Derivative (3)t(3;18)(q27;q21)t(18;16)(q21;?) involving the BCL2 and BCL6 genes in follicular lymphoma with t(3;14;18) (q27; q32; q21)

Yamamoto, Katsuya
Ono, Kanako
Katayama, Yoshio
Shimoyama, Manabu
Matsui, Toshimitsu

(Citation)
Cancer Genetics and Cytogenetics,179(1):69-75

(Issue Date)
2007-11

(Resource Type)
journal article

(Version)
Accepted Manuscript

(URL)
https://hdl.handle.net/20.500.14094/90000862

Additional der(3)t(3;18)(q27;q21)t(18;16)(q21;?) involving the *BCL2* and *BCL6* genes in follicular lymphoma with t(3;14;18)(q27;q32;q21)

Katsuya Yamamoto, Kanako Ono, Yoshio Katayama, Manabu Shimoyama, Toshimitsu Matsui

Hematology/Oncology, Department of Medicine, Kobe University Graduate School of Medicine, Kobe, Japan

Corresponding author: Toshimitsu Matsui

Address: Hematology/Oncology, Department of Medicine, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan

TEL: +81-78-382-5885

FAX: +81-78-382-5899

E-mail: matsui@med.kobe-u.ac.jp

Abstract

Follicular lymphoma (FL) is genetically characterized by t(14;18)(q32;q21) involving the *BCL2* gene (*BCL2*), and is often associated with 3q27 translocations involving the *BCL6* gene (*BCL6*). We describe here an unusual case of FL with a variant three-way translocation t(3;14;18)(q27;q32;q21). A 57-year-old man was given a diagnosis of FL, grade 2. Chromosome analysis showed 49,XY,+X,+3,t(3;14;18)(q27;q32;q21),i(6)(p10),+21. Spectral karyotyping confirmed three derivative chromosomes, der(3)t(3;18)(q27;q21), der(14)t(3;14)(q27;q32) and der(18)t(14;18)(q32;q21). However, an extra chromosome 3 was shown to be an unbalanced translocation der(3)t(3;16)(q27;?). Fluorescence *in situ* hybridization (FISH) analyses detected IGH/BCL2 fusion signal on the der(18)t(14;18)(q32;q21). FISH also demonstrated split signals of BCL2 and BCL6 on the der(3)t(3;16)(q27;?) as well as the der(3)t(3;18)(q27;q21). The results indicated that the three-way translocation involved *BCL2*, *IGH* and *BCL6*, and that the der(3)t(3;16)(q27;?) contained the 18q21 fragment including *BCL2*. It is probable that the translocation between chromosome 16 and the der(3)t(3;18)(q27;q21) occurred after duplication of the der(3)t(3;18)(q27;q21) as clonal evolution. Thus, this additional chromosome was finally described as der(3)t(3;18)(q27;q21)t(18;16)(q21;?). These findings suggest that the der(3)t(3;18)(q27;q21) involving *BCL2* and *BCL6* had a crucial role in the pathogenesis of FL with t(3;14;18)(q27;q32;q21).

1. Introduction

The t(14;18)(q32;q21) translocation is found in 80 to 90% of follicular lymphoma (FL) and about 30% of diffuse large B-cell lymphoma (DLBCL) [1]. The translocation juxtaposes the *BCL2* gene (*BCL2*) at 18q21 with the immunoglobulin heavy chain gene (*IGH*) at 14q32, and results in deregulated expression of *BCL2*, encoding a 26kDa protein that prolongs cell survival by blocking programmed cell death. Almost all cases of FL with t(14;18) have additional chromosomal alterations such as +X, +7, +12, +18, del(1)(p36), del(6)(q) and +der(18)t(14;18); many of them are correlated with morphological progression [1, 2]. In addition, complex variant translocations, occurring among chromosomes 14, 18, and one or two other chromosomes, are detected in rare cases of FL [3].

On the other hand, rearrangements of the *BCL6* gene (*BCL6*), mapped at 3q27, are observed in 28.6% to 35.5% of DLBCL and 6.4 to 14.3% of FL [4]. The most common type of *BCL6* translocations is t(3;14)(q27;q32) including *IGH*, and a variety of *IG* or non-*IG* partner genes on other chromosome loci could be involved in the translocations. These 3q27 translocations also result in deregulated expression of *BCL6*, encoding a 79kDa protein that functions as a transcription repressor with a zinc-finger motif [4].

As a result, many cases of FL have concurrent dual abnormalities, t(14;18)(q32;q21) and 3q27 translocations with the rearrangements of *BCL2* and *BCL6* [5-7], although these two aberrations were mutually exclusive in FL grade 3B [8]. Furthermore, as a variant type of t(14;18)(q32;q21), the three-way translocation t(3;14;18)(q27;q32;q21) has been found in a few cases of FL/DLBCL [9-12]. We describe here a novel case of FL with t(3;14;18)(q27;q32;q21), who had additional der(3)t(3;18)(q27;q21)t(18;16)(q21;?) involving *BCL2* and *BCL6* as clonal evolution.

2. Materials and methods

2.1. Case History

A 57-year-old man was admitted to our hospital for lymphadenopathy and edema in September 2006. He had cervical, axillar, and inguinal lymphadenopathy without hepatosplenomegaly. Computed tomography and positron emission topography disclosed the marked swelling of para-aortic lymph nodes. Peripheral blood examination showed hemoglobin 132 g/L, platelets 298 x 10^9/L and white blood cells 9.6 x 10^9/L with 1% band forms, 69% segmented neutrophils, 8% monocytes, and 22% lymphocytes without atypical lymphocytes. Serum levels of lactate dehydrogenase (LDH) and soluble interleukin-2 receptor (sIL-2R) were 164 IU/l (normal range, 117-205) and 625 U/ml (normal range, 135-483), respectively. A cervical lymph node biopsy was consistent with a FL, grade 2, according to the World Health Organization classification. Immunohistochemistry showed that lymphoma cells were positive for CD10, CD20, CD79a, BCL2 and BCL6 but negative for CD3. Surface marker analysis by flow cytometry also revealed that they were positive (more than 20%) for CD10 (40.5%), CD19 (92.2%), CD20 (95.8%), CD23 (44.0%), CD25 (63.2%), HLA-DR (99.3%) and κ chain (81.7%). Bone marrow biopsy showed slight infiltration of lymphoma cells. Therefore, he was diagnosed as having FL, clinical stage IVA. He received a total of six cycles of R-CHOP regimen (rituximab 375 mg/m^2 day 1, cyclophosphamide 750 mg/m^2 day 2, doxorubicin 50 mg/m^2 day 2, vincristine 1.4 mg/m^2 day 2, prednisolone 100 mg/body days 2-6) and remained in complete remission for more than nine months.

2.2. Chromosome analyses and spectral karyotyping

Chromosome analyses were performed using the G-banding technique on short-term culture of the cells obtained from lymph node. Karyotypes were described according to ISCN 1995 [13]. Spectral karyotyping (SKY) was carried out with a SkyPaint kit (Applied Spectral

Imaging, Migdal Ha'Emek, Israel).

2.3. Fluorescence in situ hybridization (FISH) analyses

We used LSI IGH/BCL2 Dual-Color, Dual Fusion Translocation Probe and LSI BCL6 Dual-Color, Break Apart Rearrangement Probe (Abbott-Vysis, Downers Grove, IL, USA). The LSI IGH/BCL2 Probe is a mixture of the IGH probe labeled with SpectrumGreen spanning 1.5 Mb containing the entire *IGH* locus at 14q32 and the BCL2 probe labeled with SpectrumOrange covering a region of 750 kb including the entire *BCL2* at 18q21. The expected pattern in a normal nucleus is two orange and two green signals. In a nucleus harboring a t(14;18)(q32;q21), one orange, one green and two orange/green (yellow) fusion signals representing the two derivative chromosomes are observed. The BCL6 probe is a mixture of a 300 kb 5' LSI BCL6 probe labeled with SpectrumOrange and a 600 kb 3' LSI BCL6 probe labeled with SpectrumGreen at 3q27. In a normal cell, the expected signal pattern is two orange/green fusion signals. In a cell with a BCL6 translocation, one orange, one green and one fusion signals are observed.

2.4. Southern blot analyses

High-molecular-weight DNA was extracted from lymph node cells. Ten micrograms of DNA were digested with *Hin*dIII, *Bam*HI and *Eco*RI. The digested DNA was hybridized with the 5.6 kb genomic probe covering the entire joining region (JH) of *IGH*, 1.2kb *Bam*-HI-*Hin*dIII genomic fragment containing the first exon of *BCL6* for the major translocation cluster (MTC) region, and 2.8 kb *Eco*RI-*Hin*dIII genomic fragment containing the third exon of *BCL2* for the major breakpoint region (MBR) (SRL, Inc., Tokyo, Japan) [11].

3. Results

Chromosome analysis of lymph node cells at the diagnosis of FL showed 46,XY,t(3;14;18)(q27;q32;q21),add(10)(q22)[5]/49,XY,+X,+3,t(3;14;18)(q27;q32;q21),i(6)(p10),+21[9]/46,XY[6] (Fig. 1). We describe here the former abnormal clone and the latter clone with +3 as clone A and clone B, respectively. To confirm these cytogenetic aberrations, we performed SKY analysis on two metaphase spreads of clone B and revised the karyotypes as follows (Fig. 2): 49,XY,+X,+der(3)t(3;16)(q27;?),t(3;14;18)(q27;q32;q21),i(6)(p10),+21[2]. That is, an extra chromosome 3 detected by G-banding was shown to be an unbalanced translocation between 3q27 and chromosome 16. In addition, SKY analysis confirmed the der(3)t(3;18)(q27;q21) and the der(14)t(3;14)(q27;q32) generated by the three-way translocation, whereas SKY could not visualize the small segment 14q32->14qter on the der(18)t(14;18)(q32;q21). The size of this segment was supposed to be within a range of 1-2 Mb, which is minimum genomic alteration that SKY could detect, as described in other cases with t(14;18)(q32;q21) previously [11, 14, 15].

For further characterization of these translocations, we next performed FISH analyses with IGH/BCL2 and BCL6 probes. FISH with IGH/BCL2 on metaphase spreads of clone B detected IGH/BCL2 fusion signal on the der(18)t(14;18)(q32;q21). FISH also showed that split BCL2 signals were unexpectedly located on the der(3)t(3;16)(q27;?) as well as the der(3)t(3;18)(q27;q21) (Fig. 3C). FISH on 100 interphase nuclei could distinguish clone A with two BCL2 signals from clone B with three BCL2 signals, because clone A did not include der(3)t(3;16)(q27;?) with one BCL2 signal (Fig. 3A, 3B and Table 1). On the other hand, FISH with BCL6 probe on metaphase spreads of clone B showed that 5’ and 3’ BCL6 signals were located on the der(14)t(3;14)(q27;q32) and der(3)t(3;18)(q27;q21), respectively. Furthermore, 3’ BCL6 signal was detected on the der(3)t(3;16)(q27;?) (Fig. 4C). FISH on

100 interphase nuclei also discriminated clone A with one 3’ BCL6 signal from clone B with two 3’ BCL6 signals (Fig. 4A, 4B and Table 1). These results demonstrated the involvement of *BCL2*, *IGH* and *BCL6* in the three-way translocation t(3;14;18)(q27;q21;q32).

Southern blot analyses confirmed rearrangements of *IGH* and *BCL6* in the MTC region, whereas *BCL2* was not rearranged in the MBR (Fig. 5 and data not shown).

4. Discussion

We have detected an additional der(3)t(3;16)(q27;?) and a three-way translocation t(3;14;18)(q27;q32;q21) in a case of FL by G-banding and SKY analyses. In view of the essential role of t(14;18)(q32;q21) in FL, we suppose that the three-way translocation evolved from a primary t(14;18)(q32;21) followed by the second exchange between der(14)t(14;18)(q32;q21) and chromosome 3. Furthermore, FISH analyses showed that split signals of BCL2 and BCL6 were located on the der(3)t(3;16)(q27;?) as well as the der(3)t(3;18)(q27;q21). The results indicate that the der(3)t(3;16)(q27;?) contained the 18q21 fragment including *BCL2*, although SKY could not identify chromosome 18 material on this chromosome. It is probable that the translocation between unidentified band of chromosome 16 and 18q21 of the der(3)t(3;18)(q27;q21) occurred after duplication of the der(3)t(3;18)(q27;q21) as clonal evolution. Thus, this additional chromosome was finally revised as der(3)t(3;18)(q27;q21)t(18;16)(q21;?). These results suggest that, among three derivative chromosomes generated by the three-way translocation, the der(3)t(3;18)(q27;q21) involving *BCL2* and *BCL6* had a crucial role in the pathogenesis of FL.

As shown in Table 2, three previous cases of FL/DLBCL with t(3;14;18)(q27;q32;q21) have been reported [9-12], for a total of four including the present case. As expected, FL grade 3B was not included in these cases [8]. All cases showed rearrangements of *BCL6* in the MTC region. On the other hand, *BCL2* was not rearranged with a probe covering MBR in all three cases examined by Southern blot analyses, although FISH consistently showed *BCL2* rearrangements. These findings indicate that the breakpoints of *BCL2* in these cases may be located in the region other than MBR, such as minor cluster region (mcr), 3' *BCL2* and 5' mcr [16, 17]. In any case, almost all coding exons of *BCL2* and *BCL6* were supposed to be situated on the der(3)t(3;18)(q27;q21), supporting the significant role of this derivative

chromosome. Case 1 also had two additional chromosome abnormalities involving 3q27, der(3)t(1;3)(q21;q27) and del(3)(q26q27). However, these two aberrations were shown to induce no rearrangement and no loss of *BCL6* by FISH [10]. Consequently, the present case first demonstrated clonal evolution involving *BCL6* from t(3;14;18)(q27;q32;q21).

It has been reported that the presence of *BCL6* translocation did not significantly alter the clinical features and prognoses of FL with t(14;18) [1, 5, 6]. In fact, it is unlikely that these four cases in Table. 2 had specific clinical features, including overall survival. However, Akasaka et al. [7] demonstrated that *BCL6* translocation is not necessary for transformation, but that *BCL6* translocation in FL may constitute a subgroup with a higher risk to transform into aggressive lymphoma. Further observation will be required to clarify whether FL with t(3;14;18)(q27;q32;q21) may transform to DLBCL more preferentially.

It remains to be completely elucidated how the expression of *BCL2* and *BCL6* is deregulated by t(3;14;18)(q27;q32;q21). In another similar three-way translocation t(8;14;18)(q24;q32;q21), *MYC* (exons 2 and 3) and *BCL2* were shown to be situated near the 3' and 5' *IGH* enhancer, and deregulated on the der(14)t(8;14)(q24;q32) and der(8)t(8;14)(q24;q32)t(14;18)(q32;q21), respectively [15, 18]. The presence of *IGH* on the der(8) was not evident by multicolor karyotyping, but *MYC* (exon 1)-*IGH-BCL2* triple fusion on the der(8) was confirmed by locus-specific FISH in all cases examined [15]. Recently, Rack et al. [12] proposed that the molecular mechanism of t(3;14;18)(q27;q32;q21) may be analogous to that of t(8;14;18)(q24;q32;q21). That is, in the second translocation between der(14)t(14;18)(q32;q21) and 3q27, a novel der(3)t(3;14)(q27;q32)t(14;18)(q32;q21) involving *BCL2*, *IGH* and *BCL6* might be generated if the segment 18q21->18qter was accompanied with a part of 14q32 fragment including JH and constant regions. However, in the present case, neither chromosome 14 material nor IGH signal was detected on the der(3)t(3;18)(q27;q21) by SKY and FISH analyses, respectively. Therefore, at present, it is

unknown whether there was cryptic insertion of *IGH* enhancer between *BCL2* and *BCL6*, which could be responsible for deregulation of both genes. Molecular cloning of the break-points will be essential to elucidate the mechanism of co-activation of *BCL2* and *BCL6*.

Acknowledgements

This work was supported in part by grants-in-aid for scientific research from the Ministry of Health, Welfare and Labor and from the Ministry of Education, Culture, Sports, Science and Technology of Japan (No. 19591113).

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Figure legends

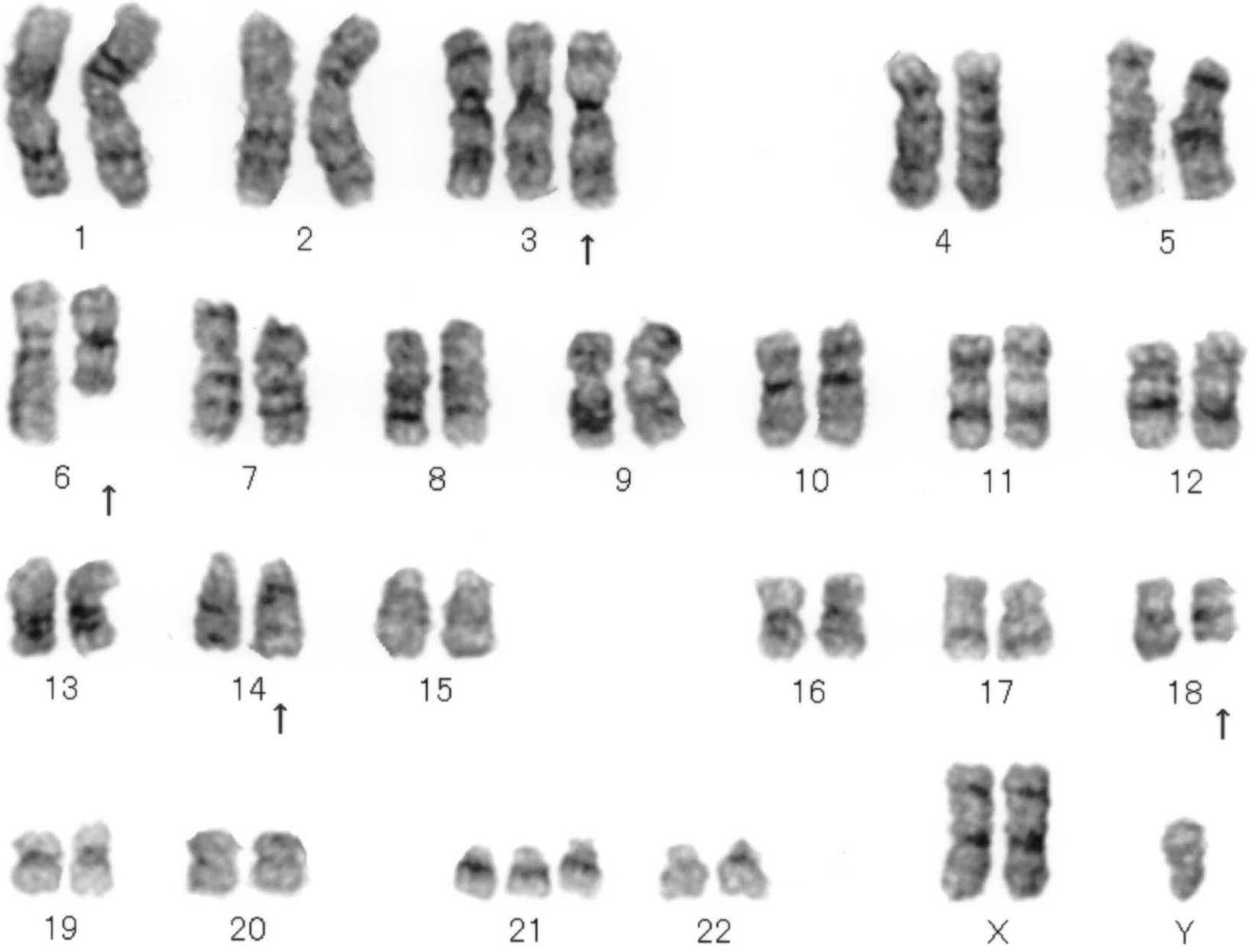
Fig. 1. G-banded karyotype of the lymphoma cells. The karyotype is 49,XY,+X,+3,t(3;14;18)(q27;q32;q21),i(6)(p10),+21. Arrows indicate rearranged chromosomes.

Fig. 2. Spectral karyotyping of the metaphase spread after spectrum-based classification. Chromosomes were assigned a pseudocolor according to the measured spectrum. The revised karyotype is 49,XY,+X,+der(3)t(3;16)(q27;?),t(3;14;18)(q27;q32;q21),i(6)(p10),+21. The grayscale images are reverse DAPI; the colored images, SKY. Arrows indicate rearranged chromosomes.

Fig. 3. FISH analyses with IGH/BCL2 probe on (A) interphase nuclei of clone A, (B) interphase nuclei of clone B, and (C) metaphase spreads of clone B. (A, B) Arrows indicate 1) IGH (green), 2) BCL2 (orange) and 3) IGH/BCL2 (orange/green) signals. (C) Arrows indicate 1) IGH on normal chromosome 14, 2) BCL2 on normal chromosome 18, 3) IGH/BCL2 on the der(18)t(14;18)(q32;q21), 4) IGH on the der(14)t(3;14)(q27;q32), 5) BCL2 on the der(3)t(3;18)(q27;q21), and 6) BCL2 on the der(3)t(3;16)(q27;?).

Fig. 4. FISH analyses with BCL6 probe on (A) interphase nuclei of clone A, (B) interphase nuclei of clone B, and (C) metaphase spreads of clone B. (A, B) Arrows indicate 1) 5’ BCL6 and 3’ BCL6 (orange/green), 2) 5’ BCL6 (orange), and 3) 3’ BCL6 (green) signals. (C) Arrows indicate 1) 5’ BCL6 and 3’ BCL6 on normal chromosome 3, 2) 5’ BCL6 on the der(14)t(3;14)(q27;q32), 3) 3’ BCL6 on the der(3)t(3;18)(q27;q21) and 4) 3’ BCL6 on the der(3)t(3;16)(q27;?).

Fig. 5. Southern blot analyses of the lymphoma cells with *BCL2* and *BCL6* probes. (A), *BCL2*; C, normal control; P, patient; 1, *Eco*RI; 2, *Hin*dIII; (B), *BCL6*; 1, *Bam*HI; 2, *Hin*dIII. Arrows indicates rearranged bands of the *BCL6* gene.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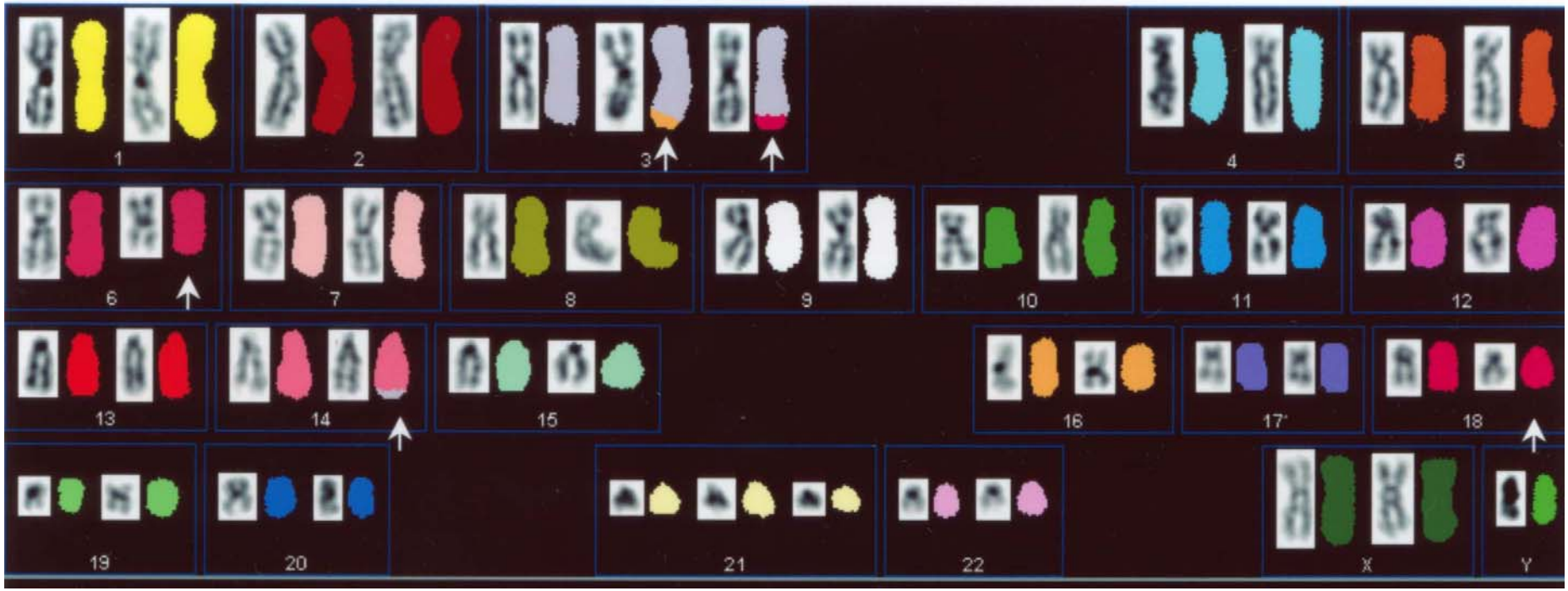
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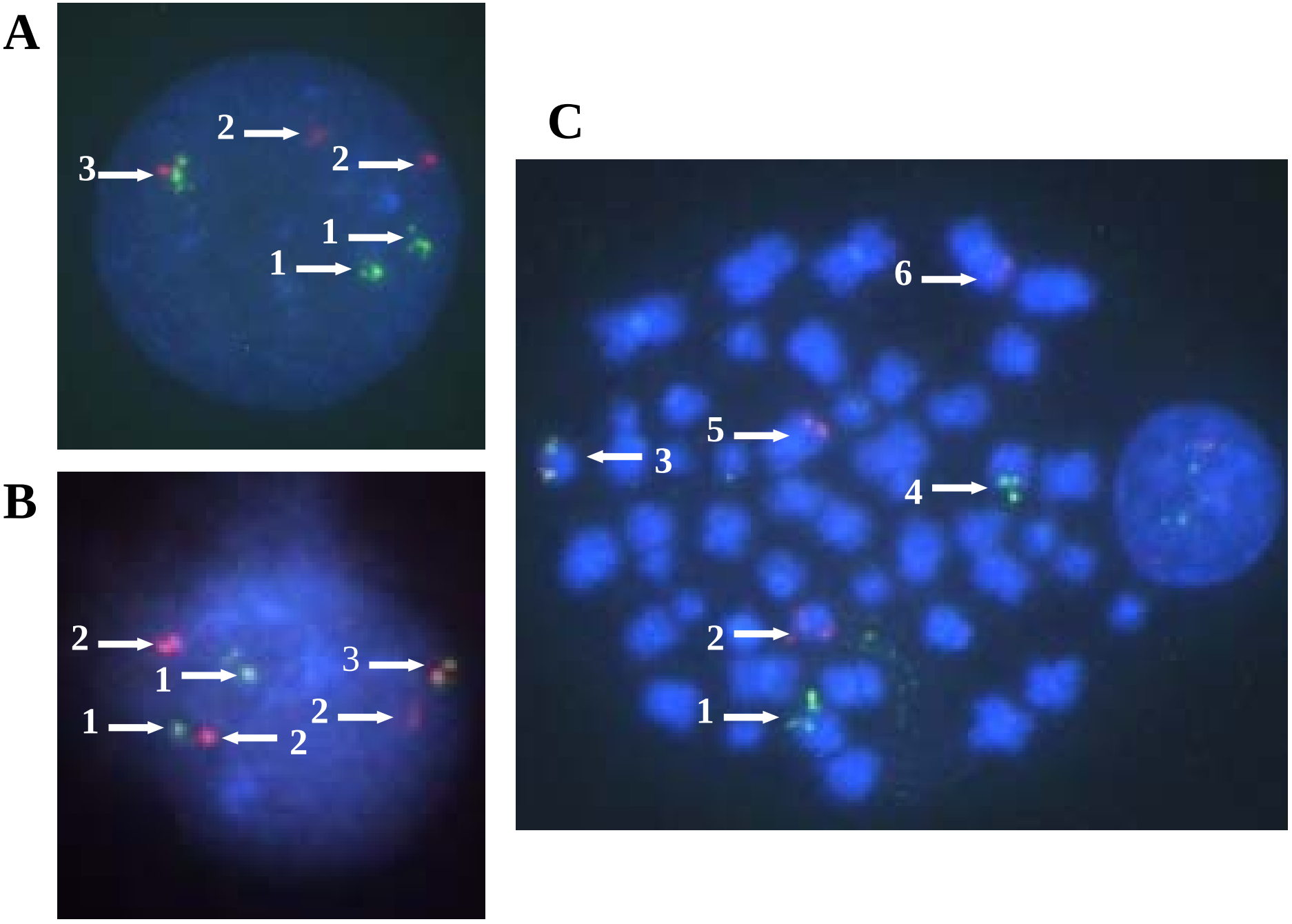
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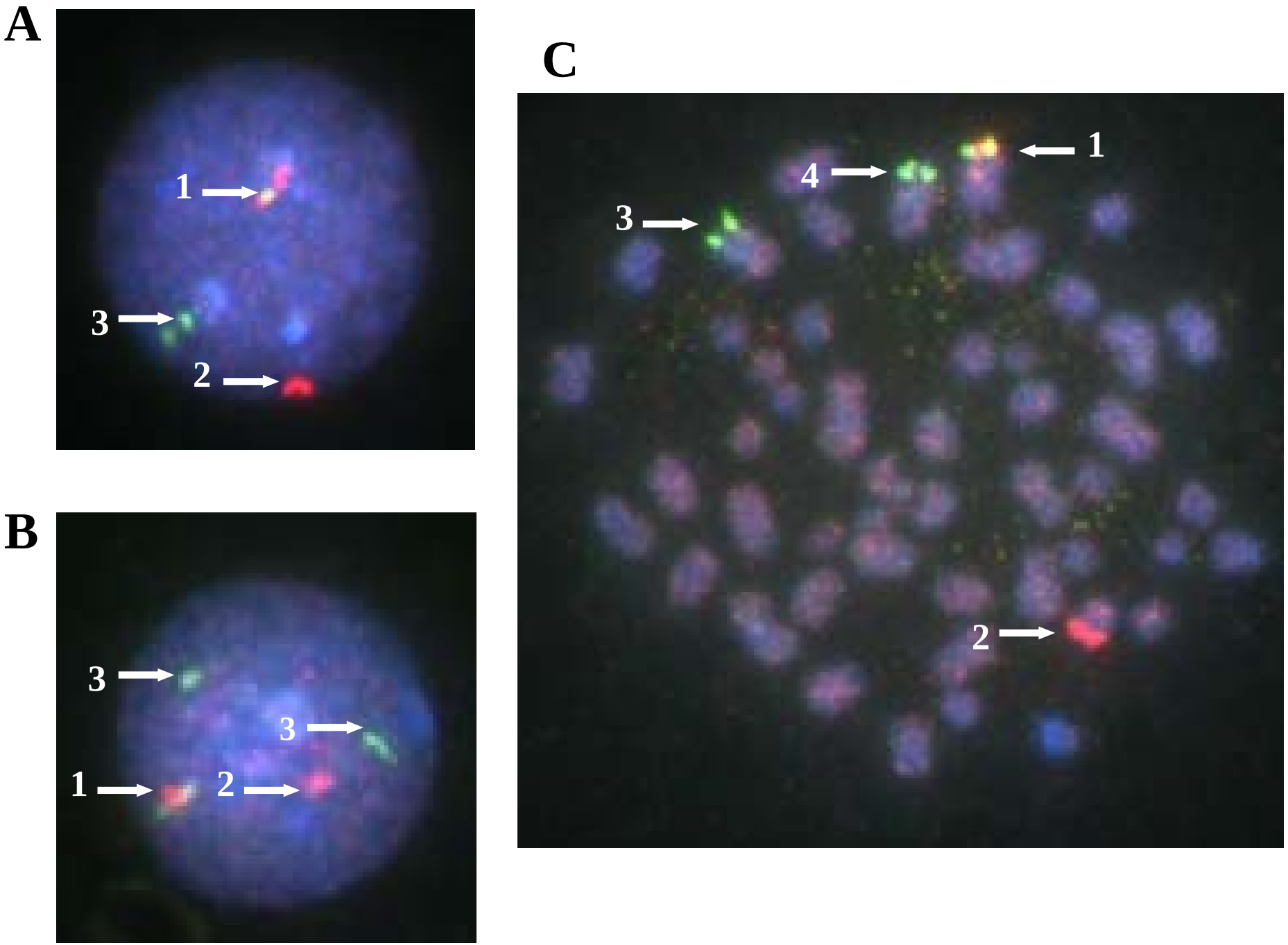
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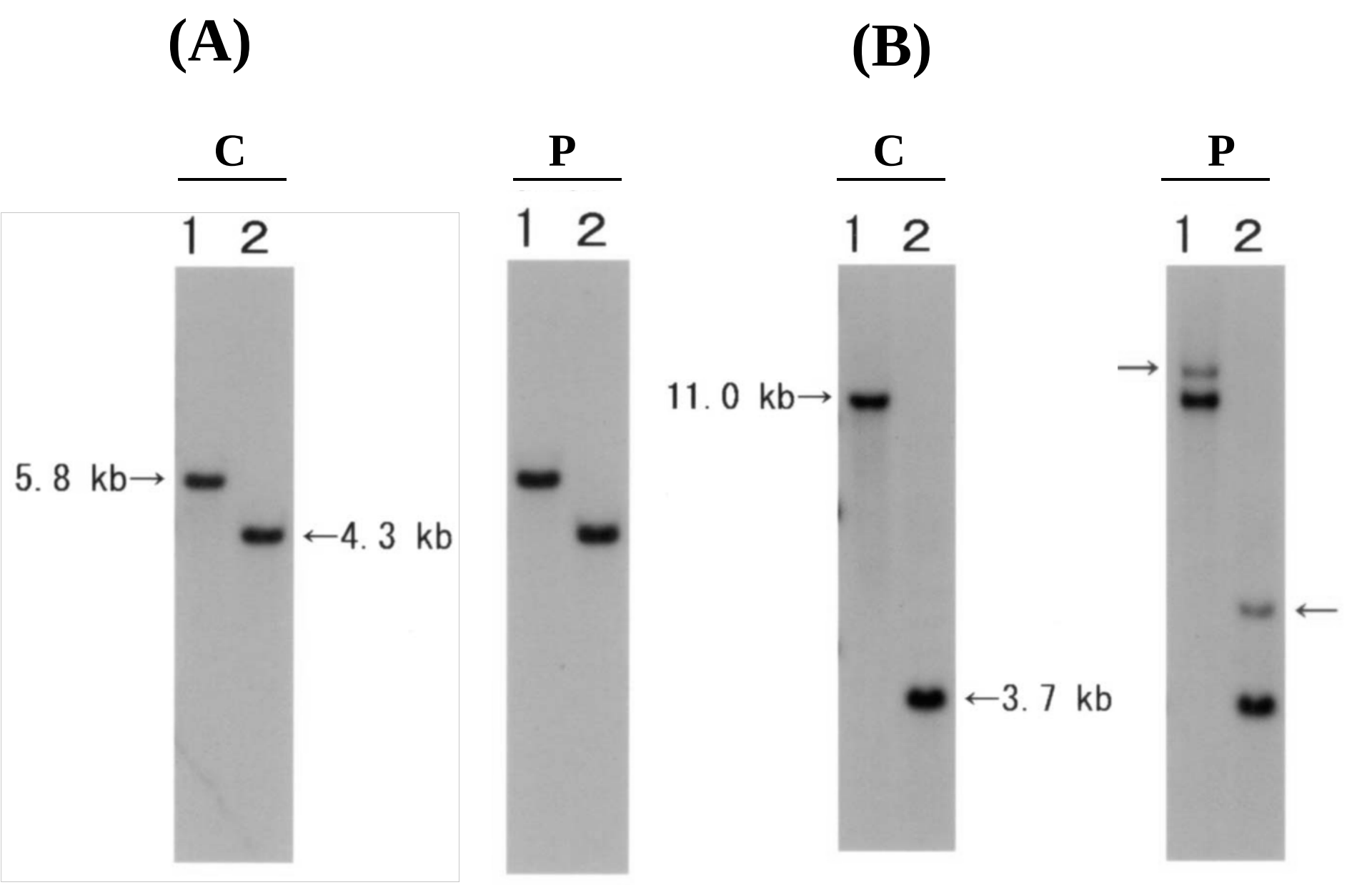
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Table 1. Results of FISH analyses on 100 interphase nuclei of lymph node cells

signals	IGH	BCL2	IGH/BCL2	Number of cells
clone A	2	2	1	8
clone B	2	3	1	32
normal clone	2	2	0	60
signals	5’ BCL6	3’ BCL6	5’ BCL6/3’ BCL6	Number of cells
clone A	1	1	1	4
clone B	1	2	1	38
normal clone	0	0	2	58

Table 2. Reported cases of lymphoma with t(3;14;18)(q27;q32;q21)

Case No.	*Age/ Sex*	*Diagnosis*	*Karyotypes*	*BCL2 MBR*	*BCL6 MTC*	*OS (mo)*	*References*
1	NA/M	DLBCL	55,XY,**t(3;14;18)(q27;q32;q21)**,del(3)(q26q27),+der(3)t(1;3)(q21;q27),+5,+6,t(8;9)(q24;p12),+11,+12,+13,+16,der(17)t(1;17)(q21;p13),+20	NA	R	NA	Roumier *et al*., 2000 [10]
2	43/F	FL, grade 2	46,XX,**t(3;14;18)(q27;q32;q21)**,i(16)(p10)[15]/46,XX[5]	G	R	36+	Okano *et al*., 2005 [11]
3	46/F	FL, grade 1	48,XX,**t(3;14;18)(q27;q32;q21)**t(18;7)(p10;?),+8,+mar[3]/46,XX[17]	G	R	18+	Rack *et al*., 2005 [12]
4	57/M	FL, grade 2	46,XY,**t(3;14;18)(q27;q32;q21)**,add(10)(q22)[5]/49,+X,**t(3;14;18)(q27;q32;q21)**,+der(3)t(3;18)(q27;q21)t(18;16)(q21;?),i(6)(p10),+21[9]/46,XY[6]	G	R	9+	Present case

Abbreviations: NA, not available; F, female; M, male; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MBR, major breakpoint region; MTC, major translocation cluster; G, germline; R, rearranged by Southern blot analysis; OS, overall survival; mo, months. + indicates alive. Boldface type highlights the translocation t(3;14;18)(q27;q32;q21).