High Resolution Copy Number Analysis of *IRF4* Translocation-Positive Diffuse Large B-Cell and Follicular Lymphomas

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Translocations affecting chromosome subband 6p25.3 containing the *IRF4* gene have been recently described as characteristic alterations in a molecularly distinct subset of germinal center B-cell-derived lymphomas. Secondary changes have yet only been described in few of these lymphomas. Here, we performed array-comparative genomic hybridization and molecular inversion probe microarray analyses on DNA from 12 formalin-fixed paraffin-embedded and two fresh-frozen *IRF4* translocation-positive lymphomas, which together with the previously published data on nine cases allowed the extension of copy number analyses to a total of 23 of these lymphomas. All except one case carried chromosomal imbalances, most frequently gains in Xq28, 11q22.3-qter, and 7q32.1-qter and losses in 6q13-16.1, 15q14-22.31, and 17p. No recurrent copy-neutral losses of heterozygosity were observed. *TP53* point mutations were detected in three of six cases with loss of 17p. Overall this study unravels a recurrent pattern of secondary genetic alterations in *IRF4* translocation-positive lymphomas.

INTRODUCTION

Translocations affecting chromosomal band 6p25 containing the *IRF4* gene have been described as recurrent changes in multiple myeloma (Iida et al., 1997; Yoshida et al., 1999; Chesi et al., 2000), aggressive B-cell lymphomas (Tamura et al., 2001; Hunt et al., 2008; Salaverria et al., 2011), chronic lymphocytic leukemia

Additional Supporting Information may be found in the online version of this article.

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(Michaux et al., 2005), ALK-negative anaplastic large-cell lymphoma (Feldman et al., 2011), and other T-cell lymphomas (Feldman et al., 2009; Pham-Ledard et al., 2010). There is compelling evidence that *IRF4* is the target gene in B-cell neoplasia. The breakpoints might be located on either side of *IRF4* and can affect the *DUSP22* gene, immediately telomeric (Morin et al., 2011) and the *EXOC2* gene centromeric to *IRF4*. In a recent study, we have described *IRF4* translocations to characterize a subset of lymphomas, which are predominantly germinal center B-cell (GCB)-type diffuse large B-cell lymphoma (DLBCL) or follicular lymphoma (FL) grade 3, share strong expression of IRF4/MUM1 and BCL6 and lack both PRDM1/BLIMP1 expression and t(14;18)/*BCL2* breaks. Moreover, these lymphomas showed a distinct gene expression profile and were associated with disease onset in childhood and young adulthood and favorable prognosis (Salaverria et al., 2011). The pattern of secondary chromosomal imbalances in these lymphomas is yet poorly defined: the copy number changes of only nine of these lymphomas have as yet been described because mostly only formalin-fixed paraffin-embedded (FFPE) material was available. Here, by applying molecular inverse probe (MIP) assay and array-comparative genomic hybridization (CGH) adapted for FFPE tissues (Zhao et al., 2004) and combined evaluation with the previously published cases, we describe a recurrent pattern of imbalances in these *IRF4* translocation-positive B-cell lymphomas.

MATERIALS AND METHODS

Patient Samples and DNA Extraction

A total of 23 *IRF4* translocation-positive lymphomas were included in the study. Twenty-one were recruited from a previously published series (Salaverria et al., 2011) and two were novel. Array 2.7K CGH data from 9 out of 21 were also previously published (Salaverria et al., 2011). The remaining samples (12 + 2) were recruited for MIP assay and array-CGH studies (Supporting Information Table 1). DNA was extracted from 12 FFPE and two fresh-frozen tissues using a phenol-chloroform extraction method (Zettl et al., 2000). The study was performed in the framework of the BFM-NHL and DSHNHL trials as well as the molecular mechanisms in malignant lymphomas (MMML) network, for which central and local institutional review board approval was obtained.

Immunohistochemical and Fluorescence *In Situ* Hybridization (FISH) Analyses

Immunohistochemical and FISH analyses were performed as previously described (Oschlies et al., 2006; Ventura et al., 2006), using commercially available (Abbott/Vysis, Des Plaines, IL) and previously described FISH probes (Supporting Information Table 2) (Nagel et al., 2009; 2010b; Eberle et al., 2011; Salaverria et al., 2011). Histological review and determination of tumor cell content in the FFPE samples was performed by two independent hematopathologists (IO and WK). The tumor cell content was greater than 35% (range from 35 to 95) (Supporting Information Table 1).

MIP Assay and Array-CGH

Eleven DNAs from FFPE material were hybridized on the MIP assay using the Oncoscan FFPE Express custom service (Affymetrix, Santa Clara, CA). Copy number determination of MIP assay has been previously described (Wang et al., 2009). Nine DNAs from FFPE material (including eight cases simultaneously analyzed by MIP assay) and two DNAs from fresh-frozen tissue were analyzed using Agilent 244K array (Agilent Technologies, Santa Clara, CA). Gains and losses were defined using Nexus 6.0 beta Discovery Edition (BioDiscovery, El Segundo, CA). Array 2.7K CGH data from nine previously published cases from the MMML network were included in the meta-analysis (Supporting Information Fig. 1 and Supporting Information Table 1) (Salaverria et al., 2011).

Mutation and SNP Analyses

TP53 mutational analysis of exons 2–11 was performed as previously described (Gross et al., 2001). Sequence variations and their functional consequences in silico were determined according to the IARC *TP53* Database (R15) (Petitjean et al., 2007). Direct sequencing of the *B2M* gene as well as of three mutations detected by MIP assay (*EGFR*, *TP53*) was performed using an ABI PRISM 3100 Genetic Analyzer system (Applied Biosystems, Foster City, CA) (Supporting Information Table 3). The *IRF4* polymorphism rs872071 was genotyped using high-resolution melting analysis in a 480 II LightCycler® (Roche Diagnostics, Mannheim, Germany).

Statistical Analysis

Statistical calculations were performed using PASW Statistics software version 18 (SPSS, Chicago,

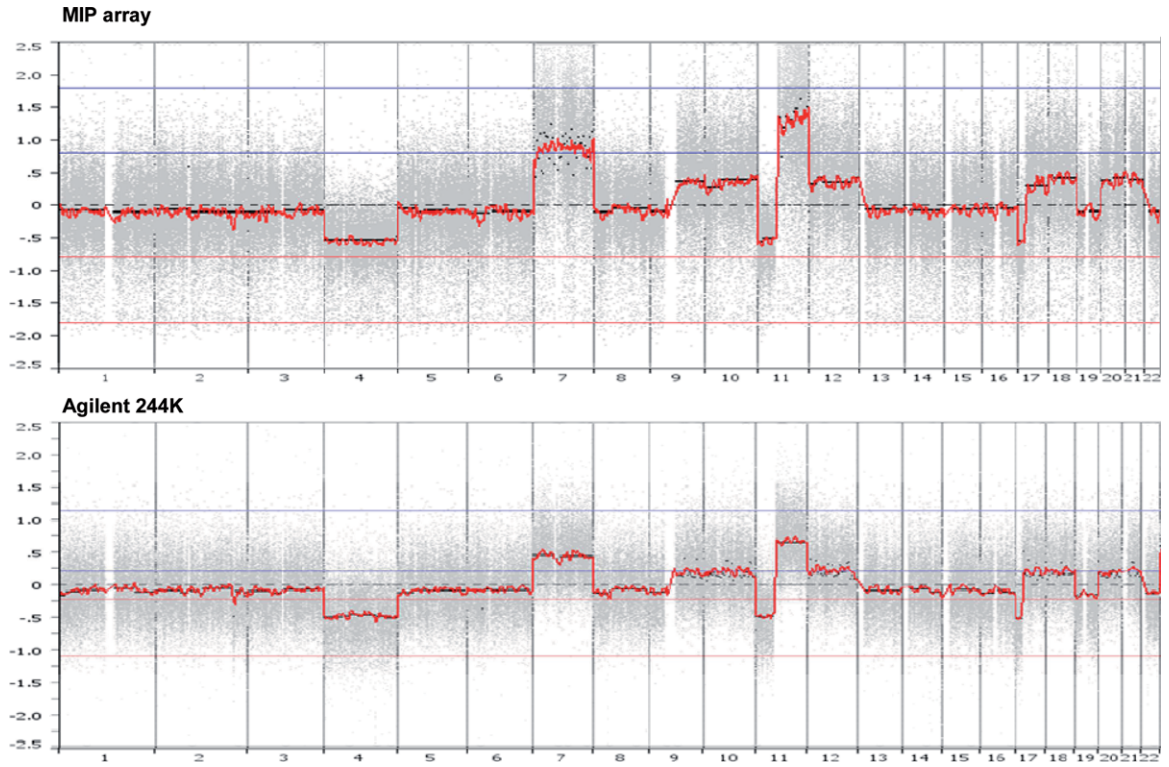

Figure 1. Raw profiles of copy number results in case ID12 using MIP assay and Agilent 244K array-CGH platforms, displayed using Nexus 6.0 beta Discovery Edition. Proportion of gains and losses are displayed from 1pter to 22qter on the *x*-axis. The case shows a complete concordance of gross imbalances in both platforms: gain/amplification of 7, 9q13-qter, 10, 11q11-qter, 12, 17q, 18, 20, and 21q, and loss of 4, 11pter-p11.12, and 17p.

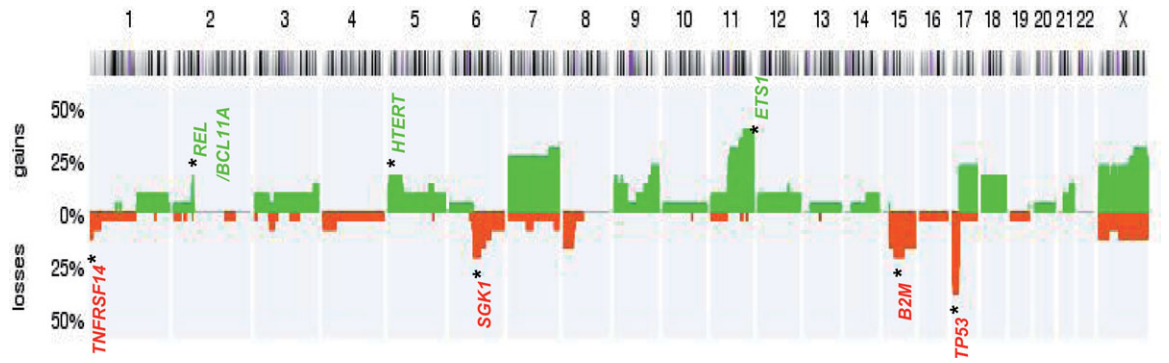

Figure 2. Copy number profiles of 23 *IRF4* translocation-positive lymphomas. On the *x*-axis, the chromosomes are represented horizontally from 1 to *x*, on the *y*-axis, the percentage of cases showing copy number alterations. Gains are represented on the positive *y*-axis and colored in green, whereas losses are represented on the negative *y*-axis in red. The most frequent alterations were gains of Xq28, 11q22.3-qter, and 7q32.1-qter, and losses of 6q13-16.1, 15q14-22.31, and 17p. Candidate genes in regions of gain are displayed in green and in regions of loss in red.

IL). Chi-Square analysis was used in order to detect the specific copy number alterations associated to age groups.

RESULTS AND DISCUSSION

To determine the pattern of chromosomal imbalances in *IRF4* translocation-positive lymphomas, we have analyzed DNA from 12 FFPE and two fresh-frozen tissues using MIP assay and array-CGH. For estimation of technical accuracy, eight of these samples were hybridized to both platforms. All eight cases showed a complete concordance of gross imbalances (Fig. 1 and Supporting Information Table 4). FISH was applied for verification of gains/amplifications in chromosome

arms 11q (*ATM/FDX* loci) (Supporting Information Fig. 2), 2p (*REL/BCL11A* loci), and 5p (*HTERT* locus) in five different samples (ID11, ID12, ID14, ID15, and ID20), and the results were in good agreement with the array-based analysis. Finally, results obtained in cases ID16 and ID22 were compared with those from metaphase analysis and again showed considerable agreement (data not shown). As these controls indicated technical validity of the MIP assay/array-CGH data from FFPE, we combined the results of the 14 cases with those from our previously published series analyzed with 2.7 K array-CGH for meta-analysis (Salaverria et al., 2011). Concordance between MIP assay/Agilent 244K array and BAC array was not tested but discrepancies due to technical biases, different materials hybridized, and analysis methods/thresholds could exist.

Sixteen of the 23 cases were classified as DLBCL, one as FL 3B, five as composite FL grade 3/DLBCL, and one as high-grade B-cell non-Hodgkin lymphoma, not further classified. Twelve samples were from male and 11 were from female patients. The mean age of the patients was 30.1 years (range 4–87 years). Twenty-two (95%) of the 23 cases displayed chromosomal alterations (Fig. 2) with a mean of six alterations per case. Children $\leq$18 years (n = 12) and adults >18 years (n = 11) presented similar numbers of copy number imbalances (6.2 vs. 5.6 imbalances; t-test P-value=0.73) (Supporting Information Fig. 3). Analogs results were found when children and young adults $\leq$40 years (n = 16) were compared with adults >40 years (n = 7) (6.3 vs. 5 imbalances; t-test P-value = 0.42).

The most frequent genetic aberrations were gains in Xq28 (9/23), 11q22.3-qter (9/23), and 7q32.1-qter (6/23) and losses in 6q13-16.1 (5/23), 15q14-22.31 (5/23), and 17p (9/23) (Fig. 2). Interestingly, three cases with deletions in 1pter-p35.2 were detected (ID1, ID8, and ID13). Deletions of this region have been associated with mutations of the *TNFRSF14* gene in FL (Cheung et al., 2010).

Copy number neutral-loss of heterozygosity (CNN-LOH) was observed in two of 11 cases hybridized to the MIP assay but lacked recurrence. The CNN-LOH affected 1q21.1-qter (ID18), and 14q31.3-qter, 16q11.2-qter, and 17q11.2-qter (ID20) (Supporting Information Table 5).

Remarkably, five cases (22%) displayed a pattern of 17p loss-17q gain suggestive of an isochromosome 17q (Scheurlen et al., 1999). Mutation analysis of the putative target gene in the deleted region in 17p, *TP53*, in six cases with 17p deletions, revealed a nonsense mutation in exon 6 (g.12706C>T, p.R213X), a consensus splice donor site mutation (g.13420G>T) and a mutation affecting the transactivation domain (g.11198C>T, p.L26F) in three of six cases (Supporting Information Fig. 4).

With regard to the other regions of recurrent imbalances, potential candidate genes are *SIK2* and *ETS1* in the gained region in 11q and *B2M* in the deleted region in 15q21.1. *SIK2* gene amplification has been demonstrated in the DLBCL cell line Karpas-422 (Nagel et al., 2010a), and *ETS1* is known to be involved in translocations in human acute leukemia (Rowley et al., 1990) and mutated in DLBCL (Morin et al., 2011). Inactivating mutations and deletions in *B2M*, encoding β2-microglobulin, have been recently described in B-cell lymphomas (Pasqualucci et al., 2011) and likely affect major histocompatibility complex class I function. We sequenced *B2M* in 16 cases but only one case (ID11) lacking chromosome 15 aberration showed both a missense and a splice site mutation in exon 1 (Supporting Information Fig. 5). As regards the deletions in 6q, it is remarkable that a recent sequencing study in a young DLBCL patient carrying a fusion between 6p25 and 14q32, juxtaposing *IGH* with the *DUSP22* gene, showed a mutation of the *SGK1* gene in 6q23 as the only recurrent mutation (Morin et al., 2011). However, *SGK1* is not located in the critical region detected in our *IRF4* translocation-positive cases. A possible candidate gene in this region is *EPHA7* at 6q16.1, a tumor suppressor gene that is inactivated in 72% of FLs. Moreover, it has been shown that knockdown of *EPHA7* drives lymphoma development in a murine FL model (Oricchio et al., 2011). Additionally, *MAP3K7* and *CASP8AP2* at 6q15 have been suggested to be potential target genes of 6q deletions in lymphoma. Specifically, mutations of *MAP3K7* have been found to deregulate the NF-kB pathway in DLBCL (Compagno et al., 2009) and *CASP8AP2* deletions have been found to be a poor prognostic marker in pediatric T-cell lymphoblastic leukemia and lymphoma (Remke et al., 2009; Callens et al., 2012).

In comparison with other GC derived lymphomas as t(14;18)-positive FL (Schwaenen et al., 2009), *IRF4* translocation-positive cases show higher frequencies of 11q gains (39% vs. 10%;

Fisher's exact test P-value <0.05) and isochromosome 17q (*22%* vs. *2%*; Fisher's exact test P-value <0.05) (Supporting Information Fig. 6).

In addition to imbalances, the MIP platform also generates genotype information. Since several studies have identified SNPs in the *IRF4* 3'UTR region to be associated with the risk of developing chronic lymphocytic leukemia and other lymphomas (Di Bernardo et al., 2008; Allan et al., 2010; Broderick et al., 2010; Crowther-Swanepoel et al., 2010), we explored the presence of the risk alleles in *IRF4* translocation-positive cases and extended the analyses by somatic genotyping in 14 cases. This was possible because one SNP at the MIP assay, rs1050976, is in complete linkage disequilibrium with the published risk SNP rs872071 (Supporting Information Table 5). Interestingly, the risk allele was depleted in the *IRF4* translocation-positive cases compared with Caucasian controls ($n = 631$) (0.35 vs. 0.47; χ^2 test P-value = 0.08). Although these results were not significant likely due to the limited size of this group of rare lymphomas, we suggest that the inherited variation in B-cell developmental genes might vary between different genetic subtypes of B-cell lymphoma.

In conclusion, our data suggest *IRF4* translocation-positive B-cell lymphomas to carry a recurrent pattern of secondary genetic alterations, including inactivation of *TP53* in a subset of these lymphomas.

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