Eur J Haematol 2000: 64: 194–200
Printed in UK. All rights reserved

EUROPEAN
JOURNAL OF HAEMATOLOGY
ISSN 0902-4441

Cytogenetic findings in a population-based series of 787 childhood acute lymphoblastic leukemias from the Nordic countries

Forestier R, Johansson B, Borgström G, Kerndrup G, Johannsson J, Heim S, the NOPHO Leukemia Cytogenetic Study Group. Cytogenetic findings in a population-based series of 787 childhood acute lymphoblastic leukemias from the Nordic countries.
Eur J Haematol 2000: 64: 194–200. © Munksgaard 2000.

Abstract: Different types of leukemia are characterized by different patterns of nonrandom chromosomal aberrations, but the frequencies with which the various karyotypic subtypes are seen differ among cytogenetic laboratories, countries, and geographic regions. During the 12-yr period 1986–1997, a total of 2054 children (<15 yr of age) were diagnosed with acute lymphoblastic leukemia (ALL) in the five Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden). Cytogenetic analyses were successfully performed in 1372 patients, 787 (57%) of whom displayed clonal chromosomal abnormalities. ALL with ⩾47 chromosomes was the most frequent cytogenetic subgroup (63%), with massive hyperdiploidy (⩾52 chromosomes) and chromosome numbers in the tri- and tetraploid range, constituting 46% of all abnormal cases. ALL-associated translocations were found at low frequencies [11q23 translocations in 3.7%, t(9;22)(q34;q11) or del(22q) in 2.2%, t(4;11)(q21;q23) in 2.0%, t(11;19)(q23;p13) in 1.4%, t(1;19)(q23;p13) in 1.3%, and t(8;14)(q24;q32) in 1%]. Two rearrangements not previously reported in childhood ALL, but recurrent in this population-based material, were identified: der(7;9)(q10;q10) and t(9;12)(q22;p11–12), the molecular genetic consequences of which are unknown. Hyperdiploid childhood leukemias, especially those with a high hyperdiploid modal number, thus seem to be more frequent and ALL-specific translocations less frequent in the Nordic countries than in other geographic regions. Although technical differences among laboratories cannot be ruled out as a cause of at least some of the frequency differences observed compared with previous studies, systematic differences in exposure to environmental oncogenic factors or in geographic/ethnic origin are an intriguing possibility.

Erik Forestier[1], Bertil Johansson[2], Georg Borgström[3], Gitte Kerndrup[4], Johann Johannsson[5], Sverre Heim[6], The NOPHO Leukemia Cytogenetic Study Group

Departments of [1]Clinical Science, Pediatrics, University of Umeå, Sweden, [2]Clinical Genetics, Lund University Hospital, Sweden, [3]Medical Genetics, University of Helsinki, Finland [4]Pathology, University of Odense, Denmark, [5]Pathology, University of Iceland, Reykjavik, Iceland, and [6]Genetics and Pathology, the Norwegian Radium Hospital, Oslo, Norway

Key words: acute lymphoblastic leukemia; childhood; bone marrow karyotype

Correspondence: Dr Erik Forestier,
Department of Clinical Science, Pediatrics,
University of Umeå, SE-901 85 Umeå, Sweden
e-mail: Erik.Forestier@Pediatri.umu.se

Accepted for publication 30 August 1999

Cytogenetic analyses of childhood acute lymphoblastic leukemia (ALL) have, during the last three decades, proved to be of both biological and clinical importance, and chromosome banding analysis remains the method of choice for genome-wide screening for the acquired genetic changes that characterize ALL. The leukemic karyotype is, together with age, white blood cell count, and immunophenotype, crucial in deciding which treatment the child should be given. Not only are certain cytogenetic aberrations associated with specific subtypes of leukemia (1), but several karyotypic features have been found to correlate with the clinical outcome even with optimal chemotherapy (2, 3). Hence, the importance of the karyotype both diagnostically and as a prognostic parameter is well established.

The frequencies of the common leukemia-associated cytogenetic abnormalities have differed substantially among studies from different centers (2, 4, 5), and it has been suggested that differences in genotoxic exposure or ethnic susceptibility could

account for at least some of the observed variability (6).

In the present study, we provide a complete population-based description of the main karyotypic features of all children with ALL and clonal cytogenetic abnormalities diagnosed in the five Nordic countries during the 12-yr period 1986–1997. In addition to establishing the frequencies of cytogenetic subgroups in childhood ALL for our population, the data generated also enabled the identification of two new recurrent ALL-associated structural chromosome abnormalities.

Materials and methods

From 1 January 1986 to 31 December 1997, 2054 patients under the age of 15 yr were diagnosed with ALL in the five Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden; total population of 22 million). At diagnosis, bone marrow samples and/or peripheral blood were processed for karyotype analysis at 15 different laboratories. The methods to prepare and stain the metaphase spreads differed among the laboratories. The 787 patients with a registered acquired clonal chromosome abnormality out of these 2054 constitute the cohort of the present study. The cytogenetic evaluation was performed at different laboratories in the Nordic countries (5 in Finland, 5 in Sweden, 3 in Denmark, 1 in Norway, and 1 in Iceland) after chromosome banding of short-term cultured leukemic cells, almost always from the bone marrow but sometimes also from peripheral blood. In some cases, the aberrations were also analyzed with fluorescence *in situ* hybridization (FISH) in order to verify a given chromosomal rearrangement or to describe it more precisely. All karyotypes after 1992 were prospectively registered in the NOPHO (Nordic Society of Pediatric Hematology and Oncology) database, whereas the 1986–1991 data were collected retrospectively. Since 1996, all karyotypes in Sweden are reviewed centrally. Insufficiently described karyotypes were reviewed by the respective laboratories and only centrally reviewed if needed. Description of karyotypes and criteria for clonality followed the recommendations of the ISCN (1995) (7). The chi-square test was used to compare statistically the differences in the frequencies of modal number subgroups.

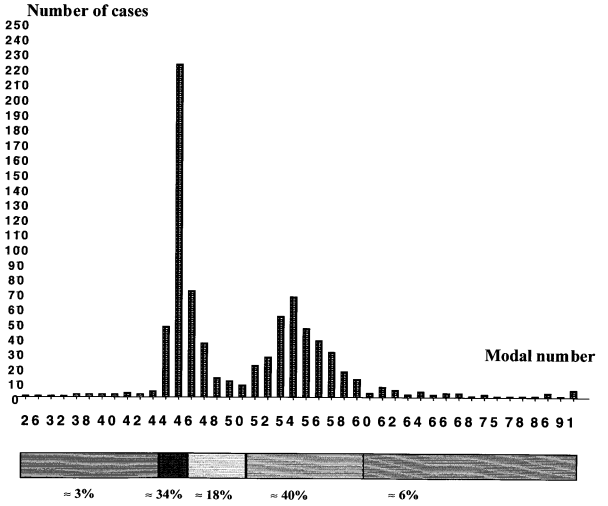

Fig. 1. Distribution of modal chromosome number among the 787 cytogenetically abnormal ALL.

Results

Patients

Cytogenetic analyses were successfully performed in 1372 ALL, 787 (57%) of which displayed clonal chromosomal abnormalities. The remaining 585 (43%) had a normal karyotype.

Modal chromosome number

Subdivision of the total material into different modal number groups was based on the recorded main modal number, differences in propensity to have additional structural abnormalities, and differences in the frequency of whole chromosome gains and losses (Table 1, Fig. 1). The vast majority of the cases (≈93%) were distributed in a bimodal fashion, with a major peak at 46 and a minor peak at 55 chromosomes (chr), with a hiatus at 51–52 chr (Fig. 1). Hypodiploid (⩽44 chr; 2.8%) and, especially, near-haploid ALL were rare, whereas cases with ⩾47 chr (63%), in particular massive hyperdiploidy (⩾52 chr; 46%), were common. The

Table 1. Incidences of modal number groups, frequencies of structural chromosomal abnormalities, and the most common gains and losses in each group among the 787 cytogenetically abnormal ALL

Modal number group [%]	Structural aberrations (%)	Gains and losses[a]
Hypodiploid (<45 chr) [2.8]	64	−9, −7, −16, −17
Moderate hypodiploid and pseudodiploid (45–46 chr) [34]	88	−9, −20, −7, −13, −18, −19, −6
Moderate hyperdiploid (47–51 chr) [18]	73	+21, +X, +8, +10, +14, +19
Massive hyperdiploid (52–60 chr) [40]	43	+21, +X, +6, +14, +10, +4, +8
Tri- and tetraploid range(>60 chr) [5.7]	36	+21, +6, +18, +X, +11, +14

[a]The numerical abnormalities are listed in decreasing frequency order.

Table 2. Frequencies of structural rearrangements among the 787 cytogenetically abnormal ALL

No. of cases (%)	Rearrangement	Comments
1 (0.1)	t(1;11)(p32;q13)	
1 (0.1)	t(1;11)(p32;q23)	
1 (0.1)	ins(1;11)(p36;q13q23)	
2 (0.3)	t(1;12)(p32;p12)	
10 (1.3)	t(1;19)(q23;p13)/der(19)t(1;19)(q23;p13)	Mode 46–47 chr; 4 cases with der(19)t(1;19)
23 (2.9)	add/der/dup(1q)	Always involving 1q25–31; mode $\geqslant$52 chr in 93%
1 (0.1)	t(3;12)(p11;p13)	
16 (2.0)	t(4;11)(q21;q23)/ins(4;11)(q21;q11q23)	10 patients below the age of 1
3 (0.4)	t(5;12)(q12;p11)	
33 (4.3)	del(6q)	Sole abnormality in 16 cases
1 (0.1)	dic(7;9)(p11–13;p11)	
3 (0.4)	der(7;9)(q10;q10)	New recurrent abnormality
1 (0.1)	t(7;14)(q36;q11–12)	
1 (0.1)	t(8;14)(q24;q21)	T-cell ALL
2 (0.3)	t(8;14)(q11;q32)	Both patients had Down's syndrome
8 (1.0)	t(8;14)(q24;q32)	All B-cell ALL
2 (0.3)	t(9;9)(p11;q11)	
2 (0.3)	t(9;11)(p21;q23)	
2 (0.3)	t(9;12)(q22;p11–12)	New recurrent abnormality
3 (0.4)	t/dic(9;12)(p11–13;p11–13)	
13 (1.8)	t(9;22)(q34;q11)	Mode 39–59 chr; sole abnormality in 3 cases
4 (0.5)	del(22q)	
16 (2.0)	del(9p)	Sole abnormality in 6 cases
2 (0.3)	i(9)(q10)	
1 (0.1)	t(10;11)(p13;q21)	
1 (0.1)	t(10;14)(q24;q11)	
2 (0.3)	t(11;14)(p13;q11)	
11 (1.4)	t(11;19)(q23;p13)	
29 (3.7)	11q23 translocations	Mode 44–47 chr. One patient had both t(1;11) and t(11;19)
15 (1.9)	del(11q)	Breakpoints at 11q23 in 5 cases
2 (0.3)	t(12;17)(p13;q21)	
4 (0.5)	t(12;21)(p12–13;q22)	Identified by FISH
36 (4.6)	t/del(12p)	Mode always $<$51 chr
1 (0.1)	t(14;18)(q32;q21)	
10 (1.3)	i(17)(q10)	Hyperdiploidy in 8 cases; sole change in 1 case
10 (1.3)	del(17)(p11–12)	Sole abnormality in 3 cases

frequencies of structural abnormalities varied from 36% in tri- and tetraploid ALL to 88% in moderately hypodiploid and pseudodiploid ALL. Among the hyperdiploid and tri- and tetraploid ALL, gain of chromosome 21 was most common. Monosomy 9 was the most frequent loss among the hypodiploid cases (Table 1). Gain or loss of a single chromosome as the sole abnormality was infrequent. Single gains were only seen for chromosomes X, 8, and 21, whereas monosomy 7 was the only loss found as a sole change.

Recurrent structural rearrangements

Recurrent structural rearrangements, i.e. abnormalities observed in two or more ALL in the present series, are listed in Table 2; single cases are also included in Table 2 if the aberration has been reported in the literature previously (8). The most frequent structural changes were t/del(12p) (4.6% of all 787 cytogenetically abnormal ALL), del(6q) (4.3%), and various 11q23-translocations (3.7%). The ALL-associated translocations t(1;19)(q23;p13), t(4;11)(q21;q23), t(8;14)(q24;q32), t(9;22)(q34;q11)/del(22q), and t(11;19)(q23;p13) were seen in 1.3%, 2.0%, 1.0%, 2.2%, and 1.4% of the cases, respectively. Two recurrent rearrangements not previously reported in ALL were identified: der(7;9)(q10;q10) in three cases and t(9;12)(q22;p11–12) in two cases.

The frequencies of breakpoints in the different chromosomes are listed in Table 3. All chromosomes except the Y chromosome were involved in structural rearrangements, with chromosomes 1, 6, 9, 11, and 12 having the highest breakpoint frequencies. Chromosome bands 11q23 and 12p11–13 (Fig. 2) were most frequently involved in translocations.

Discussion

The existing information on the frequencies of various cytogenetic abnormalities in leukemia in general, and in childhood ALL in particular, is not

Table 3. Breakpoint frequencies per chromosome among the 787 cytogenetically abnormal ALL

Chromosome	%
1	8.7
2	2.7
3	2.9
4	3.3
5	2.0
6	7.1
7	4.2
8	3.2
9	10.0
10	1.4
11	8.7
12	6.1
13	1.1
14	4.3
15	1.4
16	1.4
17	3.9
18	0.5
19	4.2
20	0.9
21	2.7
22	2.9
X	0.4
Y	0.0

very reliable: few, if any, previous studies have been population-based, and one must assume that reporting may have been biased (8). The present population-based series of ALL in children under the age of 15 yr comprises all cases in this age group in the Nordic countries during 1986–1997. The relatively low cytogenetic success rate in the total material (≈40%) most likely reflects the situation in most Western countries during this time period; indeed, it was not until 1992 that all participating Nordic countries began to require that cytogenetic investigation be done in all childhood ALL. Despite the differences in success rate among the participating institutions, we consider these 787 abnormal ALL karyotypes to be a representative, unbiased cohort for the evaluation of different aberration frequencies. No significant clinical differences were noted between the study cohort and cases with normal karyotypes or without cytogenetic information, except that T-cell ALL was less frequent in the study cohort. This strongly indicates that the group of patients with cytogenetically abnormal ALL was unselected, i.e. there has been no clinical bias in sending cases for cytogenetic investigations and no particular clinical subsets of childhood ALL are more likely to fail attempted cytogenetic investigation. Thus, we consider the study cohort to be representative of the entire population of children with ALL diagnosed and treated in the Nordic countries between 1986 and 1997.

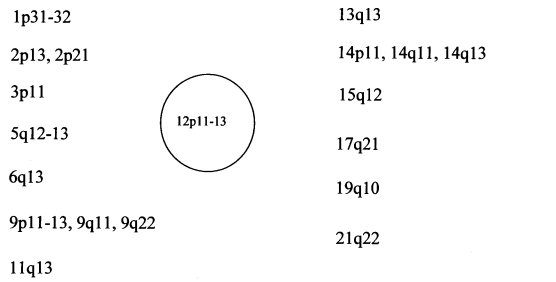

Fig. 2. Translocation partners to 12p11–13 identified in the present series.

The salient findings of the present study were that hyperdiploid ALL, especially the subgroup characterized by modal number ⩾52 chromosomes, was more common than previously reported, and that recurrent ALL-associated structural abnormalities were found at lower frequencies than described in earlier studies and reviews (Tables 4 and 5). The difference in frequency between the German/French studies (4, 5) and the present study is statistically significant ($p<0.01$) for the group of patients having ⩾51 chromosomes.

Assessing the modal chromosome number in our series, it is clear that more than 90% of the cases have either 45–51 chromosomes, i.e. moderate hypodiploidy, pseudodiploidy, and moderate hyperdiploidy, or a modal number between 52 and 60 chromosomes, i.e. massive hyperdiploidy (Fig. 1). These two modal groups differ also with regard to how often the cases display structural abnormalities (≈80% versus ≈40%; Table 1). Different dividing points between modal number groups have been proposed (9, 10) but the 51/52 dividing point suggested by Mertens and coworkers (11) fits well with our findings. We found a higher frequency of ALL with ⩾47 chromosomes (63%) and, especially, massive hyperdiploidy and chromosome number in the tri- and tetraploidy range (46%) than previously reported by other investigators (2, 4, 5, 12) (Tables 1 and 4). The distribution of gains and losses of whole chromosomes and the frequencies of structural rearrangements in the different modal groups, on the other hand, agreed well with earlier findings (4, 12) (Table 1).

Although the fraction of hypodiploid ALL has varied much (2–9%) among previous studies (4, 5, 12, 13, 14), it seems safe to conclude that it is a rare phenomenon, in particular the finding of a near-haploid karyotype (Fig. 1). Although other dividing points for hypodiploidy have been suggested, we have, both for methodological reasons and based on the modal chromosome number distribution (Fig. 1), chosen to consider modal chromosome number ⩽44 to be the true hypodiploid group.

The t(1;19)(q23;p13) was seen at a lower frequency than previously reported in comparable

Table 4. Studies reporting frequencies of modal number groups in childhood ALL[a]

Reference	Hypodiploid[b]	Pseudodiploid	Moderate hyperdiploid[c]	Massive hyperdiploid[d]	Tri- and tetraploid[e] range	>47 chr
Present series[f] $n=787$	8.8	28.2	16.6	39.1	7.2	≈63
UKALL (2) $n=502$	10.6	29.3	16.5	38.8	4.8	≈60
BFM (4) $n=618$	6.0	41.6	18.0	38.3		≈56
GFCH (5) $n=292$	6.8	39.7	14.4	37.6		≈52
Pui, review (12)	7	42	15	27		≈42

[a] All frequencies are given as percentages of cytogenetically abnormal cases.
[b] <46 chr.
[c] 47–50 chr, except for the UKALL study which had the cutoff at 49 chr.
[d] 50–59 chr in the present series and in the UKALL study; >50 chr in the other studies.
[e] >59 chr.
[f] To enable comparisons, the frequencies in the present series were recalculated using other cutoff values for the ploidy groups.

studies and reviews (2, 4, 5, 12, 15) (Table 5). This translocation (in its balanced and unbalanced form) is suggested to be one of the most common translocations in B-precursor childhood ALL (16). Today it is possible to identify this aberration by reverse transcriptase polymerase chain reaction amplification and also by flow cytometry with an antibody specific to the E2A-PBX1 chimeric protein (17, 18). These techniques cannot, however, distinguish between the balanced and unbalanced variant, and because there are studies suggesting a prognostic difference between the two, even when the patients were treated aggressively (19), chromosome banding and kryotyping are needed to discriminate between the two. Another frequent aberration involving chromosome 1 in this series was add/der/dup(1q) (2.9%), a frequency in agreement with earlier reports. The latter abnormalities seem to be secondary events, especially in conjunction with a massive hyperdiploid karyotype (20). In fact, the modal chromosome number was ⩾52 chromosomes in 93% of the present ALL with add/der/dup(1q) (Table 2).

One of the most frequently recorded structural rearrangements in this study was del(6q) (4.3%). Mostly, it was part of complex karyotypes, supporting the interpretation that it is a secondary change (21), found not only in ALL but also in non-Hodgkin lymphomas (8). However, it should be stressed that del(6q) was found as the sole anomaly in 16 of the 33 ALL with this abnormality (Table 2), indicating that it may be an early ALL-associated change as well.

Previously, 16 patients with ALL and t(8;14)(q11;q32) have been reported, four of whom had Down's syndrome (DS) (8). It is noteworthy that both patients with this t(8;14) in the present study also had DS (Table 2). Thus, six (33%) out of the now 18 reported cases have had DS. The fact that a constitutional extra chromosome 21 predisposes a child to have an ALL (22) with this translocation is intriguing. It is known that the translocation involves the *IGH* locus on 14q32 (8), but the gene on 8q11 deregulated by the re-arrangement remains to be identified.

Deletions of 9p have, during the last few years, attracted much interest because of the location on 9p of the tumor suppressor genes *CDKN2A* and *CDKN2B* and also because of the correlation between del(9p) and high-risk clinical features (23). Deletions involving 9p are frequent as secondary changes in ALL (21), suggesting that del(9p) is associated with evolution and progression of ALL. However, del(9p) was found as the sole change in

Table 5. Studies reporting frequencies of structural aberrations in childhood ALL[a]

Reference	(4;11)	t(9;22)	t(1;19)	del(6q)	t/del(12p)
Present series	2.0	2.2	1.3	4.3	4.6
UKALL (2)	2.4	2.0	3.2		7.0
BFM (4)	4.4	3.9	3.4	3.2	4.0
GFCH (5)	2.4	3.1	3.4	8.9	11.3
Pui, review (12)	2.0	3–5	5–6		
Rubnitz, review (15)[b]	4	4	5–6		

[a] All frequencies are given as percentages of cytogenetically abnormal cases.
[b] Only B-precursor ALL included.

six (38%) of the 16 cases with this abnormality in the present series (Table 2), indicating that del(9p) also may play a primary role in leukemogenesis.

The Philadelphia (Ph) chromosome, which almost always results from the reciprocal t(9;22)(q34;q11), was seen in 2.2% of all our cases with clonal aberrations: t(9;22) in 13 ALL and del(22q) in four ALL (Table 2). The Ph chromosome was found in hypo-, pseudo- as well as hyperdiploid karyotypes, with modal numbers ranging from 39 to 59 chromosomes. The frequencies of Ph-positive childhood ALL in previous studies have generally been higher (2, 4, 5, 13, 15) (Table 5). These frequency differences may, at least in part, be due to age differences because of the well known age-dependent occurrence of t(9;22) in ALL (24). The use of molecular genetic techniques increases the detection rate of t(9;22) in ALL, most likely due to the often poor chromosome morphology in ALL, particularly in cases with massive hyperdiploidy. For example, the large BFM study reported by Schlieben and coworkers (25) identified five BCR/ABL-positive cases, out of 21, that were not detected cytogenetically.

Translocations involving 11q23 were found in 3.7% of the cases (Table 2). This chromosome band is highly promiscuous (8, 26) and is known to have more than 20 translocation partners. In the present series, the identified partners, in decreasing frequency order, were chromosome bands 4q21, 19p13, 9p21, 1p32, and 1p36 (Table 2). Ten of the 16 patients with t(4;11) were less than 1 yr old, well in agreement with the fact that rearrangements of 11q23 are more common in infant leukemias (26). Deletions of 11q were found in 1.9% of our cases (Table 2), with one third of them showing breakpoints in 11q23. Whereas most 11q23-translocations involve the *MLL* gene (26), it has been suggested that deletions rarely affect this gene (27).

Rearrangements of the short arm of chromosome 12 (Fig. 2) were detected by chromosome banding in almost 5% of the cases (Table 2), making t/del(12p) the most common structural aberration in our series. Similar frequencies have been reported previously (2, 4, 5, 28) (Table 5). Some, or even many, of the 12p rearrangements may well have been cryptic t(12;21)(p13;q22), undetectable by conventional cytogenetics but known to be the most frequent structural abnormality in childhood ALL (28, 29). Only four cases with this translocation were identified (Table 2). However, this does not reflect a true frequency difference but rather the fact that FISH analyses for t(12;21) were introduced in the Nordic countries in 1997, i.e. at the end of the present study period.

Two abnormalities not included in the Catalog of Chromosome Aberrations in Cancer (8) were identified in the present series as recurrent changes: der(7;9)(q10;q10) and t(9;12)(q22;p11–12) (Table 2). The molecular genetic consequences of these abnormalities remain to be elucidated. However, the der(7;9) results in loss of 7p and 9p material, and loss of the tumor suppressor genes *CDKN2A* and *CDKN2B* on 9p could be one pathogenetically important outcome of the abnormality. The t(9;12)(q22;p11–12) is another example of the frequent involvement of chromosome 12 in leukemia-associated rearrangements (Fig. 2), and *ETV6* on 12p is obviously an attractive candidate gene in this context. The true frequencies of the cytogenetic subgroups defined by these aberrations can only be assessed when more large population-based series of karyotyped childhood ALL are described.

The possibility of an impact of geographic and/or ethnic factors on karyotypic patterns has been addressed previously. For example, the frequencies of t(9;22)(q34;q11) and +21 have been reported to vary among different geographic regions (6), a previous study of ALL in Sweden has suggested that hyperdiploid ALL are more common in that part of the world (30), and differences in t(1;19) frequencies have been detected between black and white Americans (31). Whether the cytogenetic differences between the present series and other comparable studies as regards modal chromosome numbers and ALL-specific rearrangements (Tables 4 and 5) are due to geographic and/or ethnic differences is unknown. Although technical differences among laboratories cannot be ruled out as a cause of at least some of the observed differences, systematic differences in exposure to environmental oncogenic factors or in geographic/ethnic origin are an intriguing possibility. Comparisons of population-based cytogenetic studies of ALL from different parts of the world are needed before this question can be resolved.

Acknowledgements

We are grateful to all cytogenetic laboratories in the Nordic countries for making this study possible by reporting data to NOPHO. Financial support was obtained from the Children's Cancer Fund of Sweden, the Swedish Cancer Society, the Norwegian Cancer Society, the Medical Faculty of the Universities of Umeå, the Samaritans' Research Foundation in Stockholm, the Lions' Cancer Research Foundation, and the Children's Cancer Association in Umeå.

References

1. Heim S, Mitelman F. Quantitative acute leukemia cytogenetics. Genes Chromosomes Cancer 1992;**5**:57–66.
2. Chessels JM, Swansbury GJ, Reeves B, Bailey CC, Richards SM. Cytogenetics and prognosis in childhood lymphoblastic leukaemia: results of MRC UKALL X.

Medical Research Council Working Party in Childhood. Br J Haematol 1997;**99**:93–100.
3. Forestier E, Gustafsson G, von Heideman A, *et al*. Prognostic impact of bone marrow karyotype in childhood acute lymphoblastic leukaemia: Swedish experiences 1986–1991. Acta Paediatr 1997;**86**:819–925.
4. Harbott J, Ritterbach J, Ludwig WD, Bartram CR, Reiter A, Lampert F. Clinical significance of cytogenetic studies in childhood acute lymphoblastic leukemia: experience of the BFM trials. Recent Results Cancer Res 1993; **131**:123–132.
5. Groupe Francais de Cytogénetique Hématologique. Collaborative study of karyotypes in childhood acute lymphoblastic leukemias. Leukemia 1993;**7**:10–19.
6. Johansson B, Mertens F, Mitelman F. Geographic heterogeneity of neoplasia-associated chromosome aberrations. Genes Chromosomes Cancer 1991;**3**:1–7.
7. Mitelman F, ED. ISCN: an International System for Human Cytogenetic Nomenclature. Basel: Karger, 1995.
8. Mitelman F. Catalog of Chromosome Aberrations in Cancer '98. CD-ROM. Version 1. New York: Wiley-Liss, 1998.
9. Look AT, Roberson PK, Williams DL, *et al*. Prognostic importance of blast cell DNA content in childhood acute lymphoblastic leukemia. Blood 1985;**65**:1079–1086.
10. Raimondi SC, Pui CH, Hancock ML, Behm FG, Filatov L, Rivera GK. Heterogeneity of hyperdiploid (51–67) childhood acute leukemia. Leukemia 1996;**10**:213–214.
11. Mertens F, Johansson B, Mitelman F. Dichotomy of hyperdiploid acute lymphoblastic leukemia on the basis of the distribution of gained chromosomes. Cancer Genet Cytogenet 1996;**92**:8–10.
12. Pui CH. Childhood leukemias. N Engl J Med 1995;**332**: 1618–1630.
13. Pui CH, Williams DL, Raimondi SC, Rivera GK, Look AT, Dodge RK. Hypodiploidy is associated with a poor prognosis in childhood acute lymphoblastic leukemia. Blood 1987;**70**:247–253.
14. Fenaux P, Lai JL, Morel P, *et al*. Cytogenetics and their prognostic value in childhood and adult acute lymphoblastic leukemia (ALL) excluding L3. Hematol Oncol 1989; **7**:307–317.
15. Rubnitz JE, Look T. Molecular genetics of childhood leukemias. J Pediatr Hematol Oncol 1998;**20**:1–11.
16. Pui CH, Raimondi SC, Hancock ML, *et al*. Immunologic, cytogenetic, and clinical characterization of childhood acute lymphoblastic leukemia with the t(1;19)(q23;p13) or its derivative. J Clin Oncol 1994;**12**:2601–2606.
17. Scurto P, Hsu Rocha M, Kane JR, *et al*. A multiplex RT-PCR assay for the detection of chimeric transcripts encoded by the risk-stratifying translocations of pediatric acute lymphoblastic leukemia. Leukemia 1998;**12**:1994–2005.
18. Sang BC, Shi L, Dias P, *et al*. Monoclonal antibodies specific to the acute lymphoblastic leukemia t(1;19)-associated E2A/pbx1 chimeric protein: characterization and diagnostic utility. Blood 1997;**89**:2909–2914.
19. Secker-Walker LM, Berger R, Fenaux P, *et al*. Prognostic significance of the balanced t(1;19) and unbalanced der(19)-t(1;19) translocations in acute lymphoblastic leukemia. Leukemia 1992;**6**:363–369.
20. Pui CH, Raimondi SC, Dodge RK, *et al*. Prognostic importance of structural chromosomal abnormalities in children with hyperdiploid (greater than 50 chromosomes) acute lymphoblastic leukemia. Blood 1989;**73**:1963–1967.
21. Johansson B, Mertens F, Mitelman F. Secondary chromosomal abnormalities in acute leukemias. Leukemia 1994;**8**: 953–962.
22. Berger R. Acute lymphoblastic leukemia and chromosome 21. Cancer Genet Cytogenet 1997;**94**:8–12.
23. Murphy SB, Raimondi SC, Rivera GK, *et al*. Nonrandom abnormalities of chromosome 9p in childhood acute lymphoblastic leukemia: association with high-risk clinical features. Blood 1989;**74**:409–415.
24. Tuszynski A, Dhut S, Young BD, *et al*. Detection and significance of bcr-abl mRNA transcripts and fusion proteins in Philadelphia-positive adult acute lymphoblastic leukemia. Leukemia 1993;**7**:1504–1508.
25. Schlieben S, Borkhardt A, Reinisch I, *et al*. Incidence and clinical outcome of children with BCR/ABL-positive acute lymphoblastic leukemia. Leukemia 1996;**10**:957–963.
26. Hunger SP, Cleary ML. What significance should we attribute to the detection of MLL fusion transcripts? Blood 1998;**92**:709–711.
27. Raimondi SC, Frestedt JL, Pui CH, *et al*. Acute lymphoblastic leukemias with deletion of 11q23 or a novel inversion (11)(p13q23) lack MLL gene rearrangements and have favorable clinical features. Blood 1995;**86**:1881–1886.
28. Rubnitz JE, Pui C-H, Downing JR. The role of TEL fusion genes in pediatric leukemias. Leukemia 1999;**13**:6–13.
29. Raimondi SC, Shurtleff SA, Downing JR, Rubnitz J, Mathew S, Hancock M. 12p abnormalities and the TEL gene (ETV6) in childhood acute lymphoblastic leukemia. Blood 1997;**90**:4559–4566.
30. Heim S, Bekassy AN, Garwicz S, *et al*. Bone marrow karyotypes in 94 children with acute leukemia. Eur J Haematol 1990;**44**:227–233.
31. Raimondi SC, Behm FG, Roberson PK, *et al*. Cytogenetics of pre-B-cell acute lymphoblastic leukemia with emphasis on prognostic implications of the t(1;19). J Clin Oncol 1990; **8**:1380–1388.