A novel *IGH@* gene rearrangement associated with *CDKN2A/B* deletion in young adult B-cell acute lymphoblastic leukemia

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Abstract. Acquired copy number changes are common in acute leukemia. They are reported as recurrent amplifications or deletions (del), and may be indicative of involvement of oncogenes or tumor suppressor genes in acquired disease, as well as serving as potential biomarkers for prognosis or as targets for molecular therapy. The present study reported a gain of copy number of 14q13 to 14q32, leading to immunoglobulin heavy chain locus splitting in a young adult female. To the best of our knowledge, this rearrangement has not been previously reported in B-cell acute lymphoblastic leukemia (ALL). Low resolution banding cytogenetics performed at the time of diagnosis revealed a normal karyotype. However, retrospective application of fluorescence *in situ* hybridization (FISH) banding and locus-specific FISH probes, as well as multiplex ligation-dependent probe amplification and high resolution array-comparative genomic hybridization, revealed previously hidden aberrations. Overall, a karyotype of 46,XX,del(9)(p21.3p21.3),derivative(14)(pter->q32.33::q32.33->q13::q32.33->qter) was determined. The patient was treated according to the Polish Adult Leukemia Group protocol and achieved complete remission. The results of the present study indicate that a favorable prognosis is associated with these aberrations when the aforementioned treatment is administered.

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Introduction

B-cell acute lymphoblastic leukemia (B-ALL) is a malignant neoplasm derived from B-cell progenitors. It is the most commonly occurring malignancy in pediatric patients, accounting for up to 80% of childhood leukemia cases. Thus, it is the primary cause of cancer-associated mortality in children and young adults (1,2).

Rearrangements involving the immunoglobulin (Ig) heavy chain (*IGH@*) locus on chromosomal band 14q32.33 are rare in B-ALL, occurring in <5% of childhood cases and detected in ~10% of adult patients (3,4). *IGH@* rearrangements occur more often in adolescents and appear to be associated with a favorable clinical outcome. This additionally applies to cases of B-ALL associated with genetic aberrations, including deletion (del) in 9p21.3 [cyclin-dependent kinase inhibitor 2A/B (*CDKN2A/B*)] and 9p13.3 (paired box-5) (5). In B-ALL, the most common *IGH@* rearrangements involve translocation to partner genes such as *C-MYC* in 8q24 by the well-characterized translocation t(8;14)(q24.1;q32). An additional partner is the inhibitory transcription factor *ID4* in 6p22, which is cytogenetically visible as translocation t(6;14)(q32;p22). Another translocation, t(14;19)(q32;q13), leads to overexpression of the CCAAT-enhancer binding protein (*CEBP*) gene family (6), whilst t(5;14)(q31;q32) involves interleukin-3 in 5q31 (7), and the translocations t(X;14)(p22;q32) and t(Y;14)(p11.2;q32) result in dysregulated expression of cytokine receptor-like factor 2 (8). Translocations between *IGH@* and erythropoietin receptor in 19p13 have also been reported together with other translocations appearing less frequently (9-11).

In all of the aforementioned translocations, an oncogene located close to the breakpoint of the translocation partner is activated via juxtaposing to *IGH@* regulatory sequences (4). Notably, all rearrangements involving *IGH@* at 14q32.33 possess unique biological characteristics and have been

observed to correlate with clinical, morphological and immunophenotypic characteristics.

Cryptic deletions in chromosomal band 9p21.3 involve the *CDKN2A* gene, which encodes two transcripts ($p16^{Ink4A}$ and $p14^{ARF}$), as well as the *CDKN2B* gene ($p15^{Ink4B}$). The functions of these transcripts in the cell cycle are to control the transition from G1 to S phase. The sizes of 9p21.3 deletions in patients with ALL appear to vary significantly; however, in the majority of cases, *CDKN2A* is co-deleted with *CDKN2B* and methylthioadenosine phosphorylase (12-14).

The present study reported a novel *IGH@* rearrangement associated with a deletion in *CDKN2A/B* in a young adult with B-ALL. In addition, the potential underlying mechanism of chromosome 14 rearrangement is discussed.

Patient and methods

Clinical description. A 20-year-old female presented at the Hospital Maria Sklodowska-Curie Memorial Cancer Centre and Institute (Warsaw, Poland) in November 2008 with a white blood cell count of $3.7x10^9$/l (normal range, 3.5-$10x10^9$/l), hemoglobin of 11.0 g/dl (normal range, 12.0-16.0 g/dl) and platelets of $334x10^9$/l (normal range, 125-$400x10^9$/l). In the bone marrow, ~93% blast cells (normal range, <5%) were observed. Immunophenotype was characterized by the expression of a variety of B-cell-specific antigens, with positivity for cluster of differentiation (CD)10, CD19, CD22, CD34, CD38, CD45, CD52, CD79a, terminal deoxynucleotidyl transferase and human leukocyte antigen-DR, and negativity for CD2, CD15, CD20, CD33, CD56, CD66c and cIgM. These results were consistent with common B-ALL.

The patient was treated with induction therapy, which consisted of epirubicin, vincristine and PEG-L-asparaginase, steroids, according to the Polish Adult Leukemia Group (PALG) protocol (15), with two courses of consolidation (consolidation I, vepesid, metrotrexate and dexamethasone; consolidation II, cyclophosphamide, cytosar and PEG-L-asparaginase) and maintenance treatment. From December 2011 to date, the patient has remained under the observation of an outpatient clinic, and demonstrated complete remission with no signs of minimal residual disease (MRD).

The present study was approved by the Ethical Board at the Friedrich Schiller University (Jena, Germany; approval no., 1105-04/03) and written informed consent was obtained from the patient.

Cytogenetic results at diagnoses. Banding cytogenetic analyses were performed on unstimulated bone marrow aspirate according to standard protocols (16). A total of 25 metaphases were available for cytogenetic evaluation, and were analyzed on a banding level of 300 bands per haploid karyotype (17). GTG-banding revealed a normal female karyotype of 46,XX.

Retrospective analyses

Molecular cytogenetics. Fluorescence *in situ* hybridization (FISH) was performed according to standard procedures (18) and/or according to the manufacturer's protocol.

Probes and probe sets were constructed as follows: Bacterial artificial chromosome clones of interest were identified using the Human Genome Browser Database of the Genome Bioinformatics Group at the University of California at Santa Cruz (Santa Cruz, CA, USA; http://genome.ucsc.edu/) and Ensembl Genome Data Resources of the Sanger Institute Genome Database (http://www.ensembl.org/). DNA probes (Table I) obtained from the Resources Center (Oakland, CA, USA) were labeled by polymerase chain reaction with SpectrumGreen (Green-dUTP; catalog no., 02N32-050; Abbott Molecular, Des Plaines, IL, USA), SpectrumOrange (Orange-dUTP; catalog no., 02N33-050; Abbott Molecular) or TexasRed-dUTP (ChromaTide-TexasRed-12-dUTP; catalog no., C-7631; Thermo Fisher Scientific, Inc., Waltham, MA, USA) and applied for two- or three-color FISH approaches. The FISH-banding probe sets used were as follows: Genome wide multitude multicolor banding (mMCB) and chromosome-specific high-resolution array-proven multicolor-banding (aMCB) (19-21).

In addition, commercially available probes were used: LSI *IGH* (14q32 break probe; Vysis; Abbott Molecular, Inc., Des Plaines, IL, USA), POSEIDON p16 (9p21 and 9q21 control probe; Kreatech Diagnostics, Amsterdam, Netherlands), SPEC erythroblast transformation-specific (ETS)-related gene (ERG)/TMPRSS2 TriCheck™ Probe (*ERG* in 21 q12.13-q22.3, TMPRSS2 in 21q22.3; ZytoVision GmbH, Bremerhaven, Germany), and subtelomeric probe for 14q (14q in D14S1420; Vysis; Abbott Molecular, Inc.).

A total of 10-15 metaphase spreads were analyzed with a fluorescence microscope (AxioImager Z1; Zeiss AG, Oberkochen, Germany), which was equipped with appropriate filter sets to discriminate between a maximum of five fluorochromes and the counterstain 4',6-diamidino-2-phenylindole. Image capturing and processing was performed with the ISIS imaging system (MetaSystems Hard & Software GmbH, Altlussheim, Germany).

DNA isolation. Genomic DNA was extracted from cells fixed in acetic acid-methanol (1:3) using a Puregene DNA Purification kit (Gentra Systems, Inc., Big Lake, MN, USA). DNA concentration was determined using a spectrophotometer (NanoDrop Technologies; Thermo Fisher Scientific, Inc.). The quality of DNA was assessed by agarose gel electrophoresis. DNA samples extracted from fixed cells of two healthy men and two healthy women by an identical method were used as reference samples.

Multiplex ligation-dependent probe amplification (MLPA). P377-A1 Hematologic Malignancies probemix and SALSA reagents were utilized for the present study (MRC Holland BV, Amsterdam, Netherlands). Amplified probes and Genescan 500 ROX Size Standard were separated using capillary electrophoresis using a 4-capillary ABI-PRISM 3130xl Genetic Analyzer (Applied Biosystems; Thermo Fisher Scientific, Inc.). Sizing of peaks and quantification of peak areas and heights was performed using GeneMarker software version 1.9 (SoftGenetics, LLC., State College, PA, USA). A minimum of 4 healthy control samples were included in each run.

High-resolution array-comparative genomic hybridization (aCGH). aCGH was performed with Agilent SurePrint G3 Human Genome Microarray 180 kit (Agilent Technologies, Inc., Santa Clara, CA, USA), and an oligonucleotide microarray containing ~180,000 probes 60-mer with a 17 kb average probe spacing. Genomic DNA of the patient was co-hybridized with male control DNA (Agilent Technologies, Inc.). Labeling was performed with a Genomic DNA enzymatic labeling

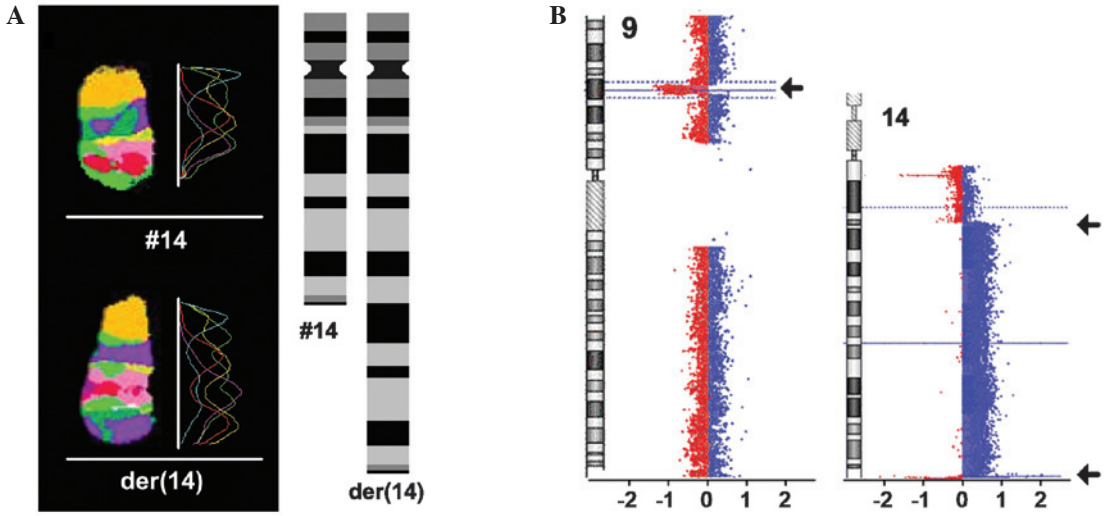

Figure 1. (A) Result of aMCB 14 probe set suggested the breakpoints of der(14) as 14q13 and 14q32.33. This was confirmed with locus-specific fluorescence *in situ* hybridization probes. For aMCB the normal (#14) and the derivative [der(14)] chromosome 14 are shown with a pseudocolor banding pattern and the corresponding underlying fluorochrome profiles. Schematic depiction of the der(14)(pter->q32.33::q32.33->q13::q32.33->qter) is also shown. (B) High-resolution array-comparative genomics revealed substantial genomic imbalances, including a loss in 9p21.3 detected initially by multiplex ligation-dependent probe amplification (result not shown) and gain of 14q13.2-q32.33 (black arrows). aMCB, high-resolution array-proven multicolor-banding; der, derivative chromosome.

kit (Agilent Technologies, Inc.), according to the manufacturer's protocol. Following hybridization, the aCGH slide was scanned and processed by Feature Extraction software version 10.7 (Agilent Technologies, Inc.), and the results were analyzed with CytoGenomics software version 2.9.1.3, using adrenomedullin 2 as an aberration algorithm.

Results

Molecular cytogenetics. G-banding at a low resolution did not reveal any chromosomal aberrations. Retrospective application of mMCB revealed only one gross chromosomal alteration, which was an inverted duplication on chromosome 14. In order to characterize the rearrangement in detail, additional FISH experiments, including aMCB for chromosome 14 (Fig. 1A) and locus-specific FISH probes (Table I), were applied, revealing the derivative (der) chromosome der(14)(pter->q32.33::q32.33 ->q13::q32.33->qter).

Dual-color FISH, using a commercially available break-apart rearrangement probe specific for *IGH*, was performed. Interphase nuclei and metaphase studies revealed splitting of the IGH variable region and 3' flanking region, located downstream of the IGH locus (data not shown). MLPA analysis revealed heterozygous deletion of $p16^{Ink4A}$, $p15^{Ink4B}$ and $p14^{ARF}$, and this was confirmed by interphase FISH (data not shown).

aCGH. aCGH revealed two large genomic imbalances: A gain of 70.6 Mb in the region of 14q13.2-q32.3 between the positions (according to the Genome Reference Consortium Human 37/Human Genome Issue 19; University of California Santa Cruz Genome Bioinformatics, Santa Cruz, CA, USA; avaliable from https://genome-euro.ucsc.edu/index.html) 35,918,265 and 106,513,022, and loss of 3 Mb in the region of 9p21.3 between the positions 21,252,517 and 24,289,720. These observations were compatible with the FISH and MLPA results (Fig. 1B).

Furthermore, aCGH revealed five small genomic imbalances with loss of copy number variants in the following: i) 3q26.32 between the positions 176,825,586 and 177,697,157 [one Online Mendelian Inheritance in Man (OMIM; http://www.omim.org/) gene, transducin (β)-like 1 X-linked receptor 1 (*TBL1XR1*), is located in this position]; ii) 10p15.3 between the positions 1,491,986 and 1,582,072 [two OMIM genes are located in this position: Adenosine deaminase, RNA-specific, B2 (*ADARB2*), and *NCRNA00168*]; iii) 16q13 between the positions 57,275,940 and 57,331,381 [two OMIM genes are located in this position: ADP-ribosylation factor-like 2 binding protein (*ARL2BP*) and plasmolipin (*PLLP*)]; iv) 21q22.2 between the positions 39,764,621 and 39,865,171 [one OMIM gene is located in this position: *ERG*]; v) Xq13.3 between the positions 47,330,212 and 47,335,227 [one OMIM gene in is located in this position: Zinc finger protein 41 (*ZNF41*; results not shown)].

Discussion

Copy number variants of specific target genes are important in the development and progression of acute leukemia and may serve as potential biomarkers for prognosis, as well as being targets for molecular therapy. Gene amplification is a significant mechanism of oncogene activation in acute leukemia. However, it is difficult to identify or resolve genomic imbalances <10 Mb in size by banding cytogenetics due to poor quality chromosomes, which may not be well-spread and may appear with indistinct margins. Molecular cytogenetic approaches, including FISH, MLPA, and aCGH, have been demonstrated to be useful for detection of previously hidden genomic imbalances (10,22). In the present study, application of the aforementioned approaches revealed a previously unreported genomic imbalance in a B-ALL case: 46,XX, del(9)(p21.3p21.3),der(14)(pter->q32.33::q32.33->q13::q32.33 ->qter). Characterization of this genomic imbalance revealed

Table I. Used probes, their location and obtained results listed according to GRCh37/hg19.

Cytoband	Location (GRCh37/hg19)	Probe	Result
3q26.32	Chr3: 177,272,863-177,430,308	RP11-114M1	Deletion on der(3) ish 3q26.3(RP11-114M1x1)[5]
3q26.32	Chr3: 177,488,843-177,646,481	RP11-91K9	Deletion on der(3) ish 3q26.3(RP11-91K9)[5]
9p21.3/ 9p11.1q11	Chr9: 21,967,751-21,975,132/ Chr9: 47,300,001-50,700,000	SPEC p16/ CEN9	Deletion on der(9) ish 9p21.3(p16x1)[8] nuc ish 9p21(p16x1)[147]/ 9p21(p16x2)[53]
14q11.2	Chr14: 20,814,125-20,814,672	RP11-332N6	1 signal on der(14)
14q11.2	Chr14: 20,940,682-21,103,092	RP11-14J7	1 signal on der(14)
14q12	Chr14: 29,511,827-29,698,386	RP11-125A5	1 signal on der(14)
14q13.1	Chr14: 32,299,162-32,460,130	RP11-501E21	1 signal on der(14)
14q13.2	Chr14: 35,335,072-35,521,841	RP11-26M6	1 signal on der(14)
14q13.3	Chr14: 36,683,813-36,704,814	RP11-259K15	2 signals on der(14)
14q21.1	Chr14:39,897,747-40,060,823	RP11-111A21	2 signals on der(14)
14q21.1	Chr14: 40,408,068-40,537,355	RP11-34O18	2 signals on der(14)
14q21.3	Chr14: 49,809,988-49,981,102	RP11-346L24	2 signals on der(14)
14q21.3	Chr14: 50,148,020-50,148,604	RP11-831F12	2 signals on der(14)
14q23.1	Chr14: 59,967,413-60,142,554	RP11-701B16	2 signals on der(14)
14q24.2	Chr14: 70,701,212-70,701,81	RP11-486O13	2 signals on der(14)
14q31.1	Chr14: 80,030,106-80,193,689	RP11-242P2	2 signals on der(14)
14q32.3	Chr14: 106,053,226-106,518,932	LSI IGH	Split signals on der(14)
14qter	Chr14: 107,038,129-107,238,316	D14S1420	1 signal on der(14)

Genome Reference Consortium Human 37/Human Genome Issue 19; Chr, chromosome; der, derivative chromosome; GRCh37/hg19; ish, *in situ* hybridization and aberrations detected in metaphase; nuc; nuclear and aberrations detected in interphase.

that the involvement of the cancer-associated oncogene *IGH@* at 14q32.33 was critical in the leukemogenic process (4).

Inversions (inv) within the long arm of chromosome 14 are common karyotypic abnormalities in T-cell lymphoid malignancies, including T-chronic lymphocytic leukemia and adult T-cell leukemia. By contrast, in B-cell-lineage ALL, inv(14)(q11q32) involving CEBP ε and *IGH@* is a rare phenomenon that is associated with improved prognosis and has been reported to be linked with complete remission (4,23,24). The positive outcome of the present study supported this observation.

To the best of our knowledge, a derivative chromosome 14, such as the one reported in the present study, has not been previously observed in ALL. Fig. 2 depicts a suggestion as to how the genetic rearrangement may have occurred. As it was a rearrangement involving an interstitial part of the long arm of chromosome 14, U-type exchange mechanisms, as reported in comparable cases from clinical genetics (25), may be discounted.

Homozygous deletions of the tumor suppressor genes *p16*^{Ink4A}, *p15*^{Ink4B} and *p14*^{ARF} at 9p21 represent a marker of unfavorable outcome. Thus, the heterozygote deletion observed in the present case may be an indication of the requirement for careful follow-up of the patient; particularly as there is evidence to suggest that the prognosis is associated with, and depends upon, the treatment received (9-13).

The present patient exhibited copy number changes in five regions, the clinical significance of which remain to be elucidated. The identification of a novel copy number change may lead to the identification of functionally important genes in leukemogenesis. Firstly, deletion of the *TBL1XR1* gene on 3q26.32 has been detected in ETS variant 6-runt-related

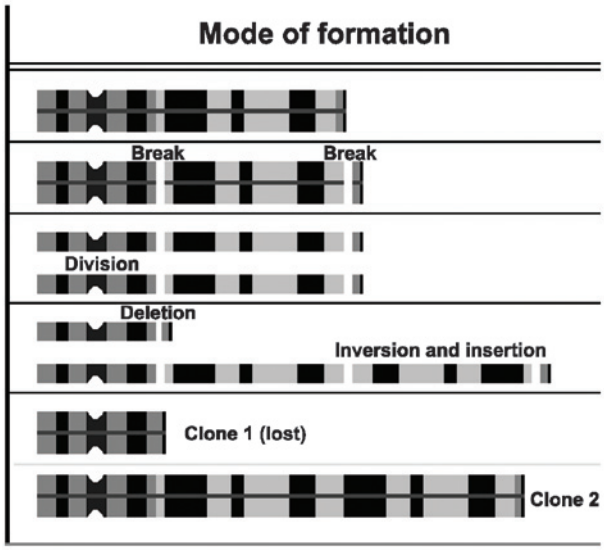

Figure 2. A suggested mode of formation for the derivative chromosome 14, as shown in Fig. 1A.

transcription factor 1-positive ALL, primary central nervous system lymphoma and diffuse B large cell lymphoma. Notably, *TBL1XR1* is widely expressed in hematopoietic tissues and may have a significant regulatory role in the nuclear factor-κB signaling pathway, suggesting that *TBL1XR1* may have a potential biological role in ALL pathogenesis (26,27).

Secondly, *ADARB2* at 10p15.3, which encodes a member of the double-stranded RNA adenosine deaminase family of RNA-editing enzymes, may possess a regulatory role in RNA editing, as well as functioning as a tumor suppressor gene. Overall, a reduction in RNA levels of *ADARB2* due to a deletion may favor cancer development and progression (28,29).

Thirdly, a recurrent deletion was identified on 21q22.22 that exclusively targets *ERG*. The *ERG* gene is a transcription factor and a member of the ETS family. The ETS family has a significant regulatory role in hematopoietic differentiation during early T- and B-cell development. Overexpression of the *ERG* gene was observed in acute myeloid leukemia and T-cell ALL and was associated with poor prognosis. Deletion of the *ERG* gene is considered to be associated with a positive outcome in older children and young adults with B-cell precursor-ALL, as was additionally observed in the present case in the form of complete remission and no indication of MRD (30,31).

Finally, to the best of our knowledge, submicroscopic losses of *ARL2BP*, *PLLP* and *ZNF41* genes were reported in the present study for the first time in ALL. *ARL2BP* is part of the ADP ribosylation factor family of RAS-associated GTPases, and has an essential role in photoreceptor maintenance and function. Homozygous mutation in the *ARL2BP* gene was identified in retinitis pigmentosa, with or without situs inversus (32). In addition, overexpression of the *PLLP* gene has been detected in malignant pleural mesothelioma (33). Furthermore, mutations in *ZNF41*, a transcription factor that is part of a cluster of human zinc finger genes on chromosome Xp11.23, have been identified in X-linked mental retardation (34).

Overall, the present study identified unbalanced acquired gross and submicroscopic rearrangements in a case of B-ALL, which had not been reported previously in this unique combination, to the best of our knowledge. The clinical consequences of the individual changes remain to be elucidated in detail. However, it is notable that treatment according to the PALG protocol achieved complete remission.

In conclusion, molecular cytogenetic approaches are a useful tool for the identification of cryptic rearrangements and potential novel target genes for prevention of leukemogenesis and progression of disease, as well as for clinical outcome predictions and selection of appropriate treatment options. The results of the present study suggested that the detection of submicroscopic alterations in B-ALL, including deletion of *TBL1XR1, CDKN2A*/*B* and *ERG* genes, that are associated with a positive outcome may be useful for diagnosis and risk stratification, particularly for future protocols that include B-ALL patients.

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