Integrative Genomics Analyses Reveal Molecularly Distinct Subgroups of B-Cell Chronic Lymphocytic Leukemia Patients with 13q14 Deletion

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Abstract

**Purpose:** Chromosome 13q14 deletion occurs in a substantial number of chronic lymphocytic leukemia (CLL) patients and it is believed to play a pathogenetic role. The exact mechanisms involved in this lesion have not yet been fully elucidated because of its heterogeneity and the imprecise knowledge of the implicated genes. This study was addressed to further contribute to the molecular definition of this lesion in CLL.

**Experimental Design:** We applied single-nucleotide polymorphism (SNP)-array technology and gene expression profiling data to investigate the 13q14 deletion occurring in a panel of 100 untreated, early-stage (Binet A) patients representative of the major genetics, molecular, and biological features of the disease.

**Results:** Concordantly with FISH analysis, SNP arrays identified 44 patients with del(13)(q14) including 11 cases with a biallelic deletion. The shorter monoallelic deletion was 635-kb long. The loss of the miR-15a/16-1 cluster occurred in all del(13)(q14) cases except in 2 patients with a monoallelic deletion, who retained both copies. MiR-15a/16 expression was significantly downregulated only in patients with the biallelic loss of the miRNA cluster compared to 13q normal cases. Finally, the natural grouping of SNP profiles by nonnegative matrix factorization algorithm showed that patients could be classified into 2 separate clusters, mainly characterized by short/biallelic versus wide/monoallelic 13q14 deletions. Supervised analyses of expression data showed that specific transcriptional profiles are correlated with these 2 genomic subgroups.

**Conclusions:** Overall, our data highlight the presence of 2 distinct molecular types of 13q14 deletions, which may be of clinical relevance in CLL. *Clin Cancer Res; 16(23); 5641–53. ©2010 AACR.*

B-cell chronic lymphocytic leukemia (CLL) is a lymphoproliferative disorder characterized by a variable clinical course: some patients progress rapidly toward more advanced stages whereas others survive for a long time without disease progression (1). Recently, considerable efforts have been addressed to the identification of genomic aberrations that could explain the pathogenetic mechanisms and the clinical heterogeneity of the disease (2–5). Deletions of 13q14, 11q22.3, and 17p13, and trisomy 12 are common in CLL and may play a role in pathogenesis and disease progression (4). 13q14 deletion occurs in approximately 50% of CLL and is associated with a favorable prognosis when present as the sole abnormality (6). Notably, 2 microRNA genes, miR-15a and miR-16-1, located at 13q14, have been reported to be downregulated in del(13)(q14) patients (7) and strongly suggest their potential role in the disease. However, the 13q14 deletion is not always accompanied by defects in miR-15a/16-1 expression, suggesting a more complex heterogeneity of the deletion itself (8, 9).

The recent introduction of microarray technology has improved the possibility of combining genome-wide DNA analyses with transcriptomic profiles, thus allowing the identification of potential candidate tumor genes related to underlying chromosomal alterations. To further elucidate the genomic complexity of the 13q14 deletion...
in CLL, we applied single-nucleotide polymorphism (SNP)-array technology to a panel of 100 untreated patients with Binet stage A disease including 44 patients with 13q deletion as assessed by fluorescence in situ hybridization (FISH). We then investigated the expression levels of the miR-15a/16 cluster by quantitative real-time PCR (qRT-PCR) and global gene expression profiling in a representative panel of cases (see flow chart in Supplementary Figure S1). The integration between genomic and expression data allowed the identification of 2 distinct molecular types of 13q14 deletion that may be of clinical relevance for the biology and the prognostic stratification of the disease.

Materials and Methods

Patients
The study included samples from 100 untreated CLL patients in Binet stage A: 60 from a retrospective collaborative Italian study (10) and 40 enrolled in an Italian prospective multicenter study (GISL O-CLL1). Eligibility required a diagnosis of a typical CLL phenotype: CD5+/CD19+ and CD23+, weak surface immunoglobulin (slg), and the monotypical expression of κ or λ light chains by neoplastic cells. Patients were selected to provide a good numerical representation of cytogenetic lesions, as assessed by FISH, and IgVH mutation status. All the patients gave their informed consent in accordance with our institutional guidelines.

Sample preparation, immunophenotype, and prognostic markers
Peripheral blood mononuclear cells were isolated by Ficoll–Hypaque gradient centrifugation (Seromed), and CD38 and ZAP-70 expression were determined by flow cytometry (11). IgVH gene usage and mutational status were established as previously described (12), with a 2% cutoff value being used to define mutated and unmutated patients. For the microarray analyses, the CLL cells were enriched by negative selection when less than 90% (11).

Translational Relevance
The 13q14 deletion represents the most common genomic aberration in CLL (50%). Although it is associated with a favorable prognosis when present as the sole abnormality, the imprecise knowledge of the genes implicated and its genetic heterogeneity have limited our understanding on the pathogenetic mechanisms contributing to the disease. Microarray technology has improved the possibility of combining genome-wide DNA with transcriptomic profiles to identify potential candidate tumor genes related to underlying chromosomal aberrations. Based on SNP array, our study shows the presence of 2 distinct molecular groups of patients with del(13)(q14) based on the deletion size and the presence of biallelic deletions. Notably, global gene expression profiling identified a significant transcriptional deregulation specifically associated with the 2 groups. Our data highlight the presence of 2 distinct molecular types of 13q14 deletion that may be of clinical relevance for the biology and the prognostic stratification of the disease.

Fluorescence in situ hybridization
The most common genomic aberrations, del(17)(p13), del(11)(q23), del(6)(q23), del(13)(q14), and trisomy 12, were investigated by interphase FISH hybridization. All of the probes are commercially available (Vysis; ref. 13).

High-density SNP arrays and data analysis
Total genomic DNA (250 ng) were processed in accordance with the manufacturer’s protocol (Affymetrix), hybridized using Affymetrix GeneChip Human Mapping 250K NspI microarrays, and subsequently scanned using a GeneChip Scanner 3000 7G. The images were acquired using the Affymetrix GeneChip Operating System (GCCOS 1.4). The accuracy of the SNP array data were confirmed by the mean and median call rates of 95.73% and 96.12% (the quality control specification for 250K arrays is a call rate greater than 93%), respectively.

The entire procedure for the copy number (CN) estimation has been fully described previously (14). Briefly, the raw data relating to the individual SNPs were extracted from CEL files and converted into signal intensities using GTYPE 4.1 and Affymetrix Copy Number Analysis Tool (CNAT 4.0.1) software. Each sample was compared with a set of 48 normal Caucasian HapMap references available on the Affymetrix web site (http://www.affymetrix.com/support/technical/sample_data/500k_data.affx) and the genomic smoothing window of the Hidden Markov Model algorithm was set at 0. After preprocessing, piecewise constant estimates of the underlying local DNA CN alterations were calculated using the DNAcopy Bioconductor package, which looks for optimal breakpoints on the basis of circular binary segmentation (15), and the median values of the estimated profiles were scaled back to a nominal multiplicity of 2. After scaling, we determined all the clusters appearing on the frequency distribution (histogram) of the SNP values for all the SNP probes using the k-means algorithm on the cumulative profile of all of the array data. The transition from one cluster to the other, namely the threshold from one CN to another, was then estimated as the meeting point of 2 Gaussian curves and approximating the distributions of mean μ and variance σ² of the 2 neighboring clusters of SNPs identified in the final clustering. Thus, the thresholds result as follows: inferred CNs of more than 2.1 and 2.5 corresponded to gain and amplification, whereas CNs of less than 1.9 and 1.34 corresponded to loss and biallelic deletion. After segmentation, the SNP dataset was compressed to 1346 probes by eliminating redundant probes to better balance less represented regions with those showing a large number of probes, as previously described (14). A probe was defined as redundant when it showed CN values identical to those of the most
contiguous upstream probe in all samples. Then a non-
negative matrix factorization (NMF) procedure adapted to
R from the original MATLAB package (16) was used
to evaluate the meaningful clusters across the whole dataset.
For each factor level from 2 to 10, NMF was repeated 100
times to build a consensus matrix, and the samples were
assigned to clusters on the basis of the consensus results.

Sequence copy number determination by quantitative
real-time PCR
Real-time PCR was performed according to a published
protocol (17) using the ABI Prism 7900 sequence detec-
tion system. Singleplex amplification reactions were
accompanied in triplicate using 40 ng of template DNA, 1X
TaqMan Universal Master Mix, no AmpErase UNG, and a
1X Primer-Probe Mix (Applied Biosystems) containing
sequence-specific primers and a fluorogenic probe.
The TaqMan RNase P Detection Reagents kit and a
Custom TaqMan Gene Expression Assay (forward primer:
5'-GCAATCTGACGAGACGGAGAT-3'; reverse primer:
5'-CAGCAGGACGTATATGACGAGAT-3'; probe: 5'-
FAM-CAGCACAAATATTG-3') were used to amplify
the ribonuclease P RNA component H1 gene mapped
within 14q11.2 (present in 2 copies in all of the subjects
and thus used as an internal standard) and the
miR-15a/16-1 cluster. The comparative ΔCt method was used for
quantification purposes. DNA samples from 10 control
individuals with 2 copies of the commonly deleted region
were selected for PCR calibration. The estimated haploid
gene CN was given by the formula $2^{\Delta\Delta C_t}$, and the
predicted CN was calculated as the closest integer number to
the estimated CN (determining Gene Copy Number using
TaqMan Real-Time PCR Assays on the 7900 HT-Quick
Reference Card; Applied Biosystems; ref. 18).

Quantification of specific gene expression
by Q-RT-PCR
Q-RT-PCR of specific genes (TP53, WBP4, PEA15,
and LGALS1) and mature miRNAs (hsa-miR-15a and
hsa-miR-16) was performed using commercial TaqMan
assays (Applied Biosystems) as previously described
(19). The relative gene and miRNA expression levels were
calculated using the $2^{-\Delta\Delta C_t}$ method (Applied Biosystems
User Bulletin No. 2) as previously described (19).
Pearson’s correlation coefficient was calculated to test
relation between gene expression and Q-RT-PCR data.

Gene expression profiling
Twenty-two CLL samples with 13q deletion included in
the retrospective database underwent gene expression
profiling (GEP) analysis. Total RNA was extracted using
the TRIzol reagent (Invitrogen) and purified using the
RNaseasy total RNA Isolation Kit (Qiagen). The biotin-
labeled complementary RNA was prepared and hybri-
dized with GeneChip Human Genome U133A Arrays
(Affymetrix Inc.), which were scanned (GeneChip Scan-
ner 3000 7G; Affymetrix Inc.) in accordance with the
manufacturer’s protocols. The probe data were converted
to expression values using the Bioconductor function for
the robust multiarray average procedure, as described
previously (20). Supervised analysis was made using
Significant Analysis of Microarrays software, version
html/; ref. 21). The cutoff point for significance at a
median false discovery rate (FDR) less than 5% (i.e., $q
< 0.05$) was determined by tuning the $\alpha$ parameter on the
FDR and controlling the $q$-value of the selected probes.
dChip software (22) was used to represent the selected
probe lists; NetAffx (https://www.affymetrix.com/analy-
sis/netaffx/) was used for the functional annotation study
of the list. The genotyping and gene expression data are
available at NCBI’s Gene Expression Omnibus through
GEO Series Accession no. GSE16746.

Statistical analysis
The data were statistically analyzed using conventional
procedures in R software (Kruskal–Wallis tests, Kendall’s $\tau$
correlations, Fisher’s exact tests, and $q$-value calculations).

Results
Molecular characteristics of the CLL patients
The main characteristics of the 100 CLL patients included
in the study are reported in Supplementary Tables S1 and
S2. Based on FISH analyses, 44 cases carried the 13q14 deletion: 34 as the sole abnormality, and the remaining
showed 11q22.3 (6 patients), 17p13.1 (2 patients),
11q22.3 and 17p13.1 deletions (1 patient), or 6q23 dele-
tion (1 patient). Biallelic 13q14 deletions were identified in
11 cases, 5 of which (CS3, CZ42, GE110, CS0100 and
LD0062) showed the presence of subclones characterized
by the biallelic deletion (ranging from 68% to 83.5%).
Trisomy 12 was present in 21 patients as a sole abnormal-
ity. Overall, the 11q22.3, 17p13.1, and 6q23 deletions
were present in 15, 7, and 2 patients, respectively. Fifty-five
cases had unmutated IgVH genes; ZAP-70 and CD38 were
expressed in 42 and 46 cases, respectively. 13q deletions
delivered in 25 of 45 (55.5%) patients with mutated IgVH
genes, 15 of 42 (35.7%) of the ZAP-70 positive patients,
and 15 of 46 (32.6%) of the CD38 positive patients.

SNP array data were concordant with FISH results
(Supplementary Tables S2 and S3). In addition, SNP arrays
detected short deletions involving the second 13q allele in
3 del(13) (q14) patients (TS12, VB0013, and PS0044);
deletions were, respectively, 467, 468, and 291-kb long
and located centromerically to the LSI D13S25 FISH probe
(Fig. 1A and B). Furthermore, SNP arrays revealed a 6q
deletion of approximately 39 Mb in length and located
upstream of the LSI MYB FISH probe in a single patient
(CZ47, data not shown). These aberrations were confirmed
by specific FISH probes in all cases (data not shown).

Characterization of the 13q deletion by SNP arrays
The SNP arrays showed that the 13q deletions varied
considerably in size, ranging from a minimum of 291 kb
(Ps0044) to a maximum of 56 Mb (CZ36; Fig. 1A and B).
Fig. 1. Chromosome 13 deletion pattern in 44 CLLs. A, monoallelic (gray lines) and biallelic losses (black lines) in the 44 deleted patients. B, the enlarged subregion spanning 13q14.2–q14.3 between physical positions 44.50 and 52.00 Mb, including the minimal monoallelic deletion. C, the localization of SNPs and the FISH probe encompassing the minimally altered region (gray bar). Gene locations and transcriptional orientation are indicated by the horizontal arrows at the bottom.
The minimal monoallelic deletion was 635-kb long spanning from SNP_A-2003314 to SNP_A-2003318 (physical position 49,635,024 bp to 50,270,550 bp; Fig. 1C); notably, the miR-15a/16-1 cluster is located upstream (~87 kb) of the centromeric SNP_A-2003314. With regard to the miR-15a/16-1 cluster, SNP array analysis depicted the following scenario: (i) retention of 2 copies of the cluster in 56 patients with a normal 13q and in 2 cases (CD0018 and CS95) showing a 13q monoallelic deletion telomeric to the cluster; (ii) retention of 1 copy of the cluster in 29 patients with a 13q monoallelic deletion and in 2 cases (CZ42 and PS0044) showing a deletion telomeric to the cluster in the second allele; (iii) loss of both copies of the cluster in the remaining 11 patients showing biallelic deletions (Fig. 1A and B; Supplementary Table S4).
The status of the miR-15a/16-1 cluster was investigated further using a custom Q-RT-PCR assay on DNA from 32 patients: 10 with biallelic deletions, 10 with monoallelic deletions, and 12 normal at 13q14 based on SNP array data. As shown in Figure 2A and B and Supplementary Table S4, the estimated CN obtained with this approach were concordant with the SNP array data ($P < 0.0001$) with 3 exceptions: 2 patients (CS3 and GE110) classified as CN $= 1$ by RT-PCR and CN $= 0$ by SNP array, who showed 2 distinct cell populations by FISH characterized by either mono- or biallelic losses, and 1 patient (RC21) classified as normal by RT-PCR and CN $= 1$ by SNP array who showed a monoallelic loss in a fraction of interphase nuclei (61%; Fig. 2A). These findings suggest that clonal heterogeneity may account for the discrepancies between the real-time PCR and SNP array data.

Furthermore, we compared miR-15a and miR-16 expressions in 78 of 100 cases including 11 with biallelic deletions, 28 with monoallelic deletions and 39 normal cases based on SNP array CN values. Cases with biallelic deletions had a miRNA expression significantly lower than cases retaining 1 or 2 copies ($P < 0.0001$ for miR-15a, $P = 0.0001$ for miR-16) whereas no statistically significant differences in miRNA expression levels could be observed between normal cases and those retaining a single copy of the cluster (Fig. 2B and C; Supplementary Table S5).

Finally, SNP array documented a loss of the RB1 gene in 28 of 44 cases with 13q14 deletion (63.6%). Two samples (CS0100 and TS12) showed a biallelic loss of the RB1 locus, which was associated with a homozygous deletion of the 13q14 FISH probe (case CS0100) or was the result of a small deletion involving the RB1 locus on the second allele (case TS12; Fig. 1B). All these findings were validated by FISH using the RB1 specific clone RP11-305D15 (data not shown).
Identification of 2 genetically distinct patient subgroups with del(13)(q14)

To identify the most significant natural grouping of genome profiles in our panel, we used the NMF algorithm. This analysis led to the identification of 4 major groups (correlation coefficient – 0.95) characterized by 13q deletion (groups I and II, 27 and 13 cases, respectively) and by trisomy 12 (group III, 21 cases), whereas no specific alteration could be associated with group IV (39 cases; Fig. 3; Table 1). Patients from groups I and II differed in the deletion size and for the occurrence of mono- or biallelic deletions: group I included samples with relatively smaller losses, 10 of which showed biallelic deletions, whereas group II included samples with larger losses. all but one (GE110) showing monoallelic deletions. The presence of 4 samples with 13q14 deletions in group IV was in all likelihood related to the fact that the inferred CN values (ranging from 1.74 to 1.85) were very close to the threshold (1.9) between monoallelic deletion and the retention of 2 copies. These "marginal" CN data are consistent with clonal heterogeneity and are in accordance with the small percentage of interphase nuclei detected by FISH showing 13q14 deletion (no more than 21% in all cases), which may affect the clustering analysis. RB1 deletion occurred in 14 of 27 cases in group I (52%), 12 of 13 in group II (92%), and 2 of 4 in group IV. Only 10 of the 44 patients with del(13)(q14) carried additional known genetic lesions, namely 11q22.3 (6 patients), 17p13.1 (2 patients), 1q22.3 (1 patient), 6q23 deletions (1 patient); however, no correlation was found with the 2 specific subgroups I and II. Finally, there was no significant association between cases within NMF groups I and II and CD38 or ZAP-70 expression or IgVH mutational status (data not shown).

Gene expression patterns associated with distinct groups of patients with 13q deletion

Fifteen cases from group I and 7 from group II, for whom RNA material was available, were profiled on GeneChip HG-U133A arrays. To verify whether the 2 groups could be divided on the basis of the differences of their expression profiles, we made a conventional unsupervised analysis using hierarchical agglomerative clustering at different levels on (i) all of the probes in the array; (ii) all of the probes mapped to the chromosome 13; or (iii) all of the probes within the 13q14 region. Notably, a significant grouping (i.e., group I and group II patients in 2 separate branches) was only detected when the 85 probes (65 genes) mapped on the 13q14 region were used (P < 0.0001; Fig. 4A). This finding indicates that, albeit differences exist between the 2 groups, these are not sufficient to drive the clustering when the global transcriptional profiling was considered (i.e., the whole matrix). Thus, we carried out a supervised analysis to characterize the specific transcriptional profiles distinguishing NMF groups I and II. We identified 76 differentially expressed probe sets, specific to 63 well-characterized genes (Fig. 4B), 10 of which were downregulated and 53 upregulated in group II compared with group I. Six of the 10 downregulated genes mapped to 13q13-q14 and exhibited a monoallelic deletion in most or all cases within group II (3 of 7 (43%) for FOXO1; 4 of 7 (57%) for EXOSC1 and WBP4; 6 of 7 (86%) for TPT1 and NUFIPI; 7 of 7 (100%) for ESD) compared with cases in group I (1 of 15 (6.7%) for EXOSC1, TPT1, ESD, FOXO1, and NUFIPI; 2 of 15 (13.3%) for WBP4). The whole list of differentially expressed genes is reported in Table 2.

We selected 2 downregulated (TPT1 and WBP4) and 2 upregulated (PEAI5 and LGALS1) genes in group II versus group I for Q-RT-PCR validation of the microarray data. The Q-RT-PCR analyses were made in a subset of 20 of 22 patients for whom RNA material was available (14 belonging to group I, 6 to group II). The correspondence between the microarray and Q-RT-PCR data were evaluated by assessing the correlation coefficients of the expression levels determined by the 2 analyses: the coefficients were 0.71 for TPT1, 0.79 for WBP4, 0.60 for PEAI5, and 0.78 for LGALS1 probe, thus indicating a very good concordance for all of the tested genes (Supplementary Fig. S2).

Discussion

This study focused on the molecular characterization of the 13q14 deletion based on SNP arrays and gene expression profiling analyses. Several aspects distinguish this from previous reports (9, 23) including a homogeneous cohort of untreated early-stage patients (Binet A), the use of highly purified CLL samples and a higher-resolution SNP array (250K NspI), the application of stringent statistics to define the genetic groups, and the integration of genomic and gene expression data in a significant number of cases. The main findings relate to the description of the topography of 13q14 deletions, the reassessment of the fate of miR-15a/16-1 cluster in relation to the genomic losses, and, perhaps more importantly, the definition of 2 major genomic groups of patients with 13q14 deletions also characterized by distinct transcriptional patterns.

Table 1. Molecular characteristics of the 4 genomic groups

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Table 2. Functional annotations of the 63 genes identified as differentially expressed among the 2 NMF groups by SAM 2-class analysis (Cont’d)

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<th>Score (d)</th>
<th>Fold change</th>
<th>q (%)</th>
<th>Cytoband</th>
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The natural grouping of genome profiles by SNP array analysis showed that the complex scenario of CN alterations affecting CLL is mainly driven by the presence of the 13q14 deletion and trisomy 12. Our SNP array approach extends previous limited evidence showing that del(13)(q14) patients are characterized by differently sized deletions. Ouillette et al. (9) documented a significant correlation between a wider deletion encompassing the RB1 gene and a higher Rai clinical stage at diagnosis or in previously treated patients. In preliminary observations on our cohort of Binet stage A patients, we did not find any significant differences in the time to treatment between the patients with shorter/biallelic (group I) or wider/monoallelic losses (group II; data not shown), although this finding awaits confirmation by ongoing prospective studies.

Our data support the notion that loss of the miR-15a/16-1 locus occurs in virtually all the CLL cases with del(13)(q14); in fact, among 44 cases with 13q deletion in our study, both copies of miRNA cluster were retained in only 2 patients with a monoallelic 13q14 deletion. Furthermore, we found that reduced miR-15a and miR-16 expression levels in patients with del(13)(q14) significantly correlated only with the presence of a biallelic loss, which is in agreement with some recent data (8, 9) but not with the older findings (7). Overall, these findings suggest a need to redefine the pathogenetic role of miR-15a and miR-16-1 in the context of the molecular subtypes of 13q14-deleted patients.

The availability and integration of GEP data allowed a more comprehensive overview of the genetic complexity of the 13q14 deletion. Indeed, this approach led to the determination of distinct transcriptional signatures associated with different groups of 13q14-deleted patients (short/biallelic versus long/monoallelic lesion) identified by the NMF algorithm. In particular, a significant gene dosage effect has been observed involving the downregulation of genes in group II (long/monoallelic deletion), 6 of which localized within the 13q14 region. Among the downregulated genes, we should note TPT1/TCTP (translationally controlled tumor protein) encoding for a highly conserved multifunctional protein acting as a prosurvival and growth stimulating factor (24), which inhibits BAX-induced apoptosis (25).

Most of the upregulated genes in group II are involved in cell motility and adhesion, regulation of cell proliferation, tumor cell migration, metastasis, angiogenesis, and apoptosis, and some of these may contribute to lymphomagenesis. This is the case of the autocrine motility factor (AMF)/glucose phosphate isomerase (GPI) gene, which is upregulated in several human cancers and encodes for a housekeeping cytosolic enzyme involved in both glycolysis and gluconeogenesis (26). The basigin gene (BSG) encodes a cell surface glycoprotein of the Ig superfamily expressed at the surface of tumor cells metastasizing in bone marrow (27) and is believed to induce matrix metalloproteinases production (28). The Galectin-1 (alias LGALS1) gene encoding a 14-kDa lectin, is overexpressed in numerous tumors including lymphomas (29) and CLL, and is

Fig. 4. Identification of gene signatures characterizing 13q14 classes. A, dendrogram of the 22 CLL samples clustered according to the expression profiles of the genes located at 13q14. B, expression profiles of the NMF CLL group I versus group II for the 76 probe sets selected by a SAM 2-class analysis. Information on chromosomes 11, 13, and 17 deletions; chromosome 12 trisomy (+, positive; −, negative; /, biallelic deletion), CD38 (+, >30%; −, <30%), ZAP-70 expression (+, >30%; −, <30%), and IgVH mutational status (+, mutated; −, unmutated) is included alongside the patient ID. The color scale bar represents the relative changes in gene expression normalized by the standard deviation, and the color changes in each row represent gene expression in relation to the mean across the samples.
implicated in abnormal mechanisms of cell adhesion, induction of apoptosis, and tumor angiogenesis (30, 31). PAK2 belongs to the p21-activated kinase family, which are well-known regulators of cytoskeletal remodeling, cell motility, proliferation, and apoptosis (32). Finally, 2 other upregulated genes, β-parvin (PARVB) and vimentin (VIM), have been reported to play a critical role in transducing signals from integrins to the actin cytoskeleton and intracellular signaling proteins (33). Low levels of PARVB correlate with low adhesion to collagen (34), whereas increased levels reduce the activating phosphorylation of AKT (35), causing propensity to apoptosis. Upregulation of VIM is thought to provide a selective advantage to tumor cells following signaling cues from mesenchymal and epithelial extracellular matrixes (36). Notably, a modulation of genes thought to act as regulators of tumor invasion and integrin-mediated cell motility and adhesion has been recently described in CLL, in particular during disease progression (37, 38).

In conclusion, our data may represent a valid contribu-
tion to the definition of the genomic profile of CLL. In particular, we provide evidence of 2 clearly distinguishable molecular subtypes among CLL patients with 13q14 deletion that may contribute toward the better understanding of the pathogenetic and clinical relevance of this lesion in CLL.

Disclosure of Potential Conflicts of Interest

No potential conflict of interest was disclosed.

Grant Support

This study was supported by grants from AIRC to A.N. (IG 4659) and F.M. (BG 6432 cofinanced by AIRC-CARICAl, Fondazione ‘Amelia Scorzetta’ and Provincia di Cosenza); All. Sezione Milano; Fondazione ‘Amelia Scorzetta’ ONLUS, Cosenza; Progetti Strategici–Ricerca Finalizzata Ministero Italiano della Salute “RIPS20063339/60” (to G.C.) and “RIPS20063401/60” (to F.M. and M.F.). and F.R.R. (Grant RR10646C9 to M.F.). The Progetto Ordinario Ricerca Finalizzata Ministero Italiano della Salute–2007 (to G.C.), Progetto Compagnia San Paolo (to G.C.,), and the Fondazione Internazionale Ricerche Medicina Sperimentale (FIRMA) provided financial and administrative assistance. L.A. and S.M. were supported by fellowships from the Fondazione Italiana Ricerca sui Cancro (FIRC).

Received 01/19/2010; revised 06/25/2010; accepted 07/24/2010; published OnlineFirst 10/14/2010.

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