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Chapter 9

Genetic Markers in the Prognosis of Childhood Acute Lymphoblastic Leukemia

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Additional information is available at the end of the chapter

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1. Introduction

Acute leukemia is a broad term used to identify several malignancies of immature hematopoietic cells. Although, variable incidences have been reported between countries, ranging from 46 to 57 cases by million children, it is considered the most common childhood cancer worldwide [1]. Acute lymphoblastic leukemia (ALL) is the most frequent subtype (75%-80% of cases; with the remaining 20-25% being of myeloid origin, AML). In ALL, B cell origin is the most frequently diagnosed (B cell ALL) representing 83%, and T cell ALL comprises 15% [2]. The total of ALL cases represents 30-40% of all types of pediatric cancer[3].

One of the major achievements in cancer therapy has been the increased cure rates for ALL, from 10% in the 60s to 76-86% today, although these favorable numbers are mainly valid for developed countries[4,5]. The improvement in ALL cure rates can be in part attributed to the assessment of conventional prognostic factors and identification of molecular markers associated with a better response to therapy. Suitable risk stratification has permitted a more personalized treatment, selecting patients for receiving standard or intensified therapy, alone or in combination with drugs against ALL specific targets, and together with an enhanced supportive care have contributed to the increase in the event-free survival (EFS) rates[4]. Conventional childhood ALL stratification is based on prognostic factors related to characteristics of the patient (age at diagnosis) and the disease itself white blood cell (WBC) count at diagnosis, immunophenotype of the leukemic cells, presence of known genetic fusions, numerical abnormalities or abnormal gene expression, and early response to therapy (evaluated by morphological methods or using a more accurate measurement such as minimal residual disease (MRD) analysis) [4–6].

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From a genetic point of view, ALL is one of the best characterized malignancies. Numerical and structural chromosomal abnormalities have been described by cytogenetic methods, fluorescence *in situ* hybridization (FISH), polymerase chain reaction (PCR), and more recently, by next generation sequencing. Chromosomal abnormalities are clonal markers of the ALL blast, since the cytogenetic and molecular analyses have revealed that approximately 75% of ALL-children present these genetic lesions [7,8]. To date, more than 200 genes have been found participating downstream of common ALL translocations [9]; interestingly, a handful of these genes are consistently affected in many subtypes of the disease paving the way to better understand homeostatic lymphopoiesis and the leukemogenic process [10].

2. Signaling and transcription factors important in lymphopoiesis and leukemogenesis

Generation of lymphoid cells is a highly ordered multi-step process that in adult mammals starts in bone marrow with the differentiation of multipotent hematopoietic stem cells (HSC) (Figure 1A). HSCs start a differentiation pathway in which the capacity to form multiple lineages is gradually lost coinciding with a gain of lineage specific functions. Thus, HSCs yield multipotent progenitor cells (MPPs) still with myeloid and lymphoid potential, which eventually give rise to lymphoid-primed multipotent progenitor (LMPP) and early lymphoid progenitor (ELP) populations, with a progressive more restrictive lymphoid program. Similarly, ELPs generate early T lineage progenitors (ETP) and common lymphoid progenitors (CLP), and these populations, although still exhibit high plasticity, preferentially give rise *in vivo* to T and B cells, respectively [11,12]. Intrinsic signaling and transcriptional programs shape this differentiation pathway guiding lineage decisions. When these developmental programs are abnormally activated or repressed, can induce the leukemogenic process.

B and T cells are characterized by their potential to express receptors with a highly diverse repertoire of specificities: the B and T cell receptors (BCR and TCR). This diverse specificity is given by a recombination process termed VDJ recombination and it is the sequential assembly and testing of the BCR and TCR what defines the B/T development pathway. The first stages (pro and pre) are characterized by recombination of the antigen binding variable sequences (heavy and light chains for the BCR, and the β, α, γ or δ chains for the TCR) (Figure 1B). The subsequent stages require elimination of auto-reactive clones, and only clones selected against self-recognition become functional mature cells. Genetic and biochemical studies have shown that all forms of the BCR and TCR are required for progression through several defined developmental checkpoints [13,14]. This is an important concept, since it illustrates that different signaling and transcription programs are operating through all developmental stages, and therefore, if an aberrant program is established, development is unable to proceed. As we will see in the following sections, the leukemic gene fusions and other genetic abnormalities produce aberrant signaling pathways or abnormal transcriptional activities, leading to a developmental arrest in specific stages, events that seem to be required and characterize B and T cell ALL.

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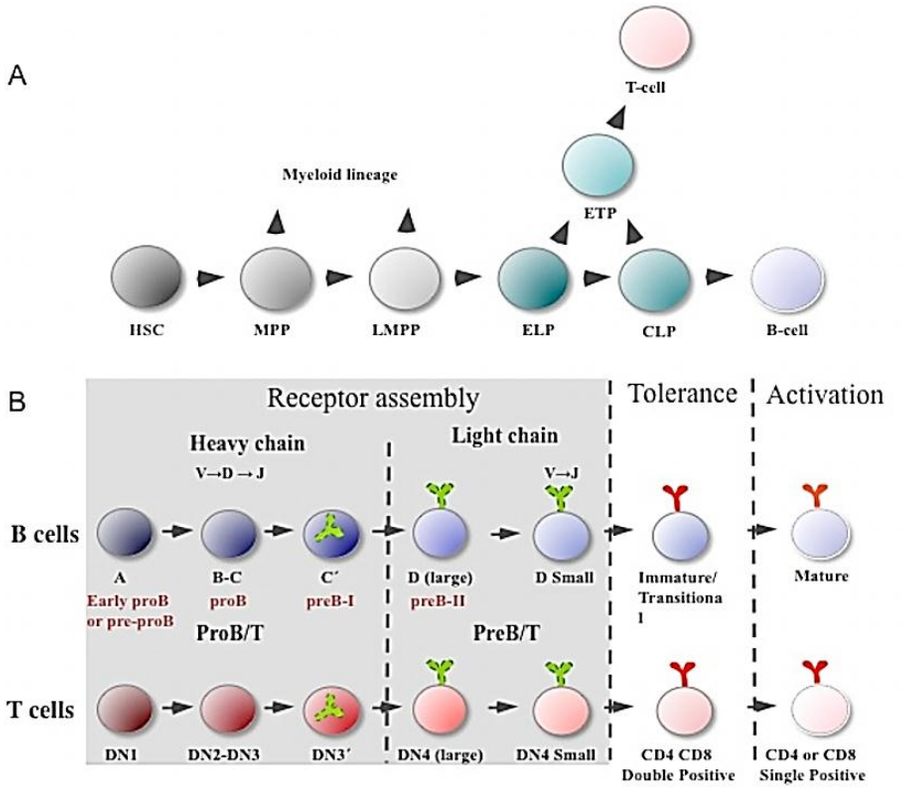


Figure 1. Schematic drawing of the early hematopoietic development. A) HSCs (hematopoietic stem cells), MPPs (multipotent progenitors), LMPPs (lymphoid-primed MPPs), ELPs (early lymphoid progenitors), CLPs (common lymphoid progenitors), ETPs (early T lineage progenitors). Important branch points during lineage decisions are shown with arrows. B) All B- and T-cell stages can be divided according to the main processes guiding development: receptor assembly, tolerance, and activation. Receptor assembly stages (light gray box) in B and T cells are differentiated by the process of VDJ recombination in the heavy (IgH) and light (IgL) chains, which are recombined in the pro-B and pre-B stages, respectively (b and a rearrangement in DN1-3 and DN4 abT cells). B cells only rearrange heavy and light chains, while T cells can follow two different pathways of TCR chains, ab and gd. Intimate contact between immature B /DP T cells and the stromal cells of the bone marrow and thymus allows those receptors capable of recognizing self-antigens to be identified and eliminated through a variety of mechanisms collectively termed "tolerance". Non-self-reactive cells transit to the mature stage where they become functional cells that could be activated and respond to foreign antigens. The nomenclature of each sub-stage in the mouse model is shown in black letters, e.g. A-D for B cells and DN1–4 for T cells; the most common human nomenclature is shown in red letters. The dashed lines separating all stages indicate checkpoints at which signaling from the pre-BCR/TCR and BCR/TCR is required for positive selection and progression along the maturation pathway. The preBCR, preTCR, and mature receptors are also illustrated in their respective stages. B cell development occurs in bone marrow and T cell development in the thymus.

Early developmental stages are the ones generally found compromised in human pediatric B and T cell ALL. These stages in B cell ALL are early proB or pre-proB (before heavy-chain recombination), preB-I (after heavy-chain recombination), and preB-II (before light-chain rearrangement) (Figure 1B). These stages are also recognized by the expression of stage specific markers, a characteristic that has helped to classify the different types of pediatric ALL. B cells are recognized by the expression of CD19 and CD10, common B cell ALL by the expression of the BCR (IgM) either in cytoplasm (preB-I) or membrane (preB-II), and preB-I can also be differentiated from preB-II cells by expression of the enzyme terminal deoxynucleotidyl transferase (TdT) [10].

T cells are recognized by the expression of CD3, CD5 and CD7. Early T cells lack expression of CD4 and CD8 (double negative or DN stages). Contrary to B cell ALL, T cell ALL clones often express markers of more advanced stages of development (for instance double positive stages). However, these clones also show a lack of expression or cytoplasmic TCRβ, indicating that transformation happened before rearrangement of this TCR component or just after, and thus arguing that transformation targeted ETP/DN1 or DN3´cells [15]. The acquisition of markers of more mature cells is probably due to marker aberrant expression or leukemia-induced developmental progression in absence of the TCR signal. Although, postnatal B cell early maturation only happens in bone marrow, T cells mature in thymus. LMPP, ELP, CLP and ETP cells are all able to leave bone marrow in response to environmental signals and complete the T cell maturation program in thymus. Therefore, ETP/DN1 cells are normal residents of bone marrow, while double positive T cells are only found in thymus. T cell transformation of very early populations also agrees with the predominant presence of the T cell leukemic clone in bone marrow [15].

Limitation of lineage choice during development is regulated by a combination of signaling pathways and transcription factors. The main receptor controlling the proB stage is the IL-7R, which is composed of an α chain (IL-7Rα) and the common cytokine receptor G chain (GC) [16,17]. Deletion of IL-7Rα or GC leads to developmental arrest at the early proB stage [18–21]. IL-7 activates three major signaling pathways: 1) JAK–STAT, 2) phosphatidylinositol 3-kinase (PI3K)–Akt and 3) Ras-Raf-Erk [22]. STAT5 (signal transducer and activator of transcription 5) is the predominant STAT protein activated by IL-7 [22,23] and STAT5 loss also arrest B cells at the early proB stage. Once the preBCR is expressed, it can take over many of the functions performed by the IL-7 receptor, since the preBCR also activates the PI3K-Akt and Ras-Raf-Erk pathways [24,25].

Downstream of IL-7 two transcription factors have been documented as the most important for cell entry into the B cell lineage: E2A/TCF3 (immunoglobulin enhancer binding factors E12/E47/transcription factor 3) and EBF1 (Early B cell Factor 1) [26–28]. On the other hand, PAX5 (Paired box 5) is the more important transcription factor for B cell commitment. Loss of E2A and EBF1 blocks entry into the B cell lineage, and loss of PAX5 redirects B cells into other lineages [28–30]. One of the main molecular functions of PAX5 (acting together with E2A, EBF1 and STAT5) is to allow VDJ recombination [31,32]. Ectopic expression of PAX5 and E2A allows VDJ recombination in non-B cells [45, 46]. Also, E2A, PAX5, IKZF1 and RUNX1, among other transcription factors, are responsible for expression of the VDJ recombinase (RAG) [33,34].

The most important cells that give rise to T cells are ELPs and CLPs. Although, both B and T cells are mainly originated from them, an important genetic difference between cells prone to the B lineage is the expression of EBF1 and PAX5, while for T cells is NOTCH1 signaling. NOTCH1 directs progenitors into the thymus and it is the master orchestrator of T cell lineage entry and development [35,36]. NOTCH contains multiple epidermal growth factor (EGF)-like repeats through which it binds its ligands DLL-1, -2, -4 (Delta-like ligand), and Jagged-1 and -2 expressed by bone marrow and thymus stromal cells. Upon ligand binding NOTCH1 initiates a series of proteolytic cleavage events, the first one catalyzed by the

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ADAM family of metalloproteinases and the second by the γ–secretase complex. This cleavage activates NOTCH1 removing the extracellular portion and translocating to the nucleus its intracellular region (ICN), where it becomes part of a large transcriptional activation complex together with CSL and histone acetylase p300. Also, ICN has a C-terminal PEST domain involved in regulation of NOTCH1 ubiquitylation and proteasome-mediated degradation, therefore controlling protein turnover [35–38].

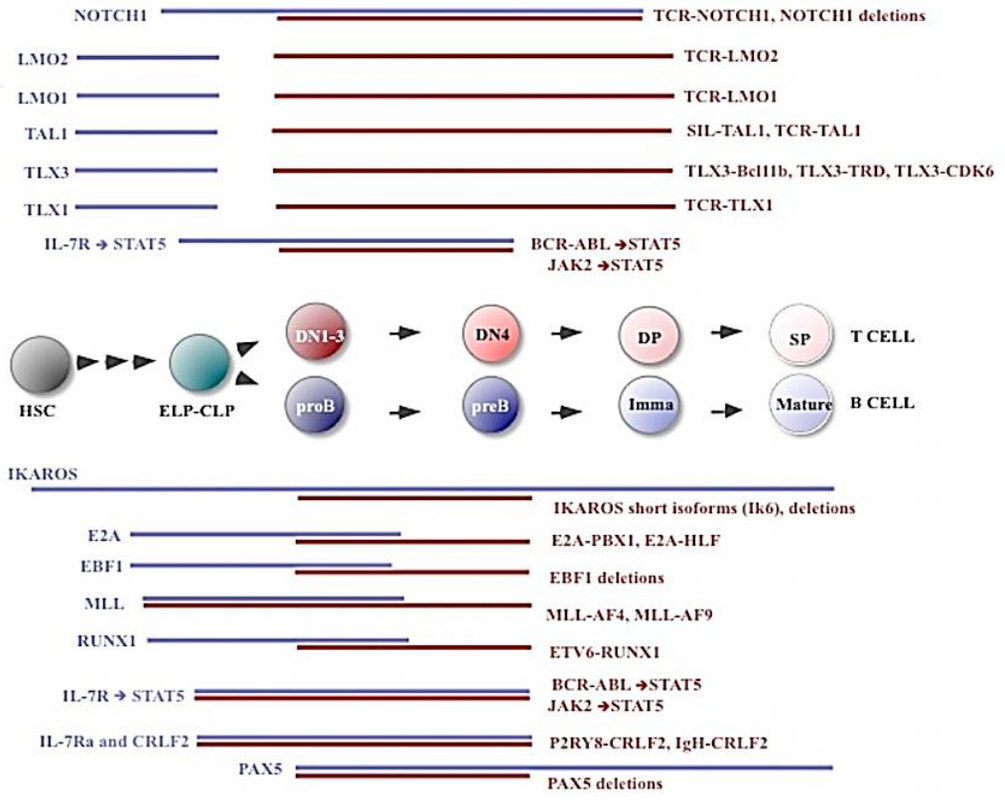


Figure 2. Schematic drawing of homeostatic and leukemic expression of acute leukemia inducing genes. Normal (in blue) and leukemic (in red) expression of receptors, signaling proteins and transcription factors is shown along the B and T cell development pathways. Homeostatic factors are shown to the left of the figure and their most common modified forms in ALL are shown to the right; the upper part showing the ones compromised in T cells and the bottom part in B cells. Developmental stages are indicated starting with the hematopoietic stem cell (HSC) and then with the early lymphoid progenitor (ELP) and the common lymphoid progenitor (CLP) and further into the T and B cell pathways. Of note, the proB and preB stages are the ones usually compromised in B cell ALL; in T cell ALL, marker expression is indicative of double positive stages but TCR recombination status shows that leukemic stages most probably belong to double negative stages. Therefore, the red line representing abnormal leukemic expression extends from DN to DP stages in T cell development. Also, several of the transcription factors compromised in T cell ALL are not normally expressed in these stages but ectopically expressed through the inducing genomic lesion.

NOTCH1 expression is importantly regulated by E2A [39], and is essential for activation of genes necessary for T cell entry and early development. Indeed, NOTCH1 expression is turned off in late stages of T cell development, forced expression of NOTCH1 in multipotent progenitor cells direct them to the T cell lineage and controls the expression of several transcription factors important for T cell early development, e.g. *HES1, Bcl11b, GATA3, TCF1, Pu1* and *RUNX1*, among many more [38]. Many of these genes are required to turn off tran-

scriptional programs of multipotent progenitor cells or other hematopoietic lineages, or for T cell specific functions such as recombinase expression or TCR recombination.

Some of the transcription factors drivers of T cell ALL are normally expressed in non-malignant thymocytes since they are essential regulators of T-cell ontogeny, while others are not expressed in normal ones, but they are rather ectopically expressed by transformed cells (Figure 2). This is contrary to B cells, in which most of the transcription factors associated with transformation fulfill an important regulatory function (Figure 2). This observation supports different mechanisms for the origin of B and T cell ALL. In agreement, *TLX1, TLX3, TAL1, LMO1* and *LMO2* gene loci remain open during TCR recombination, increasing the probability of aberrant rearrangements [39,40]. The identification of the signaling proteins and transcription factors compromised in B and T cell ALL has helped us to understand normal B and T cell development and its oncogenic counterpart, and as we will emphasize in the following sections, they have also provided an important tool to classify patients with specific genetic characteristics into risk groups matching disease prognosis.

3. Criteria for ALL risk stratification

The clinical and laboratory criteria supporting risk stratification vary among institutions, with most groups considering as high risk the following characteristics: age ≥ 10 or <1 years at presentation, WBC ≥ 50,000/μl, presence of extramedullary disease, T cell immunophenotype, presence of adverse genetic abnormalities such as t(9;22) (*BCR-ABL1*), *MLL* gene rearrangements, hypodiploidy <44 chromosomes and near haploidy. Finally, a poor response to therapy resulting in ≥ 5% bone marrow blasts at days 15, 19, 29, 35 or 43 post-treatment is also considered of bad prognosis [6].

All the above-mentioned prognostic factors are used to classify patients into two risk groups, high and standard risk. For instance, it is known that increased WBC count confers poor prognosis for B cell ALL patients and in T cell ALL, a leukocyte count greater than 100,000/μl is associated with high risk of relapse in the central nervous system. Also, patients with hyperleukocytosis, greater than 400,000/μl, are at high risk of central nervous system hemorrhage and pulmonary and neurological events due to leukostasis. However, most of these risk criteria are better understood for B cell and they are not as clear for T cell ALL patients [3]. Recently, evaluation of early response to therapy has been demonstrated being an important parameter for treatment efficacy and disease prognosis. Based on the latter criteria, it is possible to identify the group of patients that require augmented therapy to improve their outcome.

3.1. Prognostic significance of treatment response

The frequency of bone marrow or circulating lymphoblasts after one week of chemotherapy is associated with risk for relapse [41] and nowadays, this constitutes one of the most useful prognostic factors in childhood ALL. An efficient early response to treatment is determined by evaluating clearance rates of leukemic cells after the induction phase of treatment [42].

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This pharmacological response depends on numerous variables, including drug sensitivity / resistance of the leukemic cells, the dosage and the ability of individual patients to metabolize and eliminate anti-leukemic drugs [43,44].

The Berlin-Frankfurt Munster (BFM) group has traditionally employed the response to prednisone for 7 days and one dose of intrathecal methotrexate to stratify patients. Peripheral blood blast count of 1,000/μl after prednisone treatment is used as a threshold to assign patients into two groups, prednisone good responders (GR) and poor responders (PR). The ALL-BMF Group demonstrated in large series of infant patients treated with effective risk-based ALL therapy that prednisone response is a strong prognostic parameter for outcome; 75% of infants were good responders (GR) and achieved an EFS of 53% at 6 years using conventional therapy, whereas poor responder infants had an EFS of 15% [41]. The Tokyo Cancer Children´s Leukemia Group also showed that B and T cell ALL patients with high blast counts at day 8, had a 4 years EFS of 74%; in contrast, patients without blasts presented an EFS of 89% for B and 95% for T cell ALL [43]. Thus, it is well accepted that early response to prednisone treatment is a strong indicator of EFS [41]. However, this assessment is limited by the low sensitivity (5-10% blasts) of microscopy-based methods of blast quantification [45]. The morphological analysis of blasts by conventional methods easily underestimates the presence and frequency of residual cells. PCR or flow cytometry- based methods for detecting MRD are at least 100 times more sensitive.

The common principle for all MRD assessments is that leukemogenic process results in molecular and cellular changes, which distinguish leukemic cells from their normal counterparts [46]. In patients with ALL, MRD can be monitored by flow cytometry, PCR amplification of gene fusion transcripts, and PCR amplification of the B and T cell antigen receptors (BCR/TCR specific VDJ recombinants). Combining information about cell size, granularity and expression of surface and intracellular molecules, it is possible to identify by flow cytometry a phenotypic signature characteristic of leukemic cells. Flow cytometry-based identification of cell immunophenotypes allows the detection of one leukemic cell among 10,000 normal cells (0.01%) [47,48]; however, these assays require high expertise for quality results, previous knowledge of immunophenotypic profiles of normal and leukemic cells and experience to select the best markers useful for each patient [49]. Other option to distinguish leukemic from normal cells is the PCR screening of gene fusion transcripts, produced by specific chromosomal translocations, among the most common of them are: *BCR-ABL1*, *MLL-AF4*, *E2A-PBX1* and *ETV6-RUNX1* [50]. These genetic abnormalities can be detected by PCR with high sensitivities ranging from 0.1- 0.001% [51]. Clonal rearrangements of the BCR and TCR genes are also useful tools for detecting MRD. Specific VDJ rearrangements result in unique molecular signatures that can be detected by real-time quantitative PCR, with a sensitivity of 0.01-0.001% [52]. The applicability of this latter method is useful in 90% of cases, however, a leukemic blast can be associated with more than one VDJ rearrangement during disease progression; for this reason, it is recommended to use at least two different rearrangements as a target for each patient [53].

MRD studies revealed that many patients who achieve remission by traditional methods harbored residual disease predisposing them to relapse [46,48]. The most immediate ap-

plication of MRD testing is the identification of patients who are candidates for treatment intensification, since levels of MRD are proportional to the risk of relapse [51]. The most appropriate time for evaluation of MRD vary between different groups, for the ALL-BMF 95 protocol in Austria, MRD quantification by flow cytometry of bone marrow samples must be estimated on days 33 and 78 post-treatment. In the experience of St. Jude Children's Research Hospital, the presence of 0.01% residual cells on days 19, 46, or subsequent time points during treatment, is strongly associated with a high risk of relapse [54,55]. The Children's Oncology Group quantifies MRD in bone marrow on day 29 post-treatment, and ≥ 0.01% of MRD is associated with poor outcome [56]. The Dana-Farber Cancer Institute ALL Consortium, considers MRD cut-off values of 0.1% for prediction of 5-year relapse hazard [57]. Recently, the Italian cooperative group AIEOP identified 3 risk groups based on MRD values by flow cytometry of bone marrow samples on day 15 of treatment. Those risk groups are: standard (<0.01% MRD) with a 5-years cumulative incidence of relapse (CIR) of 7.5%, intermediate (0.01% - <10% MRD) with CIR of 17.5%, and high (>10% MRD) with CIR of 47.2% [58]. MRD is also useful as an independent predictor of second relapse in patients with ALL who had a previous relapse and achieved a second remission [59,60]. Notably, the time of first relapse and MRD are the only 2 significant predictors of outcome in a multivariate analysis [60].

3.2. Genetic abnormalities in ALL as prognostic factors

From a genetic point of view, ALL is one of the best characterized malignancies. Numerical and structural chromosomal abnormalities have been described by cytogenetic methods, FISH, PCR, and more recently, by next generation sequencing. Chromosomal abnormalities are clonal markers of the ALL blast, since the cytogenetic and molecular analyses have revealed that approximately 75% of ALL-children present these genetic lesions [7]. To date, more than 200 genes have been found participating, downstream of common ALL translocations. Interestingly, a handful of these genes are affected by more than one translocation, thus supporting specific mechanisms of leukemogenesis [9].

The genetic abnormalities found in ALL are basically of two types: 1) gains or losses of one or several chromosomes (numerical abnormalities) and 2) translocations generating gene fusions that encode proteins with novel functions (chimeric proteins), or that re-locate a gene close to a strong transcriptional promoter causing gene overexpression. These translocations are produced by double-strand breaks (DSB) in different chromosomes or different regions of one chromosome, that are then recombined through non-homologous end-joining mechanisms [9,61]. These events of illegitimate recombination result in juxtaposition of normally separated regions, relocating a gene or producing a chimeric fusion gene [3].

Several studies have demonstrated that the first genetic lesion in childhood ALL often occurs in uterus. Screening of many of the genetic lesions that characterize the ALL blast in blood samples from Guthrie cards supports their prenatal origin. These studies have shown the presence of the same gene fusion in blood samples collected at birth and in the leukemic blasts at diagnosis. Thus, an intrauterine origin of *MLL-AF4* has been observed in 100% of the studied cases, *ETV6-RUNX1* in 75% of cases, *E2A-PBX1* in 10% of cases and a numerical

abnormality, hyperdiploidy, in 100% of patients in one study [9]. However, it is accepted that for all mentioned cases this first oncogenic hit is not sufficient, and additional postnatal mutational events are required for disease initiation [62].

The known ALL genetic abnormalities have been relevant for the identification of genes involved in cancer and therefore for the insights in the biology of the leukemogenic process. Importantly, these genetic abnormalities are a disease signature that has been an invaluable tool for the precise disease diagnosis, prognosis and stratification into risk groups, guiding patient management and treatment choice [63]. The Third International Workshop on Chromosomes in Leukemia was the first major study demonstrating the independent prognostic significance of cytogenetic findings in ALL, providing data on clinical relevance of chromosomal recurrent aberrations, and elucidating its molecular basis and biologic consequences [64]. Given their importance, it is the main goal of this chapter to describe in detail the most important genetic abnormalities in the stratification of ALL patients, highlighting aspects of their oncogenic mechanisms, incidence and prognosis.

4. Molecular and cytogenetic subgroups in pediatric B cell ALL

As it was previously mentioned, several genetic abnormalities are characteristic of ALL and have been relevant for the identification of genes involved in cancer and therefore have given insights into the biology of the leukemogenic process, plus they have been an invaluable tool for the precise disease diagnosis, prognosis and stratification into risk groups. Several of them will be discussed in the coming sections.

4.1. *BCR-ABL1* fusion

The *BCR-ABL1* fusion is generated by a reciprocal translocation between sequences of the *BCR* (Breakpoint cluster region; do not confuse with the B cell receptor) gene located at 22q11.23, and the *ABL1* (Abelson tyrosine-protein kinase 1) gene located at 9q34.1. This translocation generates a derivative chromosome 22 known as the Philadelphia (Ph) chromosome, and was first observed in adult patients with chronic myeloid leukemia (CML), but later also in approximately 3-5% of pediatric ALL patients. The *BCR* gene contains 23 exons and encodes a 160 kD phosphoprotein of still unclear function. However, its first exon, which is normally present in the BCR-ABL1 protein, contains a serine/threonine kinase activity and SH2 binding sites [65]. On the other hand, *ABL1* is a proto-oncogene that encodes a cytoplasmic and nuclear protein tyrosine kinase implicated in cell differentiation, cell division, cell adhesion, and stress response [66,67]. The *BCR-ABL1* fusion produces a chimeric protein with cytoplasmic localization and oncogenic potential because retains the catalytic domain of ABL1 fused to the BCR domain, which mediates constitutive oligomerization of the fusion protein in the absence of physiologic activating signals, thereby promoting aberrant tyrosine kinase constitutive activity, inducing aberrant signaling and activating multiple cellular pathways [3,68–70]. Among the signaling pathways activated contributing

to leukemogenesis are JAK2 kinase/STAT5, MAP kinases and PI3K/Akt, which includes several members of the Bcl-2 family of anti-apoptotic proteins.

The Ph chromosome detected in CML varies from the one in ALL, with different *BCR* breakpoints between diseases. Two chimeric proteins with different leukemogenic potential are encoded, one of 210 kDa prevalent in CML and other of 190 kDa prevalent in childhood ALL [70,71]. *In vitro* studies showed that the 190kDa BCR-ABL exhibits a greater tyrosine kinase activity than the 210kDa form. Thus, this fusion defines one of the subgroups of ALL with the worst clinical prognosis, mainly because it leads to genetic instability through the reduction in DNA repair fidelity and by generation of reactive oxygen species, that enhance spontaneous DNA damage in tumor cells that can yield the accumulation of additional genetic mutations [72,73].

Ph positive childhood ALL is associated with older age at presentation, high leukocyte count, French-American-British (FAB) L2 morphology, and high incidence of central nervous system. Age at ALL presentation influences the prognosis of this genetic rearrangement; patients with ages ranging from one to nine years have a better prognosis than adolescents and young adults [70,74]. Thus, Ph positive is associated with a very high risk and poor prognosis. Although more than 95% of patients achieve an adequate response to induction therapy, these remissions are shallow and short-lived [6]; additionally, these patients frequently present high levels of MRD at the end of the induction therapy [75]. Ph positive ALL incidence varies among different cohorts (Table 1), ranging between 2-3% for Western European countries (Germany, Italy, Austria, Britain, Switzerland) [76–78], 1-4% for American countries (USA and Mexico) [4,79] and 7-15% for Eastern countries (China, Taiwan, Malaysia-Singapore) [63].

Intensive research efforts were done to demonstrate the BCR-ABL1 transforming activity *in vitro* and *in vivo*, as well as to describe the downstream signaling pathways and transcriptional programs affected by this translocation. These studies led to the development of successful targeted therapy with small-molecule tyrosine kinase inhibitors (TKI), such as STI571 (Imatinib mesylate, Gleevec®, Novartis Pharmaceuticals, Basel, Switzerland). This TKI has successfully been used for treatment of Ph positive CML patients [69,87] and has also permitted a better management of ALL patients. Remissions have been achieved when Imatinib has been used either as single agent or as part of combination regimens. In accordance with COG ALLL0031 trial (2002-2006), patients who received a regimen that included Imatinib achieved a 3-year EFS of 80%, which was more than the double of the EFS rate of patients treated without this agent. Although the number of treated patients was small in this study, it supported that the addition of Imatinib to intensive chemotherapy can improve the outcome of Ph positive ALL children [74,87]. Genomic studies have identified a subtype of pediatric B cell ALL Ph negative patients with a gene-expression profile similar to *BCR-ABL1* positive ones, it is thought that these "*BCR-ABL1* like" disease harbors mutations that deregulate cytokine receptor and tyrosine kinase signaling, this subset of B cell ALL patients might also be benefited by the TKI therapy [87]. "*BCR-ABL1* like" group will be mentioned in a following section.

Genetic abnormalities	Frequency in different populations (%)									Clinical implication
	Europe		America				Asia			
	UK Medical Research Council ALL97/99 [77]	ALL-BFM90 [78,80]	UKCCG [81]	StJChRH [82]	Hispanics [83]	Mexico [84]	India [4]	China [85]	Malaysia-Singapore [86]	
Numerical changes										
Hyperdiploidy >50 chromosomes	38	-	31	25	41	31	-	24	-	Excellent prognosis with anti-metabolite treatment
Hypodiploidy <44 chromosomes	-	-	-	1-2	<1	-	-	-	-	Poor prognosis
Structural changes										
t(1;19)(q23;p13) *E2A-PBX1*	4	2	-	5	5 *E2A-PBX1* or *E2A-HLF*	5	7	5	4	Improved prognosis with high-dose methotrexate treatment
11q23 rearrangements *MLL*	2	3	2	8	2	9	0	3	5	Poor prognosis
t(9;22) (q34;q11.2) *BCR-ABL1*	3	2	2	2	1	4	5	17	7	Improved early treatment outcome with imatinib
t(12;21) (p13;q22) *ETV6-RUNX1*	25	22	21	25	13	9	7	19	13	Excellent prognosis with asparaginase

-, non described

Table 1. Frequency of numerical and structural changes among B-ALL patients of different cohorts

4.2. *E2A-PBX1* fusion

The *E2A-PBX1* fusion results from the balanced translocation t(1;19)(q23;p13) or the unbalanced derivative der(19)t(1;19), that involve *E2A* (previously described as the Immunoglobulin enhancer binding factors E12/E47, also named *TCF3*) and *PBX1* (Pre-B cell leukemia

transcription factor 1) genes. *E2A* encodes two basic helix-loop-helix (bHLH) transcription factors, E12 and E47, through alternative splicing. Both transcription factors are immunoglobulin enhancer binding proteins involved in the regulation of immunoglobulin gene expression [34] and in the initiation and specification of the B cell lineage [29]. *PBX1* also encodes a transcription factor (Leukemia Homeobox 1), a member of the three amino acid loop extension (TALE) family of homeodomain proteins. PBX1 forms heterodimers with HOX family homeodomain proteins and together with them cooperatively regulates transcription of several target genes according to the HOX partner [88,89]. PBX1 regulates the self-renewal potential of HSC by maintaining their quiescence state; additionally, it modulates early stages of B-cell development. PBX1 is also important for the multi-linage potential of human embryonic stem cells (hESC) [90].

E2A-PBX1 fusion results in chimeric proteins that contain the transcriptional activation domain of E2A linked to the DNA-binding domain and HOX heterodimerization domain of PBX1. The resulting oncogenic transcription factor inappropriately activates the expression of genes normally regulated by the PBX1-HOX heterodimers [3,91]. Among the transcriptional targets of E2A-PBX1 are *WNT16* and *MerTK*. Since the WTN family is widely recognized to be involved in oncogenesis, it is possible that *E2A-PBX1* initiates the leukemogenic process through its potent expression of WNT16 [10,92]. MerTK is a receptor with a coupled tyrosine kinase activity that regulates self-renewal of bone marrow precursor cells, and although MerTK is not normally expressed in committed lymphocytes, high level expression is detected in B and T cell ALL and mantle cell lymphomas [93,94].

According to studies in different populations (Table 1), *E2A-PBX1* translocation is present in approximately 2-6% of pediatric ALL cases; however its incidence among the specific pre-B ALL subtype (the one with cytoplasmic or membrane IgM) is approximately 25% [64,95,96]. The Total Therapy Study XIIIB at St Jude Children's Research Hospital reported an incidence of 4.7%, with 5-year EFS of 80-90% [4,97]. On the other hand, the reported incidences for European countries, such as Great Britain, Germany, Italy, Austria and Switzerland, is between 2.1 and 4%, while the reported incidences for Eastern countries (Malaysia, Singapore and China) range from 4.12 to 5.37%. *E2A-PBX1* has barely been detected in Guthrie cards of B cell ALL patients, which suggests that in most cases emerges postnatally [9]. Also, the molecular breakpoints of the *E2A-PBX1* fusion in IgM positive or IgM negative cases are generally dissimilar suggesting different origins of the disease [3,98].

Clinical features of pre-B ALL positive for *E2A-PBX1*, include 5 year age at presentation, WBC count of 21-28,000/μl and pseudodiploid karyotypes [64,87,99]. Risk stratification for *E2A/PBX1* patients is controversial. It is considered of poor prognosis in adult cases, while in children it has been reported either relatively favorable or of poor prognosis. This could be explained in part by treatment differences; although it was initially considered of an unfavorable outcome, rate cures have been improved with the use of more effective therapies, such as dosage intensification with methotrexate [64,82]. Future treatment improvements could be achieved based on the discovery of pathways for treatment resistance of *E2A-PBX1* positive cells. It has been shown that *MerTK* is activated by GAS6 (Growth arrest specific 6) produced in bone marrow by mesenchymal cells, which are part of the HSC supporting

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stroma. One of the important functions regulated by GAS6 is HSC self-renewal and it is possible that the leukemic blast becomes resistant to conventional chemotherapy due to GAS6 induced quiescence. Similar to BCR-ABL1 targeted therapy, GAS6-MerTK interaction might be an important target for directed therapy [94].

Another translocation involving the *E2A* gene in ALL is t(17;19)(q22;p13), present in 1% of children, which produces the fusion of *E2A* to *HLF* (Hepatic leukemia factor). *HLF* is a member of the bZIP family of transcription factors and the E2A-HLF fusion protein contains the transcriptional activation domain of E2A linked to the DNA-binding and protein-protein interaction motifs of HLF. The resulting chimeric protein most probably activates the transcription of genes normally regulated by HLF. It is suggested that E2A-HLF inhibits apoptosis through the aberrant up-regulation of SLUG and LMO2, which are anti-apoptotic factors in normal hematopoietic progenitor cells [10,100].

4.3. *MLL* translocations

Myeloid/lymphoid or Mixed lineage leukemia gene (*MLL, MLL1, ALL1, TRX*, and *HTRX*) is the human homologue of the *Drosophila melanogaster* trithorax gene; it is located at 11q23 and consists of 36 exons. It encodes a 430 kDa DNA binding protein that positively regulates *HOX* gene expression through methylation of lysine 4 of histone 3 (H3K4) [101]. MLL is a large multi-domain protein, the N-terminus contains three short AT-hook motifs (ATH 1–3), which are thought to mediate DNA binding. There are two speckled nuclear localization sites (SNL1 and SNL2) immediately C-terminal to the ATH motifs that are followed by a transcriptional repression domain consisting of two functional subunits, RD1 and RD2. RD1 contains a DNA methyltransferase (DMT) homology domain with a CxxC zinc-finger motif that might recruit transcriptional repressors. RD2 recruits histone deacetylases HDAC1 and HDAC2. There is also a plant homology domain (PHD) zinc-finger motif that might mediate protein-protein interactions and a C-terminal SET (Su(var)3-9, enchancer-of-zeste, trithorax) domain that possesses histone H3 lysine 4 (H3K4) methyltransferase activity [95]. Despite RD1 and RD2, MLL is thought to be primarily a transcriptional activator due to its methyltransferase activity and to the transcriptional activation domain, which recruits the transcriptional co-activator CBP (CREB-binding protein). MLL is thought to be a master gene for epigenetic transcriptional memory regulation.

MLL in its mature form consists of two non-covalently associated subunits, an N-terminal 320 kDa fragment (MLL_N) and a C-terminal 180 kDa moiety (MLL_C), which are both core components of the MLL complex and result from the cleavage of nascent MLL by an aspartic protease named taspase 1. The MLL_N fragment is thought to bind DNA regulatory regions of clustered *HOX* genes as part of a multi-subunit complex that includes components of the basal transcription machinery and mediate transcriptional repression of *HOX* genes. However, in the presence of MLL_C, the MLL_N complex can lead to transcriptional activation. The MLL_C subunit contains the SET motif and associates with at least four proteins that modify chromatin for efficient transcription through methylation, acetylation and nucleosome remodeling processes [101,102]. *MLL* gene is ubiquitously expressed in haematopoietic cells including stem and progenitor populations, and *HOX* genes are direct targets of MLL dur-

ing development [7,95,102]. Also, MLL is a key constituent of the mammalian DNA damage response pathway, and it is reported that deregulation of the S-phase checkpoint mediated by *MLL* aberrations contributes to the pathogenesis of human *MLL* positive leukemias [103].

Most *MLL* translocations initiate within a well-characterized 8.3 kb breakpoint cluster region that encompasses exons 5-11. This region is AT-rich, contains Alu, LINE, and MER repetitive sequences, putative DNA topoisomerase-II cleavage recognition sites, as well as a scaffold and matrix attachment region (SAR/MAR); these elements have been proposed to play a direct or indirect role in promoting 11q23 rearrangements [104]. The proposed mechanisms that yield *MLL* translocations include recombination of Alu elements, recombination mediated by topoisomerase-II poisons, and an error prone non-homologous end joining (NHEJ) of DSB [101,104]. *MLL* fusions are diverse, since it has been found in more than 70 different translocations with numerous partner genes. The most frequent are *AF4, AF9, ENL, AF10, ELL* and *AF6*. *MLL-AF4* results from the translocation t(4;11)(q21;q23) that is commonly found in patients younger than one year of age (infant ALL), while *MLL-AF9* is generated by the translocation t(9;11)(p22;q23) that is more frequently seen in secondary, therapy-induced malignancies. Although infrequent, other type of rearrangement involving *MLL* is the partial tandem amplification [7].

All *MLL* fusions encode proteins that share a common transcriptional regulator function capable of regulating HOX genes expression. Some of the *MLL* fusion partners are themselves chromatin modifiers that function in histone acetylation, whereas other fusion partners can recruit histone methyl-transferases, such as DOT1; methylation at lysine 79 of histone H3 catalyzed by DOT1 has been recognized as a hallmark of chromatin activated by MLL fusion proteins [7,102,104]. MLL fusion proteins efficiently transform hematopoietic cells into leukemic cells with stem cell-like self-renewal properties [7].

MLL translocations define subgroups of high risk ALL with specific clinical and biological characteristics associated to adverse prognosis. These subgroups include infant acute leukemia (IAL), therapy-related leukemia (a subtype of leukemia developed by patients previously treated with etoposide after a cancer episode) and T cell ALL [102]. *MLL* translocations are found in approximately 10% of all human leukemias including ALL, AML and biphenotypic (mixed lineage) leukaemia, this latter one is characterized by the expression of both myeloid and lymphoid antigens such as CD14 and CD19 in the leukemic blast [7,102]. *MLL* translocations are particularly frequent (70-80%) in high risk IAL.

MLL-AF4 is one of the leukemia-inducing genetic rearrangements documented to emerge *in utero* during fetal hematopoiesis. Concordant *MLL-AF4* positive leukemia studies in identical monozygotic twins demonstrated that both siblings share the same breakpoints, although the disease usually presents at different times in each twin [105]. Moreover, *MLL-AF4* can be detected in archived neonatal blood from Guthrie cards in IAL or in ALL patients. This evidence coupled with the short period of latency observed in patients that develop IAL, strongly suggests that some leukemia-driving gene fusions can be acquired prenatally [9,62,95]. These observations have raised the question if *in utero* exposition to specific environmental mutagens can induce *MLL* breakage and anomalous recombination events. *In vitro* and *in vivo* assays have identified bioflavonoids, hormones and insecticides

as potential inductors of *MLL* aberrations [80,106–110]. Additionally, the best-known inductor of *MLL* aberrations is etoposide, which is a DNA topoisomerase-II inhibitor commonly used as a chemotherapeutic agent. Etoposide induced genetic aberrations might be due to increased concentrations of DNA topoisomerase-II DNA cleavage complex. 11q23 rearrangements, particularly those that generate *MLL-AF9* fusions, are found in 5-15% of secondary therapy-related leukemias [104,107,111–113].

As mentioned before, the frequency of *MLL* rearrangements in IAL, particularly the *MLL-AF4* fusion, is approximately 80%; however, this frequency diminishes in older children with ALL. *MLL* rearrangements incidences reported from American countries ranged from 2.2-3.3%, while for European countries (Germany, Italy, Austria, UK and Switzerland) was between 2.1-6%. The incidence of *MLL* rearrangements in Eastern countries (China, Taiwan, Malaysia and Singapore) also ranged from 2.1-4.9%. The estimated 5-year EFS for patients with *MLL* translocations ranged between 30-40% [4] and therefore it is considered of very bad prognosis.

4.4. *ETV6-RUNX1* fusion

RUNX1 (Runt-related transcription factor 1 and also known as *AML1* or *CBFα2*) is a gene that maps in 21q22.3. *RUNX1* encodes a transcription factor that contains a Runt domain essential for interaction with transcription factor CBFβ and for DNA binding [114]. The RUNX1-CBFβ heterodimer is a master regulator of early hematopoietic genes transcription. *ETV6* (E-Twenty-Six, also named *TEL*), is localized in 12p13.1, belongs to the *ets* transcription factor family, and contains two major domains: ETS and helix-loop-helix (HLH). ETV6 participates in fetal hematopoiesis of all lineages [115,116]. A substantial proportion (7-25% of children and 2% of adults, Table 1) of ALL patients present the *ETV6*/*RUNX1* fusion as a result of the translocation t(12;21)(p13;q21). The chimeric protein from this fusion contains the N-terminal region of ETV6 fused to almost all RUNX1, including the Runt domain. The ETV6 fragment losses the DNA binding domain but retains the protein binding domain that interacts with cellular proteins with transcriptional repression activity, N-CoR and mSin3a, producing stable repression complexes at the promoters of RUNX1 target genes. mSin3a transcriptional repressor function is due to a histone deacetylase activity(HDAC) [10] but the ETV6-RUNX1 fusion has additional repressor functions through sequestration of transcriptional complexes and competitive inhibition of the wild-type ETV6 activity [10,116].

Several abnormalities secondary to *ETV6-RUNX1* fusion have been detected, such as *ETV6* loss, *ETV6*/*RUNX1* duplication and extra copies of *RUNX1* originated by trisomy 21. Recently, it has been described that *ETV6* loss occurs postnatally in more mature cells than the *ETV6-RUNX1* fusion. Analysis of this deletion revealed an unexpected similarity with SINE and LINE retrotransposons, suggesting their participation in this loss of heterozygosity-like mechanism of ETV6 loss. These findings are consistent with Greaves′ double hit model of leukemogenesis for this subtype of ALL [117].

ETV6/*RUNX1* positive patients have been defined as a group with excellent outcome at 5 years follow-up, which cannot be identified by standard prognostic features [118,119]. In several studies based on different populations, this subgroup represented about 25% of cas-

es with B cell precursor immunophenotype [120]; and this genetic marker could also be found in T cell ALL [81]. Other studies support different incidence rates for *ETV6/RUNX1* fusions depending on ethnicity and geographic origin [83,85,121,122] (Table 1). In particular, the lowest frequencies have been described for Hispanic [83,121] and Oriental patients [85,123], compared to patients from West Europe and the United States. Given this difference, further studies should be conducted looking for environmental and genetic etiologic factors, including exposure to leukemogenic agents, analysis of predisposition genes associated to ALL and genetic ancestry in different populations.

Several studies have supported that *ETV6-RUNX1* positive patients have an excellent outcome in clinical trials after treatment with corticosteroids, vincristine, and asparaginase [82]. Nevertheless, *ETV6/RUNX1* has been considered as a non-significant prognostic factor in other studies, since this fusion has been found in relapsed patients [124,125]. In spite of their excellent initial treatment response, and favorable short-term outcome, up to 24% of patients relapse [124], and this usually occurs in patients out of treatment, often several years after cessation of treatment and occasionally as long as 10 to 20 years later [125]. Efforts have been made for obtaining a better understanding about the origin of relapses in this group of ALL patients. Analyses of copy number abnormalities (CNAs) have provided evidence that *ETV6-RUNX1* positive patients have an average of 6 CNAs at diagnosis, with increasing abundance of these CNAs at relapse, and the genes involved in CNAs usually include cell cycle regulator genes [125,126].

The clonal origin of relapse has been investigated comparing CNA profiles from matched *ETV6/RUNX1* positive patients at diagnosis and relapse. Genes associated with cell cycle control (cyclin-dependent kinase inhibitors *CDKN2A, CDKN2B, CCNC)* were found deleted in relapsed patients. As a novel finding, trisomy 16 was observed as a recurrent abnormality, although its significance is presently unknown [125]. A model of abnormalities acquisition from diagnosis to relapse has been proposed; mutations detected recurrently or known to be involved in a leukemogenic pathway were classified as driver mutations, while mutations defined as non-recurrent or without a known function in leukemogenesis were considered passenger mutations. Four genetic profiles have been proposed with this analysis: 1) diagnosis and relapse clones with the same abnormalities; 2) relapse clones with acquired extra driver mutations; 3) relapse clones with losses and gains of driver mutations and 4) relapse clones without all original CNAs but with a novel profile of genetic alterations [125]. At least 3 of these groups support that clones present at diagnosis are responsible for relapses occurring months or years after treatment cessation. In one patient with a remission lasting 119 months a backtracking FISH analysis was performed, and a low number of leukemic subclone was identified at presentation whose genotype matched that observed in the relapse clone. This patient showed clonal diversity at diagnosis and the relapse subclone probably remained due to active mechanisms of chemotherapy resistance and quiescence. The authors suggested that this case of relapse represents an effect of a dormant clone with low proliferative capacity and associated drug insensitivity rather than a mutation-induced resistance effect [125]. This patient might exemplify the genetic variation sometimes observed between initiating and relapse clones. Thus, this study argues that evolutionary genetic

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changes between the leukemic blast at presentation and relapse most probably are due to the frequency and intrinsic genetic characteristics of the relapsed clone.

More recently, it has been shown that genes associated with glucocorticoid mediated apoptosis could be deleted in *ETV6/RUNX1* relapsed patients. One of the most altered genes is the Bcl2 modifying factor (BMF), whose deletion is often detected at diagnosis and relapse. The glucocorticoid receptor NR3C1, and genes of the mismatch repair pathways are also deleted, but this was only observed at relapse. All these genes participate in apoptosis induced by gluococorticoids, supporting that a drug resistance mechanism could contribute to the episode of leukemia relapse, e.g. *BMF* deletions leading to survival of a specific leukemic clone after gluococorticoid treatment [126]. This information is relevant for future evaluation of *ETV6/RUNX1* patients and perhaps this genetic lesion should be diagnosed in ALLs together with BMF, NR3C1 and other CNAs as a guide for novel treatment approaches.

4.5. Hyperdiploidy

Hyperdiploidy with 51-65 chromosomes is also a frequent abnormality, 25-41% of ALL patients present this numerical aberration [10,83,85] and are generally associated with a favorable outcome (Table 1). This includes age 3-5 years and relative low WBC count at presentation, B cell precursor immunophenotype [127] and a 5-year EFS estimate of 85-95% when patients are treated with anti-metabolite based therapy [4,127]. Leukemic lymphoblasts in this subgroup have a high propensity to undergo apoptosis *in vitro* and *in vivo*, and accumulate greater quantities of methotrexate and its active polyglutamate metabolites than other ALL subgroups. These features are probably very important for the associated good prognosis of this subtype of ALL.

High hyperdiploidy can be detected by cytogenetic analysis or flow cytometry. This latter technique measures the DNA content of the leukemic blasts in comparison to the normal cell pool and DNA content of 1.16 is considered as a prognostic indicator of favorable outcome. However, it is recommended to perform additional cytogenetic studies to detect specific chromosome gains, and discard the presence of additional genetic rearrangements, which could also influence disease outcome. About 50% of hyperdiploid cases present additional abnormalities as duplications of 1q or isochromosome 17q, this last abnormality confers adverse prognosis [128]. High hyperdiploidy is often characterized cytogenetically by massive aneuploidy, originating a non-random gain of specific chromosomes, including some or all of +X, +4, +6, +10, +14, +17, +18, and +21; trisomies and tetrasomies of other chromosomes are also present in this group of patients [127].

In spite of the excellent prognosis associated to this genetic subtype, about 25% of the patients develop adverse events, indicating outcome differences and genetic subgroups between high hyperdiploid patients. For this reason, diverse studies have been performed trying to identify prognostic characteristics in these ALL patients. Based on cytogenetic studies and survival analyses, specific trisomies have been found associated to prognosis. Results from univariate analyses informed that gain of individual chromosomes 6, 4, 10 and 18 improves prognosis, in contrast, trisomy 5 confers worse prognosis

[129–131]. Currently, the Children's Cancer Group (CCG) and the Pediatric Oncology Group (POG) consider the presence of simultaneous trisomies of chromosomes 4, 10, and 17 as a favorable prognostic factor [132].

Analysis by SNP array of high hyperdiploid patients have been performed and revealed that 80% presented CNAs, which are not detected by traditional cytogenetic methods. An association between duplication of 1q and +5 has often been observed, and also uniparental isodisomies of chromosomes 9 and 11, gains of chromosomes 17q and 21q, deletions and microdeletions of *ETV6*, cyclin-dependent kinase inhibitor 2A (*CKDN2A*), *PAX5* and PAN3 poly(A) specific ribonuclease subunit homolog (*PAN3*). Interestingly, partial deletions of AT rich interactive domain 5B (*ARID5B*) were also detected [127] and polymorphisms of this gene were recently associated to susceptibility for developing ALL, particularly associated with the high hyperdiploid subtype [133].

ALL cases with 47-50 chromosomes have an intermediate prognosis [71], near-triploidy (69 to 81 chromosomes) [134] have a response to therapy similar to that of non-hyperdiploid, and ALL cases with near tetraploidy (82 to 94 chromosomes) have a high frequency of T cell immunophenotype (see T cell ALL section) and frequently harbors a cryptic ETV6-RUNX1 fusion [135]. These tetraploid leukemias, although significantly less common, have a worse prognosis than the ones with 51-65 chromosomes. The genetic reason for this differential prognosis is presently unclear.

4.6. Hypodiploidy

The hypodiploid ALL is defined as leukemic blasts with less that 46 chromosomes and it is present in 6-7% of patients with childhood ALL. Three different subgroups have been defined according to the number of chromosomes, which are also important for disease outcome: near-haploid ALL (less than 30 chromosomes), low hypodiploid ALL (33-39 chromosomes) and high hypodiploid ALL (42-45 chromosomes). Near-haploidy is observed approximately in 0.5% of ALL cases and it is most frequently associated with females, and together with low hypodiploidy is related with the worst prognosis. Also, children with near-haploidy tend to be younger than those with low hypodiploidy [134,136]. Most of the hypodiploid ALL patients belong to the high hypodiploid group.

The pattern of chromosome loss in near-haploidy is not random as there is preferential retention of two copies of chromosomes 6, 8, 10, 14, 18, 21, and the sex chromosomes. In rare cases, an apparent hyperdiploid genome is observed but the number of chromosomes results from doubling haploid or near-haploid chromosome content. In these cases, although there is an increased in the total number of chromosomes, this ALL is still characterized by losses of specific chromosomes. This ALL is frequently wrongly diagnosed without a careful cytogenetic and DNA content analysis [136], and an appropriate diagnosis is important as near-haploidy defines a rare type of ALL associated with short remission duration and poor prognosis. Therefore, a clear diagnosis of the total chromosome number is essential to stratify patients into the appropriate risk group.

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5. Molecular and cytogenetic subgroups in pediatric T-cell ALL

T cell ALL is a neoplastic disorder characterized by malignant transformation of early thymocytes [37]. It accounts for approximately 10-15% of pediatric ALL cases [2,37,137–139] and tends to present clinically with high circulating blast cell counts, mediastinal masses, and often central nervous system involvement [37,140]. Therefore, it is a high risk ALL with a relapse rate of about 30% within the first 2 years following diagnosis [15,139]. T cell ALL is caused by genetic alterations leading to a variety of changes that can affect cell cycle control, unlimited self-renewal capacity, impaired differentiation and loss of sensitivity to death signals [37]. As previously described, T cell ALL shares some chromosome rearrangements with B cell ALL; however, about 50% of T-ALL patients have recurrent chromosomal translocations specific of this subtype. The most common chromosome abnormalities include rearrangements affecting the *TCR* regulatory elements: juxtaposing promoter and enhancer elements from the *TCRA/D* locus (T-cell receptor α/δ, 14q11) and *TCRB* (T-cell receptor β, 7q34) to developmentally important transcription factor genes such as homeobox genes (*TLX1, TLX3*); helix-loop-helix genes (*TAL1/SCL, TAL2, LYL1*) or LIM-domain genes (*LMO1, LMO2*) (Table 2) [15,37,139–142]. Other important genetic abnormalities frequently targeted during malignant transformation of T cells are interstitial deletion on *TAL1/SCL* and *NOTCH1* point mutations (Table 2). Translocations not involving *TCR* loci have also been described, relevant examples are the gene fusion *CALM-AF10* and the episomal recombination between *NUP214* and *ABL1* genes (Table 2) [35,141].

TCR-mediated translocations in T-ALL				
Genetic abnormalities	**Frequency (%)**	**Function**	**Outcome**	**References**
t(10;14)(q24;q11) TLX1-TCR α/δ	4-10	Homeodomain transcription factor Spleen development	Good	[37,38,143]
t(7;10)(q35;q24) TCR β-TLX1				
t(1;14)(p32;q11) TAL1-TCR α/δ	3	bHLH transcription factor HSC survival	Undefined	[15,37]
t(7;9)(q34;q34.3) TCR β-NOTCH1	<1	Transmembrane receptor T-cell development	Poor	[35–38]
Non-TCR-mediated translocations and mutations in T-ALL				
t(5;14)(q35;q32) TLX3-BCL11b	20	Homeodomain transcription factor Neural development	Poor	[37,38,137]
1p32 deletion SIL-TAL1	17	bHLH transcription factor	Undefined	[15,37]
NOTCH1 mutations	>50	Transmembrane receptor T-cell development	Poor	[35–38]

HSC, Hematopoietic Stem Cell

Table 2. Translocations and mutations in T-ALL

5.1. Impaired differentiation caused by defects in transcription factors expression/ function

5.1.1. Deregulation of TLX1 and TLX3 Homeobox genes

Homeobox genes (*HOX*) are divided into two classes: class I *HOX* genes (*HOXA-D*) and class two *HOX* genes (*TLX1* and *TLX3*). Class II *HOX* genes have been extensively studied In T cell ALL and from them *TLX1* has been found activated in 4-10% of childhood T cell ALL, most frequently by t(10;14)(q24;q11) and t(7;10)(q35;q24) chromosomal translocations [36,37,40,137,143–145]. Both rearrangements lead to the transcriptional activation of *TLX1* gene by re-location of *TLX1* coding sequences under the transcriptional control of the TCR regulatory sequences (Table 2) [36,37,40,137]. *TLX1* is not normally expressed in healthy T cells. Interestingly, overexpression of TLX1 has also been observed in absence of known translocations, suggesting that other mechanisms of up-regulation are involved. Epigenetic changes mediated by promoter demethylation can also lead to *TLX1* aberrant expression [36,137,145]. *TLX1*+ T cells are virtually all arrested at a developmental stage phenotypically similar to the early cortical (CD1+) CD4+CD8+ "double-positive" stage of thymocyte development (early cortical thymocytes) [40]. However, these leukemic T cells lack preTCR expression suggesting that the oncogenic event occurred very early in development (probably to ETP/DN1 cells) and *TLX1* aberrant expression helped the cell to bypass the first developmental checkpoints until the cells were finally arrested at the double positive stage [139]. The favorable clinical outcome of patients with this phenotype might support the arrest in the double positive stage, since it is characterized by lack of expression of anti-apoptotic genes because of the tolerance and negative selection mechanisms that are at work to eliminate self-reactive T cell clones [35–37,143–145].

The cryptic chromosomal translocation t(5;14)(q35;q32) juxtaposes *TLX3* to the distal region of *BCL11B* producing a strong expression of *TLX3*, a genetic lesion present in approximately 20% of childhood T cell ALL (Table 2) [15,35–37,137,141]. Like *TLX1*, *TLX3* is not expressed during normal T cell development [36]. Rare variants of t(5;14) have also been reported: t(5;14)(q32;q11) involving *TRA/TRD* and t(5;7)(q35;q21) involving *CDK6* [35–37]. Some studies indicated that *TLX3* confers a bad response to treatment, but this is controversial since variation has been found between different populations [139]. It is possible that the prognostic meaning of *TLX3* overexpression might be influenced by the presence of additional altered oncogenes such *NUP214-ABL1* or *NOTCH1* [15,37].

5.1.2. Deregulation of TAL1, a basic Helix-Loop-Helix (bHLH) gene

Two different models have explained the oncogenic potential and transformation mechanism of *TAL1*: 1) inappropriate activation of *TAL1* target genes and 2) through a dominant-negative mechanism in which *TAL1* binds to and inhibits the normal activity of the E2A (E47)/HEB transcription factor complex. The second mechanism suggests that E2A proteins may directly regulate cell cycle in thymocyte precursors [35,37,146]. *TAL1* maps on chromosome 1p32 and abnormal function of this gene is one of the most common transcriptional defects in childhood T cell ALL (Table 2); in 17% of patients *TAL1* activation is a conse-

quence of a cryptic interstitial deletion that generates a *SIL-TAL1* fusion, and in 3% of patients, t(1;14)(p32;q11) juxtaposes *TAL1* to TCR transcriptional regulatory elements causing its ectopic expression [37]. Ectopic *TAL1* expression is associated with a maturation arrest of thymocytes. TAL1 protein could also induce overexpression of BCL2A1, resulting in anti-apoptotic activities in the stage of T cell development arrest and a poor response to therapy, particularly in young children [35,37,147,148].

It is documented that *TLX3* expression confers a poor response to treatment, whereas *TLX1* activation is significantly associated with a better prognosis in T cell ALL. A high percentage of cryptic abnormalities of *TLX1*, *TLX3* and *TAL1* genes (both translocations and deletions), are mostly detected only using FISH with specific probes for each type of alteration [35]. Recently, quantitative RT-PCR and expression microarrays have permitted a better and technically simpler T cell ALL classification based on the differential oncogene expression pattern [35]. Most probably, these new methodologies will positively impact the outcome of T cell ALL patients, allowing for a better disease sub-typing and assignment of treatments with better therapeutic responses.

A novel subgroup of early T cell precursor leukemia has been reported, characterized by simultaneous expression of T cell/ stem-cell/myeloid markers and very poor prognosis when treated with standard intensive chemotherapy. Interestingly, this subgroup includes a part of those patients with *LYL1* and *LMO1* overexpression [2].

5.2. Activation of the NOTCH1 signaling pathway

The first alteration described affecting *NOTCH1* in T cell ALL was t(7;9)(q34;q34.3), which couples the coding sequences of the *NOTCH1* ICN to the *TCR β* locus. This alteration is present in <1% of T cell ALL patients [36,38,138]. Currently, gain-of-function mutations in *NOTCH1* are reported in >50% of all T cell leukemia patients. *NOTCH1* mutations are mainly observed in the HD and PEST domains. Mutations in HD result in NOTCH1 constitutive activation and cell transformation. These HD NOTCH1 mutants are observed in an average of 44% of T cell ALL patients. The deletion of the PEST domain enhances NOTCH1 intracellular signaling and is present in 30% of patients. Both, HD and PEST mutations together are found in 17% of cases, and have a synergistic effect on NOTCH1 activation [35,38,138]. *NOTCH1* mutations are found in all developmental subtypes of T cell ALL, supporting that these mutations might occur very early in T cell progenitors [35], and in general, they represent a marker of poor prognosis in patients with T cell ALL (Table 2) [138]. Zhu and cols reported that the outcome of patients with *NOTCH1* mutations varies according to the concomitant expression of *TLX1* and/or *TLX3*. Patients additionally positive for *TLX3* expression, have worse prognosis than those with *TLX1* expression since the latter ones tent to show prolonged survival [138].

Glucocorticoids are normally used to treat T cell ALL patients and glucocorticoid resistance have been mapped to NOTCH1 aberrant expression. Recently, a combination therapy with glucocorticoids and GSIs in a mouse model of resistant to treatment T cell ALL show promising results, arguing that NOTCH1 inhibitors in combination with traditional anti-leukemic drugs might improve disease prognosis in patients with NOTCH1 mutations [149].

6. New prognostic markers detected by genomic variation assays and gene expression evaluation in childhood ALL

The previously described genetic abnormalities in ALL influence the aggressive behavior of leukemic cells and the response to treatment in an important manner. Unfortunately, those abnormalities are not 100% predictive of disease outcome. More recently, genome wide analysis has identified genes associated with risk to relapse in patients with primary gene fusions and hyperdiploidy. These studies have also found novel gene abnormalities probably leading to altered signaling pathways and gene expression patterns in the leukemic blast. Nowadays, many novel cryptic translocations, mutations, deletions, and abnormal expression profiles are considered useful outcome markers in children with ALL and several of these more common markers will be further detailed in this section.

6.1. *CASP8AP2*

The Caspase-8-Associated Protein 2 gene, also known as FLICE associated Huge Protein (*CASP8AP2* or *FLASH*), is located at 6q15. *CASP8AP2* encodes a protein with multiple functions; although it has been traditionally recognized as a key mediator of apoptosis, several studies have demonstrated that also participates in cell division [150], NF-kappaB signaling [151,152], c-Myb activation [153,154], S phase progression [155], histone transcription and 3′-end maturation of histone mRNAs [155–157]. CASP8AP2 interacts with the death-effector domain (DED) of caspase 8 and hence it plays an important regulatory role in Fas-mediated apoptosis.

The clinical significance of *CASP8AP2* was first reported in Flotho and cols study [158], in which differences in expression levels were associated with *in vivo* responses to multiagent chemotherapy. *CASP8AP2* expression was analyzed in 99 patients enrolled in St Jude Total Therapy Study XIII and patients were divided into 3 groups according to expression. Patients with high expression levels had significantly better EFS rates and lower cumulative incidences of relapse than those with intermediate or low *CASP8AP2* expression. The pro-apoptotic function of CASP8AP2 and its low expression in leukemic blasts from patients with persistent MRD, suggest that this gene could be a powerful predictor of treatment response in childhood ALL. Furthermore, Flotho and cols [159] identified a signature of 14 genes associated with MRD, and *CASP8AP2* was among the signature genes with a low level expression. Other genes down regulated in these high risk patients were the H2A histone family member Z (*H2AFZ*), budding uninhibited by benzimidazoles 3 homolog (*BUB3*) and CDC28 protein kinase regulatory subunit 1B (*CKS1B*). All these patients showed suboptimal responses to remission induction therapy and they eventually relapsed [159].

Analyses of *CASP8AP2* as a prognostic marker used for risk stratification have been made in leukemic patients from different populations. In a cohort of 39 newly diagnosed ALL patients enrolled in Beijing Children`s Hospital (BCH)-ALL 2003 protocol, the bone marrow expression of *CASP8AP2* at diagnosis was an useful indicator for relapse. In the same study, 106 patients enrolled in Chinese Children´s Leukemia Group (CCLG)-ALL 2008 protocol were also analyzed, and patients with low *CASP8AP2* expression present-

ed higher relapse rates, lower relapse free survival and lower overall survival, in comparison to the high-expression group [160].

Biologic basis of the variation of *CASP8AP2* expression could be deletions at band 6q15-16.1, which are often detected in patients with T cell ALL. This abnormality results in down regulation of *CASP8AP2* expression and poor response to early treatment. In 73 T cell ALL samples obtained from patients enrolled in the multicenter ALL-BFM 1990, ALL-BFM 1995 and ALL-BFM 2000 protocols, deletion 6q15-16.1 was associated with unfavorable MRD levels. Although deletion 6q15-16.1 involves several genes, *CASP8AP2* was the single gene with a better association between the deletion and the less efficient induction of apoptosis by chemotherapy [161].

The usefulness of *CASP8AP2* expression as a potential marker of early response to treatment and relapse is still controversial. Yang et. al. [157] failed to show prognostic significance for this gene expression in a group of 78 B cell ALL and 12 T cell ALL newly diagnosed patients enrolled in the Taiwan Pediatric Oncology Group (TPOG). Further studies should be performed in ALL children from different populations and measuring different treatment protocols in order to clarify the prognostic significance of *CASP8AP2*.

6.2. *IKZF1*

The *IKZF1* or *LyF1* gene encodes Ikaros, a transcription factor located on chromosome 7p12, whose largest transcript comprises 6 zinc finger domains in 7 exons; four of these fingers are required for DNA binding and the other 2 for homo and heterodimeric associations with other Ikaros family members, for example Helios and Aiolos [162].

IKZF1 encodes 11 isoforms through a mechanism of alternative splicing, each isoform containing a different set of zinc finger domains dictating differential DNA binding capabilities. Five of these isoforms (Ik-1, Ik-2, Ik-2A, Ik-3 and Ik-3A,) are considered as "long" and functional, because they conserve at least 3 N-terminal DNA binding domains, which permit them entering to the nucleus and presenting high transcriptional activity. The remaining isoforms are referred as "short" (Ik-4, Ik-4A, Ik-5, Ik-6, Ik-7 and Ik-8) and have 2 or less N-terminal DNA binding domains. They are unable to bind DNA with high affinity, do not enter the nucleus, therefore neither activate transcription, but retain the protein binding domains and then the ability to form homo and heterodimers. This group might act as non-DNA-binding dominant-negative isoforms, reducing Ikaros activity. In particular, Ik-6 is not efficiently translocated to the nucleus, resulting in null transcriptional activity [162,163].

Ikaros plays an essential role in development and differentiation of lymphoid and myeloid lineages. It acts as a tumor suppressor and as a regulator of gene expression through a chromatin remodeling function. In normal cells, long Ik-1 and Ik-2 isoforms are more expressed than the predominantly dominant-negative isoforms, Ik-3, Ik-4, Ik-5 and Ik-6 [162,163]. During alternative splicing Ikaros is susceptible to loss the amino-terminal DNA-binding domain, leading to increased expression of specific isoforms, in particular Ik-6, which is strongly associated with B and T cell ALL [164–166].

On the other hand, SNP array analysis of B cell ALL children has revealed deletions of complete *IKZF1* locus; there were also deletions of coding exons 3 through 6, resulting in Ik-6 expression in B-ALL patients. It has also detected point mutations (R111, L117fs, G158S, H224fs, S402fs and E504fs); in particular G158 attenuates the DNA-binding activity and might act as a dominant-negative Ikaros allele. [167]. Approximately 28% of high risk B cell ALL patients, and 9% of unselected risk patients show *IKZF1* deletions [167,168]. Deletions in *IKZF1* in unselected B cell ALL Asian patients are present in 10-15%; this incidence is similar to the one previously seen in Caucasian countries [85,157].

"Short" and "long" isoforms can be expressed in leukemic cells from both B and T cell ALL patients, however, the frequency and expression levels seem to vary between specific immunophenotype and genetic subgroups [169,170]. For instance, Ph positive B cell ALL patients tend to have higher levels of Ik-6 in contrast to Ik-1 and Ik-2 [170]. Interestingly, one study found that *IKZF1* is deleted in 84% of Ph positive B cell ALL patients, supporting its important role in the pathogenesis of this genetic subtype [168]. Ik-6 has also been found overexpressed in patients with the *MLL-AF4* fusion [171].

Regarding prognosis, there is a strong correlation between mutations, deletions in *IKZF1* or presence of non-functional Ikaros isoforms, and poor outcome in both B and T cell ALL patients. Nevertheless, this association is independent of the presence of the *BCR-ABL1* fusion, since both Ph positive and negative patients have poor outcome when *IKZF1* is altered [167,168]. Furthermore, approximately 35% of ALL relapsed cases, this condition also contributes to chemotherapy resistance [172,173]. Events of relapse have been predicted in 79% of non-high risk ALL patients based in both MRD and *IKZF1* deletions [174]. Recently, a novel high risk ALL subgroup called "*BCR-ABL1* like" has been identified, 39% of them presented *IKZF1* deletions or mutations and they had a highly unfavorable prognosis as that found in the Ph positive B cell ALL group. About 20% of the total of B cell ALL patients belong to this "*BCR-ABL1* like" subgroup [175].

6.3. *JAK2*

The *JAK2* gene is located on 9p24 and encodes a kinase that belongs to the JAK family of protein tyrosine kinases (JAK1, JAK2, JAK3 and TYK2). All members of the JAK family are activated by tyrosine phosphorylation and participate in proliferation, differentiation, and cellular migration processes after activation. Additionally, JAK2 regulates apoptosis during hematopoiesis. After JAK2 is activated, this tyrosine phosphorylates STAT5 leading to its dimerization, nuclear translocation and regulation of its target genes. The JAK/STAT pathway is the main signaling mechanism for numerous cytokines and growth factors. Mutations in different members of the JAK family are associated with inflammatory disease, erythrocytosis and childhood ALL [176,177].

Recently, it has been shown that the mutation R683, within the JAK2 pseudokinase domain, is present in approximately 3-4% of childhood ALL patients [178]. About 10% of high risk B cell ALL patients are R683+, however, the incidence is increased in patients with Down syndrome (18-28%) [179–181]. The incidence of *JAK2* mutations is about 10% in the high-risk "*BCR-ABL1* like" group [182]. *JAK2* mutations have also been observed in cell lines MHH-

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CALL4 and MUTZ5, derived from B cell ALL patients without Down syndrome [183]. *JAK2* mutations in ALL are significantly associated with poor outcome and the prognosis is worse when are associated with *IKZF1* deletions; this is an important observation since it has been estimated that 87% of high risk ALL cases harbor *JAK2* mutations together with *IKZF1* deletions [182].

6.4. *CRLF2*

The *Cytokine receptor-like factor 2* or *CRLF2* gene also termed thymic stromal lymphopoietin receptor *(TSLPR*), encodes a type I cytokine receptor. This gene is located in the pseudoautosomal region 1 (PAR1) at both sex chromosomes, X (Xp22.3) and Y (Yp11.3). CRLF2 forms a heterodimeric receptor with IL7Rα which binds the thymic stromal lymphopoietin (TSLP) ligand. CRLF2 plays an important role during T cell and dendritic cell development, promotes B cell survival and proliferation, and is involved in inflammation, allergic responses and malignant transformation [183,184].

Approximately 40% of children with B cell ALL have *CRLF2* cryptic genetic alterations, which induce abnormal signaling during B cell development [178]. *CRLF2* is involved in 2 types of genomic rearrangements: 1) an interstitial deletion within the PAR1 region of chromosome X or Y that places the *CRLF2* gene under the transcriptional control of the *P2RY8* promoter (*P2RY8-CRLF2*), and 2) two cryptic chromosomal translocations t(X;14)(p22; q32) and t(Y;14)(p11;q32), both involving the locus of the B cell antigen receptor heavy chain (fusion *IGH-CRLF2*) [183,185,186]. PAR1 deletions seem to be more frequent than *IGH-CRLF2* translocation, however some groups report that translocation is the most frequent; these observations are still controversial. *CRLF2* rearrangements are associated with aberrant overexpression of *CRLF2* in B cell ALL patients and might contribute to the pathogenesis of the disease [187–190]. Approximately 50% of patients with high *CRLF2* expression present a *CRLF2* rearrangement. However, in a few studies, low *CRLF2* expression has been detected in ALL with the *P2RY8-CRLF2* rearrangement. This low expression could result from a low frequency of the leukemic clone with the *P2RY8-CRLF2* lesion within the heterogeneous pool of leukemic blasts, further studies will be necessary to clarify it [85,187,190].

About 5-7% of Caucasian non-selected B cell ALL patients present *CRLF2* rearrangements and overexpression. This frequency increased to 16-19% in high risk B cell ALL patients; for this reason *CRLF2* abnormalities have been associated with adverse prognosis [85,178,183,186,189–191]. Occurrence of *CRLF2* abnormalities differs among ALL populations, this is probably influenced by the ethnic origin. Harvey and colleagues found that 35.3% of Hispanic/Latin high risk B cell ALL patients have *CRLF2* rearrangements and high expression of its protein [188], this fact could explain in part the poor response to treatment observed in this group [178,187–190]. *CRLF2* analysis by different groups have demonstrated that rearrangements in this gene do not coexist with other non-random ALL chromosomal abnormalities [186,189,190]; except for a couple of *BCR-ABL1* positive patients that showed a high *CRLF2* expression, but not genomic alterations of the gene [187].

Rearrangements and overexpression of *CRLF2* and *JAK2* mutations are particularly abundant in B cell ALL children with Down syndrome, coexistence of both lesions have been

found in up to 45-60% [178,186]. For this group of patients, *CRLF2* rearrangements are more frequent than other ALL aberrations as high hyperdiploid, *ETV6-RUNX1, E2A-PBX1* and *MLL-AF4*. A point mutation in *CRLF2* (F232C) has been identified in 9% of Down syndrome cases leading to *CRLF2* overexpression [191]; it has been proposed that this alteration could be the first leukemogenic event in these children [178,183].

A strong interaction among *IKZF1* deletion, *CRLF2* overexpression and *JAK2* mutations has been described in B cell ALL. Recent studies support that 100% of B cell ALL patients with *JAK2* mutations have *CRLF2* overexpression, however, the opposite is not true. Analyses of different children ALL populations have identified coexistence of these abnormalities: 81% of Hispanic/Latin patients present *CRLF2* overexpression and *IKZF1* deletions, and 69% of them have *JAK2* mutations [188]; in 40% of Caucasian patients with *CRLF2* overexpression *IKZF1* deletions have been found [189]; 95% of Chinese patients with *JAK2* mutations also present high *CRLF2* expression [85]. In Dutch children with Down syndrome, deletions of *IKZF1* were found in 35%, *JAK2* mutations in 15% and *CRLF2* overexpression in 62% of cases [192].

According to these observations, it has been speculated that *IKZF1* deletion, *CRLF2* overexpression and *JAK2* mutations collaborate during B lymphoid transformation perturbing the normal lymphoid development. Furthermore, cooperative mutations could contribute to increase the risk of relapse and promoting therapy resistance and treatment failure. Particularly, *CRLF2* alterations might be the first step in carcinogenic signaling, given that its overexpression is associated with activation of the STAT5 pathway through tyrosine phosphorylation in primary B-cell progenitors [183,189,193].

7. Conclusions

Progress in risk adapted treatment of childhood ALL can currently cure up to 80% of patients. Prognostic factors including patient and disease characteristics as well as response to treatment, play a key role in stratification. Through exhaustive genetic characterization of ALL, gene fusions, point mutations, deletions and gross losses or gains of genetic material have been associated to prognosis. Recently, gene expression and comparative genomic hybridization microarrays have identified new potential genetic markers for predicting outcome. These markers have been evaluated in order to recognize patients prone to relapse, even when they present low risk characteristics by conventional parameters of risk stratification. Based on those studies, gene signatures, mutations and signaling pathways no previously associated to ALL have been identified. Detected abnormalities are involved in diverse cellular processes, as cell cycle progression, cell death, and regulation of gene expression. These activities directly influence how the leukemic blast responds to treatment, and have an important role in the relapse process. Novel genetic alterations that have been associated with poor outcome in ALL patients are rearrangements/mutations that trigger *CRLF2* overexpression; *JAK2* mutations; *IKZF1* deletions and mutations, and down expression of *CASP8AP2*. Genomic analysis of relapse leukemic clones has also been useful detect-

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ing novel genetic abnormalities that influence the aggressive behavior of leukemic cells and in consequence the response to treatment. Recently, new mutations have been found in patients with high hyperdiploidy or with *ETV6-RUNX1* fusion. These recent findings are important in the stratification of these subgroups of patients. ALL is one of the best characterized malignancies at the genetic level, and the increased survival of ALL patients in recent years is without a doubt due to the knowledge of the genes involved in ALL etiology. Next generation technologies and discovery of new genetic markers will keep providing a better understanding of the disease and a more comprehensive biological frame to stratify patients into more reliable risk groups. This knowledge will also reveal potential therapeutic targets that could yield personalized treatments, increasing the number of cured ALL children with less adverse sequelae.

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