Haematologica 2000; 85:908-912
original paper

Hematology & Medicine

Deletions at 11q23 in different lymphoma subtypes

YING ZHU,* OUTI MONNI,* KAARLE FRANSSILA,° ERKKI ELONEN,# JUHANI VILPO,^ HEIKKI JOENSUU,@ SAKARI KNUUTILA*

**Department of Medical Genetics, Haartman Institute and Helsinki University Central Hospital, University of Helsinki, Helsinki; Departments of °Pathology, #Internal Medicine, and @Oncology, Helsinki University Central Hospital, Helsinki; ^Department of Clinical Chemistry, Tampere University Hospital and University of Tampere Medical School, Tampere, Finland*

ABSTRACT

Background and Objectives. **Chromosome band 11q23 is frequently deleted in various types of neoplasm. The region represented by yeast artificial chromosome (YAC) clone 755b11 at 11q23 has been shown to be the minimal common region of deletion in mantle cell lymphoma (MCL) and B-cell chronic lymphocytic leukemia (B-CLL). The aim of the study was to determine the frequencies of 11q23 deletion in different lymphoma subtypes.**

Design and Methods. **We performed fluorescence *in situ* hybridization (FISH) analysis with YAC755b11 on either peripheral blood or lymph node biopsy (LN) specimens of patients diagnosed as having MCL (47), CLL/small lymphocytic lymphoma (SLL) (62), diffuse large cell lymphoma (DLCL) (17), follicular lymphoma (FL) (9), and Hodgkin's disease (HD) (11). Fifteen cases of reactive or normal lymph node biopsies were studied as controls.**

Results. **Forty of the 161 (25%) samples exhibited deletions in the region represented by YAC755b11. The 11q23 deletion was found only in MCL (23, 49%), CLL/SLL (13, 21%) and DLCL (4, 24%). Three cases were classified as Richter's syndrome and they all exhibited the deletion at 11q23. The deletion frequencies in the blood specimens of typical CLL (30%) and lymph node specimens of CLL/SLL (13%) were remarkably different.**

Interpretation and Conclusions. **Our study demonstrated that the 11q23 deletion is not common in lymphomas other than MCL, CLL and DLCL. It also showed the possible correlation of the 11q23 deletion with the transformation of localized lymphoma to CLL, and with the development of Richter's syndrome.**

Key words: 11q23, deletion, MCL, CLL/SLL, DLCL

Correspondence: Sakari Knuutila, Ph. D., Department of Medical Genetics, Helsinki University Central Hospital, P.O. Box 400, (Haartmaninkatu 3, 4th floor) FIN-00029 HUS, Helsinki, Finland. Phone: international +358-9-19126527 – Fax: international +358-9-19126788 – E-mail: sakari.knuutila@helsinki.fi

Cytogenetic and loss of heterozygosity (LOH) analyses have shown that chromosome band 11q23 is frequently deleted in numerous types of neoplasm, such as breast,[1] ovarian[2] and colorectal carcinomas,[3] malignant melanomas,[4] and in lymphoproliferative disorders.[5] This region has been suggested to harbor novel tumor suppressor gene/genes. Recent results by comparative genomic hybridization (CGH) and fluorescence *in situ* hybridization (FISH) on mantle cell lymphoma (MCL)[6,7] and B-cell chronic lymphocytic leukemia (B-CLL)[8,9] revealed that the deletion at chromosome band 11q23 was frequent in these two diseases (49% in MCL, 30% in B-CLL). Stilgenbauer *et al.* narrowed the minimal common region of deletion in B-CLL and MCL down to a 2-3 Mb region, including the region represented by yeast artificial chromosome (YAC) clone 755b11. Among the 43 cases studied, two had translocation breakpoints within the region represented by YAC755b11[5] Monni *et al.* identified the minimal common region of deletion in MCL to be the region represented by YAC755b11.[7] The probe YAC755b11 was also used to identify a new subset of B-CLL characterized by extensive nodal involvement and inferior prognosis.[10] We, therefore, chose YAC755b11 as a probe and performed FISH analysis on 161 cases of lymphoproliferative disorders in order to study the frequencies of the occurrence of 11q23 deletion in other types of lymphoma and to explore the usefulness of the 11q23 deletion as a clinical marker.

Design and Methods

Patients

FISH analysis was performed on 161 cases (Table 1), comprising 47 cases of MCLs, 62 CLL/SLLs (small lymphocytic lymphoma), 17 DLCLs (diffuse large cell lymphoma), 9 FLs (follicular lymphoma), 11 HDs (Hodgkin's disease), and 15 reactive or normal lymph nodes. All cases in the study were collected from cases that were sent to the chromosome and molecular cytogenetic laboratory of Helsinki University Central Hospital for routine analysis. Consecutive cases were collected for each histologic subtype. For MCL and CLL/SLL, the periods of case gathering were longer than those for the other subtypes. Forty-one of the cases of MCLs and 30 of the CLL/SLL have been studied before.[7,9]

All lymphomas were classified according to the

Revised European-American Classification of Lymphoid Neoplasms (REAL).[11] In addition to morphology, immunohistologic analysis was performed on each case. MCL tumor cells were positive for CD20, CD5, CyclD1, and negative for CD23. CLL/SLL tumor cells were positive for CD20, CD5, and CD23. DLCL tumor cells were positive for CD20. FL tumor cells were positive for CD20 and about 80% of the cases were positive for Bcl-2. Cases of Hodgkin's disease without lymphocytic predominance were $CD30^+$ and $CD15^{+/-}$ for large cells, and $CD3^+$ for the majority of small cells. Lymphocyte predominant HD were $CD20^+$, $CD3^-$, $CD15^-$, and $CD30^-$ for large cells, $CD20^+$ for most of the small cells in nodules, and $CD3^+$ for the cells surrounding large cells.

Preparation for FISH analysis

Forty-one MCL and 29 CLL/SLL samples were embedded in paraffin, whereas all the others were either blood or fresh tissue samples.

The nuclei from paraffin-embedded tissues were extracted as described elsewhere with slight modifications.[12,13] Briefly, four 30 µm sections were deparaffinized with xylene at 55°C (three times for 30 min, once for 25 min) and at 67˚C for 20 min, which was followed by treatment in 100%, 95%, 70%, and 50% ethanol series and in water (twice) at room temperature for 10 min each. After deparaffinization the sections were digested in 1 mL of Carlsberg's solution (0.1% Sigma protease XXIV, 0.1 M Tris, 0.07 M NaCl, pH 7.2) for 1 h at 37˚C and vortexed vigorously for 20 min. The nuclear suspension was filtered through nylon net (pore size 55 µm) and the nuclei yield was checked microscopically.

Cells were separated from fresh tissue samples and cultured overnight in RPMI media [80%RPMI 1640, 20% fetal calf serum, 0.29 mg/mL L-glutamine, 100 mg/mL streptomycin, 100 U/mL penicillin, 0.1 µg/mL colcemid (all from Gibco, Grand Island, NY, USA)]. Peripheral blood of leukemia patients was collected and mononuclear cells were isolated and cultured with optimal mitogen stimuli as described previously.[14] After harvesting, cells were hypotonically treated (0.075 M KCl, 15 min, 37°C) and fixed with methanol-acetic acid (3:1).

Fluorescence in situ hybridization

DNA probes. YAC clones 755b11 and 953a4 were purchased from CEPH-Généthon (Paris, France). Both YACs were tested by polymerase chain reaction (PCR) with their corresponding markers. Their correct chromosomal locations were confirmed by FISH analysis on normal lymphocyte metaphase preparations. The yeast was grown in AHC media for 4-6 days and DNA was extracted from the yeast using a glass bead-phenol procedure.[15]

Fluorescence in situ hybridization (FISH). The probe was labeled with biotin-14-dATP (Gibco BRL, Paisley, UK) by nick translation and single-color FISH was performed. We consider this to be sufficient because either a control probe was used or G-banding, FISH, and/or CGH analysis were performed. The hybridization mixture contained approximately 1 µg labeled DNA, 25 µg human Cot-1 DNA (Gibco BRL), and 25 µg herring sperm DNA (Sigma Chemical Co., Bornem, Belgium) dissolved in 50% formamide and 10% dextran sulfate in 2×SSC. The hybridization mixture was denatured at 75˚C for 5 min. To remove excess cytoplasm, the sample slides were pre-treated with pepsin (0.01 mg/mL in 0.01 M HCl; Sigma, St. Louis, MO, USA) at 37°C for 7 min and dehydrated in 70%, 85%, and 100% ethanol for 5 min each. The slides were denatured in 70% formamide/2×SSC (pH 7) at 65°C for 2 min, followed by dehydration in 70%, 85%, and 100% ethanol for 2 min each. The paraffin-embedded samples were treated in 1 M sodium thiocyanate at 70°C for 15 min, followed by treatment with pepsin (5 mg/mL in 0.05 M HCl) at 37°C for 20 min and dehydrated in 70%, 85%, and 100% ethanol for 5 min each. The slides were denatured in 70% formamide/2×SSC (pH 7) at 75°C for 5 min, followed by dehydration in 70%, 85%, and 100% ethanol for 2 min each. After applying the denatured hybridization mixture onto the slides, the slides were incubated at 37°C for 2 days.

Detection and analysis. Probes labeled with biotin were visualized by fluorescein-isothiocyanate (FITC; Sigma). Only slides with high hybridization efficiency, indicated by clear and strong signals in more than 90% of the nuclei, were analyzed. From each preparation a minimum of 200 morphologically intact and non-overlapping nuclei and metaphase spreads were scored. Images were captured using an Olympus fluorescence microscope (Tokyo, Japan) connected to a cooled charge coupled device (CCD) camera and the ISIS digital image analysis system (MetaSystems GmbH, Altlussheim, Germany).

Controls. The cut-off level was defined by the mean value plus three times the standard deviation (SD) of the frequency of control cells exhibiting only one signal (mean 7.8%; SD 3.3%; cut-off level 17.7%). In addition, paraffin-embedded tissues were tested by a chromosome copy number control probe YAC953a4 mapped to 11p13. Fresh preparations were karyotyped and abnormalities of chromosome 11 were taken into consideration in the interpretation of the results.

Table 1. FISH results and clinical data from patients with lymphoproliferative disorders and the controls.

	No. of cases	*Age (average)*	*F/M*	*No. of 11q23 deletion cases (%)*
MCL	47	45-90 (65)	19/28	23 (49%)
CLL/SLL - Blood	30	48-79 (64)	8/22	9 (30%)
CLL/SLL - Lymph node	32	38-84 (63)	9/23	4 (13%)
DLCL	17	40-83 (65)	9/8	4 (24%)
FL	9	41-75 (59)	6/3	0 (0%)
HD	11	10-76 (37)	7/4	0 (0%)
Reactive or normal lymph node	15	12-54 (29)	6/9	0 (0%)

F/M: no. of females/males; MCL: mantle cell lymphoma; CLL: chronic lymphocytic leukemia; SLL: small lymphocytic lymphoma; DLCL: diffuse large cell lymphoma; FL: follicular lymphoma; HD: Hodgkin's disease.

Results

Out of the 161 samples studied, 40 (25%) had deletions in the region represented by YAC755b11. Twenty-three out of the 47 MCL cases (49%) had deletions. There was no difference in frequencies among blastoid variant cases and cases with normal morphology. Out of the 62 CLL/SLL cases studied, 13 (21%)

had deletions. One of the patients with the deletion later developed DLCL. This patient is considered to have Richter's syndrome. Four out of the 17 (24%) DLCL were found to have deletions. The disease history of these patients showed that two of them had previously been diagnosed as having CLL. They are also Richter's syndrome patients. None of the 9 FLs, 11 HDs or the 15 reactive or normal lymph node specimens had the deletion. The percentage of cells showing deletions ranged from 22% to 95% (mean, 72%). The FISH results are summarized in Table 1.

Table 2 summarizes the chromosome imbalances detected by G-banding, FISH, and/or CGH analysis of the patients with the 11q23 deletion.

There was no difference in the deletion frequencies between males and females (MCL, p=0.86; CLL/SLL, p=0.74; DLCL, p=1.00, chi-square test or Fisher's exact test). Similarly, there was no difference in age at diagnosis between those with the deletion and those without the deletion in any of the histologic types of lymphoma (MCL, p=0.89; CLL/SLL, p=0.17; DLCL, p=0.82, the Mann-Whitney test).

The deletion was clearly more common in MCL than in the other types of lymphoma (MCL vs. CLL/SLL: p=0.0021, chi-square test; MCL vs. DLCL: p=0.069, chi-square test). The deletion was as common in CLL/SLL as in DLCL (p=1.00, Fisher's exact test).

Discussion

Our study shows that the 11q23 deletion is frequently present in MCL (49% of cases), less so in CLL/SLL (21%) and in DLCL (24%), and absent in FL and HD. However, for HD, we ought to consider that the analysis was not conducted exclusively on Reed-Sternberg cells that are considered to be the malignant cell population.[16] Previous studies on MCL and CLL have shown similar results, with deletion frequencies of 46% in MCL[17] and 20% in CLL.[10] The frequencies of 11q23 deletion are now reported for the first time for DLCL, FL and HD.

Patients with CLL can sometimes develop DLCL and they are then said to have Richter's syndrome. Our study included three Richter's syndrome cases. One was diagnosed as having CLL at the time of this study and clinical follow-up showed that this patient later developed DLCL. The other two were diagnosed as DLCL at the time of study and their records showed them to have been previous CLL patients. Interestingly, all of them had the deletion. Although the material is small, the current results suggest that the deletion is associated with the transformation of CLL into DLCL. CLL patients whose tumor cells have deletions in this region could be more prone to develop Richter's syndrome. Genes that cause the transformation might reside in this particular region.

CLL and SLL are considered one disease entity because the tumor cells are morphologically and immunohistochemically similar. In the present study, we analyzed 30 blood specimens of typical CLL and 32 lymph node specimens of CLL/SLL. The difference in the frequencies of the deletion was clear between blood and lymph node specimens. Nine out of 30 (30%) blood specimens of the typical CLL cases had 11q23 deletions, whereas only 4 lymph node specimens out of 32 (13%) CLL/SLL cases had the deletion. The differences in the deletion frequencies between blood and lymph node specimens in CLL/SLL suggest that the deletion is related to the transformation of local lymphoma into a general hematologic disease, such as CLL. Our hypothesis finds support also in a recent study, which demonstrated a differential expression pattern of functionally relevant adhesion molecules and cell signaling receptors on CLL cells with or without 11q22.3-q23.1 deletion.[18] Sembries *et al*. suggested that the 11q deletion may have impaired several cellular pathways in CLL cells, changing the migratory properties of these cells within lymphoid organs and in peripheral blood. Unfortunately, our limited archival material did not allow us to carry out a more detailed study on paired specimens of cases of CLL and Richter's syndrome, or on paired blood and lymph node specimens from patients with CLL/SLL.

The 11q deletion was detected in almost half of the MCL cases, which makes the 11q23 deletion a candidate diagnostic marker for MCL and suggests that the deletion is associated with the pathogenesis of MCL. However, a previous study[7] showed that there may not be any association between the presence of the deletion and clinical parameters, such as blastoid transformation, survival, International Prognostic Index score, and Ann Arbor stage. We did not perform any clinical correlation analysis in the present study because of difficulties in obtaining clinical data and the fact that our material is, after all, too limited to allow a proper statistical analysis. In the future, the newly developed tissue microarray technique[19] will be able to be applied to a large number of tumor samples and further insights will be gained on the clinical implication of the 11q23 deletion.

Several genes located at 11q23 have been found to be involved in tumorigenesis. The *ATM* gene has been shown to have a pathogenic role in MCL[17] and CLL.[20] The *ATM* gene is about 1.8 Mb proximal to the region represented by YAC755b11. Therefore we presume that other genes may also be involved. The *PPP2R1B* gene, which has been shown to be mutated in some colon and lung carcinomas,[21] is located very close to the region represented by YAC755b11. So far, its possible involvement in lymphomas has not been reported. The gene encoding the protein radixin, *RDX*, is also located in this area. Radixin belongs to the ERM (ezrin/radixin/moesin) protein family. Radixin and the rest of the ERM family members act as links between the plasma membrane and actin cytoskeleton. These proteins are involved in a variety of cell functions, such as cell adhesion, migration, and the organization of cell structure, and are highly homologous, both in protein sequence and functional activity, with merlin/schwannomin, a neurofibromatosis-2-associated tumor-suppressor protein.[22,23] However, a recent report showed that radixin is not expressed in human blood lymphocytes, monocytes, or neutrophils.[24]

In conclusion, we screened 161 specimens by FISH analysis with YAC755b11 as a probe. The region represented by YAC755b11 is the most frequently deleted in MCL. The deletion also occurs in CLL/SLL and DLCL, but not in FL or HD. All three Richter's syndrome cases had the deletion. The deletion frequen-

Table 2. Chromosome imbalance detected by G-banding, FISH, and/or comparative genomic hybridization (CGH) analysis of the patients with 11q23 deletion evaluated by FISH analysis with YAC755b11 as the probe.*

Patient No.	sex/age	FAB	Chromosome imbalance by G-banding, FISH, and/or CGH analysis
1	M/54	CLL/SLL(B)	46,XY,del(11)(q14q24)[1]/46,idem, del(13)(q?14q?32)[1]/46,idem, t(3;10)(p13-21;q25-26), del(13)(q?14q?32)[6]/46,XY[6]
2	M/64	CLL/SLL(B)	46,XY,del(7)(q32q36), del(11)(q21q23)[6]/46,idem, del(6)(q?21q?24)[4]/46,XY[7]
3	M/72	CLL/SLL(B)	47,XY,+12[2]/46,XY[25]
4	F/69	CLL/SLL(B)	46,XX,del(11)(q13q23), del(13)(q12q21)[7]/46,XX[9]
5	M/68	CLL/SLL(B)	46,XY,+8,del(6)(q?23), del(11)(q?14), del(13)(q?14q?22), -20[cp9]/46,XY[5]
6	M/71	CLL/SLL(B)	46,XY,del(11)(q?22q?24)[2]/46, XY[18]
7	M/62	CLL/SLL(B)	46,XY,del(11)(q?13), del(13)(q?14)[2]/46, XY[15]
8	M/67	CLL/SLL(B)	46,XY[20]
9	F/77	CLL/SLL(B)	46,XX[2]
10	F/71	CLL/SLL(L)	46, XX, +?2, -4, +2mar, inc rev ish enh(5q)
11	F/71	CLL/SLL(L)	46, XX
12	M/50	CLL/SLL(L)	46, XY rev ish dim (11q21q23, 13q14q22)
13	F/83	DLCL	45, XX, add(1)(p?32), -4, +7, -11, -18, +1 mar, inc [7]/45, XX, -1, -2, +7, add(9)(p?), -11, -17, -18, +2mar, inc [5]/45, XX, -1, -9, -11, -18, +r(?), +2 mar, inc [3]/46, XX
14	M/40	DLCL/Richter's	46, XY, -8, -9, -9, -11, -11, -14, +21, +5 mar, inc rev ish enh(8q22qter), dim(11q22)
15	M/67	DLCL/Richter's	46-48, XY, del(6)(q?), del(11)(q?), -18, +1-2 mar, inc [cp10]
16	F/74	DLCL	46-49, XX, t(1;?)(p?;?), +8, t(10;?)(p?11;?), +15, 2-4 mar, inc [cp15]/92-96, idem× 2 [cp5] rev ish enh(8,15), amp(8q22qter, 10p), dim(1p11p32)
17	M/53	MCL	arev ish normal
18	F/73	MCL	46, XX rev ish normal
19	M/55	MCL	45, XY, t(3;?)(q2;?), del(6)(q?21), t(11;?)(q?;?), -12, -13,-14, der(13q14q), -18, +3-5 mar, inc [cp13]/46, XY [3] rev ish enh(3q21qter), dim(17p12pter)
20	F/68	MCL	46-47, XY, t(11;14)(q13;q32), 4-5 mar, inc/92-94 idemx2 rev ish enh(7pterq32, 15q15qter), dim(11q14q23, 15q11q15)
21	F/53	MCL	ish t(3)(wcp3+) rev ish enh(3q23qter), dim(17p)
22	M/71	MCL	47, XY, +Y, ?del(6)(q?), mar, inc ish t(3)(wcp3+) rev ish enh(Y, 3q13, 15q22q24), dim(6q14qter, 11q22)
23	F/63	MCL	40-45, 2-3 mar, inc [10]
24	M/45	MCL	ish t(11;14)(wcp11+) rev ish dim(1p13p22, 9pterq22, 11q22, 13q21qter)
25	M/63	MCL	46, XY rev ish dim(1p22p31, 6q15qter, 9pterq22, 11q22q23)
26	F/75	MCL	rev ish dim(1p22, 9,13)
27	F/80	MCL	46, XX, t(11;14)(q13;q32), 2-3 mar, inc rev ish dim(13q21q22)
28	M/60	MCL	rev ish dim(6q21-qter, 11q22)
29	M/63	MCL	46, XY, del(1)(p?), t(11;14)(q13;q32), del(6)(q?), del(13)(q?), inc rev ish dim(1p21p22, 6q21q22, 13q21q32)
30	M/63	MCL	46, XY, t(11;14)(q13;q32), inc ish t(11;14)(q13;q32)(wcp11+) rev ish enh(7p), dim(11q22)
31	M/65	CLL/SLL(L)	Not studied.
32	M/87	MCL	Not studied
33	F/86	MCL	Not studied
34	M/78	MCL	Not studied
35	M/60	MCL	Not studied
36	F/74	MCL	Not studied
37	M/69	MCL	Not studied
38	F/63	MCL	Not studied
39	F/61	MCL	Not studied
40	M/62	MCL	Not studied

**Cytogenetic changes are described according to the International System for Human Cytogenetic Nomenclature (ISCN). CLL/SLL(B): blood specimen from a patient with chronic lymphocytic leukemia / small lymphocytic lymphoma; CLL/SLL(L): lymph node specimen from a patient with chronic lymphocytic leukemia / small lymphocytic lymphoma; DLCL: diffuse large cell lymphoma; Richter's: Richter's syndrome; MCL mantle cell lymphoma; M: male; F: female.*

cies in the blood specimens of typical CLL and lymph node specimens of CLL/SLL were remarkably different. These findings provide functional clues towards the search for novel cancer-related genes in this area and may have diagnostic and prognostic value.

Contributions and Acknowledgments

YZ, HJ and SK were the principal investigators and designed the study. YZ wrote the paper, OM analyzed part of the samples, KF diagnosed all the cases, EE and JV collected clinical data, and HJ managed the statistical data. All the authors

revised the manuscript and contributed to its intellectual content. The order of the names was a joint decision of all authors.

The criteria for the order of names were involvement in laboratory research, clinical data management, and writing and reviewing the manuscript. The order of the names was decided on the basis of each individual contribution to the above criteria.

Funding

This work was supported by the Sigrid Jusélius Foundation, the Finnish Cancer Society, the Foundation for the Finnish Cancer Institute, and Helsinki University Central Hospital Research Funds, in Finland.

Disclosures

Conflict on interest: none.

Redundant publications: no substantial overlapping with previous publications.

Manuscript processing

Manuscript received May 15, 2000; accepted August 23, 2000.

Potential implications for clinical practice

- The high frequency of 11q23 deletion in MCL suggests that 11q23 deletion can be used as a diagnostic marker for MCL. Its prognostic use in MCL should be studied further.
- The possible correlation of the 11q23 deletion with the transformation of localized lymphoma to CLL and with the development of Richter's syndrome may also be useful in the prognosis of these diseases.

References

1. Hampton GM, Mannermaa A, Winquist R, et al. Loss of heterozygosity in sporadic human breast carcinoma: a common region between 11q22 and 11q23.3. Cancer Res 1994; 54:4586-9.
2. Foulkes WD, Campbell IG, Stamp GWH, Trowsdale J. Loss of heterozygosity and amplification on chromosome 11q in human ovarian cancer. Br J Cancer 1993; 67:268-73.
3. Keldysh PL, Dragani TA, Fleischman EW, et al. 11q deletions in human colorectal carcinomas: cytogenetics and restriction fragment length polymorphism analysis. Genes Chromosome Canc 1993; 6:45-50.
4. Tomlinson IPM, Gammack AJ, Stickland JE, et al. Loss of heterozygosity in malignant melanoma at loci on chromosome 11 and 17 implicated in pathogenesis of other cancers. Gene Chromosome Canc 1993; 7:169-72.
5. Stilgenbauer S, Liebisch P, James MR, et al. Molecular cytogenetic delineation of a novel critical genomic region in chromosome bands 11q22.3-q23.1 in lymphoproliferative disorders. Proc Natl Acad Sci USA 1996; 93:11837-41.
6. Monni O, Oinonen R, Elonen E, et al. Gain of 3q and deletion of 11q are frequent aberrations in mantle cell lymphoma. Gene Chromosome Canc 1998; 21:298-307.
7. Monni O, Zhu Y, Franssila K, et al. Molecular characterization of the deletion at 11q22.1-q23.3 in mantle cell lymphoma. Br J Haematol 1999; 104:665-71.
8. Karhu R, Knuutila S, Kallioniemi OP, et al. Frequent loss of the 11q14-q24 region in chronic lymphocytic leukemia: a study by comparative genomic hybridization. Gene Chromosome Canc 1997; 19:286-90.
9. Zhu Y, Monni O, El-Rifai W, et al. Discontinuous deletions at chromosome band 11q23 in B-cell chronic lymphocytic leukemia. Leukemia 1999; 13:708-12.
10. Döhner H, Stilgenbauer S, James MR, et al. 11q deletions identify a new subset of B-cell chronic lymphocytic leukemia characterized by extensive nodal involvement and inferior prognosis. Blood 1997; 89: 2516-22.
11. Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study group. Blood 1994; 84:1361-92.
12. Heiden T, Wang N, Bernhard T. An improved Hedley method for preparation of paraffin-embedded tissues for flow-cytometric analysis of ploidy and S-phase. Cytometry 1991; 12:614-21.
13. Hyytinen E, Visakorpi T, Kallioniemi A, Kallioniemi OP, Isola JJ. Improved technique for analysis of formalin-fixed, paraffin-embedded tumors by fluorescence in situ hybridization. Cytometry 1994; 16:93-9.
14. Larramendy ML, Siitonen SM, Zhu Y, et al. Optimized mitogen stimulation induces proliferation of neoplastic B-cells in chronic lymphocytic leukemia - significance for cytogenetic analysis. Cytogenet Cell Genet 1998; 82:215-21.
15. Hoffman C, Winston FA. Ten minute DNA preparation from yeast efficiently releases autonomous plasmids for transformation of Escherichia coli. Gene 1987; 57:267-72.
16. Teerenhovi L, Lindholm C, Pakkala A, Franssila K, Stein H, Knuutila S. Unique display of a pathologic karyotype in Hodgkin's disease by Reed-Sternberg cells. Cancer Genet Cytogen 1988; 34:305-11.
17. Stilgenbauer S, Winkler D, Ott G, et al. Molecular characterization of 11q deletions points to a pathogenic role of the ATM gene in mantle cell lymphoma. Blood 1999; 94:3262-4.
18. Sembries S, Pahl H, Stilgenbauer S, Döhner H, Schriever F. Reduced expression of adhesion molecules and cell signaling receptors by chronic lymphocytic leukemia cells with 11q-deletion. Blood 1999; 93:624-31.
19. Kononen J, Bubendorf L, Kallioniemi A, et al. Tissue microarrays for high-throughput molecular profiling of tumor specimens. Nat Med 1998; 4:844-7.
20. Schaffner C, Stilgenbauer S, Rappold GA, Döhner H, Lichter P. Somatic ATM mutations indicate a pathogenic role of ATM in B-cell chronic lymphocytic leukemia. Blood 1999; 94:748-53.
21. Wang S, Esplin E, Li J, et al. Alterations of the PPP2R1B gene in human lung and colon cancer. Science 1998; 282:284-7.
22. Trofatter JA, MacCollin MM, Rutter JL, et al. A novel moesin-, ezrin-, radixin-like gene is a candidate for the neurofibromatosis 2 tumor suppressor. Cell 1993; 72: 791-800.
23. Wilgenbus KK, Milatovich A, Francke U, Furthmayr H. Molecular cloning, cDNA sequence, and chromosomal assignment of the human radixin gene and two dispersed pseudogenes. Genomics 1993; 16:199-206.
24. Shcherbina A, Bretscher A, Kenney DM, Remold-O'Donnell E. Moesin, the major ERM protein of lymphocytes and platelets, differs from ezrin in its insensitivity to calpain. FEBS Lett 1999; 443:31-6.