Collaborative Study of Karyotypes in Childhood Acute Lymphoblastic Leukemias

Groupe Français de Cytogénétique Hématologique

(Participants listed in Appendix)

A collaborative study carried out by the Groupe Français de Cytogénétique Hématologique collected 411 successful karyotypes of childhood acute lymphoblastic leukemias. Karyotypes showed a clonal abnormality in 292 patients (71%). The distribution of ploidy groups was: pseudodiploidy in 116 karyotypes (28.2%), hyperdiploidy >50 chromosomes in 110 karyotypes (26.8%), hyperdiploidy 47–50 chromosomes in 46 karyotypes (11.2%) and hypodiploidy in 20 karyotypes (4.9%). One-half of the patients with hyperdiploidy >50 chromosomes also had a structural abnormality, with a partial trisomy 1q in one fourth of them. Similar translocations, candidate for new recurrent changes were identified: t(9;9)(p13;q13), t(7;9)(q11;p11), t(7;12)(q11;p12–13), t(4;12)(q13;p12), and t(1;17)(q12–21;p13). Within recurrent translocations, the three t(10;11)(p13–14;q14–21) displayed a T-cell phenotype. In T-cell leukemias, a new area of recurrent breakpoints (5q31–35) was observed and deletions 6q were more frequent in this lineage. Correlations of cytogenetic results with clinical and hematological data revealed that, within hyperdiploidy >50 chromosomes, patients with structural changes were older than patients without. Patients with 9p changes showed some of the features usually observed in lymphomatous leukemias. Even with a short follow-up, differences in outcomes were observed. Patients with hyperdiploidy >50 chromosomes fared the best and those with pseudodiploid karyotypes did worse than patients with other karyotypes. Patients with random translocations did not share the poor outcome of patients with recurrent translocations.

INTRODUCTION

Cytogenetic studies of childhood acute lymphoblastic leukemias (ALL) reveal recurrent changes, correlated with immunophenotypic, clinical and hematological patterns. Favorable prognostic significiance of hyperdiploidy >50 chromosomes was the first one to be identified and has been recognized in every report to date (1–8). Translocations have then shown an independent and adverse predictive value (9). However, as therapy progressed, the relative impact of different prognostic factors needed to be reevaluated in the light of contemporary protocols.

A collaborative study of a large number of patients makes it possible to identify new recurrent changes, to assess correlations and to evaluate the prognostic value of cytogenetic factors as therapies evolve. In the present report by Le Groupe Français de Cytogénétique Hématologique (GFCH), 411 childhood ALL were analyzed, with this aim in mind.

MATERIALS AND METHODS

Patients

A collaborative study of the GFCH, collected 411 karyotypes of childhood ALL (below the age of 16 years) from March 1987 to 1990. Diagnosis of ALL was based on morphologic and cytochemical criteria of the French–American–British (FAB) classification. Leukemias of B-cell lineage were broken down into five groups: early early B (DR+ CD19+), early B (DR+ CD19+ CD10+), pre-pre-B (DR+ CD19+ CD10+ CD20+), pre-B (DR+ CD19+ CD10+ CD20±, intracytoplasmic immunoglobulin or CIg) and mature B-ALL (surface immunoglobulin or SIg). Leukemias of T-cell lineage were classified in four differentiation stages: early T (CD2+ CD5+ CD7+), common T (CD2+ CD5+ CD7+ CD1+ CD3± CD4+ CD8+), and late T (CD2+ CD5+ CD7+ CD1− CD3+ CD4± CD8±) and (CD2+ CD5+ CD7+ CD1− CD3+ CD4− CD8−). Myeloid markers were tested in most patients. For every antigen tested, reactivity was considered to be positive when percentages of expression were >30% for lymphoid, and >20% for myeloid markers. Immunophenotypes were reviewed by a member of the GEIL group (10).

Therapeutic regimens varied with different participants: FRALLE protocol was used in 44.7% of cases (11), EORTC in 38.4% of cases (12) and other regimens in 16.9% cases (13).

Cytogenetics Methods

At diagnosis, chromosome analyses were carried out mainly from bone marrow (390 karytoypes), and seldom from peripheral blood (21 karyotypes). Most samples were cultured for 24 h without mitogen (347 karyotypes), whereas direct techniques and 48 h cultures were performed in 101 and 34 samples respectively. RHG banding was most commonly used (338 cases), whereas GTG, QFQ and CBG bandings were performed in 87, 34 and 18 cases, respectively. Chromosomes were classified according to the ISCN 1985 nomenclature (14).

Standard criteria to define a clone were used: at least two metaphases with the same extra chromosome or with identical structural changes, or a minimum of three metaphases with the same missing chromosome. Karyotypes were classified within usual ploidy groups: pseudodiploidy, hyperdiploidy >50 chromosomes, hyperdiploidy 47–50 chromosomes and hypodiploidy. A karyotype was considered to be complex when at least three different structural abnormalities were present in the same clone.

Each karyotype was critically reviewed by all the participants of the GFCH group in two successive workshops before being recorded in the study. Cytogenetic eligilibity criteria were

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successful banding and, when no abnormality was found, the complete karyotype of at least 20 metaphases with good banding. A quality score was given to each case from 1 (poor but interpretable banding) to 3 (good banding).

Statistical Methods

For each patient included in our study, the following dates were recorded: date of first complete remission (CR), date of first relapse, date of death or date of last follow-up (except for two patients unaccounted for at 9 and 20 months of complete remission).

Hypotheses of no differences for discrete variables were tested using Pearson χ^2 statistics for a two-way frequency table (at $a = 0.05$) and the rank test of Kruskal and Wallis for continuous variables.

Event-free survival (EFS) was measured from the date of CR to the date of first relapse or last follow-up in CR. Patients dying in CR were censored at the time of death. Patients who never achieved CR were assigned an EFS of 0 month. Differences were tested with the log-rank test and curves were plotted from life tables calculated using the method of Kaplan and Meier.

We first compared the EFS of patients within different ploidy groups (normal karyotypes, pseudo, hyper >50, hyper 47–50, hypo), then the EFS of patients with and without translocations. Partially identified derivatives were included in translocations and the patients with t(8;14) translocations were excluded from statistical analysis of the outcome. To further investigate patients with translocations, we compared the group of recurrent translocations known to confer poor prognosis; t(9;22), t(4;11), t(1;19), to the group of random translocations. Recurrent but rare translocations were excluded from this test. To study the prognostic value of various combinations of risk factors, Cox regression was used.

RESULTS

Karyotypes and Immunophenotypes

Clonal abnormalities were found in 292 patients (71%) distributed among 116 pseudodiploidies (28.2%), 110 hyperdiploidies >50 chromosomes (26.8%), 46 hyperdiploidies 47–50 chromosomes (11.2%), 20 hypodiploidies (4.9%) (see Table 1).

Table 1. Distribution of Chromosomal Abnormalities within Ploidy Groups.

	Number of Cases (%)	Structural Changes	t[a]	9p[b]	12p[b]	6q[b]	mar[c]	Complex Karyotypes[d]	Clonal Evolution[e]
Whole sample	411 (100)	228	142	40	35	28	68	44	66
Normal karyotype	119 (28.9%)	0	0	0	0	0	0	0	0
Pseudodiploidy	116 (28.2%)	116	93	29	17	19	13	17	20
Hyperdiploidy >50	110 (26.8%)	59	16	0	3	1	31	9	32
Hyperdiploidy 47–50	46 (11.2%)	38	21	7	10	7	19	12	9
Hypodiploidy	20 (4.9%)	15	12	4	5	1	5	6	5

[a] Translocations.
[b] Structural changes with or without loss of material.
[c] Markers: unidentifiable structural changes.
[d] Complex karyotypes: presence of at least three different structural changes.
[e] Clonal evolution: simultaneous presence of related clones.

Table 2. Distribution of Immunophenotypes within the Main Chromosome Groups.

	Immunophenotype										
	B phenotype 334 patients (81.2%)						T phenotype 56 patients (13.6%)				
	B[a]	DR+ CD19+	CD10+	CD20+	Clg+	IgS+	T[a]	CD7+ CD5+ CD2+ CD1− CD3− CD4− CD8−	CD7+ CD5+ CD2+ CD1+ CD3− CD4+ CD8+	CD7+ CD5+ CD2+ CD1+/− CD3+ CD4+/− CD8+/−	CD7+ CD5+ CD2+ CD1− CD3+ CD4− CD8−
Normal karyotype (n = 113)	19	12[b]	50[b,c]	8	2	0	4	4	13	0	1
Pseudodiploidy (n = 109)	14	5	37[b,f]	15[c]	7[b]	5	7	3	14	0	1
Hyperdiploidy >50 (n = 107)	19	4	59[b,c]	20	1	1	0	2	1	0	0
Hyperdiploidy 47–50 (n = 43)	4	4	19	5	5[c]	2	1	2	1	0	0
Hyperdiploidy (n = 19)	6	2	4	4	1	0	2	2	0	0	0
9p (n = 39)	5	4[b,c]	11[b,d]	7	2	2	0	1	6	0	1
12p (n = 33)	6	0	19[d]	4	2	0	0	2	0	0	0
6q (n = 26)	3	0	10[c]	3	1	0	2	2	4	0	1

[a] Number of markers insufficient to determine the maturation stage.
[b] T marker present in one case.
[c] Myeloid marker(s) present in one case.
[d] Myeloid marker(s) present in two cases.
[e] Myeloid marker(s) present in three cases.
[f] Myeloid marker(s) present in five cases.

In hyper >50, modal numbers ranged from 51 to 61 with a peak at 55 chromosomes, and nonrandomly gained chromosomes ranged in decreasing order: chromosome 21 (trisomic in 24, tetrasomic in 66 cases), chromosome 6, chromosome 14, chromosome 4, chromosome 18, chromosome 17, chromosome X and chromosome 10. Except for chromosome 21, gains usually led to trisomies. More than one-half of patients (53.6%) also had a structural abnormality. Deletions, duplications, translocations, isochromosomes and markers were found. Translocations were random, except for two t(9;22)(q34;q11), and four derivatives involving the long arm of chromosome 1. Extra chromosomes were equally distributed within the groups with and without structural changes but modal numbers peaked at 57 chromosomes in the group with structural abnormalities. Only two triploid and three tetraploid karyotypes were observed.

In hyper 47–50, modal numbers were 47 in 36 karyotypes, 48 in six karyotypes, 49 in one karyotype and 50 in three karyotypes. Eight karyotypes were characterized by numeric only abnormalities and an extra chromosome 21 was the sole frequent gain.

In hypo, the most common modal number was 45. No karyotype with less than 44 and no haploid cases were recorded. Chromosomes 20 and X were nonrandomly lost.

Immunophenotypes of ploidy groups are shown in Table 2. The hyper >50 group was mainly associated with early B (DR+, CD19+, CD10+) or with pre-pre-B-cell phenotypes (DR+, CD19+, CD10+, CD20+). Immature B (DR+, CD19+) and mature (CIg+ or SIg+) phenotypes, as well as T-cell phenotypes were seldom observed in this hyperdiploid group. Normal and pseudodiploid karyotypes showed the highest proportion of T-cell ALL with a predominance of common thymocytes in both cases.

Structural changes were observed in all ploidy groups (see Table 1) . Translocations were present in all ploidy groups but in only 14.5% of hyper >50 karyotypes. Conversely, the incidence of markers was higher in hyper >50 and in hyper 47–50 than in other groups, thus accounting for the difficulty in obtaining good banding in hyperdiploid cells. Structural changes were more complex in hyper 47–50 (26% cases) and in hypodiploidy (30% cases) than in other groups. Clonal evolution, defined by the presence of related clones, was found to be equally distributed within all ploidy groups.

Most recurrent changes in ALL were observed in this series. Their frequencies and immunophenotypes are shown in Table 3. Four t(1;19)(q23;p13) translocations were balanced, whereas in six other cases, the derivatives 1 were lost and two normal chromosomes 1 were present. Deletions 9p, 6q, isochromosomes 9q, translocation t(9;9) were associated with t(1;19) in four out of six karyotypes with secondary changes. Two variant Philadelphia chromosomes Ph^1, t(9;16;22)(q34;q24?;q11) and t(9;14;22)(q32;q32;q11) were described. Ph^1 chromosome was the only abnormality

Table 3. Frequencies and Immunophenotypes of the New Recurrent Translocations and of Other Recurrent Changes.

Number of Cases	Frequency (%)	Chromosomal Abnormalities	Immunophenotype									
			B Phenotype						T Phenotype			
			B Lineage[a]	DR+ CD19+	CD10+	CD20+	CIg+	SIg+	CD7+ CD5+ CD2+ CD1− CD3− CD4− CD8−	CD7+ CD5+ CD2+ CD1+ CD3− CD4+ CD8+	CD7+ CD5+ CD2+ CD1+/− CD3+ CD4+/− CD8+/−	CD7+ CD5+ CD2+ CD1− CD3+ CD4− CD8−
New recurrent translocations												
2	(0.5%)	t(9;9)(p13;q13)	−	−	−	1	−	−	−	1	−	−
2	(0.5%)	t(7;9)(q11;p11)	−	−	−	1	−	1	−	−	−	−
2	(0.5%)	t(7;12)(q11;p12-13)	−	−	−	1	−	−	1	−	−	−
2	(0.5%)	t(4;12)(q13;p12)	−	−	1	−	1	−	−	−	−	−
2	(0.5%)	t(1;17)(q12-22;p13)	−	1	1	−	−	−	−	−	−	−
Recurrent changes												
10	(2.4%)	t(1;19)(q23;p13)	1	−	5[c,d]	2	2[c]	−	−	−	−	−
9	(2.2%)	t(9;22)(q34;q1)[b]	−	−	8[c]	1	−	−	−	−	−	−
8	(1.9%)	t(8;14)(q24;q32)	−	−	3[e]	−	−	5	−	−	−	−
7	(1.7%)	t(4;11)(q21;q23)[f]	1	2[c]	−	−	−	−	−	−	−	−
3	(0.7%)	t(10;11)(p13-14;q14-21)	−	−	−	−	−	−	2	1	−	−
3	(0.7%)	i(9q)	−	−	1	−	−	−	−	1	−	1
2	(0.5%)	t(11;14)(p13;q11)	−	−	−	−	−	−	−	2	−	−
2	(0.5%)	t(9;12)(p23;p12)	−	−	2[c]	−	−	−	−	−	−	−
2	(0.5%)	dic(9;12)(p13;p11)	−	−	1[c]	1	−	−	−	−	−	−
1	(0.1%)	dic(7;9)(p11;p11)	−	−	−	1	−	−	−	−	−	−
1	(0.1%)	t(10;14)(q24;q11)	−	−	−	−	−	−	−	1	−	−

[a] Number of markers insufficient to determine the maturation stage.
[b] Two of them were variant: t(9;16;22)(q34;q24?;q11) and t(9;14;22)(q32;q32;q11).
[c] Myeloid marker present in one case, and in two t(9;22) cases.
[d] CIg not tested in four cases.
[e] SIg not tested in two cases.
[f] Two were undifferentiated.

in two patients. Ph[1] chromosomes were associated with hyperdiploidy >50 chromosomes, with a standard pattern of extra chromosomes (57 and 59 modal numbers) in two patients, whereas a monosomy 7 (either complete or limited to 7p) was present in two patients. One-half of the t(8;14)(q24;q32) translocations were single changes, whereas partial trisomy 1q was observed in two of the four karyotypes with other changes. Six of the seven t(4;11)(q21;q23) and two of the three t(10;11)(p13-14;q14-21) translocations were primary, whereas all isochromosomes 9q were secondary changes.

New recurrent translocations were identified (see Table 3). Two of them involved the short arm of chromosome 12: two t(7;12)(q11;p12), one associated with T-cell ALL and the other with B-cell ALL, and two t(4;12)(q13;p12) observed in early and pre-B leukemias.

Two new recurrent changes involved the short arm of chromosome 9. One of them affected both chromosomes 9: t(9;9)(p13;q13) and was differentiated from i(9q) by CBG banding. A third translocation, t(9;9)(p11;q13), with a close but different break on 9p was also observed. In two patients, they were the only

Table 4. Translocations Involving the Short Arm of Chromosome 9.

Sex/Age (years)	AHSMC	WBC (10^9/l)	Hb (g/dl)	FAB	Phenotype[a]	Karyotype
F/11.3	− − + − −	11.6	9.4	L1	Early early B	50,XX, +12, +21, +22,t(2;9)(q21;p21)
M/3.5	+ + + + −	43.4	9.2	L1	Common T	46,XY,der(3)t(3;9)(p25;p11),t(7;9)(q35;q33-34),i(9q),inv(14)(q11q32)
M/8.8	− + + − −	35	8.9	L1	Early early B	46,XY,t(3;9)(p22;p23)
M/14.5	+ + + − −	150	7.8	L2	Pre-pre-B	45,XY,dic(7;9)(pll;p11)
F/1.3	+ + − − −	200		L1	Pre-pre-B	45,XX, −7,der(9)t(7;9)(q11;p11),
M/4	+ + + − −	55	4.7	L1	Mature B	46,XY, −7, −12,der(9)t(7;9)(q11;p11), +mar1, +mar2
M/9.1	+ + + + −	10.7	11.6	L1	Common T	46,XY,t(9;9)(p11;q11)
F/10.6	+ + + − −	6.5	9.7	L1	Early B	46,XX,der(19)t(1;19)(q23;p13),der(9)t(9;9)(p13;q13)
M/11.7	+ + + − −	130	10	L1	Common T	46,XY,t(9;9)(p13;q13)
F/6.3	+ + + −	7.5	8.5	L1	Pre-B	46,XX,der(9)t(9;10)(p22;q11)
M/9.1	+ + + − −	1.5		L1	Early B[b]	46,XY, +8,dic(9;12)(p13;p11)/45,XY,dic(9;12),del(17) (p13)[c]
F/14.9	+ − − − −	2.9	6.9	L2	Pre-pre-B	46,XX, +8,dic(9;12)(p13;p11)
F/5.7	− − + − −	15.3	7.5	L1	B lineage	44,XX, −10, −17,t(9;12)(p11;p12),der(7q)
M/8.7	+ + + − −	39	6.4	L1	Early B[b]	46,XY,t(9;12)(p23;p12),der(9)t(9;12)
M/4.7	+ + + − −	5.6	3	L1	Early B	46,XY, −15,t(9;12)(p23;p12),del(6q),del(13q), +mar
M/2.2	− + + − −	17.5	5.7	L2	Early B	47,XY,t(9;12)(p23;q14), +der(12)t(9;12),del(12)(p12)
M/1.2	+ + + − −	36.9	5.4	L1	Early B	45,XY, −18,der(9)t(9;18?)(p21;q12)

Only fully identified translocations are shown.
AHSMC, Adenopathies, hepatomegaly, splenomegaly, mediastinal mass, central nervous system; WBC, white blood cell count; Hb, Hemoglobin.
[a] Phenotype: early early B, DR+ CD19+;early B, DR+ CD19+ CD10+; pre-pre-B, DR+ CD19+ CD10+ CD20+; pre-B, DR+ CD19+ CD10+ CD20+ Clg1+; mature B, Slg+; early thymocyte, CD7+ CD2+ CD5+ common thymocyte, CD7+ CD2+ CD5+ CD1+ CD3− CD4+ CD8+.
[b] Presence of myeloid markers.
[c] Case already published (15).

Table 5. Translocations Involving the Short Arm of Chromosome 12.

Sex/Age (years)	AHSMC	WBC (10^9/l)	Hb (g/dl)	FAB	Phenotype[a]	Karyotype
M/3.7	+ + + − −	11.6	5.4	L2	Early B	46,XY,t(1;12)(p22;p11),der(6q)/46,XY,t(5;12)(q14;p11)
M/3.2	− + + − −	8.4	5.1	L1	Early B	46,XY,t(2;12;22)(p12-13;p13;q11)
F/3.7	+ + + − −	38	5.1	L1	Mature B	50,XX, +10, +16, +21, +21,t(3;12)(q23;p12), del(6q),der(19)t(19;?)(p13;?)
M/3.1	+ + + − −	35.6	5	L1	Early B	47,XY,t(4;12)(q13;p12),del(1q),del(2q),der(3q),del(6)(q21q25), +mar
M/4.6	+ + + − −	9	6.6	L1	Pre-B	46,XY,t(4;12)(q13;p12), +der(1)t(1;?)(p36;?)
M/5.3	− + + − −	2.8	8.8	L1	Pre-pre-B	46,XY, −7, −9, −15,t(4;12;15)(q25;p12?;q21), +mar1, +mar2, +mar3
F/1.6	− + + − −	56.2	5.3	L1	Early B	47,XX, +10,t(5;12)(p11;p11)
F/7.4	+ − + − −	5.1	9.7	L2	Early T	45,XX, −7,der(12)t(7;12)(q11;p12),del(6)(q16q22),
M/3	− − + − −	12.1	8.3	L1	Pre-pre-B	45,XY, −7, −20,der(12)t(7;12)(q11;p13), del(7)(p22)
F/5.7	− − + − −	15.3	7.5	L1	B Lineage	44,XX, −10, −17,t(9;12)(p11;p12),der(7q)
M/4.7	+ + + − −	5.6	3	L1	Early B	46,XY, −15,t(9;12)(p23;p12),del(6q),del(13q), +mar
M/8.7	+ + + − −	39	6.4	L1	Early B[b]	46,XY,t(9;12)(p23;p12),der(9)t(9;12)
M/9.1	+ + + − −	1.5		L1	Early B[b]	46,XY, +8,dic(9;12)(p13;p11)/45,XY, dic(9;12),del(17)(p13)[c]
F/14.7	+ − − − −	2.9	6.9	L2	Pre-pre-B	46,XX,dic(9;12)(p13;p11)
M/1.8	+ + + − −	7.3	7.1	L1	Early B	46,XY,t(12;12)(p11-12;q13)

Only fully identified translocations are shown.
AHSMC, Adenopathies, hepatomegaly, splenomegaly, mediastinal mass, central nervous system WBC, white blood cell count; Hb, hemoglobin.
[a] Phenotype: early early B, DR+ CD19+; early B, DR+ CD19+ CD10+; pre-pre-B, DR+ CD19+ CD10+ CD20+ pre-B, DR+ CD19+ CD10+ CD20+ Clg+;mature B, Slg+; early thymocyte, CD7+ CD2+ CD5+; common thymocyte, CD7+ CD2+ CD5+ CD1+ CD3− CD4+ CD8+.
[b] Presence of myeloid markers.
[c] Case already published (15).

changes. Two t(7;9)(q11;p11) were also found. Two out of five translocations involving 9p expressed T-cell immunophenotypes.

Two translocations t(1;17)(q12-22;p13) were observed in hyperdiploid karyotypes, one in hyperdiploidy >50 and the other in tetraploidy.

All chromosomes, except chromosome Y, were affected by translocations. Those involving the short arm of chromosome 9 constituted 12%, and those involving the short arm of chromosome 12, 10.5% of all translocations. They are listed in Tables 4, 5 and 6 respectively, with their immunophenotypes, clinical and hematological data.

The recurrent breakpoints were 9p (40 cases), 12p (35 cases) and 6q (28 cases). Their distribution within ploidy groups and immunophenotypes are shown in Tables 1 and 2 respectively. Most of 9p abnormalities (30 cases) were associated with del(9p), due to simple deletion in five cases and to unbalanced translocations in 25 cases. These were the only changes in one third of karyotypes.

Table 6. Translocations Involving all Chromosomes, Except Those with 12p and 9p.

Sex/Age (years)	AHSMC	WBC (10^9/l)	Hb (g/dl)	FAB	Phenotype[a]	Karyotype
M/2.3	+ + + − −	127	7.2	L2	Early early B	46,XY,t(1;2)(p21;q32),der(19)t(1;19)(q23;p13),del(6q),i(9q)
F/2.9	+ + + − −	14.6	5.1	L1	Mature B	61,XX,+2,+4,+5,+6,+8,+8,+10,+11,+12,+14,+17,+18,+21,+21,+22,der(5)t(1;5)(q11;q14)
M/11.9	− + + − −	10.3	9.6	L3	Pre-pre-B	46,XY,der(6)t(1;6)(q11;q11),t(8;14)(q24;q32)
F/3	+ − + − −	16.7	6.4	L1	Early B	57,XX,−10,−10,+11,+14,+21,+21,der(6)t(1;6)(q22;q15),+mar(?3)
F/13.6	+ + + − −	9.7	8.6	L2	B lineage	47,XX,der(7)t(1;7)(q11;p21),t(1;19)(q23;p13)+i(1q)
F/6.8	+ + + + −	104	6.7	L1	Common T	46,XX,t(1;11)(p34;q21)
M/4.7	+ − − + −	10.1	12.2	L3	B lineage	46,XY,der(12)t(1;12)(q11;q24),t(8;14)(q24;q32),der(22)t(1;22)(q11,q13)
F/2.8	− − − − −	3.3	8.6	L1	Early B	57,XX,+X,+4,+5,+6,+10,+14,+15,+18,+21,+21,+der(17)t(1;17)(q11;p13)
F/4.7	− − + − −	2	7.3	L1	Early early B	94,XXXX,+der(17)t(1;17)(q11;p13) ×2
F/5	+ + + + −	77	2.7	L1	B lineage	46,XX,der(21)t(1;21)(q11;q22)
F/9.2	− + + + −	30.6	8.2	L2	T lineage	46,XX,t(2;5)(p14;q32)
F/5.7	+ + + − −	17.8	8.7	L1	Early B	46,XX,t(2;5)(q22;q34),del(13)(q13q21)
M/14	− − − − −	1.2	11	L2	Early B	55,XY,+X,+4,+6,+8,+9,+10,+14,t(2;14)(p11;q32),+mar1,+mar2
F/5.6	+ − + − −	36	7.9	L1	Pre-pre-B	45,XX,−20,t(2;22)(q11;p11?),del(7p),
F/2.7	+ + + − −	59	5.1	L1	ND	44,XX,−11,−15,t(3;5)(p22,q35),der(9)t(9;?)(p24;?),del(12)(p12)
M/7.3	+ − + − −	68	11	L1	Pre-pre-B	46,XY,t(3;10;19)(q23;q11;q11)
M/3.9	+ + + − −	22.6	3.6	L1	Early B	54,XY,+X,+4,+6,+10,+14,+17,+18,+21,der(11)t(3;11)(q21?;p15?)
M/11.4	− − − − −	3.7	7.6	L2	Early B[b]	46,XY,−12,der(3)t(3;12)(q11;q11),del(9)(q21q23),+mar
M/2.7	+ + − + −	46.9	10.5	L2	T lineage	46,XY,t(4;20)(q31;q12),der(3)t(3;?)(q24;?),(dup(11) (p12p14)
F/6.3	− − − − −	15.1	7.8	L1	Early B	46,XX,der(21)t(4;21)(q25;p13)?,del(4)(q13)
M/2.6	− + + − −	11	7.2	L1	Early B	46,XY, −1,t(5,6)(q12,q23),der(12)t(12;?),(p1?;?),+mar
M/7.8	+ + + − −	6.5	6.2	L2	Early B[b]	55,XY,+X,+4,+6,+10,+14,+18,+18,+19,+21,t(5;8)(q15;q13)
M/,1.3	+ − − − −	10.5	7.7	L1	Early B	46,XY,t[5;inv(7)(p13q32)](q12;q32)
F/10.9	+ + + + −	110	7	L1	Common T	46,XX,t(5;14)(p13−14;q32),t(10;14)(q24;q11)
M/5.6	+ + + − −	26	8.5	L2	Pre-pre-B	46,XY,t(6,8)(q21;q13),del(9p)
F/10.9	− − + − −	10	13.3	L2	Pre B[c]	46,XX,der(6)t(6;13)(q15;q22),del(9)(p21)der(19)t(1;19)(q23;p13)
F/11.8	+ + + − −	1.8	6.8	L1	Early early B	45,XX,t(6;15)(p22;q26),del(3)(p14),der(18)t(18;?)(p11;?)
F/8.3	+ − + − −	240	8.7	L2	Pre-pre-B	46,XX,der(7)t(7;9)(p13;q12)
M/11.3	+ + + − −	11.8	8.7	L2	Pre-pre-B	47,XY,+X,−21,t(7;11)(p13;q21),+mar [del(1p)?]
F/1.4	− + + − −	3.1	9.3	L1	ND	46,XX,t(7;15)(q22;q13)
F/10.4	+ + + − −	8.7	8	L1	Pre-pre-B	46,XX,t(8;14)(q11;q32)
M/1.8	+ + + − −	72.2	5.9		B lineage	47,XY,der(17)t(8;17)(q11?;q23?) × 2,der(9)t(9;?)(p1?;?),del(12)(p12)
M/1.8	+ + + − −	47	6.8	L1	Pre-B	46,XY,r[der(9)t(9;13)(q31;q14)],der(13)t(9;13)(q31;q14)
M/14.9	+ + + − +	296	10.1	L2	Common T	46,XY,der(11)t(11;14)(p13;q11),t[der(14);17][?;p12]
M/9.6	+ − + + −	46.3	10.4	L1	Early T	48,XY,+6,+17,t(11;15)(q23;q14)
M/8.3	+ + − − −	6.8	9.1	L1	ND	47,XY,+8,der(15)t(11;15)(q?;p11),t(1;20)(q23;q13),del(6)(q13q21)
M/4.3	− + + − −	24	8.6	L1	Early B	46,XY,t(13,14)(q34;q24),del(6)(q11q16),ins(X;12)(q22q28;p12)?
M/11.8	+ − − + −	11.4	12.4		Common T	46,Y,t(X;13)(p22;q12)?,del(6)(q15q22)

Only fully identified translocations are shown.
AHSMC, adenopathies, hepatomegaly, splenomegaly, mediastinal mass, central nervous system; WBC, white blood cell count; Hb, hemoglobin; ND, not determined.
[a] Phenotype: early early B, DR+ CD19+;early B, DR+ CD19+ CD10+; pre-pre-B, DR+ CD19+ CD10+ CD20+; pre-B, DR+ CD19+ CD10+ CD20+ Clg+; mature B, Slg+; early thymocyte, CD7+ CD2+ CD5+; common thymocyte, CD7+ CD2+ CD5+ CD1+ CD3− CD4+ CD8+.
[b] Presence of myeloid markers.
[c] Presence of one T marker.

Table 7. Correlations between Ploidy Groups, and Clinical and Hematological Data.

	Whole Sample $n = 411$	Normal $n = 119$	Pseudodiploidy $n = 116$	Hyperdiploidy		Hypodiploidy <46 $n = 20$	p
				>50 $n = 110$	47–50 $n = 46$		
Age							
Median years	4.67	5.07	5.49	3.76	4.57	4.58	NS
<2 years (%)	10.2	7.6	13.8	10	8.7	0	NS
>10 years (%)	18.3	16.8	25	12.7	15.2	5	NS
Males (%)	55.4	58	60.3	46.3	67.4	35	0.05
Hemoglobin, median (g/dl)	7.9	7.6	8.35	8.1	7.55	7.7	NS
Mediastinal mass (number of cases)	45	17	21	4	2	1	0.001
White blood cells							
Median ($\times 10^9$/l)	11.5	10.7	21.7	6.45	18.7	15.3	0.00001
$>50 \times 10^9$/l (%)	9.8	26	36	2	12	4	0.001
FAB L2 (%)	18	11.8	22.4	17.3	10.87	30	NS
Platelet, median ($\times 10^9$/l)	62	89	53	61.5	65	30	0.0003

NS, not significant.

Seven of 40 cases with 9p changes had a T-cell phenotype. However, although T-ALL were slightly more frequent in patients with 9p change (17.5%) than in patients without (12.6%), the difference was not significant.

The 12p abnormalities showed a loss of material in 23 karyotypes, either due to deletion (nine cases) or to unbalanced translocations (14 cases). They were the only changes in eight patients and were associated with B-cell phenotype in 31 patients. Both patients with a T-cell phenotype showed either a single deletion 12p or two deletions, del(12p) and del(6q).

Breaks in the long arm of chromosome 6 led to partial deletions in 26 out of 28 instances. Simple deletions were more frequent (21 cases) than unbalanced translocations (five cases). Regardless of breakpoint sites, the 6q22 band was lost in all patients. These 6q deletions were seldom the only changes (two instances) and were more frequently found in T-ALL (13%) than in B-ALL (5.3%) ($p < 0.06$). Furthermore, the two patients with del(6q) as the sole change displayed a T-cell phenotype.

A partial trisomy for the long arm of chromosome 1 was observed in 23 karyotypes. This partial trisomy was mainly associated with hyper >50 (10 duplications and four derivatives involving 1q) but also with t(1;19) (six derivatives) and with t(8;14) (two derivatives). A recurrent partial monosomy involved the short arm of chromosome 7 in 15 patients.

The chromosomal regions affected in T-ALL were in decreasing order: 6q in seven, 9p in seven, 11p (p11 to p14) in six, 5q (q31 to q35), in four and 14q11–12 in four patients. The 7q35 area was affected in only one patient and no break was observed in 7p15.

No new recurrent breakpoint was identified in B-ALL and the 11q23 breaks were found in ALL expressing immature antigens, or both B lymphoid and myeloid markers.

Six constitutional abnormalities were found: four trisomies 21, one inv(9)(p11q13), and one balanced translocation t(3;19)(q23;p13). No acquired change occurred in these patients.

Clinical and Hematological Data

Correlations between these data and ploidy groups are shown in Table 7. Hyperdiploidy >50 was characterized by a concentration of low risk factors, as opposed to high risk factors, mainly associated with pseudodiploidy. Within the hyper >50 group, patients with structural abnormalities had a higher median age (4.37 years) than patients without (3.39 years) ($p < 0.002$).

Patients with 9p changes (Table 8) displayed high leukocyte counts, frequent splenomegaly but also tended to be older and present with T-ALL more frequently than patients without.

Comparison of hematological data between patients with and without 12p abnormalities did not reveal differences, except for a lower level of hemoglobin in patients with 12p changes ($p = 0.03$). No adverse prognostic factor was found in these patients.

This short follow-up ranging from 6 to 48 months (median 23 months), only allows interim data. Because percentages of complete remissions were identical in the three main therapy protocols, and because the distributions of known prognostic factors (age, organ involvement, leukocytosis, immunophenotypes) and of different cytogenetic groups were similar in the three

Table 8. Clinical and Hematological Data of Patients with and without 9p Changes.

	Patients without 9p $n = 370$	Patients with 9p $n = 39$	p
Median age (years)	3.71	5.6	NS
Males (%)	54.7	62.5	NS
Splenomegaly (%)	62	82	0.006
Mediastinal mass (%)	10	17.5	NS
White blood cells			
Median ($\times 10^9$/l)	10.8	25.5	0.05
$>50 \times 10^9$/l %	17.8	35.8	0.009
Hemoglobin (g/dl)	7.9	8	NS
FAB: L2 (%)	17.6	23	NS
T-ALL	12	17.5	NS

NS, not significant.

main protocols, we studied the patients as a group in statistical analyses. However, each statistical test was carried out after adjustment for protocol.

Even in this short follow-up, the outcomes of various ploidy groups displayed different patterns (Figure 1). Patients with hyper >50 fared the best, with 85% of patients in complete remission as opposed to 65.5% of patients with pseudodiploidy after a 2-year median follow-up ($p < 0.003$). Within the hyper >50 group, no difference was detected between patients with and without structural changes.

Translocations were studied as a group, then broken down in two groups: high risk translocations including t(9;22), t(4;11) and t(1;19), which are also the most frequent, and other translocations including random translocations but excluding recurrent but rare translocations. Patients with translocations relapsed earlier than patients without ($p = 0.009$). However, this negative impact was only due to high risk translocations (47% of failures at a 2-year follow-up), since patients with random translocations fared as well as patients without translocation (20% of failures at a 2-year follow-up). Within the high risk group, EFS were different for t(9;22),t(4;11) and t(1;19) (see Figure 2). Among nine patients with t(9;22), only one is still in complete remission. Two of them, observed with standard hyper >50, relapsed after one and five months. Patients with t(4;11) relapsed later than those with t(9;22), but only three of the seven patients are still in complete remission. Two of them are infants and another is 14 years old. Patients with t(1;19) experienced the best outcomes. Four out of ten patients failed therapy: one did not achieve remission and three relapsed after 7, 13 and 14 months. Three of these four failures had unbalanced translocations.

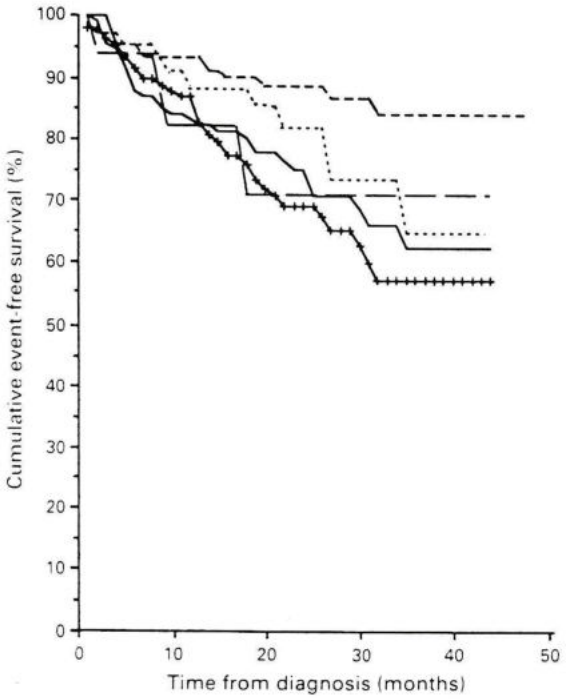

Figure 1. Proportions of patients in event-free survival showed significant differences ($p < 0.004$) when the ploidy groups were compared. The number of patients (n) and the proportions of patients in EFS at 48 months follow-up are indicated. ---, Hyperdiploidy >50 chromosomes, $n = 110$, EFS 84.71%; ———, hypodiploidy, $n = 20$, EFS 71.11%; . . . , hyperdiploidy 47–50 chromosomes, $n = 46$; EFS 64.66%; ——, normal, $n = 119$, EFS 62.59%; + + +, pseudodiploidy, $n = 116$, EFS, 56.95%.

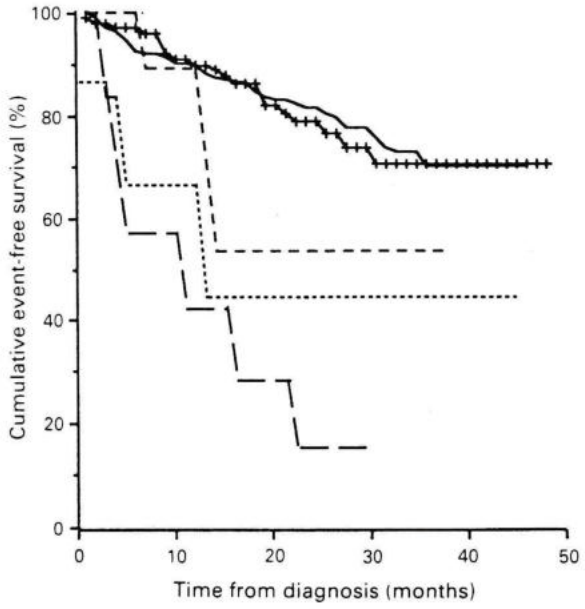

Figure 2. Comparison of patients with specific translocations, random translocations and without translocation revealed significant differences of EFS ($p < 0.0001$). Recurrent but rare translocations were excluded from this test. The number of patients (n) and proportions of patients in EFS at 48 month follow-up are indicated. For specific translocations, t(9;22), t(4;11), t(1;19) were pooled in a group. This group was used in the log-rank test (EFS of this group = 40%). Kaplan–Meier curves are shown for each translocation to better visualize the evolution of each one. ——, Random translocation, n = 99, EFS 70.64%; + + +, without translocation, $n = 269$, EFS 70.10%; ---, t(1;19), $n = 10$, EFS 53.33%; . . . , t(4;11), n = 7, EFS 44.4%; ———, t(9;22), $n = 9$, EFS 14.29%.

DISCUSSION

The collaborative study conducted by the GFCH enabled us to analyze 411 karyotypes of childhood ALL. The rate of clonal abnormalities was in keeping with most series in literature. (3–6,16–21). However, with improved banding techniques, some authors have detected more pseudodiploid karyotypes (22,23).

Hyperdiploidy >50 chromosomes showed a structural change in one-half of the patients, similar to Pui's series (24). However, the distribution of these changes revealed that one-fourth of them led to partial trisomy 1q.

As in previous reports, immunophenotypes of hyperdiploidy >50 chromosomes were early B-cell phenotypes in most patients. Pseudodiploid and normal karyotypes showed the highest proportions of T-cell phenotypes. However, unlike Raimondi who has reported more early thymocytes in normal than in pseudodiploid karyotypes, we observed that common

thymocytes were most frequently seen in both groups.

All recurrent translocations exhibited the expected phenotypes, with the exception of three t(10;11)(p13–14; q14–21) in which an immature T-cell phenotype was found. This translocation has so far been seen in immature B-cell ALL and also in myeloid AL. We have thus postulated that this translocation might affect an early pluripotent stem cell, capable of differentiating in both (T or B) lymphoid and myeloid lineages (27).

Similar translocations, candidates for new recurrent changes, were found. Two involved the short arm of chromosome 12: t(4;12)(q13;p12) and t(7;12)(q11;p12). Raimondi *et al.* first reported a t(7;12)(q11;p12) (28), then reassigned the breakpoint in 7p (29). Two new translocations involved the short arm of chromosome 9. One of them affected both chromosomes 9: t(9;9)(p13;q13) in two patients and t(9;9)(p11;q13) in one patient. Translocations t(9;9)(cen;cen) already reported (19,30,31) and found as only changes in our study, are good candidates for primary translocations. Two patients presented with t(7;9)(q11;p11) while another had the recurrent dic(7;9)(p11;p11). Thus, both dic(7;9) and t(7;9) are likely to be recurrent changes in ALL. The t(1;17) observed in two of our patients has not been reported in literature. Finally, four of the five new recurrent changes identified involved either 9p or 12p.

Structural rearrangements clustered in expected chromosomal areas 9p, 12p and 6q, with a deletion in most instances. The distribution of B- and T-cell phenotypes between these changes were in agreement with data in the literature for 9p and 12p, (28,32,33) but the significant association of deletions 6q with T-cell phenotypes has not been reported to our knowledge in childhood ALL.

Two other recurrent changes were found: partial trisomy for the long arm of chromosome 1 and partial deletion for the short arm of chromosome 7.

A new chromosomal region frequently involved in T-ALL was identified: 5q31 to 5q35. IL9 gene, the T-cell growth factor located in 5q31, might be involved in these malignancies (34).

Within the group hyperdiploid >50, patients with structural changes were older than patients without. Given the known high risk factor of age, this age distribution might affect the outcome of the two groups. The follow-up of our study did not enable us to evaluate the potential predictive value of this feature. Pui has reported a poorer prognosis for patients with structural changes after a 6-year follow-up but has not observed differences in ages (24).

Patients with pseudodiploidy fared worse than all other cytogenetic groups. This poor outcome is not surprising, given the proportions of high risk factors and of translocations in this group. However, at a 2-year follow-up, the random translocations did not show such an outcome thus differing from Williams's data in which all translocations were identified as the strongest indicators of therapy failure (9). These data might have been affected by progress in therapy. A longer follow-up is needed to verify the pronostic value of random translocations.

The differences in outcomes between t(9;22), t(4;11) and t(1;19) are in agreement with data observed with current therapies (35–37). As in our study, better results have been obtained for t(1;19) and to a lesser extent for t(4;11), while no improvement has yet been observed for t(9;22). The two patients with t(9;22) in a standard hyper >50 experienced early relapses, thus stressing the prevalence of the negative impact of t(9;22) over the favorable effect of hyper >50. Furthermore, the two patients with either complete or partial monosomy 7 did not achieve remission.

The patients with 9p showed some of the clinical and hematological features usually associated with lymphomatous diseases. This association has been debated (31,33,38) but our results, comparable to Murphy's (32), suggest that it might very well exist. No correlation between other cytogenetic groups, 6q, 12p and risk factors was observed.

This extensive study contributed new data on childhood ALL: recurrent chromosomal abnormalities and cytogenetic-hematologic correlations. The prognostic value of chromosomal changes observed at this step need to be corroborated by a longer follow-up. With this aim in mind, the GFCH has been recording the evolutions of all patients.

Appendix: Participants

The following lists participants in this study with their centre of research (number of patients studied in parentheses.)

D. Germain, C. Charrin, M.P. Pages, N. Phillipe and G. Souillet (*Lyon*; 72); A.M. Capodano, D. Hairion, M. Perrimond and G. Michel (*Marseille*; 60); N. Dastugue, A. Robert, H. Rubie and P. Colombies (*Toulouse*; 58); J. Van den Akker, C. Perrot (*Paris (St Antoine)*; 35); M.J. Grégoire, S. Gilgenkrantz, P. Bordigoni, C. Schmitt, D. Sommelet (*Nancy*; 28); C. Verellen-Dumoulin, J.M. Libouton, G. Cornu, C. Vermylen, J.L. Michaux (*Brussels (St Luc)*; 24); J.L. Laï, M. Zandecki, B. Nelken, J.P. Jouet, M. Deminatti (*Lille*; 23); M.F. Bertheas, D. Frappaz, C. Vasselon, J. Fraisse, F. Freycon (*St Etienne*; 22); C. Bastard, A. Rossi, F. Bernaudin, J.P. Vannier (*Rouen*; 12); F. Mugneret, B. Favre (*Dijon*; 11); D. Leroux, D. Plantaz, C. Bachelot (*Grenoble*; 11); C. Barin, C. Moraine (*Tours*; 10); S. Raynaud, A. Deville, A. Thyss, P. Philip, N. Ayraud (*Nice*; 9); C. Leonard, G. Tchernia, J.P. Dommergues (*Paris (Bicêtre)*; 9); J.L. Huret, E. Benz Lemoine, J. Tanzer (*Poitiers*; 9); D. Riviere, E. Pluchon-Riviere, M.J. Lebris, M.C. Leglise, J.F. Abgrall (*Brest*; 5); F. Uettwiller, A. Boilletot-Babin, J.V. Ruch, F. Oberling (*Strasbourg (H. Hautepierre)*; 3); M. Lessard, P. Boutard (*Laval*; 2); D. Viguié (*Paris (Hôtel Dieu)*; 2); C. Stoll, P. Lutz (*Strasbourg (H. Civil)*; 2); A. Verhest (*Brussels (H.Erasme, I.Bordet)*; 1); M. Poissonnier, P. Gruyer (*Versailles*; 1); A. Bernheim, A.M. Venuat (*Villejuif*; 1); G. Faure and M.C. Béné (*Immunophenotyping Revue-Groupe*, GEIL); F. Kohler and G. Nisand (*Informatic-Statistics*, CHU Nancy-Brabois).

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