ADAM3A deletion is associated with high-risk features in acute lymphoblastic leukemia

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Abstract. Acute lymphoblastic leukemia (ALL) is a malignant proliferation of lymphoid cells characterized as a heterogeneous disease at demographic, clinical and genetic levels. Copy number alterations (CNAs) are defined as secondary abnormalities subsequently required for the establishment of the leukemic clone. As the risk stratification of ALL is partly based on genetic analysis, different genomic tools are increasingly being used to screen for novel genetic biomarkers. In the present study, through array-comparative genomic hybridization (aCGH), CNAs in 12 *ADAM* genes were investigated and their association with clinicopathological features in 16 pediatric ALL cases was evaluated. The most frequent amplification was found in *ADAM6* (94%), and deletion was more common in *ADAM3A* (31%). *ADAM3A* deletion were associated with male patients (P=0.025), leukocytosis (P=0.007) and high-risk cases (P=0.004). However, the effects of aberration on *ADAM* genes still needs to be fully defined in hematological malignancies, particularly in leukemia. The findings of the present study corroborate those of previous studies that suggest that *ADAM* genes play a role in carcinogenesis.

Introduction

Acute Lymphoblastic Leukemia (ALL) is characterized by primary and secondary genetic aberrations, which lead the initiation and progression of the leukemic clone (1,2). Primary abnormalities are often chromosomal translocations, whereas secondary abnormalities are usually copy number alterations (CNAs) and point mutations, which may be present in only a subset of leukemic cells (2).

Chromosomal abnormalities are used as biomarkers to provide subtype, outcome and therapeutic response information. The application of genomic tools either in cases with or without an established abnormality revels copy number alterations, which can be used alone or in combination as prognostic information (3).

Initially, the role of a disintegrin and metalloproteases (ADAMs) proteins was limited to the fusion of gametes; however, due to their adhesion properties in intercellular interactions, their involvement in tumor biology has also been suggested (4).

Members of the ADAM family are currently an object of considerable scientific attention, due to their role in numerous signaling pathways associated with carcinogenesis, such as phosphoinositide 3-kinase (PI3K), Notch and transforming growth factor (TGF)-β (5-7). Research concerning ADAMs often focuses on their role in carcinogenesis and as potential targets of novel anticancer therapies (8,9).

The properties of ADAMs mentioned above render them an important object of interest in cancer. Thus, the present study investigated CNAs in 12 different *ADAM* genes that have been implicated in carcinogenesis and associated their CNA status with the clinicopathological data of ALL pediatric patients. The findings of the present study demonstrate that the deletion of *ADAM3A* is significantly related to leukocytosis and high-risk cases.

Patients and methods

Patients. In the present study, 16 ALL pediatric patients (5±3 years old) treated at Octávio Lobo Children's Cancer Hospital were selected for *ADAMs* copy number investigation by array-comparative genomic hybridization (aCGH). The patients were classified by immunophenotyping and morphology. The phenotypic diagnosis was performed by flow cytometry at Octávio Lobo Children's Cancer Hospital, using peripheral blood and/or bone marrow samples and staining-lyse-wash protocols. The diagnosis for ALL includes an acute leukemia orientation cell line screening

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test: CyMPO/CD79a/CD45/CD3c; CD19/CD7/CD45/CD34; the following combinations were used to classify B-ALL: CD34/CD20/CD19/CD10; CyIgM/CD13/CD19/CD22; nTdt/CD33/CD19/CD38 and nTdt/CD7/CD3c/CD10; CD8/CD7/CD4/CD3s; CD2/CD1a/CD5/CD7 for T-ALL cases. Gene fusions were investigated through reverse transcription-polymerase chain reaction (RT-PCR). The blood samples were collected prior to cancer treatment between 2017 and 2019 (Table I).

The age at diagnosis and white blood cell (WBC) count were the criteria for assigning the prognostic risk of ALL, according to the National Cancer Institute (NCI) (10): i) High-risk, WBC count >50x10^9 cells/μl, age ≤1 year, or age ≥10 years; and ii) standard risk, WBC count ≤50x10^9 cells/μl, or between 1 and 10 years of age. Cases with *BCR-ABL1 or MLL-AF4* also were assigned to the NCI high-risk group. Written consent forms were obtained from all parents of the patients. The present study was approved by the Octávio Lobo Children's Hospital Ethics Committee (CAAE: 00905812.1.0000.00.18).

RT-PCR. Total RNA was extracted from blood samples using the RNeasy Mini kit (Qiagen GmbH). RT-PCR was performed using a High Capacity c-DNA Reverse Transcription kit (Applied Biosystems; Thermo Fisher Scientific, Inc.), according to the manufacturer's instructions. Multiplex PCR was performed to identify the fused transcripts using the primers listed in Table II. The reactions were performed in a GeneAmp Thermal Cycler 2720 (Applied Biosystems; Thermo Fisher Scientific, Inc.).

Briefly, 1 μl of 10 ng cDNA was added to 4.25 μl nuclease-free water (Ambion; Thermo Fisher Scientific, Inc.); with 6,25 μl of GoTaq Colorless Master Mix (Promega Corp.) and 0,5 μl of each primer. The following profile was used: Denaturation at 95˚C for 3 min, followed by 35 cycles of 94˚C for 2 min, 61˚C for 1 min and 70˚C for 2 min in each cycle. The final extension at 70˚C by 30 min was carried out to guarantee the complete elongation of all PCR products.

PCR products were viewed on agarose gel electrophoresis performed by 30 min at 100 V with 1% agarose gel in a TBE buffer (Tris-Borate-EDTA) stained with SYBR® Safe DNA Gel Stain (Life Technologies; Thermo Fisher Scientific, Inc.). The visualization of possible bands on the gel was performed using a Safe Imager 2.0 Blue Light Transiluminator (Invitrogen; Thermo Fisher Scientific, Inc.).

aCGH. Genomic DNA was extracted from peripheral blood by Pure Link Genomic DNA Mini kit (Invitrogen; Thermo Fisher Scientific, Inc.). aCGH was performed using Agilent 4x180k CGH + SNP microarray (Agilent Technologies, Inc.). Following DNA extraction, a restriction enzyme digestion step and labeling with fluorochrome cyanine 5 were performed using random primers and exo-Klenow fragment DNA polymerase. DNA control was labeled with fluorochrome cyanine 3. DNA samples from the patients and controls [controls were samples of human genomic DNA (male or female) used as reference sample, which were supplied with the Agilent aCGH kit] were combined and hybridized on the microarray. Data were analyzed using Agilent's CytoGenomics v5.0 software.

Statistical analysis. Statistical analysis for comparisons of the CNAs between subgroups and pathological features of the patients was performed using the Chi-squared test (two-sided) or Fisher's exact test, as appropriate. The analyses were performed using the PASW Statistics program. P-values <0.05 were considered to indicate statistically significant differences.

Table I. Clinicopathological data.

Characteristic	aCGH (n=16)
Male:female	8:8
Median age (years)	6.5
Median WBC count (x10^9/l)	73
Immunophenotype[a]	
B-cell lineage	16
T-cell lineage	
Karyotypic alterations investigated[b]	
TCF3-PBX1 (n)	6
BCR-ABL1 (n)	1
MLL-AF4 (n)	
ETV6-RUNX1 (n)	
NCI risk	
High (n)	7
Standard (n)	9
Deaths (%)	3
	81

[a]Data obtained by flow cytometry; [b]data obtained by RT-PCR. NCI, National Cancer International; WBC, white blood cell count. Patients at high risk were considered those with a WBC count >50x10^9 cells/μl, an age of ≤1 year, or an age of ≥10 years. Patients with standard risk were those with a WBC count ≤50x10^9 cells/μl, or an age between 1 and 10 years.

Results

All samples exhibited at least one aberration to one of the investigated *ADAM* genes (Table III). These genes are described in the literature as being associated with the carcinogenesis of numerous types of cancer. For the 12 genes investigated, only *ADAM29* exhibited no changes. The most frequent aberrations were amplifications of *ADAM6* (94%). Notably, *ADAM3A* was deleted in 31% of the samples whilst it was amplified in 31%. It is noteworthy that 8 of these gene alterations have not been previously associated with ALL (Table III).

The occurrence of gene aberration according to the NCI risk group, sex, age and cytogenetic findings in at least 2 samples is presented in Table IV. Deletions involving *ADAM3A* were significantly associated with male patients (P=0.025), leukocytosis (P=0.007) and NCI-HR cases (P=0.004). We did not find significant results correlating any other genes (Table IV).

A total of 5 patients (31%) were hyperdiploid. The majority of the detected chromosomal gains corresponded to trisomies, gain of chromosomes X, 6 and 3 were the most frequent. A hypodiploid patient with loss of chromosomes 2, 3, 9, 11, 12, 18, 19 and 20 was also identified (data not shown). However, no significant results were found associating any numerical chromosomal abnormalities.

Table II. Nucleotide sequence of RT-PCR primers.

Genes	Primers (5'-3')	Size (bp)	Position	Exons
TCF3	CTACTCCCCGGATCACTCAA	20	1086-1105	13
PBX1	AGGCTTCATTCTGTGGCAGT	20	3893-3912	2
MLL	CGCCCAAGTATCCCTGTAAA	20	4071-4090	8
AF4	GAGCATGGATGACGTTCCTT	20	1546-1565	8
BCR	TCGCAGAACTCGCAACAGT	19	1707-1725	1
ABL	ACACCATTCCCCATTGTGAT	20	284-303	3
ETV6	TCTCTCATCGGGAAGACCTG	20	1191-1210	5
RUNX1	TGCGGTAGCATTTCTCAGC	19	619-637	5
SIL	TCCTACCCTGCAAACAGACC	20	73-92	1
TAL1	AGGCGGAGGATCTCATTCTT	20	1250-1269	4

Table III. Frequency of alterations in ADAM genes found in childhood ALL samples.

Gene	Cytoband	N (%)	Aberration type	Studies concerning these genes in cancer (Refs.)
ADAM3A[a]	8p11.23	5 (31%)	Amp	(16,17)
		5 (31%)	Del	(12,14,19)
ADAM6[a]	14q32.33	15 (94%)	Amp	(33-36)
ADAM8[a]	10q26.3	2 (12%)	Amp	(4[b],39[b],5)
ADAM9[a]	8p11.22	1 (6%)	Amp	(4[b])
ADAM10	15q21.3	1 (6%)	Del	(11,14,38,40-45)
ADAM12[a]	10q26.2	3 (19%)	Amp	(4,39[b])
ADAM15[a]	1q21.3	1 (6%)	Amp	(4,39[b])
		1 (6%)	Del	
ADAM17	2p25.1	1 (6%)	Del	(9,14,41-45)
ADAM22[a]	7q21.12	1 (6%)	Amp	(8,4[b],39[b])
		1 (6%)	Del	
ADAM28	8p21.2	1 (6%)	Amp	(14,46-50)
ADAM29	4q34.1	0	Not detected	(4,39[b])
ADAM33[a]	20p13	2 (12%)	Amp	(4,39[b])

[a]Alterations that have not been previously described in B-ALL; [b]review by Zadka *et al* (4) and Mullooly *et al* (39). ALL, acute lymphoblastic leukemia; Del, deletion; Amp, amplification.

Discussion

In the present study, the *ADAM* genes investigated exhibited a low frequency of CNAs, with the exception of the *ADAM6* gene, which was amplified in 94% of the samples and *ADAM3A* (amplified in 31% and also deleted in 31% of cases) (Table III). This similar frequency between *ADAM3A* aberrations is probably due the intra- and inter-heterogeneity of malignant cells or the reduced sample size.

The ADAM protein family includes 29 members that are known to play an important role in the regulation of cell adhesion, the activation of oncogenic receptors (Notch and HER2), tumorigenesis, in cell migration and in the production of cytokines and growth factors; however, the specific functions of the majority of *ADAM* genes are not yet fully understood (11-13).

Concerning other members of *ADAM* family, overexpression of *ADAM28* was found in lung and breast carcinomas, while loss of expression of *ADAM23* was found in breast tumors (14). *ADAM17* has been shown to be involved in EGFR regulation and their overexpression in astrocytes promotes an increase in cell proliferation and invasion (14).

ADAM3A is located at chromosome 8p11.23, the locus that exhibits a strong association with cancer (13). *ADAM3A* amplifications have been observed in squamous cell carcinoma of the conjunctiva and in a subtype of B-cell lymphoma (15,16). The amplification of genes located on 8p11.23 has been linked to tumor development and metastasis (17,18); however, in the present study, no significant clinicopathological association with *ADAM3A* amplification was found.

As regards deletions of *ADAM3A*, these have been previously identified in high-grade gliomas, cribriform

Table IV. Frequency of specific gene deletion or amplification according to the clinicopathological data in at least 2 ALL samples.

	ADAM6 amplification		*ADAM3A* deletion		*ADAM8* amplification		*ADAM12* amplification		*ADAM33* amplification	
Characteristic	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent
HR	7	0	5	2	2	5	3	4	0	7
SR	8	1	0	9	0	9	0	9	2	7
P-value	0.362		0.004[d]		0.175		0.062		0.475	
≤1 years of age	1	0	0	1	0	1	0	1	0	1
>1 to ≤10 years of age	12	1	4	9	1	12	2	11	1	11
>10 years of age	2	0	1	1	1	1	1	1	1	2
P-value 1[a]	0.773		0.511		0.773		0.671		0.763	
P-value 2[b]	NC		0.386		0.386		0.386		0.505	
P-value 3[c]	0.684		0.591		0.257		0.254		0.371	
WBC >50	5	0	2	3	1	4	1	4	0	5
WBC ≤50	10	1	3	8	1	10	2	9	2	9
P-value	0.482		0.999		0.540		0.982		0.541	
Leucopenia	2	0	0	2	1	0	1	1	1	1
Leucocytosis	9	1	5	5	1	9	1	9	0	10
P-value	0.640		0.469		0.181		0.3182		0.166	
Leucocytosis	9	1	5	0	1	9	1	9	0	10
Normal	4	0	0	4	0	4	1	3	1	3
P-value	0.511		0.007[d]		0.511		0.468		0.285	
Leukopenia	2	0	0	2	1	0	1	1	1	1
Normal	4	0	0	4	0	4	1	3	1	3
P-value	NC		NC		0.200		0.540		0.540	
Male	7	1	5	3	2	6	3	5	0	8
Female	8	0	0	8	0	8	0	8	2	6
P-value	0.301		0.025[d]		0.466		0.200		0.466	
CT^+	6	1	1	6	1	6	1	6	2	5
CT^-	9	0	4	5	1	8	2	7	0	9
P-value	0.437		0.307		0.466		0.686		0.175	

HR, NCI high risk; SR, NCI standard risk; CT^+, positive for any gene fusion; CT^-, negative for all gene fusions; NC, not calculated. [a]P-value derived from comparison between ≤1 year of age vs. >1 to ≤10 years of age; [b]P-value derived from comparison between ≤1 year of age vs. >10 years of age; [c]P-value derived from comparison between >1 to ≤10 years of age vs. >10 years of age; [d]P≤0.05, denotes statistically significant differences between groups with and without aberration.

neuroepithelial tumors and extranodal NK/T cell lymphoma of the nasal type (12,14,19). Dun *et al* (20) found frequent 8p11.23 deletion as secondary genetic abnormalities in cases *ETV6-RUNX1*-positive leukemia. However, to the best of our knowledge, the present study is the first to describe *ADAM3A* deletion in leukemia. It is important to note that all samples with *ADAM3A* deletion investigated herein were negative for the gene fusions *ETV6-RUNX1*, *BCR-ABL1, MLL-AF4* or *TCF3-PBX1* (Table I).

Furthermore, deletions on the short arm of chromosome 8 (8p) are common in different tumor types (20-24), suggesting that tumor suppressor genes on 8p are frequently co-deleted reinforcing the functional role of those genes in carcinogenesis (24).

In the present study, the deletion of *ADAM3A* was associated with high-risk cases (NCI-risk) and leukocytosis. This finding is consistent with the observation that CNAs in 8p11 (both amplification and deletion) are commonly associated with a more aggressive tumor phenotype (24), which is the case for high-risk ALL patients.

Of note, *ADAM3A* deletion also exhibited an association with male patients. These results indicate a potential sex-specific association between *ADAM3A* deletion in the study population of the present study. One explanation could be the fact that males are generally more exposed to carcinogenesis than females (25). However, the exact reasons for this apparent sex-specific association and the risk of leukemia cannot be fully explained.

Leukocytosis typically occurs in response to hematological malignancies and inflammation, among others conditions (25,26). Among the mechanisms that connect inflammation to cancer are intrinsic factors, which include acquired genetic alterations affecting oncogenes, tumor suppressors and genome stability genes that contribute

to the activation of the inflammatory pathways (26,27). Several molecular and cellular signaling pathways have been identified as links between inflammatory processes and cancer development (27,28).

Moreover, in different types of cancer, the inflammatory process often determines the development of a tumor and has an impact on the course and prognosis of the disease (28,29). Elevated levels of certain metalloproteinases have been reported in some types of inflammatory responses (29,30). ADAM proteins are expressed among others, by human lymphocytes, and they can interact with adhesion proteins located on the surface of other leukocytes (30,31).

The capacity of certain ADAMs to differentiate immunologically competent cells suggests that they play an important role in immunological processes (31,32). Dendritic cells, B cells and monocyte subpopulations also express these proteins, which indicates the important roles of ADAMs in cancer prognosis (4,32,33).

Thus, it was hypothesized that *ADAM3A* may act as a tumor suppressor in ALL. It was suggested that *ADAM3A* deletion, alone or combined with other tumor suppressor genes in this genomic region, plays an important role in leukemic transformation, contributing to the activation of inflammatory pathways.

There are few studies available regarding the role of *ADAM6* in cancer; however, they demonstrate a potential association in cancer development, similar to the other members of the ADAM family (34-37).

Studies *in vitro* on different types of tumor cells (6,38-40) have demonstrated that the biological function of *ADAM10* can be cell type-specific, that is, depending on the substrate activated by this gene.

Liu and Chang (41) demonstrated that the protease PILP-1-induced death of leukemia cells was mediated through the downregulation of *ADAM17* and the subsequent inactivation of Lyn and Akt. Several studies have focused on the importance of *ADAM17* upregulation in tumor malignancy (42-44). Thus, based on these studies, the suppression of *ADAM17* protein expression may have potential for cancer therapy.

ADAM28 is overexpressed in several cancer types and is related to cell proliferation and lymph node metastasis (45-48). The overexpression of *ADAM28* is asscoiated with relapse and is potentially regulated by the PI3K/Akt pathway, suggesting that *ADAM28* may be a novel biomarker for evaluating relapse in B-ALL and as a potential therapeutic target in B-ALL patients (49).

In B-CLL culture, *ADAM28* knockdown has been shown to decrease the release of CD200 (a membrane glycoprotein of the immunoglobulin superfamily), indicating that *ADAM28* plays a role in the shedding of CD200 from B-cell CLL cells (50).

In conclusion, the present study reinforces that aCGH allows the identification of novel genes associated with cancer and emphasizes the need for including the investigation of submicroscopic aberrations as additional markers for risk stratification. Through this technique, recurrent aberrations in *ADAM* genes were identified in the present study, particularly in *ADAM3A* and *ADAM6*, suggesting that these genes may have important functions in carcinogenesis. Thereby, *ADAM3A* deletion can be related to leukemic process in patients with high-risk characteristics. Although the sample size was limited, the results of the present study should be considered, taking into account that the associations observed were concordant with those of previous studies mentioned above. There is substantial evidence supporting the involvement of *ADAMs* in cancer formation or progression. Thus, the effects of the aberration on these genes need to be fully defined in hematological malignancies, particularly in leukemia.

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Availability of data and materials

The data and material that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

JABG was involved in the conceptualization and methodology of the study, and in the investigation, writing and preparation of the original draft, and visualization. FARMJr was involved the methodology and investigative aspects of the study. MPCDS was involved in the study methodology. AVW and EHCDO were involved in providing resources, study methodology and visualization. ASK was involved in the conceptualization of the study, study supervision and visualization, and in the writing, reviewing and editing of the manuscript. All authors reviewed and approved the final manuscript.

Ethics approval and consent to participate

The Octávio Lobo Children's Cancer Hospital Ethics Committee approved the present study (CAAE: 00905812.1.0000.00.18). The parents of the patients provided consent to participate in the study by signing a Consent Form allowing the use of biological samples and clinical data.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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