Genetic Alterations in Pediatric Acute Lymphoblastic Leukemia

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Introduction

Acute Lymphoblastic Leukemia (ALL) is a malignant clonal proliferation of precursor limphoid cells, B and T.

Despite this hematologic tumour can occur at all ages, it is the most prevalent malignancy in **childhood** and it has a preponderance in males over females. Specifically, in Spain it comprised 28,5% of childhood malignancies between 1983 and 2002.

ALL is a multistep process associated with the acquisition of **genetic and epigenetic alterations** in the leukemic blast cells, that varies according to the age *(Figure 1)*, and it is a **heterogeneous disease** composed of multiple biological subgroups. (*Figure 2)*

Proliferation and accumulation of blasts cells in the bone marrow results in a suppression of hematologic processes, causing **symptoms** that reflect bone marrow failure (pancytopenia), as anaemia, thrombocytopenia and neutropenia.

It can be distinguished different methods of **diagnosis**. Firstly, the morphological diagnosis is made with an assessment of the bone marrow. Secondly, it is important flow cytometry, that is the standard procedure for ALL diagnostic and subclassification and also allows to detect minimal residual disease. In addition, cytogenetics, FISH and karyotyping, are an important step in ALL classification because conventional karyotyping can be helpful in identification of recurrent translocations and gain and loss of chromosomal material. Next-generation sequencing approaches are important to comprehensively identify genetic alterations in the genome and transcriptome.

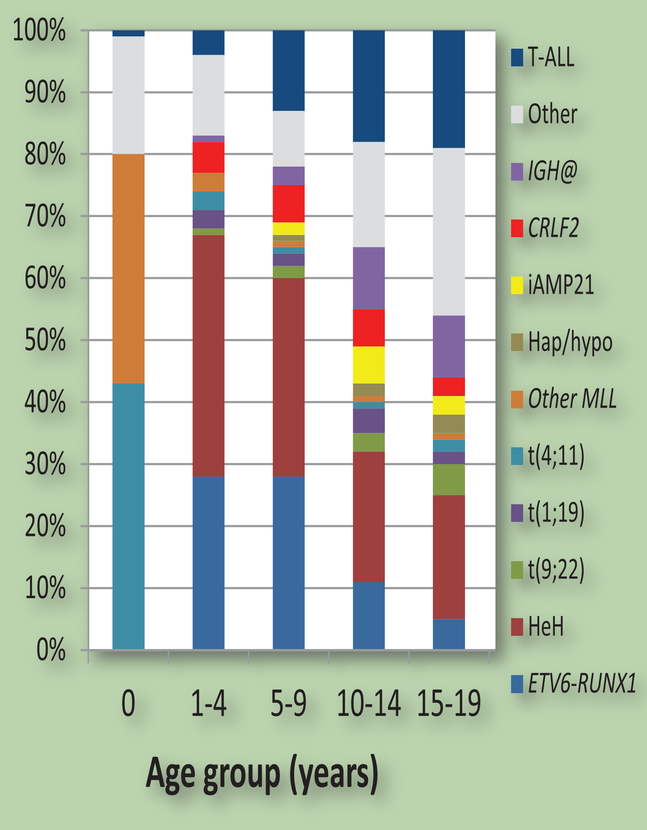

Figure 1. Distribution of different cytogenetic subgroups according to age. *(1)*

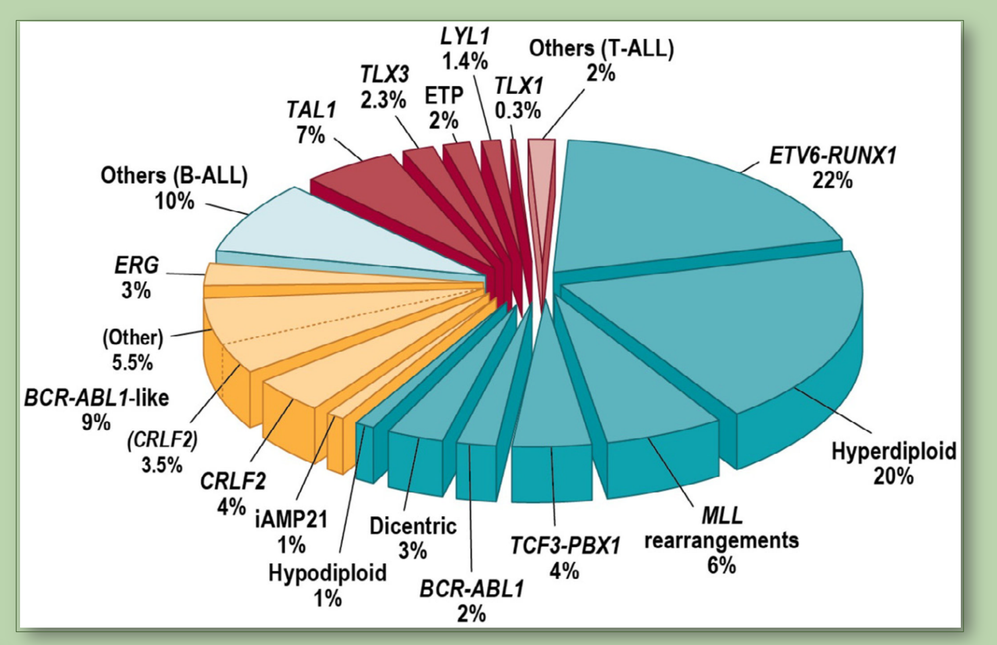

Figure 2. Subclassification of childhood ALL. Blue wedges refer to B-progenitor ALL, yellow to recently identified subtypes of B-ALL, and red wedges to T-lineage ALL. B-ALL correspond to the 85% and T-ALL to the 15% of all cases. *(2)*

Aim of the project

The aim of this project is do a review of the main genetic alterations in pediatric ALL and its prognosis, using articles published between 2012 and 2015 and searched in PubMed.

Results

Approximately 75% of childhood ALL cases have recurrent genetic abnormalities, including aneuploidy, chromosomal arrangements and submicroscopic DNA mutations.
Childhood ALL is considered a sporadic disease, but predisposition exists in <5% of cases, as occurs in Down Syndrome. Patients with this syndrome have 20-fold increased incidence of ALL.

It is noteworthy that many of the involved genes are related with key roles in lymphoid development, cell cycle regulation and tumour suppression, apoptosis regulators, lymphoid signalling, transcriptional regulators, and chromatin structure and epigenetic regulators.

In **B-ALL** should be highlighted **numerical abnormalities**, that may involve ploidy changes or gain or loss of individual chromosomes (aneuploidy). It is important that ploidy is considered an imperative prognostic factor in childhood ALL. In this type of alterations, it can be distinguished hight hiperdiploidy, low hiperdiploidy, hipodiploidy and near haploidy. *(Table 1)*
Furthermore, there are **recurrent translocations**, such as ETV6-RUNX1 and MLL with different partners, and **genic alterations**, such as iAMP21 or PAX5 mutation. *(Table 2)*

T-ALL is characterized by a worse prognosis compared to B-ALL. In this subgroup there are also translocations involving T-receptor and chromosomal and subchromosomal alterations. Early-T precursor is a new subgroup in T-ALL that has 10% frequency and a poor outcome.

Finally, there are also important **epigenetic alterations**, as DNA metilation, histone modification and miRNA alterations. In this cases the primary genetic sequence is normal but there are other factors that affect gene expression. It should be noted that are reversible events that could be targeted with therapeutic agents. *(Figure 3)*

Alteration	Number of chromosomes	Prevalence (%)	Prognosis
High Hyperdiploidy	51-67	25-30	Good outcome
Low Hyperdiploidy	47-50	-	Poor outcome
Hypodiploidy	<46	5-8	Good outcome with 45 chromosomes and poor outcome with <45, especially with 33 to 44 chromosomes
Near Haploidy	23-29	0,7- 2,4	Poor outcome

Table 1. Genetic alterations in B-ALL: aneuploidy. *Table modified of (3) (4)*

Type of Alteration	Affected Genes	Locus	Functional Consequences	Prevalence (%)	Prognosis
Recurrent translocations	ETV6-RUNX1	t(12;21)(p13;q22)	Altered expression of RUNX1 regulated genes	25	Good outcome
	BCR-ABL1	t(9;22)(q34;q11)	Constitutive tyrosin-kinase protein activation	3-5	Poor outcome
	MLL-partners	(11q23)	MLL codifies a metiltransferase-histone required for hematopoietic regulation	80% in <1 year; 10% children	Poor outcome
	TCF3/E2A-PBX1	t(1;19)(q23;p13)/ der(19)t(1;19)(q23;p13)	Anormal PBX1 activation and transactivation of different genes	6	Poor outcome
	IGH@	14q32	Juxtaposition of IGH@ elements with transcription factor and cytokine receptor	<5	Poor outcome
	BCR-ABL1-like	-	IKZF1 and CDN2A/B deletions, JAK2 mutations, CRLF2 rearrangements	10-12	Poor outcome
Genic alterations	CRLF2	PAR1 (Xp22.3)/(Yp11.3)	IKZF1 alteration, JAK1 mutation, implies constitutive STAT pathway activation	5-7	Poor outcome
	iAMP21	Intrachromosomal amplification of cr21	3 or more copies of RUNX1	2	Poor outcome
	IKZF1	7p12.2	Loss of function of IKAROS transcription factor	14	Poor outcome
	JAK1/2	(1p32.3-p31.3)/(9p24)	Alteration of cytokine signalling and asociated with IKZF1 and CDKN2A/B mutation	10	Increased risk of LLA
	PAX5	(9p13)	Inactivating mutation of the transcription factor	32	No impact
	TP53	(17q13.1)	Loss of tumour suppression genes function	3	Poor outcome
	CREBBP	16p13.3	Alteration of transcriptional regulation	19% relapses	-

Table 2. Genetic alterations in B-ALL: translocations and genic alterations. *Table modified of (2) (3) (5) (6) (7) (8)*

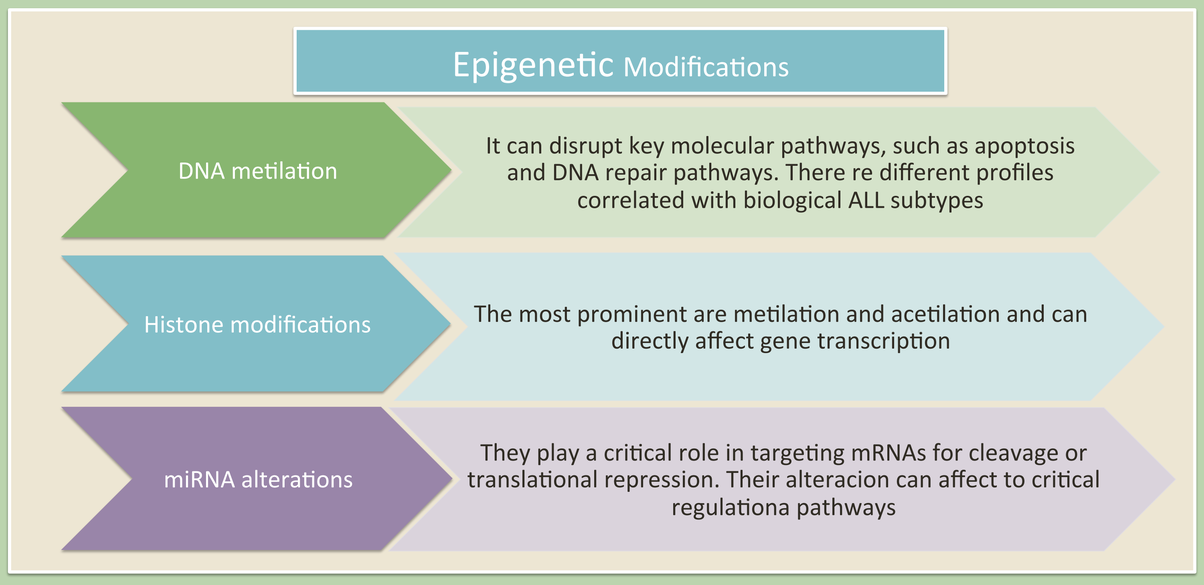

Figure 3. Different types of epigenetic modifications, as DNA metilation, histone modification, miRNA alterations

Conclusions

In this kind of cancer predominate B-progenitor tumours, with genetic and epigenetic alterations. It is important to have in mind that with the analysis and the risk stratification in function of genetic alterations it can be made a prognosis approximation with the aim to administrate the best therapy.

As this kind of cancer is the most frequent in childhood, it will be successful to carry out studies to improve diagnostic and therapeutic approaches.

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