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The origin of deletion 22q11 in chronic lymphocytic leukemia is related to the rearrangement of immunoglobulin lambda light chain locus

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ABSTRACT

The technology of array comparative genomic hybridization (array-CGH/aCGH) enabled the identification of novel genomic aberrations in chronic lymphocytic leukemia (CLL) including the monoallelic and biallelic deletions affecting 22q11 locus. In contrast to previous publications, we hypothesized that the described 22q11 deletions are a consequence of the rearrangement of immunoglobulin lambda light chain locus (IGL) segments surrounding several protein-coding genes located in this region. Indeed, using array-CGH and PCR analysis we show that all deletions ($n = 7$) affecting the 22q11 locus in our cohort ($n = 40$) are based on the physiological mechanism of IGL rearrangement. This demonstrates that this loss of genetic material is likely not pathogenic and in fact is merely a marker of IGL rearrangement.

1. Introduction

Chromosomal aberrations examined by classical karyotype analysis or fluorescent in situ hybridization (FISH) can be detected in ≥80% of chronic lymphocytic leukemia (CLL) patients. Deletions of 13q14, 17p13, 11q23, and trisomy 12 are frequently used to define prognosis of CLL patients [1–3]. The precise molecular analysis of these regions allowed for the elucidation of the affected genes (like miR-15a-16-1, *TP53*, *ATM*) and understanding of their functions in CLL pathogenesis and/or progression [2,4]. Recently, array comparative genomic hybridization (array-CGH) enabled the identification of other genomic aberrations in CLL cells with potential pathogenetic relevance [5–8].

Significantly, several groups have performed array-CGH analysis in large cohorts of CLL patients and described the monoallelic and biallelic deletions of chromosome 22q11 in CLL [7,9–11]. The largest study by Gunn et al. [9] identified these deletions in 15% of CLL cases (28/187) and analyzed their size in detail. In that study, 22q11 deletion was the second most frequent abnormality after 13q deletion in 187 CLL cases screened by BAC array-CGH. The subsequent breakpoint mapping based on agilent human genome 44K CGH arrays led to the description of minimally deleted region (0.34 Mb) containing protein-coding genes PRAME (preferentially expressed antigen in melanoma), GGTLC2 (gamma-glutamyltransferase light chain 2), ZNF280A (zinc finger protein 280A), and ZNF280B (zinc finger protein 280B) [9]. Authors suggested that the PRAME gene is the candidate tumor-suppressor localized in 22q11 [9], because it was previously associated with the biology and aggressiveness of both solid tumors and myeloid hematological malignancies [12–15].

The repeated description of cases with aberrations in 22q11 locus prompted us to characterize in detail such deletions and their possible consequences on gene expression. This genomic region contains the segments (subgenes) for immunoglobulin lambda light chain (IGL) together with above-mentioned protein coding genes and one microRNA gene (miR-650) [16]. This is a unique feature of IGL locus, because immunoglobulin kappa light chain locus (IGK) or heavy chain locus (IGH) does not contain any protein-coding genes or microRNAs. Recently, we reported that the microRNA gene (miR-650) located in this locus can be activated by specific rearrangement of IGL [16]. However, in contrast to previous authors, we hypothesized that the described deletions at 22q11

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Table 1
Results of I-FISH and array-CGH analysis in 40 CLL patients (ND stands for "not determined").

Sample ID	Age at diagnosis/sex	IGHV germ-line homology	Chromosome 17		Chromosome 11		Chromosome 13		Chromosome 12		Array-CGH-chromosome 22				Immunoglobulin locus rearrangement	
			FISH del(17)(p13)	Array-CGH-locus 17p13	FISH del(11)(q23)	Array-CGH-locus 11q23	FISH del(13)(q14)	Array-CGH-locus 13q14	FISH trisomy 12	Array-CGH-trisomy 12	Array-CGH-deletion at 22q11	Array-CGH-Start of the del. (1st del.probe)	Array-CGH-End of the del. (last del.probe)	Array-CGH-size of the del. (bp)	Immunoglobulin lambda light chain locus rearrangement	Detection of utilized IGLV segments
CLL01	69/M	99%	Neg	Neg	98%	del 11q14.1-q23.2	98%	del 13q14.2-3	Neg	Neg	Yes	21004565	21514827	510262	Yes	IGLV3-21
CLL02	71/F	100%	Neg	Neg	92%	del11q22.1-q23.2	Neg	Neg	70%	amp 12p + amp 12q11-q15	Yes	20747615	21514827	767212	Yes	IGLV6-57
CLL03	69/F	100%	43%	del 17p11.1-p13.3	Neg	Neg	82%	del 13q14.3	Neg	Neg	Yes	21174548	21514827	340279	Yes	IGLV5-39
CLL04	44/F	100%	Neg	Neg	Neg	Neg	18%	Neg	Neg	Neg	Yes	21174548	21514827	340279	Yes	IGLV1-44
CLL05	64/F	100%	98%	del 17p	Neg	Neg	Neg	Neg	Neg	Neg	Yes	21174548	21514827	340279	Yes	IGLV1-44
CLL06	69/F	ND	Neg	Neg	Neg	Neg	70%	del 13q14.2-3	Neg	Neg	Yes	21004565	21514827	510262	Yes	IGLV1-51
CLL07	57/F	100	Neg	Neg	Neg	Neg	80%	del 13q14.2	Neg	Neg	Yes	20894376	21514827	620451	Yes	IGLV3-19
CLL08	75/F	96.50%	73%	del 17p11.1-p13.3	Neg	Neg	62%	del 13q14.3	Neg	Neg	No	–	–	–	Yes	IGLV2-23
CLL09	71/M	100%	85%	del 17p	Neg	Neg	Neg	Neg	Neg	Neg	No	–	–	–	Yes	IGLV2-5
CLL10	50/M	100	Neg	Neg	85%	del 11q22.1-23.2	30%	del 13q14.2	Neg	Neg	No	–	–	–	Yes	IGLV2-23
CLL11	83/M	100%	9%	Neg	Neg	Neg	Neg	del 13q14.3	Neg	Neg	No	–	–	–	Yes	IGLV3-21
CLL12	61/F	93.50%	Neg	Neg	Neg	Neg	86%	del 13q14.2-q14.3	74%	12	No	–	–	–	Yes	IGLV3-27
CLL13	56/F	100	Neg	Neg	Neg	Neg	Neg	del 13q 14.1–14.2	Neg	Neg	No	–	–	–	Yes	IGLV2-8
CLL14	66/M	ND	62%	del 17p	Neg	Neg	62%	del 13q13.3-q21.33	Neg	Neg	No	–	–	–	Yes	IGLV2-14
CLL15	68/M	100%	35%	del 17p11.1-p13.3	Neg	neg	25%	del 13q14	Neg	Neg	No	–	–	–	Yes	IGLV3-21
CLL16-40 ($n=25$)	Average age: 63 F/M: 6/19	>98% $n=21$ <98% $n=1$ ND $n=3$	del $n=8$ undel $n=16$ ND $n=1$	del $n=8$ undel $n=17$ ND $n=0$	del $n=6$ undel $n=18$ ND $n=1$	del $n=6$ undel $n=19$ ND $n=0$	del $n=13$ undel $n=11$ ND $n=1$	del $n=13$ undel $n=12$ ND $n=0$	+12 $n=5$ neg $n=19$ ND $n=1$	+12 $n=5$ neg $n=20$ ND $n=0$	No	–	–	–	No	IGKV (kappa IG light chain)