Molecular Cytogenetic Analyses of Immunoglobulin Loci in Nodular Lymphocyte Predominant Hodgkin's Lymphoma Reveal a Recurrent *IGH-BCL6* Juxtaposition

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Chromosomal translocations juxtaposing different oncogenes to the immunoglobulin (*IG*) loci are the hallmark of various B-cell lymphomas. Because the tumor cells in nodular lymphocyte predominant Hodgkin's lymphoma (NLPHL) are also derived from B cells, we examined whether NLPHL harbors chromosomal translocations that affect *IG* loci. Fluorescence *in situ* hybridization was applied to 24 NLPHL cases using probes flanking the *IGH*, *IGK*, and *IGL* loci as well as the *BCL6* gene. Fourteen of these cases were additionally analyzed by combined immunofluorescence and fluorescence *in situ* hybridization. Chromosomal breakpoints in the *IGH* locus were detected in five NLPHL. All these cases also contained a *BCL6* breakpoint. Triple-color interphase cytogenetics demonstrated the presence of an *IGH-BCL6* juxtaposition, indicating a t(3;14)(q27;q32) in all five cases. There was no evidence for breakpoints affecting the *IGK* or *IGL* loci. Our results show that translocations juxtaposing the *BCL6* oncogene next to the *IGH* locus are recurrent in NLPHL. (*J Mol Diagn* 2005, 7:352–356)

Nodular lymphocyte predominant Hodgkin's disease (NLPHL) is a rare type of B-cell lymphoma characterized by a nodular or a nodular and diffuse tumor proliferate.¹ Large neoplastic cells, the lymphocytic and histiocytic (L&H) cells, lie within in a large mesh network of follicular dendritic cells that are filled with nonneoplastic lymphocytes. They usually account for only ~1% of the neoplastic infiltrate and express B-cell markers.^{2–4} Analysis of rearranged immunoglobulin (*IG*) genes showed a derivation from germinal center B cells selected for expression of a functional antigen receptor.^{5–8} The cytogenetic background of NLPHL is poorly characterized.⁹ Clonal karyotypes of only approximately a dozen NLPHL cases

studied by conventional cytogenetics have been published. Most of these karyotypes were hyperploid with multiple unresolved chromosomal changes. Comparative genomic hybridization from microdissected L&H cells of NLPHL revealed recurrent genomic imbalances.¹⁰

In early B-cell differentiation the immunoglobulin genes of B-cell precursors are rearranged. By class switch recombination, germinal center B cells change the isotype of the expressed B-cell receptor. During the process of somatic hypermutation, nucleotide substitutions, deletions, and duplications are induced into rearranged V-genes. Each of these three processes involves double-strand DNA breaks that enable chromosomal translocations to take place.¹¹ Chromosomal translocations juxtaposing oncogenes into the *IG* heavy-chain (*IGH*) locus at band 14q32 or less frequently the light-chain lambda (*IGL*) and kappa (*IGK*) loci, located at 22q11 and 2p12, respectively, are the hallmark of several mature B-cell lymphomas. These translocations result in deregulated expression of the oncogenes coming under the control of *IG* enhancers.^{11,12} One of these oncogenes, *BCL6*, encoding a transcriptional repressor, is located at 3q27. The *BCL6* gene is frequently translocated to *IG* but also non-*IG* partners in germinal center derived B-cell lymphomas. Just recently, an interphase cytogenetic study has reported translocations with breakpoints in the *BCL6* locus in 11 of 23 NLPHLs.¹³

Considering the B-cell origin of the L&H cells of NLPHL and the high incidence of translocations in *IG* loci in B cell, it is reasonable to assume that translocations in *IG* loci might also occur in NLPHL. Thus, we investigated a series of 24 NLPHLs by fluorescence *in situ* hybridization (FISH) for translocations involving the *IGH*, *IGL*, and *IGK* loci. To corroborate the findings by Wlodarska and colleagues¹³ in an independent series we also studied all cases for breakpoints involving the *BCL6* gene. To verify the FISH results we further analyzed 14 of the cases from

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which sufficient material was available by combined fluorescence immunophenotyping (FICTION technique) for CD20 and FISH for *IGH* and *BCL6* breakpoints.

Materials and Methods

Patient Material

Frozen tumor tissue samples from 24 patients with a NLP HL diagnosis were originally submitted for diagnostic purposes.

Histology and Immunohistochemistry

Morphology of the tumors was analyzed using histological sections stained with Giemsa. For immunohistochemistry, CD15 and CD20 antibodies (DakoCytomation, Hamburg, Germany) were applied and detected using the UltraVision detection system (Lab Vision Corp., Fremont, CA). In all cases, the neoplastic L&H cells proved to be CD15-negative and CD20-positive.

FISH and FICTION

Cell nuclei were extracted out of 40- μ m-thick frozen sections by mechanical separation in ice-cold phospho-buffered saline with a nylon net with 10- μ m aperture diameters. Nuclei were gently dehydrated through an ethanol series of increasing grade (79%, 85%, and 96%). After collecting them on cytopins nuclei were pretreated for 5 minutes at 37°C with 0.0005% pepsin, fixed for 2 minutes in 1% paraformaldehyde, and again dehydrated through an ethanol series.

The dual-color break-apart assays LSI *IGH* and LSI *BCL6* were obtained from Vysis (Downers Grove, IL). FISH was performed following the manufacturer's instructions. FISH analyses for the detection of chromosomal breakpoints in the *IGL* and *IGK* loci were performed using recently established dual-color flanking probes.¹⁴ Cases harboring signal constellations indicative for chromosomal breakpoints in both the *IGH* locus and *BCL6* gene were further studied with a triple-color FISH assay to detect the presence of an *IGH/BCL6* juxtaposition. This assay was composed of the LSI *IGH* dual-color probe in combination with a previously published *BCL6* probe set¹⁵ labeled with diethyl aminomethyl coumarin.¹⁶ The performance of this three-color probe was tested in negative controls and t(3;14)(q27;q32)-positive non-Hodgkin lymphomas.

Combined immunophenotyping and interphase cytogenetics (FICTION technique) was performed on frozen sections from 14 cases included in the FISH analyses in which suitable material was still available. Briefly, 5- μ m-thick frozen sections were thawed and dried for 30 minutes at room temperature, fixed in acetone for 10 minutes, and air-dried. Slides were incubated for 30 minutes at room temperature with a primary monoclonal antibody anti-CD20 (DakoCytomation, Hamburg, Germany) diluted (1:50) in PBS-nonfat milk buffer. Detection of the

primary antibody was performed with a rabbit anti-mouse antibody conjugated with Alexa-594 (1:100; Molecular Probes, Leiden, The Netherlands) and incubated for 30 minutes at room temperature. After immunophenotyping, slides were fixed in Carnoy's fixative (ethanol:acetic acid, 3:1) for 10 minutes and in paraformaldehyde solution (1%) for 1 minute. Then, slides were dehydrated through increasing ethanol concentrations (70%, 85%, and absolute) and air-dried. LSI *IGH* or LSI *BCL6* (1.5 μ l) were applied to the cell-containing area of the slide and covered with a round 10-mm coverslip. Both probe and target DNA were simultaneously denatured at 70°C for 7 minutes and incubated overnight at 37°C. Posthybridization washes were performed according the rapid wash protocol provided by Vysis. 4,6-Diamidino-2-phenylindole was used as DNA counterstaining. A minimum of 10 CD20+ large cells were scored whenever possible (Table 2). Slides were analyzed using an Axioskop-2 fluorescence microscope (Zeiss, Göttingen, Germany) equipped with appropriate filter sets (AHF, Tübingen, Germany) and documented using the ISIS imaging system (MetaSystems, Altlusheim, Germany).

Results

All FISH experiments with extracted nuclei were blindly evaluated using recently defined criteria¹⁷ by two independent investigators (C.R. and J.I.M.-S.). Larger nuclear size and the frequent hyperploid genomic status were used as criteria to identify putative L&H cells. At least 10 cells meeting these criteria were evaluated per case. Fifty small diploid cells were scored as internal negative controls. The diagnostic cut-offs for the *IGH*, *IGL*, and *IGK* probes were calculated as mean of false-positive results in negative controls plus three times the SD and were 9.2%, 13.3%, and 9.6%, respectively. These cut-offs are slightly higher as those previously published,^{14,17} most likely due to the different nature, preservation, and preparation of the samples studied in the present series. For the *BCL6* probe, the cut-off was virtually zero because no split signals were detected in any small diploid cells.

Of the 24 NLP HL samples analyzed by FISH with the probe flanking the *IGH* locus 3 cases (13%) showed a significant number of putative L&H cells with a signal pattern indicating a chromosomal breakpoint in the *IGH* locus. As the number of putative L&H cells with signal patterns indicative for translocations affecting the *IGL* and *IGK* loci did not exceed the cut-off level in any of the 24 cases studied we did not detect any breakpoints affecting *IG* light chains. A significant number of large atypical cells with signal patterns indicating the presence of a breakpoint in the *BCL6* locus were detected by FISH in four (17%) patients (Table 1).

To prove the FISH results and to demonstrate that the chromosomal changes detected by FISH were present in the L&H cells, FICTION analyses were attempted in all 14 cases in which sufficient cryopreserved material was still available. Putative L&H cells were identified by virtue of their larger cell and nuclear size, and expression of the CD20 antigen. In the FICTION analyses, the frequent

Table 1. Summary of the FISH and FICTION Analyses for the Detection of Breakpoints in the *IGH*, *IGL*, *IGK*, and *BCL6* Loci

		<i>IGH</i>	<i>IGK</i>	<i>IGL</i>	<i>BCL6</i>
FISH results	Total (n)	24	24	24	24
	Cases with breakpoint (n)	3	0	0	4
	Percentage of cases with breakpoint	13%	0%	0%	17%
	Total cases (n)	13	nd	nd	12
FICTION results	Cases with breakpoint (n)	5*	nd	nd	5*
	Percentage of cases with breakpoint	38%	nd	nd	42%

**BCL6/IGH* juxtaposition indicating the presence of a t(3;14)(q27;q32) was proven by triple-color interphase cytogenetics in all five cases. nd, not done.

hyperploid nature of L&H cells was not considered because truncation of the nucleus by cryosection can lead to artificial signal loss. Of 13 evaluable cases, presence of an *IGH* breakpoint was confined to the CD20+ large cell population in the 3 NLPHL cases in which such a breakpoint was also identified by FISH. Two additional cases with CD20+ L&H cells containing breakpoints in the *IGH* locus were detected by FICTION (Figure 1A, Table 1, cases NP1 and NP19, Table 2). FICTION analyses with CD20 and *BCL6*, which were evaluable in 12 cases, revealed signal constellations indicating breaks in the *BCL6* locus in the CD20+ L&H cells of 5 cases, including the 4 cases detected by FISH and 1 additional NLPHL without evidence for a *BCL6* break by FISH (Table 1, case NP1; Table 2).

All five NLPHL with signal patterns indicating *IGH* breaks also displayed *BCL6* signal patterns indicative of a breakpoint. The simultaneous occurrence of breakpoints in the *IGH* and *BCL6* loci suggested the presence of a t(3;14)(q27;q32). To investigate the presence of this translocation, these cases were studied by FISH (three cases) or FICTION (two cases) simultaneously applying differentially labeled probes for *IGH* and *BCL6*. All five cases showed a signal pattern indicative for a t(3;14)(q27;q32) translocation in all putative L&H cells evaluated (Figure 1B, Table 2).

Discussion

In this study we analyzed the *IG* heavy- and light-chain loci of 24 NLPHL cases for chromosomal translocations in an open approach using FISH and FICTION techniques. The comparison of the results obtained by FISH and FICTION in this study clearly shows that FICTION seems to be the more sensitive and therefore the more qualified technique for interphase cytogenetic analyses of NLPHL. The FICTION analysis can be restricted to the CD20+ atypical large-cell population, which might be missed by FISH due to its low frequency. Moreover, it cannot be ruled out that the mechanical separation of cell nuclei through a nylon net damages large nuclei, especially nuclei of L&H cells, more frequent than those of small cells so that the samples finally collected on cytopins for FISH analyses may be depleted of L&H cell nuclei. However, although the L&H cells are considered to be frequently hyperploid, as also shown in this study by FISH, the majority of the CD20+ atypical large cells suggestive for L&H cells in 9 of the 13 cases evaluated by FICTION displayed two co-localized signals for *IGH* and *BCL6*. This discrepancy is most likely due to sectioning artifacts in the thin cryosections. Alternatively, it could also indicate that hyperploidy is not a consistent phenomenon in NLPHL.

Figure 1. A: Combined immunophenotyping and FISH for the detection of CD20 and breakpoints in the *IGH* locus in case NP19. The CD20-positive large cell (blue) displays a split of the signals flanking the *IGH* locus indicating the presence of a translocation. The CD20 antigen detected with Alexa-594 (red fluorescence) is displayed in blue. **B:** Triple-color FISH assay for the detection of the t(3;14)(q27;q32) translocation juxtaposing the *BCL6* and *IGH* loci (false color display) in case NP20. This probe set was made of the LSI *IGH* flanking probe (*IGH* telomeric in green and *IGH* centromeric in red) combined with a *BCL6*-spanning probe labeled in DEAC (pale blue signals). The small nucleus on the right displays the regular signal constellation: two red/green co-localizations indicating intact *IGH* gene and two pale blue signals pointing to intact *BCL6* alleles. The large nucleus on the left shows multiple split of green and red signals indicating a breakpoint in the *IGH* locus. Disrupted red and green signals co-localize with pale blue *BCL6* signals pointing to a t(3;14)(q27;q32) translocation involving the *BCL6* and *IGH* loci as well as the presence of several derivative chromosomes. This signal pattern was found recurrently in this case.

Table 2. Detailed Results of the FICTION Analyses for the Detection of Breakpoints in the *IGH* and *BCL6* Loci

Case	Large CD20+ cells evaluated			
	<i>IGH</i>		<i>BCL6</i>	
	Signal pattern	No. of cells scored	Signal pattern	No. of cells scored
NP1	1F,1R,1G*	17	1F,1R,1G*	15
			1F	2
			2F	3
NP2	2F	10	2F	10
NP3	2F	5	2F	5
	4F	1	3F	1
	5F	1		
NP4	2F	10	NE	
NP5	NE		NE	
NP6	1-2F,1-2R,1-2G	10	1-2F,1-2R,1-2G	10
NP7	2F	7	2F	6
	3F	1	3F	3
	4F	2	4F	1
NP8	2F	10	2F	10
NP9	2F	10	2F	10
NP10	2F	10	2F	10
NP11	1-2F1-2R1-2G	10	1-2F1-2R1-2G	10
NP19	0-1F,0-1R,0-1G*	10	1-2F,0-1R,0-1G	10
NP20	0-1F,1-2R,1-3G	10	0F,1-2R,1-3G	10
NP21	2F	10	2F	10

*Not detected by FISH; bold letters point to signal constellations indicating the presence of a translocation. In all these cases, the *BCL6/IGH* juxtaposition proven either by FISH or FICTION.

F, fusion of red and green signals, ie, intact allele; R, isolated red signal; G, isolated green signals; NE, not evaluable.

So far, recurrent chromosomal aberrations affecting 14q32 have not been described in NLPHL by classical cytogenetics. This might be due to the scarcity of cytogenetic data, the presence of many unresolved changes and the subtelomeric location of the *IGH* locus which can lead to cryptic translocations.¹⁸ In this study, translocations affecting the *IGH* locus are reported for the first time, which were present in 38% of the NPLHLs analyzed by FICTION. *BCL6* was identified as the partner gene in all cases with *IGH* breaks studied herein suggesting the presence of a translocation t(3;14)(q27;q32). The proportion of cases with *BCL6* breakpoints in this series of NLPHL is similar to that of the recently published independent collective of 23 patients samples.¹³ The incidence of translocation t(3;14)(q27;q32) found in NLPHL seems similar to the frequency observed in diffuse large B-cell lymphoma^{19,20} and progression from NLPHL to diffuse large B-cell lymphoma has been described.^{21,22}

The variant translocations involving *IGL* and *IGK* represent ~5 to 10% of all *IG* translocations in B-cell lymphomas.²³⁻²⁵ We did not detect any breakpoints affecting *IG* light-chain loci in the present series, which might be simply due of the small sample size or the fact that FISH is less sensitive than FICTION to detect chromosomal breakpoints if the tumor cell content is low. In this context, it is noteworthy that a translocation t(3;22)(q27;q11) affecting *BCL6* and *IGL* has been previously detected in two NLPHL,^{10,26,27} suggesting recurrent deregulation of *BCL6* in NLPHL also by juxtaposition next to *IG* light-chain loci. Moreover, a recent publication has reported the presence of heterogeneous translocation partners of *BCL6* affecting non-*IG* loci in chromosome bands 9p13, 7p12, and 4q32.²⁷ In contrast to the obvious het-

erogeneity of *BCL6* partners in NLPHL, *IGH* was the only translocation partner of *BCL6* in the present series.

Summarizing the data presented herein and those from the independent series by Wlodarska and colleagues,¹³ it can be assumed that *BCL6* activation by juxtaposition predominantly to *IG* loci is the first recurrent chromosomal change in NLPHL, which is shared with other germinal center-derived B-cell neoplasms. Future studies are required to elucidate whether the presence of *BCL6* translocations defines a subgroup of NLPHLs with a distinct biological behavior as recently described in follicular lymphoma.²⁸

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