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# Low-Grade B-Cell Lymphomas With Plasmacytic Differentiation Lack *PAX5* Gene Rearrangements

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**The chromosomal translocation t(9;14)(p13;q32) has been reported in association with lymphoplasmacytic lymphoma (LPL). Although this translocation involving the paired homeobox-5 (*PAX5*) gene at chromosome band 9p13 and the immunoglobulin heavy chain (*IgH*) gene at 14q32 has been described in ~50% of LPL cases, the actual number of cases studied is quite small. Many of the initial cases associated with t(9;14)(p13;q32) were actually low-grade B-cell lymphomas with plasmacytic differentiation other than LPL. Thus, we analyzed a series of low-grade B-cell lymphomas for *PAX5* gene rearrangements. We searched records from the Department of Pathology, Stanford University Medical Center for low-grade B-cell lymphomas, with an emphasis on plasmacytic differentiation, that had available paraffin blocks or frozen tissue. We identified 37 cases, including 13 LPL, 18 marginal zone lymphomas (nodal, extranodal, splenic, and α-heavy chain disease), and 6 small lymphocytic lymphomas. A novel dual-color break-apart bacterial artificial chromosome probe was designed to flank the *PAX5* gene, spanning previously described *PAX5* breakpoints, and samples were analyzed by interphase fluorescence *in situ* hybridization. All cases failed to demonstrate a *PAX5* translocation, indicating that t(9;14)(p13;q32) and other *PAX5* translocations are uncommon events in low-grade B-cell lymphomas with plasmacytic differentiation. This study also confirms recent reports that found an absence of *PAX5* rearrangements in LPL, suggesting the reassessment of *PAX5* rearrangements in LPL. *(J Mol Diagn 2005, 7:346–351)***

Recent studies[1–3] have called into question the association of t(9;14)(p13;q32) and lymphoplasmacytic lymphoma (LPL), both medullary (ie, Waldenström's macroglobulinemia) and extramedullary. Initially described in a CD30-positive diffuse large B-cell lymphoma cell line, KIS-1,[4] this translocation involves the paired homeobox-5 (*PAX5*) gene at 9p13 and the immunoglobulin heavy chain (*IgH*) gene at 14q32.[5] After its initial characterization, further studies found the t(9;14)(p13;q32) associated with LPL.[6,7] Encoding B-cell-specific activator protein, a B-cell transcription factor, the *PAX5* gene has been thought to contribute to the development of lymphoma when brought into close proximity of the *IgH*.[8] The incidence of this translocation has been cited in at least one textbook as involving ~50% of LPL,[9] when in fact only a small number of cases have been previously studied.

In reviewing previous reports of t(9;14)(p13;q32) in the literature, as concisely summarized by Cook and colleagues,[1] only 2 of 20 cases were classified as LPL using World Health Organization criteria.[6] The remaining cases had a variety of diagnoses including plasmacytoid small lymphocytic lymphoma, diffuse large noncleaved cell lymphoma, splenic marginal zone lymphoma, diffuse large B-cell lymphoma, follicular mixed lymphoma, α-heavy chain disease, plasma cell leukemia, and primary effusion lymphoma.[4–6,8,10–14] Small lymphocytic lymphoma of the plasmacytoid subtype (working formulation) is often assumed to correlate with LPL (World Health Organization classification), but this category included many other lymphoma types that are now better characterized. By definition, the World Health Organization criteria are stringent for the diagnosis of LPL, excluding plasmacytoid variants of other lymphomas.[9] The heterogeneity of lymphomas associated with t(9;14) is also illustrated by previous reports of sequenced *PAX5* breakpoints as shown in Figure 1: a plasmacytoid small lymphocytic lymphoma (1052),[6] a splenic marginal zone lymphoma (MZL-1),[10] a diffuse large B-cell lymphoma (895),[8,11] α-heavy chain disease (MAL),[12,13] and the KIS-1 cell line.[4,5]

Given the frequency of low-grade B-cell lymphomas other than LPL associated with t(9;14), we chose to investigate the incidence of the *PAX5* gene rearrangement in a series of low-grade B-cell lymphomas with an emphasis on plasmacytic differentiation. We developed a dual-color break-apart bacterial artificial chromosome (BAC) probe spanning all previously sequenced *PAX5* rearrangements (Figure 1). Our series of cases was investigated for *PAX5* gene rearrangements using interphase fluorescence *in situ* hybridization (FISH) on both

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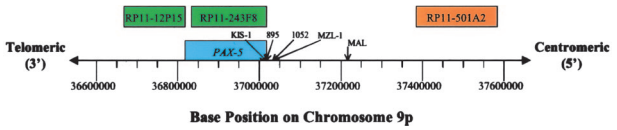


**Figure 1.** PAX-5 FISH probe design. BACs RP11-12P15 and RP11-243F8 (labeled green) span the *PAX5* gene and ~250-kb telomeric (3′) to the *PAX5* gene. RP11-501A2 (labeled red) localizes to a region centromeric (5′) to previously described breakpoints. **Arrows** indicate sequenced *PAX-5* translocations described in the literature.[4–6,8,10–13] Base position identified using the UCSC Genome Browser, *http://genome.ucsc.edu.*

touch preparations (TP) from frozen tissue and paraffin-embedded tissue (PET).

## Materials and Methods

### Patient Samples and Controls

Records from the Stanford University School of Medicine, Department of Pathology, were reviewed from 1984 to 2002 for cases of low-grade B-cell lymphoma with an emphasis on plasmacytic differentiation specifically targeting LPL and its morphological mimics including marginal zone lymphomas and small lymphocytic lymphomas with plasmacytic differentiation. Thirty-seven samples were identified with adequate tissue available, either frozen or formalin-fixed PET. All samples were reviewed including hematoxylin and eosin-stained sections, immunohistochemical stains, flow cytometry studies, and molecular genetic studies, if available. None of the cases had classical cytogenetic studies performed. Samples were classified by the authors (T.G., D.A.) using the World Health Organization criteria.[15] The additional description of plasmacytic differentiation was added to those cases of low-grade B-cell lymphomas that met World Health Organization criteria for small lymphocytic lymphoma, nodal and extranodal marginal zone lymphoma, and that showed increased numbers of plasma cells and plasmacytoid cells.

The KIS-1 cell line, a CD30-positive diffuse large B-cell lymphoma cell line, that has previously been shown to have the t(9;14)(p13;q32) rearrangement and overexpress the *PAX5* gene product was used as a positive control.[4,5] The presence of a t(9;14) was confirmed by conventional karyotype and FISH analysis, including whole chromosome paint probes for chromosomes 9 and 14 (Vysis, Downers Grove, IL) and the core binding factor $\beta$ (CBFB) break-apart probe specific for band 16q22 (Vysis). The karyotype was further supported by use of the Chromoprobe Multiprobe System, Octachrome whole chromosome paint assay (Cytocell Ltd., Adderbury, Banbury, UK). Negative controls included formalin-fixed paraffin-embedded tonsil and frozen tonsil, obtained from patients with reactive follicular hyperplasia on routine pathology examination.

### Probe Design

A *PAX5* break-apart FISH probe was designed to label 5′ and 3′ ends of previously reported *PAX5* breakpoints as shown in Figure 1.[5,6,8,10–13] BAC clones RP11-12P15, RP11-243F8, and RP11-501A2 were located using the University of California, Santa Cruz Genome Browser (*http://genome.ucsc.edu*) and obtained (BACPAC Resources, Children's Hospital Oakland Research Institute, Oakland, CA). BAC DNA was isolated using a Large-Construct kit (Qiagen Inc, Valencia, CA), and labeled using the Vysis Nick Translation kit. BACs 3′ to previously reported *PAX5* breakpoints (RP11-12P15, RP11-243F8) were labeled using Spectrum Green dUTP, while the BAC 5′ to previously reported *PAX5* breakpoints (RP11-501A2) was labeled with Spectrum Orange d-UTP. Probes were resuspended in Hybrisol 50 [50% formamide/2× saline sodium citrate (SSC) + 0.1 g/ml dextran sulfate]. On hybridization, the resulting pattern should be two fusion (2F) signals in nuclei lacking a *PAX5* rearrangement and one red, one green, and one fusion (1R1G1F) signal in nuclei containing a *PAX5* translocation. Probe location was confirmed by standard FISH procedures on normal metaphases and the KIS-1 cell line.

### FISH

PET samples were prepared in a modification of the protocol described by Paternoster and colleagues[16] in which nuclei are extracted from core biopsies obtained from PET. Slides were pretreated using a Vysis VP 2000 processor. Settings included: 1) 20 minutes in room temperature, 0.2 N hydrochloric acid; 2) distilled water ($dH_20$) rinse; 3) 30 minutes in 80°C Vysis pretreatment reagent (no. 30-801250); 4) $dH_2O$ rinse; 5) 10 minutes in 37°C protease I (10% pepsin); 6) $dH_2O$ rinse; 7) 10 minutes in room temperature, 10% buffered formalin; 8)

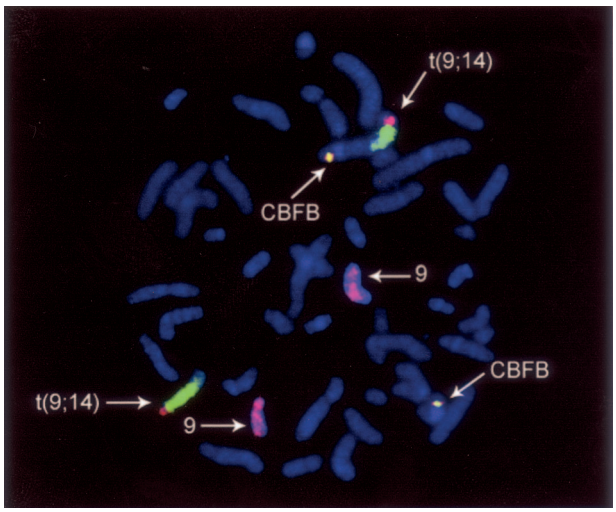


**Figure 2.** Co-hybridization of KIS-1 metaphase spread with the dual-color CBFB probe specific for band 16q22 and differentially labeled whole chromosome paint probes for chromosomes 9 and 14 show two chromosomes consisting primarily of chromosome 9 material (labeled red) and representing a normal 9 homolog and a derivative 9 consistent with a translocation t(9;14). Two additional rearranged chromosomes are identified, a derivative chromosome 14 (labeled green) with a small distal chromosome 9 segment (labeled red), and a complex derivative chromosome 16 [der(16)] identified by the CBFB probe and containing distal juxtaposed red chromosome 9 and green chromosome 14 segments.

$dH_2O$ rinse; 9) dehydration in room temperature ethanol series; and 10) air dry. After the addition of probe, slides were placed in a HYBrite hybridization instrument (Vysis), denatured 8 minutes at 80°C, and hybridized overnight (~16 hours) at 37°C. Slides were then washed 2 minutes in 0.4× SSC/0.3% Nonidet P-40 (NP-40) (Vysis) at 73°C and 5 to 60 seconds in room temperature 2× SSC/0.1% NP-40. Slides were air-dried and counterstained with 4′,6-diamidino-2-phenylindole (DAPI II) (Vysis).

TP were prepared from frozen tissue samples using standard methods. Slides were soaked in Carnoy's fixative for 15 minutes and allowed to air dry. Optimal FISH results were obtained by 1) pretreatment of 30 minutes in 37°C 2× SSC; 2) dehydration in ethanol series; 3) air dry; 4) denaturation 5 minutes in 73°C 70% formamide/2× SSC; 5) dehydration by ethanol series; 6) air dry; 7) denature probe 5 minutes at 73°C; 8) apply probe, cover with 22 × 22 mm coverslip (VWR Scientific, Brisbane, CA), seal with rubber cement; and 9) hybridize in HYBrite hybridization instrument (Vysis) at 37°C overnight. Post-hybridization washes and counterstaining were the same as for the PET samples.

Hybridized slides were analyzed using the CytoVision 3.0 Genus capture system (Applied Imaging, San Jose, CA) with an Olympus BX51 fluorescent microscope (Olympus America, Melville, NY) using 82000 and 83000 series triple pass filter sets (Chroma Technology Corp., Rockingham, VT). Break-apart of probe signals was defined by a distance of more than two signal widths between two differently labeled probe signals. Using these criteria, two to three sets of 100 consecutive intact interphase nuclei were examined for the number of green, red, and fusion signals, resulting in a total of 200 to 300 nuclei reviewed for each sample. Background levels for both TP and PET samples were determined by scoring a total of 1000 nuclei each of respective negative controls from a series of separate experiments. The maximum range of abnormal signals (ie, a split signal pattern, 1R1G1F) per 200 nuclei plus 2 SD was calculated as the background level of abnormal signals for TP and PET-negative control samples. Hence, a case was considered to demonstrate a *PAX5* gene rearrangement if the percentage of nuclei with a split signal pattern was above this threshold (maximum range, +2 SD).

**Table 1.** Summary of Clinical, Pathological, and Tissue Types Studied

| Case | Age/sex | Diagnosis | Tissue | PET or TP |
|---|---|---|---|---|
| 1 | 52M | LP | LN | PET |
| 2 | 62M | LP | SPL | PET |
| 3 | 73 F | LP | SPL | PET |
| 4 | 64M | LP | SPL | PET |
| 5 | 58 F | LP | SPL | PET |
| 6 | 51M | LP | SOFT | TP |
| 7 | 53M | LP | LN | TP |
| 8 | 44 F | LP | LN | TP |
| 9 | 86 F | LP | LIV | TP |
| 10 | 64M | LP | LUNG | TP |
| 11 | 74M | LP | LUNG | TP |
| 12 | 39M | LP | BM | TP |
| 13 | 73 F | LP-DLBCL | LN | TP |
| 14 | 62 F | NMZ-P | LN | TP |
| 15 | 74M | EMZ-P | SKIN | TP |
| 16 | 77M | EMZ-P | CONJ | TP |
| 17 | 80 F | EMZ-P | CONJ | TP |
| 18 | 52 F | EMZ-P | STO | TP |
| 19 | 67 F | EMZ-P | CONJ | TP |
| 20 | 38 F | EMZ-P | CONJ | TP |
| 21 | 64M | EMZ-P | ORBIT | TP |
| 22 | 58 F | SMZ | LN | PET |
| 23 | 62 F | SMZ | SPL | PET |
| 24 | 42M | SMZ | SPL | PET |
| 25 | 58 F | SMZ | SPL | PET |
| 26 | 66 F | SMZ | SPL | PET |
| 27 | 40M | SMZ | SPL | PET |
| 28 | 73M | SMZ | SPL | PET |
| 29 | 46 F | SMZ | SPL | PET |
| 30 | 66 F | SMZ | SPL | TP |
| 31 | 66 F | SLL-P | LN | TP |
| 32 | 74 F | SLL-P | LN | PET |
| 33 | 63M | SLL-P | LN | TP |
| 34 | 65 F | SLL-P | LN | TP |
| 35 | #F | SLL-P | LN | TP |
| 36 | 65M | SLL | LN | TP |
| 37 | 62M | AHCD | INT | TP |

All cases were negative for *PAX5* translocations by FISH analysis.

M, male; F, female; LP, lymphoplasmacytic lymphoma; DLBCL, diffuse large B-cell lymphoma; NMZ-P, nodal marginal zone lymphoma with plasmacytic differentiation; EMZ-P, extranodal marginal zone lymphoma with plasmacytic differentiation; SMZ, splenic marginal zone lymphoma; SLL-P, small lymphocytic lymphoma with plasmacytic differentiation; AHCD, α heavy-chain disease; LN, lymph node; SPL, spleen; LIV, liver; BM, bone marrow; CONJ, conjunctiva; INT, intestine; SOFT, soft tissue; STO, stomach; #, age not available.

## Results

### Clinical and Pathological Data

Of the 37 samples examined, 17 were from male patients and 20 were from female patients, with ages ranging from 38 to 86 years (mean, 61 years). Pathological diagnoses included 13 LPL, with 1 case containing areas of both LPL and diffuse large B-cell lymphoma, 1 nodal marginal zone lymphoma with plasmacytic differentiation, 7 extranodal marginal zone lymphomas with plasmacytic differentiation, 9 splenic marginal zone lymphomas, 6 small lymphocytic lymphomas (of which 5 showed plasmacytic differentiation), and 1 case of α-heavy chain disease. The sites of tissue biopsies included lymph node ($n = 12$) and extranodal sites ($n = 25$) as listed in Table 1.

### KIS-1 Cell Line

Standard cytogenetics of the KIS-1 cell line supported by FISH analysis revealed a karyotype consistent with that previously reported,[4] with additional karyotypic evolution. The line is described here using the International System of Human Cytogenetic Nomenclature[17] as follows: 48~49, Y,dup(X)(q?q?),del(1)(q42),add(4)(q31),del(8)(p11.2),der(9)t(9,14)(p13;q32),dup(11)(q13q32),t-(12,13)(p10;p10),−14,der(14)t(9,14)(q22;q32),+15, der(16)(9pter→9p13:14q32→14q11.2:2?→2?: 16p?-11.2→16qter),add(17)(p11.2),+20,der(22)t(1,22)(q12;q13),+2~3mar.ish der(16)(WCP9+,RP11 501A2+, WCP14+,WCP2+,CBFB+,WCP16+)[cp10].

All KIS-1 cell line metaphase cells ($n = 100$) analyzed with the *PAX5* break-apart probe showed a fused 5′ to 3′ *PAX5* chromosome signal consistent with a normal 9 homolog, a discrete 5′ *PAX5* signal consistent with the derivative chromosome 9 [der(9)t(9,14)], a discrete 3′ *PAX5* signal on a large chromosome morphologically consistent with the complex der(16) chromosome, and an atypical double and diffuse 3′ *PAX5* signal pattern on a medium-sized metacentric chromosome. The atypical 3′ *PAX5* double signal suggested a duplication/amplification of 3′ *PAX5* signals and could not be correlated by karyotype or FISH paint with a specific chromosome. These results were supported by FISH studies with whole chromosome paint probes and CBFB probe for band 16q22 (Figure 2). A corresponding signal pattern of one red:three green:one fusion (1R3G1F) was observed in 43% of interphase nuclei examined ($n = 300$) (Figure 3). A pattern of 1R4G1F was seen in another 52% of interphase nuclei ($n = 300$), which may reflect either sister chromatid separation or additional karyotypic heterogeneity within the KIS-1 cell line. Based on the karyotype and FISH analyses, the complex der(16) is interpreted as the likely site of 3′ *PAX5-IGH* gene rearrangement in the KIS-1 line.

## *Interphase FISH Analysis*

Review of negative control slides yielded threshold levels, calculated as the maximum range +2 SD for split signals per 200 nuclei, of 3.1% for PET and 9.4% for TP samples using the *PAX5* break-apart probe. Using these criteria all samples examined were negative for a *PAX5* translocation with ranges of split signals of 0 to 3.0% for PET and 0 to 6.4% for TP cases (Figure 4). The results for case 20 showed 86.5% nuclei with a normal signal pattern (2F), 6.4% split signals (1R1G1F), and 7.1% abnormal signals (1G1F) from analysis of 300 TP nuclei. The pattern of one green: one fusion signal may be the result of poor hybridization or a microdeletion involving 9p13. This signal pattern was not observed in significant numbers in other cases. Case 22 revealed a duplication of chromosome 9 with 65% normal signal pattern (2F) and 35% aneuploid (4F) signals from analysis of 200 PET nuclei (Figure 5), confirmed by FISH with telomeric chromosome 9p and 9q probes.

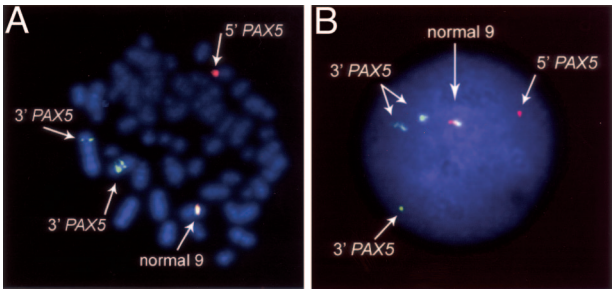


**Figure 3.** KIS-1 metaphase (**A**) and interphase nuclei (**B**) hybridized with *PAX5* probe. Red signals correspond to the centromeric (5′) end of the *PAX5* probe on chromosome 9p13, whereas green signals indicate the telomeric (3′) portion of the probe. A fusion signal indicates an intact *PAX5* gene. Separate red and green signals (split signal) indicate a *PAX5* rearrangement.

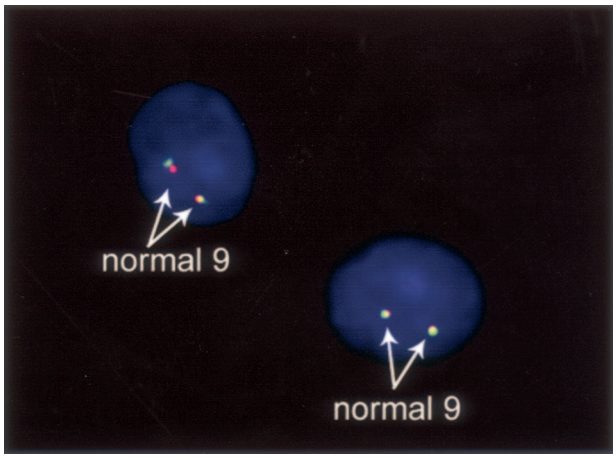


**Figure 4.** Representative interphase nuclei from case 27 hybridized with *PAX5* probe. Two fusion signals indicate intact *PAX5* genes with no translocation.

## *Discussion*

We analyzed a series of 37 low-grade B-cell lymphomas, including 13 LPLs, for evidence of *PAX5* rearrangements using interphase FISH and a novel dual-color break-apart BAC probe. We found no evidence of *PAX5* gene rearrangements, suggesting t(9;14) and *PAX5* translocations are uncommon events in these types of lymphomas. These results confirm recent reports[1–3] that found a lack of t(9;14) in LPL. Cook and colleagues[1] examined a series of 14 previously published cases of nodal or other extramedullary LPLs using a novel BAC contig probe for *PAX5* and an *IgH* dual-color, break-apart probe (Vysis), and investigated for the presence of t(9;14) using paraffin section interphase FISH. The authors found no evidence of *PAX5* or *IgH* translocations. Schop and colleagues[2] investigated a total of 74 patients with Waldenström's macroglobulinemia (IgM >1.5 g/dL and clonal lymphoplasmacytic infiltrate in bone marrow) and using conventional cytogenetics (37 samples), multicolor metaphase FISH (5) and interphase FISH (42) failed to identify IgH

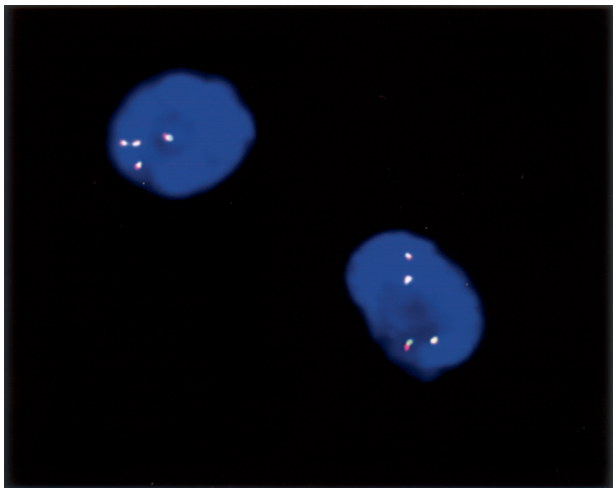

**Figure 5.** Representative interphase nuclei from case 22 hybridized with *PAX5* probe. Four fusion signals indicate duplication of chromosome 9, confirmed by FISH with telomeric 9p and 9q probes (data not shown).

translocations or t(9;14). Waldenström's macroglobulinemia is a clinicopathological syndrome, which is most commonly associated with the pathology of LPL, although the relationship between the two entities is somewhat controversial.[18] Finally, Mansoor and colleagues[3] studied 37 bone marrow cases of LPL/Waldenström's macroglobulinemia by conventional cytogenetics, and while t(9;14) was not identified, other chromosomal abnormalities were described. In this study, LPL/Waldenström's macroglobulinemia was defined by the presence of a monoclonal IgM paraprotein, bone marrow involvement by a neoplasm comprised of small lymphocytes with plasmacytoid differentiation and flow cytometry immunophenotypic studies demonstrating a monotypic B-cell population lacking co-expression of CD5, CD10, and CD23. Thus, our findings and recent studies all concur that t(9;14) and *PAX5* rearrangements are uncommon events in LPL.

Despite textbooks and review articles citing ~50% of LPL are associated with t(9;14)(p13;q32),[9,17] the initial retrospective analysis of t(9;14) identified only 8 cases with the translocation out of a series of 426 karyotypic abnormal non-Hodgkin lymphomas.[6] Of these eight cases, four cases were diagnosed as small lymphocytic lymphoma of the plasmacytoid type and an additional two cases had previous lymph node biopsies with similar morphology. This morphology is generally assumed to correspond to LPL using World Health Organization criteria, although other lymphoma types could be included in the category of small lymphocytic lymphoma, plasmacytoid. Hence, only 1.4% of karyotypic abnormal non-Hodgkin lymphomas in the original study had t(9;14) and LPL morphology. The other initial study showing that t(9;14)(p13;q32) involves the *PAX5* gene included three LPLs (all from a previous study)[6] and four diffuse large cell lymphomas with known t(9;14) or other translocations of 9p13.[7] In summary, the number of reported cases of LPL associated with t(9;14) and *PAX5* rearrangements is quite small.

*PAX5* rearrangements are not unique to LPL, and have been described in association with other types of non-Hodgkin lymphomas. The t(9;14)(p13;q32) has been reported in association with plasmacytoid small lymphocytic lymphoma (a broad category in the working formulation that corresponds to LPL, but also to marginal zone lymphoma and other lymphoma subtypes, using World Health Organization criteria), splenic marginal zone lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, $\alpha$-heavy chain disease, primary effusion lymphoma, and plasma cell leukemia, among others.[4–6,8,10–14] Given the frequency of low-grade B-cell lymphomas in this list and the morphological overlap of marginal zone lymphomas and LPL, we chose to broaden the search for *PAX5* rearrangements. We were unable to find *PAX5* translocations in either LPL or other low-grade B-cell lymphomas, including splenic marginal zone lymphomas, small lymphocytic lymphomas, nodal and extranodal marginal zone lymphomas, and $\alpha$-heavy chain disease.

In summary, although t(9;14) and *PAX5* translocations may occur in some cases of LPL, it is distinctly uncommon. In addition, from our review of the literature the association of t(9;14) and *PAX5* rearrangements with LPL is not unique to this subtype of lymphoma.

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