Near-Haploidy and Low-Hypodiploidy in B-Cell Acute Lymphoblastic Leukemia

Subjects: Hematology
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B-cell acute lymphoblastic leukemia (B-ALL) is characterized by an uncontrolled proliferation of blood cells in the bone marrow. Hypodiploidy with less than 40 chromosomes is a rare genetic abnormality in B-cell acute lymphoblastic leukemia (B-ALL). This condition can be classified based on modal chromosome number as low-hypodiploidy (30–39 chromosomes) and near-haploidy (24–29 chromosomes), with unique cytogenetic and mutational landscapes.

hypodiploidy near-haploidy B-cell acute lymphoblastic leukemia

1. Introduction

Acute lymphoblastic leukemia (ALL) is a neoplasm arising from lymphoid precursor cells and can be classified as B-ALL or T-ALL based on the immunophenotype of the neoplastic cells [1]. The global incidence of ALL is ~3 cases per 100,000 people and shows a bimodal distribution, with a predominant peak early in life (1 to 15 years) and a second, much lower, peak in older groups (>55 years) [2] (**Figure 1**). ALL has a slightly higher incidence in males, with a male-to-female ratio of 1.2:1 [3]. The disease is characterized by the uncontrolled proliferation of leukemic cells, which invade the bone marrow (BM), peripheral blood (PB), and other hematopoietic tissues including spleen, liver, and lymph nodes, resulting in a hematopoietic displacement which is responsible for the cytopenias frequently observed at diagnosis. ALL cells also infiltrate commonly the central nervous system (CNS).

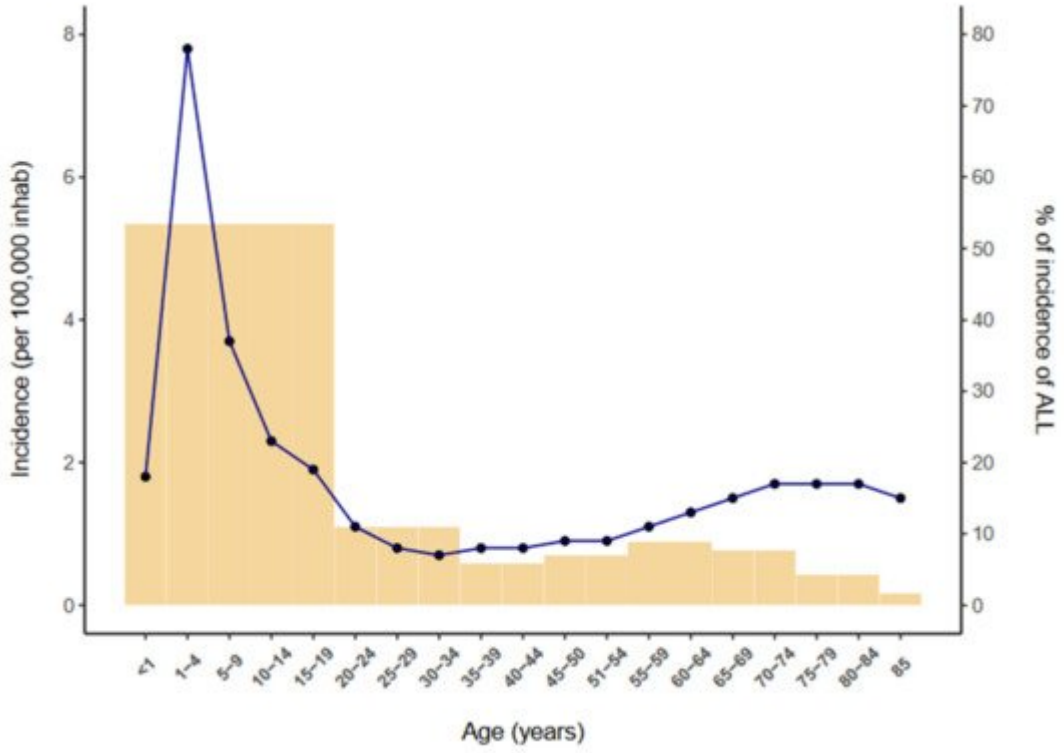

Figure 1. Incidence of ALL per 100,000 inhabitants by age (2014–2018) according to the SEER database [2].

B-cell precursor ALL (B-ALL) accounts for 80–85% of ALL cases and is characterized by small-medium sized leukemic blast cells staining almost always positive for the B-cell antigens CD19, cytoplasmic CD79a and CD22. Although BM and PB are involved in most cases, B-ALL occasionally presents with primary nodal or extranodal sites (B-lymphoblastic lymphoma), which predominantly affect skin, soft tissue, bone and lymph nodes [4].

2. Definition of Hypodiploid B-ALL Subgroups

Hypodiploidy -the loss of one or more whole chromosomes- is a rare cytogenetic finding (≤7%) in children and adults with B-ALL and is generally an adverse prognostic marker [5][6][7][8][9][10][11][12][13][14][15][16]. Most cases (~80%) of hypodiploid B-ALL present with 45 chromosomes and are classified as near-diploid B-ALL, a clinically distinct entity characterized by rearrangements that form dicentric chromosomes but that does not have outcomes as poor as those associated with hypodiploid B-ALL [11].

3. Cytogenetic Characterization of B-ALL with Hypodiploidy <40 Chromosomes

Hypodiploid cases with <40 chromosomes can be further subdivided into two groups based on the bimodal distribution of chromosome numbers: (i) near-haploidy, with 24–29 chromosomes (**Figure 2**A), and (ii) low-hypodiploidy, with 30–39 chromosomes (**Figure 2**B,C) [17] (**Table 1**). Although the modal number of chromosomes is variable, the most recurrent modal numbers are 25–28 for near-haploid and 33–39 for low-hypodiploid B-ALL [18].

Based on conventional chromosome banding analyses, hypodiploidy with <40 chromosomes shows a non-random loss of chromosomes: in near-haploid B-ALL, retained disomies generally comprise chromosomes 8, 10, 14, 18, 21, X and Y [11][12][19][20] whereas in low-hypodiploid cases, retained disomies are more variable and typically comprise chromosomes 1, 5, 6, 8, 10, 11, 14, 18, 19, 21, 22, X and Y, with retained disomies for chromosomes 1, 6, 11 and 18 being the most frequently observed. The most typically lost chromosomes are chromosome 3, 7, 9, 15, 16 and 17 [11][12][19][21][22]. The non-random retention of chromosomes suggests that these chromosomes may harbor specific genes that enhance the oncogenic potential of leukemic cells.

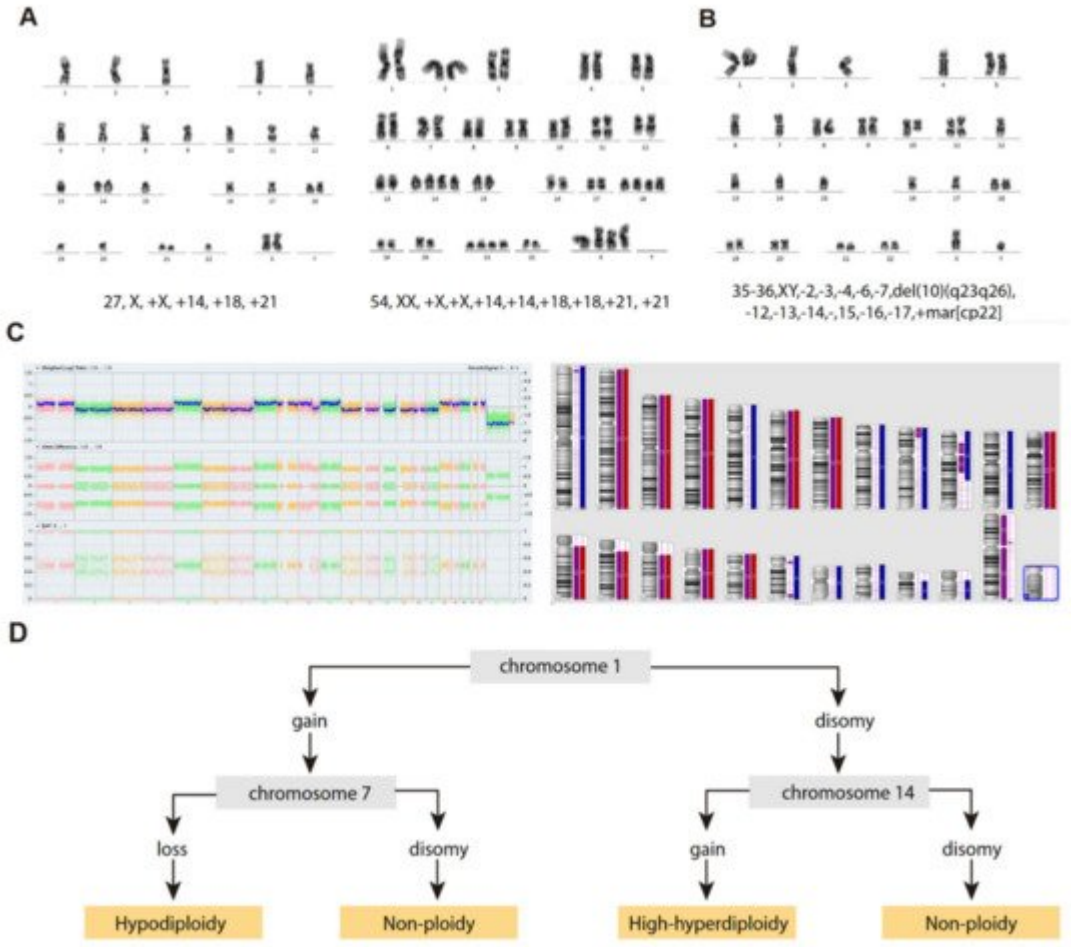

Figure 2. Cytogenetic characterization of B-ALL with <40 chromosomes. (**A**) G-banded karyotype of near-haploid B-ALL leukemic cells. *Left panel*, near-haploid clone. *Right panel*, chromosomally-doubled clone of the same patient. (**B**) G-banded karyotype of low-hypodiploid B-ALL leukemic cells. Karyotype formulas are indicated below. (**C**) SNP-array karyogram obtained for the low-hypodiploid B-ALL patient in B. *Right panel*, blue bars indicate chromosomal disomies of the duplicated/near-triploid clone, red bars indicate chromosomal losses, and purple bars indicate absence of heterozygosity. *Left panel*, Log2 ratio plot detailing whole chromosomal view for each chromosome, the figure demonstrates pattern of low-hypodiploidy where chromosomes with the lowest Log2 ratio represent the monosomies and a partial deletion of chromosome 10. Allele difference plot and B-allele frequency plot (BAF; BB, AB and AA alleles) indicates copy-neutral loss of heterozygosity. (**D**) Algorithm proposed by Creasey

et al. [22] to distinguish hypodiploid with <40 chromosomes and high-hyperdiploid B-ALL cases based on specific chromosomal gains.

Table 1. Cytogenetic characteristics of B-ALL patients with <40 chromosomes.

Age (Years)	Near-Haploid					Low-Hypodiploid					Reference
	MN	Retained chr	Lost chr	Doubled Clone	Frequency	MN	Retained chr	Lost chr	Doubled Clone	Frequency	
1–18	25–28	8, 10, 14, 18, 21 and sex chr.		yes	0.0046	30–40	1, 19, 21, 22 and sex chr.	3, 7, 13, 16, 17	yes	0.41	[7]
1–10	24–28	8, 10, 14, 18, 21 and sex chr.	7, 13, 14, 20, X	yes	0.0042	33–44		7, 13, 14, 20, X	nr	0.79	[9]
2–15	23–29	14, 18, 21 and sex chr.		yes	0.0039	33–39	1, 2, 5, 6, 8, 10, 11,12, 14, 18, 19, 21, 22 and the sex chr.	7, 17	yes	0.39	[11]
15–84	-	-	-	-	-	30–39	1, 5, 6, 8, 10, 11, 15, 18, 19, 21, 22, X, Y	3, 7, 15, 16, 17	66 to 78 chr	0.05	[23]
15–55	-	-	-	-	-	33–39	nr	nr	nr	0.0008	[11]
15–55/>55	<30				0.0016	32–39	1	2, 3, 7, 9, 13, 15, 16, 17, 20, 4	64–74	3.85%	[24]

Age (Years)	Near-Haploid					Low-Hypodiploid					Reference
	MN	Retained chr	Lost chr	Doubled Clone	Frequency	MN	Retained chr	Lost chr	Doubled Clone	Frequency	
1–9/>10	24–29	14, 18, 21 and sex chr.	nr	nr	nr	33–39	nrec	3, 7, 16, 17	nr	nr	[25]
<31	24–31	14, 18, 21 and sex chr.	nr	yes	0.008	32–39	1, 8, 10, 11, 18, 19, 21 and 22	nr	nr	0.0064	[26]

Abbreviations: chr, chromosomes; MN, modal numbers; nr, non-reported; nrec, non-recurrent.

an exact mosome y, some d 22 [21].

The presence of hypodiploid doubled clones has been observed in ~60–65% of patients with near-haploid and low-hypodiploid B-ALL in different studies, and is commonly observed as a mosaic with both hypodiploid and hyperdiploid (doubled) clones visible by standard cytogenetics, fluorescence in situ hybridization (FISH) or flow cytometry analysis of DNA content [7][11][12][26]. Furthermore, the doubled clone may be the only one detected at diagnosis, leading to the manifestation known as “masked hypodiploidy”, which is clinically challenging since patients can be erroneously classified and treated for high-hyperdiploid B-ALL while being at higher risk of treatment failure. It has been reported that there is no difference in clinical outcome for patients with “masked hypodiploidy”, those who are mosaic for a doubled clone and a hypodiploid clone, and those who have only a hypodiploid clone [12][28][26]. In addition, the hypodiploid clone tends to be quantitatively more frequent at relapse, suggesting that the actual hypodiploid clones may be more chemoresistant than their hyperdiploid (doubled) counterparts [10][29].

4. Molecular Characterization of Hypodiploid B-ALL with <40 Chromosomes

In addition to the massive genetic losses, both near-haploid and low-hypodiploid B-ALL show characteristic and differentiated gene expression profiles, in addition to specific mutational and focal copy-number alteration (CNA) landscapes, those excluding whole chromosome losses [19]. Notably, near-haploid and low-hypodiploid B-ALL presenting with or without doubled clones show similar transcriptional and mutational profiles [19], most likely explaining the similar clinical outcomes between patients with and without chromosomal doubling [7][12][26].

4.1. Near-Haploid B-ALL

The mutational landscape of near-haploid B-ALL is characterized mainly by the presence of alterations involving receptor tyrosine kinases and activating RAS signaling alterations, with >70% of patients showing mutations or focal CNA involving genes in these pathways (**Table 2**) [19][21][30]. The different RAS signaling alterations have been shown to be mutually exclusive, suggesting that, in contrast to the convergent evolution for RAS mutations observed in infants with MLL-rearranged B-ALL [31], a single alteration in the pathway is sufficient to maintain constitutive RAS-pathway activation. Focal deletions or point mutations in *NF1* gene are the most recurrent genetic alterations of near-haploid B-ALL (≥44% of patients) [13][19][32].

Table 2. Molecular characteristics of hypodiploid <40 chromosomes B-ALL (Adapted from Holmfelt et al., 2013 [19]).

Genes	Cellular Pathway	Near-Haploid B-ALL			Low-Hypodiploid B-ALL		
		Mutation	Focal Deletion	Focal DEL + Mut	Mutation	Focal Deletion	Focal DEL + Mut
NF1	RTK/RAS pathway	11/68 (16%)	16/68 (24%)	3/68 (4%)	0	2/34 (6%)	0
KRAS		2/68 (3%)	0	0	0	0	0
NRAS		10/68 (15%)	0	0	0	0	0
PTPN11		1/68 (1%)	0	0	0	0	0
FLT3		6/68 (9%)	0	0	0	0	0
CRLF2		0	2/68 (3%) *	0	0	0	0
MAPK1		1/68 (1%)	0	0	0	0	0
GAB2		0	2/68 (3%)	0	0	1/34 (3%)	0
EPHA7		0	2/68 (3%)	0	0	0	0
RASA2		0	2/68 (3%)	0	0	0	0
IKZF1	B-cell development	0	3/68 (4%)	0	0	1/34 (3%)	0
IKZF2		1/68 (1%)	0	0	0	18/34 (53%)	0
IKZF3		1/68 (1%)	8/68 (12%)	0	0	1/34 (3%)	0
PAX5		1/68 (1%)	4/68 (6%)	0	0	2/34 (6%)	0
EBF1		0	0	0	0	0	0

Genes	Cellular Pathway	Near-Haploid B-ALL			Low-Hypodiploid B-ALL		
		Mutation	Focal Deletion	Focal DEL + Mut	Mutation	Focal Deletion	Focal DEL + Mut
VPREB1	Cell cycle and apoptosis	0	3/68 (4%)	0	0	2/34 (6%)	0
CDKN2A/B		0	15/68 (22%)	0	0	8/34 (24%)	0
TP53		2/68 (3%)	0	0	31/34 (91%)	0	0
RB1		2/68 (3%)	3/68 (4%)	1/68 (1%)	5/34 (15%)	8/34 (24%)	0
ETV6	Hematopoiesis	1/68 (1%)	3/68 (4%)	1/68 (1%)	0	0	0
Histone cluster (6p22)	Histone-related	0	13/68 (19%)	0	0	1/34 (3%)	0
ARID1B		0	2/68 (3%)	0	0	0	0
PAG1	BCR signalling	1/68 (1%)	6/68 (9%)	0	0	1/34 (3%)	0
ARPP21	Calmodulin signalling	0	1/68 (1%)	0	0	0	0
SLX4IP (C20orf194)	Telomere length maintenance	0	2/68 (3%)	0	0	0	0
CUL5	Ubiquitin pathway	0	2/68 (3%)	0	0	0	0
FAM53B	Wnt signalling	0	2/68 (3%)	0	0	0	0
PDS5B (APRIN)	Cohesin complex	0	2/68 (3%)	0	0	0	0
ANKRD11	Cell adhesion	0 [19][21][30][33]	0	0 [19][21]	0	2/34 (6%)	0
DMD		0	0	0	0	1/34 (3%) [19][34]	0

* one patient encoding P2RY8-CRLF2.

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found in homozygosity in virtually all low-hypodiploid B-ALL cases due to the very recurrent loss of chromosome 17. *TP53* mutations are frequently found in non-tumor hematopoietic cells in 50% of the cases of childhood low-hypodiploid B-ALL [21][30], suggesting that these cases may be a manifestation of Li-Fraumeni syndrome or other germline *TP53* cancer-predisposing mutations [19][33][34]. Accordingly, genetic counseling is recommended for children with low-hypodiploid B-ALL carrying *TP53* mutations, and their relatives [35][36]. In contrast to childhood

cases, *TP53* mutations in low-hypodiploid adult B-ALL are somatic, are not found in healthy hematopoietic cells, and not detectable in remission samples [19][21].

5. Etiology of Hypodiploidy in B-ALL

Genomic analyses of these subtypes have been difficult given the limited number of cases; however, a study on a small cohort of 8 near-haploid and 4 low-hypodiploid B-ALL samples suggested that the massive loss of chromosomes is the primary oncogenic event, with other oncogenic insults occurring after hypodiploidy [20]. This is consistent with similar analyses in high-hyperdiploid B-ALL cases, the most frequent aneuploid entity in B-ALL, indicating that chromosome gains were the primary oncogenic event [37][38]. Thus, similar pathogenic mechanisms involving gross aneuploidies may be shared in these B-ALL subtypes. Furthermore, the genomic landscape of near-haploid and low-hypodiploid B-ALL subtypes, as well as that of high-hyperdiploid subtypes, is characterized by aneuploidy and subtype-specific mutations, with significant fewer microdeletions and structural chromosomal rearrangements in comparison with other cytogenetic subtypes containing structural chromosomal reorganizations [19][37]. Collectively, these data strongly suggest that hypodiploidy has a direct impact on cell transformation and leukemogenesis rather than being solely a passenger event. The fact that severe hypodiploidy is observed in a wide spectrum of neoplasms further indicates that it is indeed a major contributor of tumorigenesis [39].

6. Outcome and Treatment Strategies for B-ALL with Hypodiploidies <40 Chromosomes

6.1. Relationship of Genetic and Clinical Features with Patient Outcome

The EFS is not significantly different between patients with near-haploid or low-hypodiploid B-ALL, including those cases with “masked hypodiploidy” [13][14][35]. In some cases, hypodiploidy may accompany other primary genetic abnormalities, such as *BCR-ABL1*, *TCF3-PBX1*, *ETV6-RUNX1* and *KMT2A* rearrangements, which modulate the prognosis of the disease. Accordingly, some authors have suggested that these patients should be treated based on the primary structural abnormalities rather than the hypodiploidy, and on their MRD values after induction [14]. The high presence of germline *TP53* mutations among patients with low-hypodiploidy confer an increased risk of relapse in this group and is associated with the development of secondary neoplasms [14]. Therefore, it is highly recommended that all patients with low-hypodiploidy B-ALL are tested for germline *TP53* mutations [14][40]. Strikingly, the germline *TP53* mutations in these cases have been associated with increased mortality due to second neoplastic malignancies following hematopoietic stem cell transplantation (HSCT), highlighting the importance of the germline study in low-hypodiploid B-ALL to assess HSCT versus less toxic alternative therapies [16][41][42].

6.2. Current Treatment Protocols

Different study groups, such as the UKALL, NOPHO, AALL0031 and COG studies, consistently stratify near-haploid and low-hypodiploid B-ALL subtypes as high-risk based on the poor prognosis of the patients, which does

not depend on treatment era or on the NCI risk group in which they are classified [14][16][43]. In view of the poor prognosis of patients with hypodiploid B-ALL, they have been classically treated with high-dose chemotherapy followed by allogeneic transplantation. However, different studies assessing the impact of HSCT on B-ALL with near-haploidy and low-hypodiploidy failed to demonstrate a clear benefit of HSCT in MRD positive or negative patients [13][14][35][44]. Notwithstanding these findings, the outcome of hypodiploid B-ALL with <40 chromosomes has been substantially improved by MRD-guided therapy, which intensifies treatments based on the MRD EOI status [13].

6.3. Novel Therapeutic Targets and Approaches to Treat B-ALL with <40 Chromosomes

New treatments aiming to target recently identified biological drivers of hypodiploidies as well as immunotherapy strategies are currently being explored to achieve better responses before HSCT or to be used as alternative approaches. The recent discovery of near-universal *TP53* alterations in low-hypodiploid B-ALL has highlighted a key role for this gene in leukemogenesis. Investigation of this germinal mutation in this population is recommended when evaluating treatment with chemotherapy and HSCT. It remains to be demonstrated, however, whether therapies directed at this genetic lesion have an effect on low-hypodiploidy [36]. The anti-apoptotic protein BCL-2, has been identified as an effective therapeutic target for hypodiploid B-ALL with <40 chromosomes [45], and the efficacy of BCL-2 inhibitors (mainly venetoclax) has been demonstrated in ex vivo models of B-ALL with near-haploidy and low-hypodiploidy, especially in cases with elevated levels of the apoptosis-related factors BIM or BAD.

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