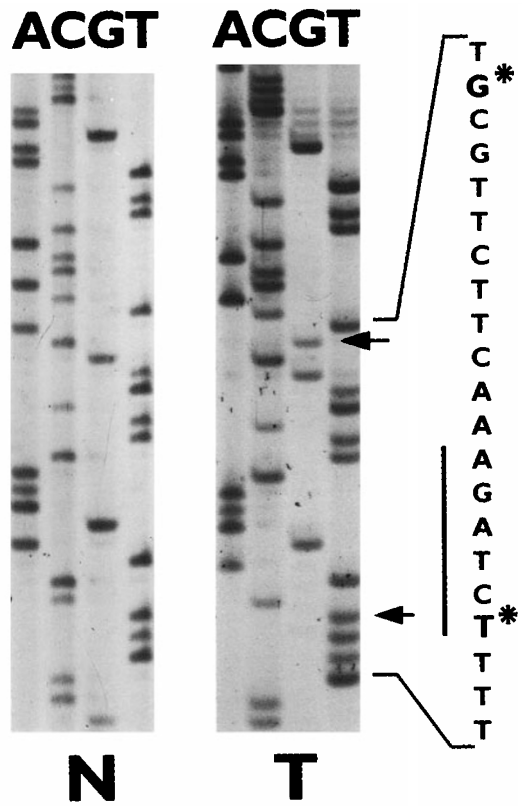

Figure 3 *BCL6* mutations detected by sequencing in tumor 1254. A mutation in the exon 1 region that generated a new *Xba*I restriction site is shown. The sequence shown here represents the antisense strand. Arrow points to the mutation, the solid line on the side indicates the *Xba*I site. DNA sequence derived from the normal counterpart of the patient 1254 was used as a negative control

Discussion

The majority of B cell NHLs exhibit recurring chromosomal translocations involving the *IG* genes and several proto-oncogenes. At the molecular genetic level, such translocation analysed in the greatest detail comprise those associated with Burkitt's lymphoma (BL) and FL, wherein the expression of *MYC* and *BCL2* genes, respectively, is deregulated as a result of translocations which juxtapose these genes with one of the *IG* loci (Dalla-Favera *et al*., 1982; Taub *et al*., 1982; Bakhshi *et al*., 1985). In contrast, translocations affecting *BCL6* are promiscuous and involve multiple gene partners, in addition to the *IG* genes. More than 17 different chromosomal sites have been identified which participate in translocations with 3q27 (Bastard *et al*., 1992; Ye *et al*., 1993a; Wlodarska *et al*., 1995). We have recently shown that heterologous promoters fused to *BCL6* in these translocations lead to its persistent expression beyond its developmentally regulated point of downregulation during B-cell development, leading to lymphomagenesis (Chen *et al*., 1998).

Here we report the molecular genetic analysis of the t(2;3)(q21;q27) translocation subset comprising one case each of FSCL, FMxL, and DLCL. To date, this translocation has been reported in four cases of NHL (Kornblau *et al*., 1991; Konishi *et al*., 1990; Bloomfield *et al*., 1983; Benitze *et al*., 1992), thus identifying a new subset of recurring translocation in NHL. Notably, the t(2;3)(q21;q27) translocation was the only chromosomal abnormality in case 1254.

No *BCL6* rearrangements associated with the chromosomal translocation was detected within the MBR or 100 kb 5′ of the *BCL6* locus in any of the three tumors by Southern blot and/or FISH analysis, suggesting the presence of variant breakpoint(s) at a distance from *BCL6*. Consistent with this finding, in a recent study by us, 50% of NHL with 3q27 chromosomal rearrangements failed to exhibit *BCL6*-MBR rearrangements (Chaganti *et al*., 1998). Wlodarska *et al*. (1995) also were unable to detect a *BCL6*-MBR rearrangement in a case of NHL with a t(1;3)(q21;q27) translocation by FISH analysis. In one tumor (1562) we localized the 3q27 breakpoint to the recently identified ABR, 200–270 kb telomeric to *BCL6*. This and other possible distant breakpoints may harbor long range regulatory element(s) capable of deregulating *BCL6* expression. Studies of BL translocations have shown that the t(8;14)(q24;q32) translocation breakpoints can be as far as 300 kb

upstream or downstream of *MYC*, in addition to the apparent cluster region surrounding the first exon (Joos *et al*., 1992; Axelson *et al*., 1994). Alternatively, other oncogene(s) upstream of *BCL6* may be deregulated by the translocation(s) or exert long-range influence on *BCL6* expression.

As previously noted in the other DLCLs, the *BCL6* gene in all these cases studied exhibited mutations and/or deletion in the region spanning the exon1-intron1 boundary. By RT–PCR analysis of *BCL6* expression in tumor 1254, we have shown that the allele with the deletion probably is silent, possibly due to loss of the preferred promoter (pb) 3′ of the first exon. The fact that the mutated allele appeared to be the only expressed allele in this translocation is consistent with the role of mutation in *BCL6* activation. The mutation analysis of the three tumors with the t(2;3)(q21;q27) translocation reported here is also consistent with our previous observation that *BCL6* mutation is independent of rearrangement by translocation.

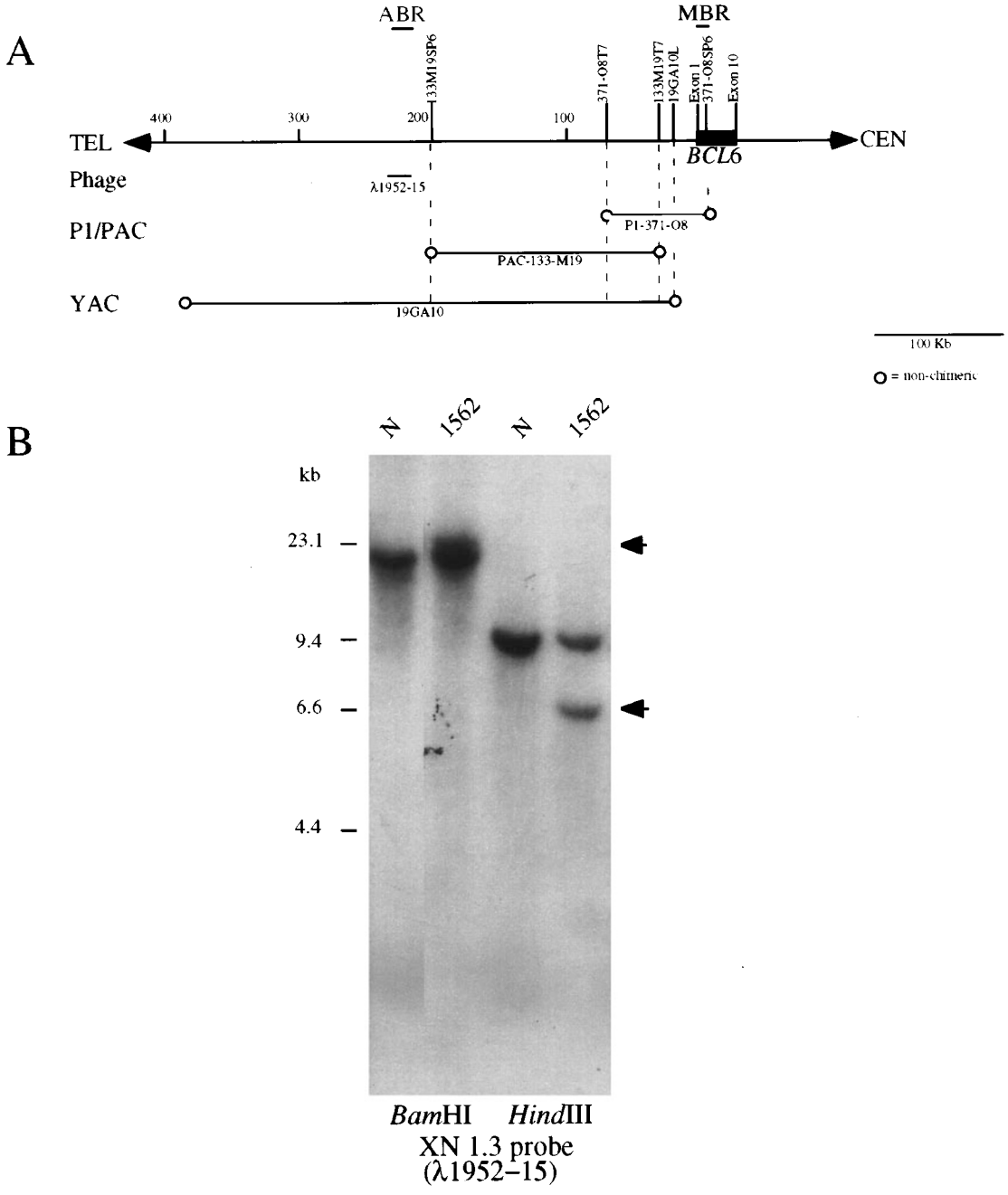

Figure 4 Mapping the 3q27-ABR breakpoint in tumor 1562. (**a**) Schematic representation of a 400 kb contig of P1, PAC, and YAC clones from the genomic region of 3q27. The positions of *BCL6* and associated MBR are indicated. The ABR is located approximately 200–270 kb 5′ (telomeric) to the *BCL6* gene as determined by a combination of PFGE and hybridization analysis (Butler *et al*., 1997). The ends of P1, PAC, and YAC clones serve as markers of overlap between adjacent clones, and are named according to their clone of origin, followed by their primer derivation (T7 or SP6 for P1/PAC) or orientation (left (L) or right (R) for YAC). The point of overlap between clones is indicated by the vertical dashed lines on the map. Probe XN 1.3 was isolated from a genomic phage λ-15-1952 contained within the ABR. (**b**). Southern blot showing rearrangement in tumor 1562 DNA using probe XN 1.2 from ABR. Arrowheads indicate the rearranged restriction fragments

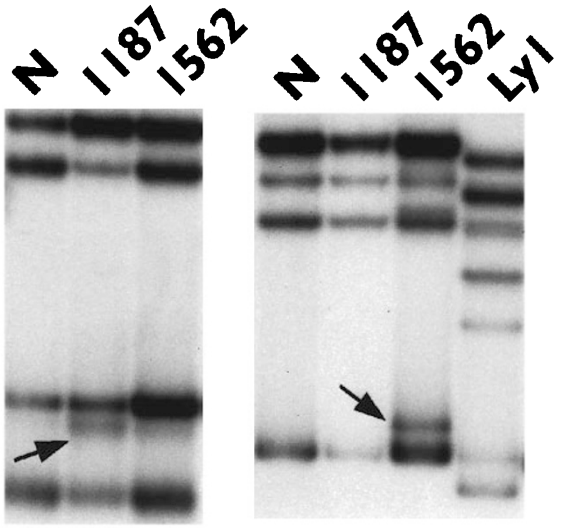

Figure 5 Mutations in the first exon/intron boundary of *BCL6* detected by PCR/SSCP analysis. Representative results from PCR products E1.11 and E1.14 at the exon-intron 1 boundary from tumors 1187 and 1562. Arrows point to bands representing conformation changes. DNA from placenta (N) and Ly1, a DLCL cell line previously documented to have a mutation (Migliazza *et al*., 1995) were used as negative and positive controls, respectively

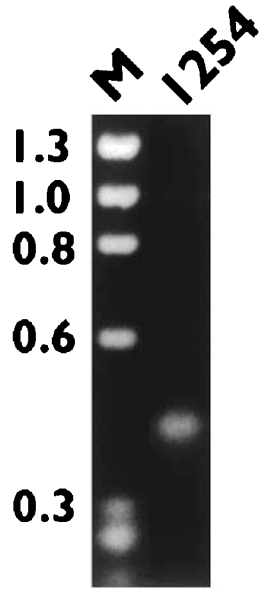

Figure 6 *BCL6* expression detected by 5′ anchor RT–PCR. The first strand cDNA derived from patient 1254 was subjected to PCR amplification with 5′ anchor forward primer (GIBCO/BRL) and reverse primer 567. The fragment sizes of the marker ϕX174 RF DNA/*Hae*III are indicated

Materials and methods

Tumor ascertainment and cytogenetics

Tumors 1187, 1254 and 1562 were part of a previously described ascertainment of NHL at the Memorial Sloan-Kettering Cancer Center (MSKCC) (Offit *et al*., 1994). The tumors were diagnosed based on histopathologic, immunophenotypic, and immunogenotypic analysis as described previously (Offit *et al*., 1994). Cytogenetic analysis of disaggregated lymph node cells was performed following short-term culture, chromosome preparation, and G-banding, according to conventional methods. Each tumor specimen revealed a t(2;3)(q21;q27) translocation. Case 1187 was a 54-year-old male with follicular small-cleaved cell lymphoma (FSCL) with the chromosomal complement: 48,XY, t(2;3)(q21;q27),i(6)(p10),+12,der(12)t(1;12)(q21;q22),t(14;18) (q32;q21),+21[10]. Case 1254 was a 74-year-old female with a DLCL with the chromosomal complement: 46,XX, t(2;3)(q21;q27) [2] /46, XX [23]. Case 1562 was a 72-year-old female with a follicular mixed lymphoma (FMxL) with the chromosomal complement:43-46, XX, t(2;3) (q21;q27), t(3;8) (q27;q13), del(6) (q21q27), −10,−16,+mar1,+mar2, +mar3[cp15].

Fluorescence in situ *hybridization (FISH) analysis of BCL6 genomic locus*

The PAC clone 133M19 which covers the 100 kb upstream of *BCL6* was labeled with biotin-14-dUTP by nick translation and hybridized to interphase nuclei from tumor cells. Hybridization signals were visualized with FITC-conjugated avidin (Oncor) following staining with propidium iodide.

Analysis of BCL6 rearrangements by Southern blotting and cloning of the rearranged bands

Genomic DNA from the the tumor biopsies and placental control DNAs were digested with the restriction enzymes *Bam*HI and *Xba*I, electrophoresed on a 0. 8% agarose gel, and transferred to a nylon membrane (Oncor). The blot was hybridized sequentially with the *BCL6*-MBR probes pGS4.0 (a 4 kb *Sac*I fragment), pGRB5.1 (a 5.1 kb *Eco*RI/*Bam*HI fragment), and pGFB1.8 (a 1.8 kb *Bam*HI fragment) (Figure 2a). In the case of tumor 1562, DNA digested with *Hind*III and *Bam*HI was also hybridized with the ABR probe XN 1.3. A genomic library of tumor 1254 was prepared by *Sau*3A partial digestion of DNA followed by ligation into lambda GEM-11 (Promega). The library was screened with the pGS4.0 probe. Positive clones were selected and mapped. Rearranged fragments were subcloned into pGEM-7Zf(−) (Promega) and sequenced.

Mutation analysis and expression of BCL6 alleles by RT–PCR

Genomic DNAs isolated from tumors 1187, 1562, Lyl, a DLCL cell line (Tweeddale *et al*., 1987) (positive control) and placenta (negative control) were amplified by PCR with primers spanning the first exon and the 5′ end of the first intron as previously described (Migliazza *et al*., 1995). SSCP analysis was performed according to described methods (Xu *et al*., 1994). For 5′ anchor RT–PCR analysis, total RNA was isolated from a snap-frozen sample of tumor 1254 using the RNAgents reagent (Promega). 5′RACE analysis of the *BCL6* transcripts was performed using the 5′RACE kit (GIBCO/BRL) following manufacturer's recommendations. The primers used for cDNA amplification were as previously described (Ye *et al*., 1997), except that the reverse primer 567 (AGGGTT-GATCTCAGGATC) at exon 4 was also used for the final amplification. The final PCR product was subcloned into PGEM-T (Promega) and sequenced.

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