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Molecular cytogenetic delineation of a novel critical genomic region in chromosome bands 11q22.3–923.1 in lymphoproliferative disorders

(chromosome 11/tumor suppressor gene/B-cell chronic lymphocytic leukemia/non-Hodgkin lymphoma/fluorescence *in situ* hybridization)

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ABSTRACT **Aberrations of the long arm of chromosome 11 are among the most common chromosome abnormalities in lymphoproliferative disorders (LPD). Translocations involving *BCL1* at 11q13 are strongly associated with mantle cell lymphoma. Other nonrandom aberrations, especially deletions and, less frequently, translocations, involving bands 11q21-923 have been identified by chromosome banding analysis. To date, the critical genomic segment and candidate genes involved in these deletions have not been identified. In the present study, we have analyzed tumors from 43 patients with LPD (B-cell chronic lymphocytic leukemia, $n = 40$; mantle cell lymphoma, $n = 3$) showing aberrations of bands 11q21–923 by fluorescence *in situ* hybridization. As probes we used Alu-PCR products from 17 yeast artificial chromosome clones spanning chromosome bands 11q14.3–923.3, including a panel of yeast artificial chromosome clones recognizing a contiguous genomic DNA fragment of ≈9-10 Mb in bands 11q22.3–923.3. In the 41 tumors exhibiting deletions, we identified a commonly deleted segment in band 11q22.3–923.1; this region is ≈2-3 Mb in size and contains the genes coding for *ATM* (ataxia telangiectasia mutated), *RDX* (radixin), and *FDX1* (ferredoxin 1). Furthermore, two translocation breakpoints were localized to a 1.8-Mb genomic fragment contained within the commonly deleted segment. Thus, we have identified a single critical region of 2–3 Mb in size in which 11q14–923 aberrations in LPD cluster. This provides the basis for the identification of the gene(s) at 11q22.3–923.1 that are involved in the pathogenesis of LPD.**

Structural abnormalities of the long arm of chromosome 11 (11q) are recurring aberrations in various types of lymphoproliferative disorders (LPD; refs. 1 and 2). A number of genes have been identified which reside at the breakpoints of reciprocal translocations. The translocation t(11;14)(q13;q32), which is strongly associated with mantle cell lymphoma (MCL), results in the fusion of the *BCL1* locus to the *IgH* locus, which is thought to deregulate the *CCND1* gene (3–6). The *MLL* gene in chromosome band 11q23, rearranged in acute leukemias (7, 8), has been shown to be involved in rare cases of non-Hodgkin lymphoma (NHL; ref. 9). Other genes of pathogenetic significance in hematopoietic neoplasms mapping to 11q23 include *RCK*, *PLZF*, and *LPC*. *RCK* has been cloned from the t(11;14)(q23;q32) breakpoint of the RC-K8 lymphoma cell line and maps telomeric of *MLL* in band 11q23 (10). The *PLZF* gene was identified in a case of acute promyelocytic leukemia with the variant t(11;17)(q23;q21) and maps centromeric of *MLL* (11). Most recently, *LPC* (lymphoma proprotein convertase) has been cloned from the breakpoint of a t(11;14)(q23;q32) occurring in a case of primary mediastinal B-cell lymphoma (12). *LPC* is located proximal to the *MLL* gene.

Besides balanced translocations, deletions of 11q are recurring aberrations in LPD and were among the first chromosome abnormalities described in B-cell chronic lymphocytic leukemia (B-CLL). In a compilation from the *Catalog of Chromosome Aberrations in Cancer* (1), the most common structural aberrations resulting in loss of chromosomal material in LPD or NHL were deletions affecting 11q14–925 (13). The most frequently deleted band in this report was 11q23, which was therefore suspected to be the locus of a novel tumor suppressor gene. However, there is only scarce data on the molecular characterization of the genomic region affected by these deletions. In a study by Kobayashi *et al.* (14), 15 hematologic neoplasms (mostly acute myeloid leukemias and myelodysplastic syndromes, and three NHLs) and a NHL cell line with 11q deletions were analyzed using fluorescence *in situ* hybridization (FISH). In 14 of 16 tumors, a commonly deleted segment at 11q23.1 containing the neural cell adhesion molecule gene (*NCAM*) was found. The *BCL1* locus at 11q13 and the *MLL* gene at 11q23.3 were located outside the critical region. However, the resolution of the deletion map was limited, since the applied probes were scattered along a large genomic region.

In the current study, we have characterized deletions and translocations affecting chromosome bands 11q21–923 in 43 LPD tumors. For interphase FISH, 17 clones from a contig map of yeast artificial chromosome (YAC) clones encompassing bands 11q14.3–923.3 were selected as probes (ref. 15; M.R.J., unpublished data). Since overlapping YACs were applied, it was possible to systematically delineate the extent of the deletions at the molecular level. A single critical region of 2–3 Mb was identified in bands 11q22.3–923.1, where all deletions and translocations clustered.

MATERIALS AND METHODS

Tumor Samples. Tumors from 43 patients with LPD exhibiting deletions ($n = 41$) or translocations ($n = 2$; Table 1, tumor nos. 10 and 30) of chromosome bands 11q21–923 were studied. These aberrations were identified by G-banding ($n = 15$; tumor nos. 1–15 in Table 1) or interphase cytogenetic analysis ($n =$

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Abbreviations: LPD, lymphoproliferative disorder(s); MCL, mantle cell lymphoma; NHL, non-Hodgkin lymphoma; B-CLL, B-cell chronic lymphocytic leukemia; FISH, fluorescence *in situ* hybridization; YAC, yeast artificial chromosome.

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Table 1. Mapping of deletions and translocations involving chromosome bands 11q14–23 in tumors from 43 patients with LPD using FISH

Chromosome 11	Band 11q	YAC	*D11S*	Gene	Tumor Number 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43
	14.3	810e11	*1342*		di	di	di	del	di	di	del	del	del		del		di	di	del	del	del	del		di	di	del	di	del	del	di	di	di	di					di		di		del			di		
	21	963h7	*917*		del	del			del						del		del	del				del	di	del	di			del	del	del	del	di	di		di	di	di	del	di	di	di		di		del		
	22.1-22.3	966e4	*876*	*PGR*	del		di	del				del			di						del		del	del	del	del	di				del	di			di	di		del	del	del		del	di	del		
	22.3	950c12	*2000*	*GRIA4*	del	del	del		di		del				del	del				del		del	del	del			di	del	del	del	del		del		di	del	del	del	del	del		del	del	del	di	di
	22.3-23.1	890c12	*384*	*ACAT1*					del																		del								di	del	del								del	del
	22.3-23.1	801e11	*1778*	*ATM*	del			del	del	del	del	del		di		del		del			del	del	del			del	del	del	del	del		del	del		del					del		del	del	del	del	del
	22.3-23.1	975h6	*927*	*RDX*	del				del				del	di		del	del		del	del	del										del		di							del						
	22.3-23.1	755b11	*1893*	*FDX1*		del	del		del				del	3		del						del	del	del	del	del	del	del	del	del	del	del	del	3	del	del	del	del	del	del	del		del	del	del	del	del
q13	22.3-23.1	888h8	*424*	*CRYAB/PTS*							del		di																					di	di												
q14	23.1	913g9	*1987*	*PTS/NCAM*				del			del	del	di		del		del		del																di												
q21 q22	23.1	957e4	*1327*	*DRD2/PLZF*	del	del	del			del	del			di	del			del			del						del			del		del									del					
q23	23.1	943b7	*1793*	*PLZF*	del	del	del	del	del		del		del		del				del	del		del	del		del	del	del	del	del	del		del	del	del		di	del	del	del	del	del	del		del		del		
q24 q25	23.2-23.3	939b12	*908*		di	di	del	del	di		di				del				del	del		del		di	del					del	di		di			del	del	di	di	del		del		del	del	del
	23.3	785e12	*1340*	*APOC3*	di		di	di	di						del				del	del		del		di	3					del							del	del	di		del		del	del		del	di
	23.3	665e10	*2086*	*CD3D/MLL*	di	di	di	di	di		di	del			di		del	del	di	di					di	3			del		di		di		di	di	di		di	di	di	del					
	23.3	13HH4		*MLL*	di	di	di		di	del	di	del	del	di	di	del	del	del	di	di	del	del	di	del	di	3	del	del		del		del	di	di				di		di		del	del	del	del	di	di
	23.3	874d2	*1345*				di	di							di					di	del					3													di							

Chromosome 11 ideogram, band designation, and YAC clones used as probes with corresponding DNA-loci and genes are shown. del, Deletion (one fluorescence signal); di, disomy (two fluorescence signals); 3, three fluorescence signals (translocation in tumor nos. 10 and 30; partial trisomy in tumor no. 22).

28; tumor nos. 16–43 in Table 1). Based on morphology and immunophenotype, the tumors were classified as B-CLL (n = 40) and MCL (n = 3; tumor nos. 2, 3, and 23 in Table 1). The three cases of MCL were shown to carry the t(11;14)(q13;q32) by chromosome banding analysis (tumor nos. 2 and 3 in Table 1), or by interphase FISH (tumor no. 23 in Table 1). None of the B-CLL tumors exhibited the t(11;14) as detected by interphase FISH (data not shown). Mononuclear cells were obtained from blood, lymph node, or splenic tissue and either directly harvested or used for short term culture as described (16). After hypotonic treatment (0.075 M KCl for 16 min at 37°C), cells were fixed (methanol/acetic acid, 3:1) and dropped onto glass slides.

YAC Probe Set. A sequence-tagged-sites (STS) contig map of YAC clones from chromosome region 11q14-q23 was constructed by one of us (M.R.J., unpublished data; ref. 15). A panel of 17 YAC clones was selected for this study (Table 1; DNA marker and/or gene are given in parentheses, order from centromere to telomere): 810e11 (*D11S1342*); 963h7 (*D11S917*); 966e4 (*D11S876*; *PGR*); 950c12 (*D11S2000*; *GRIA4*); 890c12 (*D11S384*; *ACAT1*); 801e11 (*D11S1778*; *ATM*); 756a6 (*ATM*; not indicated in Table 1); 975h6 (*D11S927*; *RDX*); 755b11 (*D11S1893*; *FDX1*); 888h8 (*D11S424*; *CRYAB* and *PTS*); 913g9 (*D11S1987*; *PTS* and *NCAM*); 957e4 (*D11S1327*; *DRD2* and *PLZF*); 943b7 (*D11S1793*; *PLZF*); 939b12 (*D11S908*); 785e12 (*D11S1340*; *APOC3*); 665e10 (*D11S2086*; *CD3D* and *MLL*); and 874d2 (*D11S1345*) (15, 17, 18). All clones were derived from the Centre d'Étude du Polymorphisme Humain library (Généthon, Fondation Jean Dausset, Paris, France). Clones 950c12 through 785e12 recognize a contiguous genomic fragment in chromosome bands 11q22.1-q23.3 of 9–10 Mb size. A second YAC clone (13HH4) recognizing the *MLL* gene was generously provided by B. D. Young (St. Bartholomew's Hospital, London; ref. 19).

FISH. Alu-PCR derived DNA from the YAC clones was labeled and hybridized as probe by dual-color FISH as described (20–22). Interphase screening for 11q aberrations was performed with YAC 755b11 and a differently labeled YAC clone mapping to another chromosomal region as internal control. Signal numbers were enumerated in 200 nuclei for each fluorochrome. Images were captured using a cooled charged coupled device camera linked to an Apple Macintosh computer.

RESULTS

Based on G-banding analysis, 13 B-CLL (tumor nos. 1 and 4–15) and two MCL (tumor nos. 2 and 3) tumors with deletions of chromosome bands 11q21-q23 (n = 14) or, in one case (tumor no. 10), a balanced translocation t(X;11)(q13;q23) were initially selected for deletion/translocation mapping. Dual-color FISH was performed by hybridization of differently labeled YAC probes (Fig. 1*A*). In the 14 tumors with 11q deletions, we found a commonly deleted segment extending from YAC clones 890c12 to 943b7 (Table 1). The estimated size of this consensus deletion was 7–8 Mb. The breakpoint of the t(X;11)(q13;q23) was localized to the 1.8-Mb genomic segment recognized by YAC clone 755b11 (Fig. 1*B*), which was also contained in the critical segment of the deletion cases (tumor no. 10, Table 1).

We subsequently screened >200 LPD tumors, mainly B-CLL, by FISH using YAC clone 755b11 as diagnostic probe. We identified 27 tumors (tumor nos. 16–29 and 31–43) with an 11q deletion. By FISH mapping using clones 950c12 to 785e12, which recognize a contiguous genomic fragment in bands 11q22.1-q23.3, we further narrowed down the commonly deleted segment: tumor no. 31 exhibited a small interstitial deletion comprising only YAC clones 755b11, 975h6, and 801e11 (Table 1). The estimated size of this region is 2–3 Mb. Tumor no. 22 had both an interstitial deletion (single hybridization signal with YAC clones 810e11 to 939b12) and a partial trisomy 11 (three signals with YAC clones 785e12 to 874d2) in the same cell clone (Table 1).

One tumor showed a small third hybridization signal when YAC 755b11 was used for FISH (Table 1, tumor no. 30). In this case, YAC 801e11 and YAC 975h6 were combined as one probe and hybridized together with YAC 888h8 and YAC 913 g9 as the second probe. In 76% of nuclei, a single red-green doublet signal was present, whereas the second red and the second green signal were spatially unrelated (Fig. 1*C*). Cohybridization of YAC 755b11 and YAC 888h8 re-

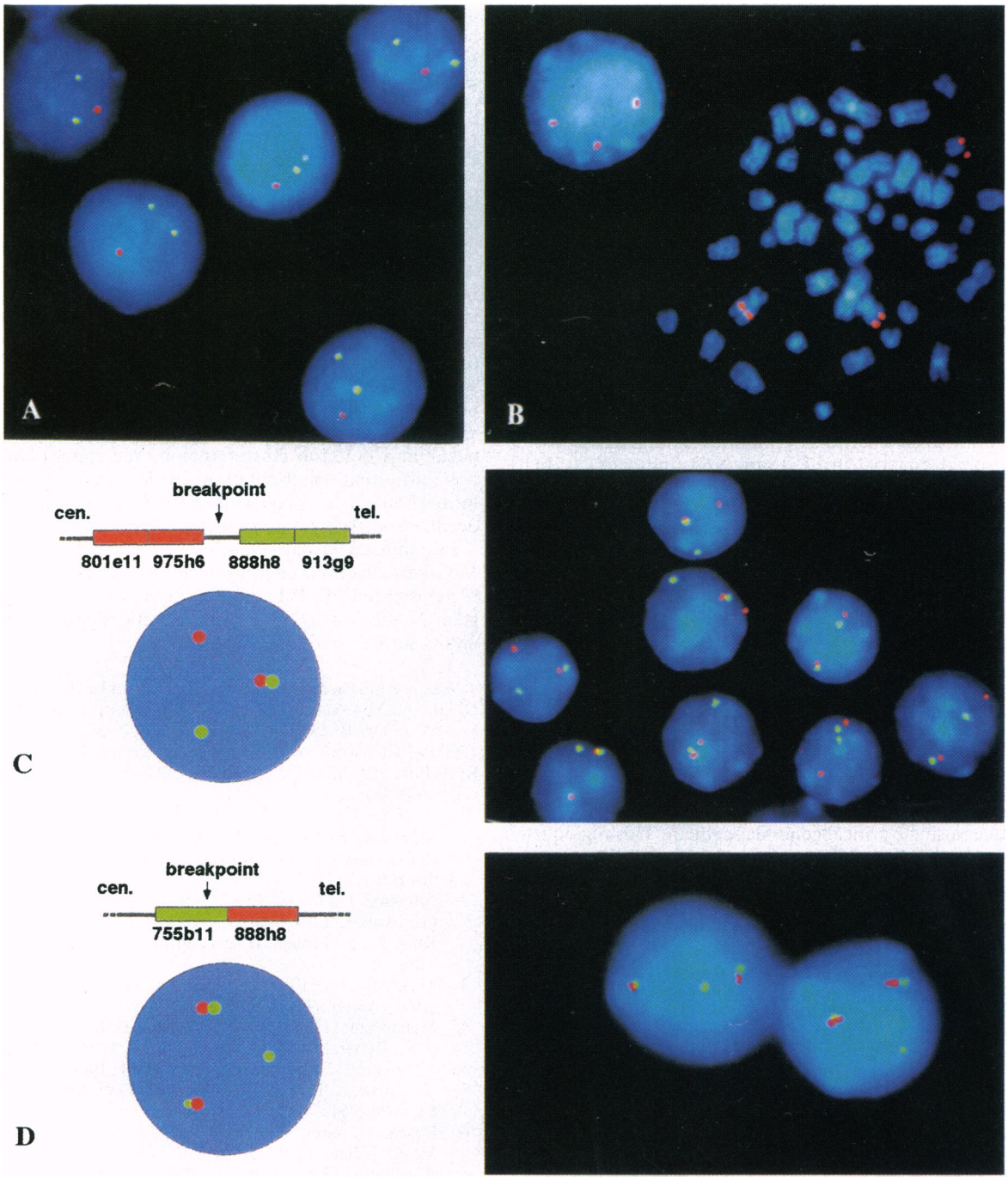

FIG. 1. Analysis of deletions and translocations involving chromosome bands 11q21–923 in lymphoproliferative disorders using FISH. (*A*) Tumor exhibiting a deletion of YAC 755b11 (single red signal in five nuclei); two signals of the control probe (green) are present in all nuclei, indicating a high hybridization efficiency. (*B*) Identification of a YAC clone spanning the breakpoint of the t(X;11)(q13;q23) in tumor no. 10: one of the 755b11 signals (red) is split on metaphase cell and interphase nucleus; the normal chromosome 11 is at 4 o'clock, the derivative der(11) is at 8 o'clock, and the der(X) is at 1 o'clock. (*C*) Scheme and FISH image illustrating hybridization of 801e11/975h6 (red) and 888h8/913g9 (green) to nuclei from tumor no. 30; separate red and green signals are seen in 7 of 8 nuclei, indicating a translocation in the genomic segment between the two YAC pools. The remaining nucleus shows juxtaposition of both red and green signals, as is expected in normal nuclei. (*D*) Scheme and FISH image of the translocation breakpoint in tumor no. 30 within YAC 755b11 (green). Note the colocalization of the smallest green signal with one of the two YAC 888h8 (red) signals, indicating that the breakpoint had occurred within the telomeric portion of YAC 755b11 (closer to 888h8). The other red-green doublet signal represents the normal chromosome 11.

sulted in three 755b11 signals with the small 755b11 signal colocalizing with one of the 888h8 signals (Fig. 1*D*). This signal pattern indicates that the translocation in this tumor had occurred in the distal part of the genomic fragment identified by 755b11.

In addition, we searched for 11q deletions/translocations not involving the region identified by clone 755b11. Therefore, we analyzed 49 B-CLL tumors, which exhibited two hybridization signals with 755b11 on initial screening using a panel of YAC clones proximally and distally flanking 755b11. This panel included the following YAC clones (DNA marker/gene): 810e11 (*D11S1342*); 966e4 (*PGR*); 756a6 (*ATM*); 975h6 (*RDX*); 913g9 (*PTS* and *NCAM*); 665e10 (*CD3D* and *MLL*); and 13HH4 (*MLL*). None of the 49 cases exhibited 11q aberrations using these clones as diagnostic FISH probes.

DISCUSSION

In LPD, deletions of distinct chromosomal regions have been identified that point to putative tumor suppressor genes being involved in the pathogenesis of these tumors (13). By molecular techniques, deletions involving band 13q14 have been identified as the most common genetic abnormalities in B-CLL, and a novel tumor suppressor locus of potential pathogenetic significance is suspected to reside in close vicinity to the *RB1* gene (23–26). Using restriction fragment length polymorphism (RFLP) analyses of tumors from 71 patients with NHL, Gaidano *et al.* (27) identified two commonly deleted regions on 6q, one at 6q21–923 and one at 6q25–927. Deletions or point mutations of the *TP53* tumor suppressor gene have been shown to be present in B-CLL in ≈15% of cases (28, 29). These mutations have been associated with resistance to therapy and short survival (29). In a recent compilation of the data from the *Catalog of Chromosome Aberrations in Cancer* (1), deletions of bands 11q21–925 were the most common structural abnormalities leading to the loss of chromosomal material in LPD and NHL tumors (13). In agreement with this report, we have found 11q deletions in ≈18% of patients with LPD in a series of >200 (H.D., unpublished results). Deletions were identified by FISH using YAC clone 755b11 mapping to 11q22.3–923.1.

The current study was aimed at the molecular characterization of the critical region of the 11q deletions observed in these tumors. In the 41 tumors exhibiting deletions, we have identified a commonly deleted region in chromosome bands 11q22.3–923.1 that is 2–3 Mb in size. In the two other tumors exhibiting translocations of band 11q23, the translocation breakpoints were located within the 1.8-Mb YAC clone 755b11, which was contained in the critical region of the deletion cases. Screening at other loci along chromosome bands 11q14–923 failed to detect aberrations outside this consensus region. Thus, our results indicate that 11q deletions in LPD affect a single critical genomic segment. This region is located proximal of the *MLL* gene and contains the genes encoding *ATM*, *RDX*, and *FDX1*. The *NCAM* gene, previously discussed as a candidate tumor suppressor in hematologic neoplasms with 11q deletions (14), was lost in many tumors but was not contained within the minimally deleted segment. Two other genes at 11q21–923, which have potential significance in the malignant transformation, are *MRE11* [meiotic recombination (*S. cerevisiae*) 11 homolog] and *IL1BC* (interleukin 1 beta convertase). *MRE11*, the recently cloned human homolog of a yeast gene involved in recombinational DNA repair, was located by FISH to chromosome band 11q21; thus, the gene most likely resides proximal of the consensus deletion (30). The *IL1BC* wild-type gene product leads to apoptosis in fibroblasts, a function that is lost in mutant forms of *IL1BC* (31, 32). *IL1BC* is located between the YAC clones 966e4 and 950c12 of our probe set and therefore outside the minimally deleted segment.

A candidate tumor suppressor gene mapping to the critical region at 11q22.1–923.1 is the recently cloned *ATM* gene, which, when mutated, is thought to be the gene predisposing to the autosomal recessive trait ataxia telangiectasia (18). Patients suffering from this disease have a markedly elevated risk to develop malignant tumors, especially of the lymphoid tissue (33). The function of the *ATM* gene product is not fully established; however, several nonmammalian genes that are involved in cell-cycle checkpoint control show homology to the *ATM* gene product (ref. 34 and references therein). Two other genes, *RDX* (radixin) and *FDX1* (ferredoxin 1; previous name *ADX*, adrenodoxin), are contained within the critical region. *RDX* encodes a cytoskeletal protein that interestingly shows homology to the *NF2* tumor suppressor gene product (35, 36). *NF2* gene mutations and deletions have been found in tumors that are not typically observed in individuals affected by neurofibromatosis-2 but have so far not been reported in hematologic malignancies (37, 38). YAC clone 755b11, which is split by the two translocations and deleted in all other tumors studied, contains *FDX1*, a gene that codes for an iron-sulfur protein involved in mitochondrial electron transport (39, 40). To our knowledge, *FDX1* has so far not been linked to the pathogenesis of malignant disease.

The two translocation breakpoints within the 1.8-Mb genomic segment contained in the critical region may point to a novel gene of pathogenetic significance in LPD. Translocations commonly lead to the activation of protooncogenes or to chimeric fusion genes of oncogenic potential (41). However, translocations involving chromosome band 13q14 in B-CLL have been demonstrated to be accompanied by submicroscopic deletions and have led to the identification of a genomic segment likely containing a novel tumor suppressor locus (23, 24). Likewise, the translocation breakpoints at 11q22.3–923.1 found in the current study may disrupt a tumor suppressor gene, particularly since they occur in a deletion cluster region. We cannot exclude the possibility that small deletions, which are beyond the resolution limit of the probes used for FISH in our study, have occurred at the two chromosome breakpoints.

In summary, we have identified a single critical region of 2–3 Mb where deletions and translocations affecting bands 11q21–923 cluster in LPD. Whether one of the known genes or a novel gene in this region is of pathogenetic significance in LPD awaits further study.

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