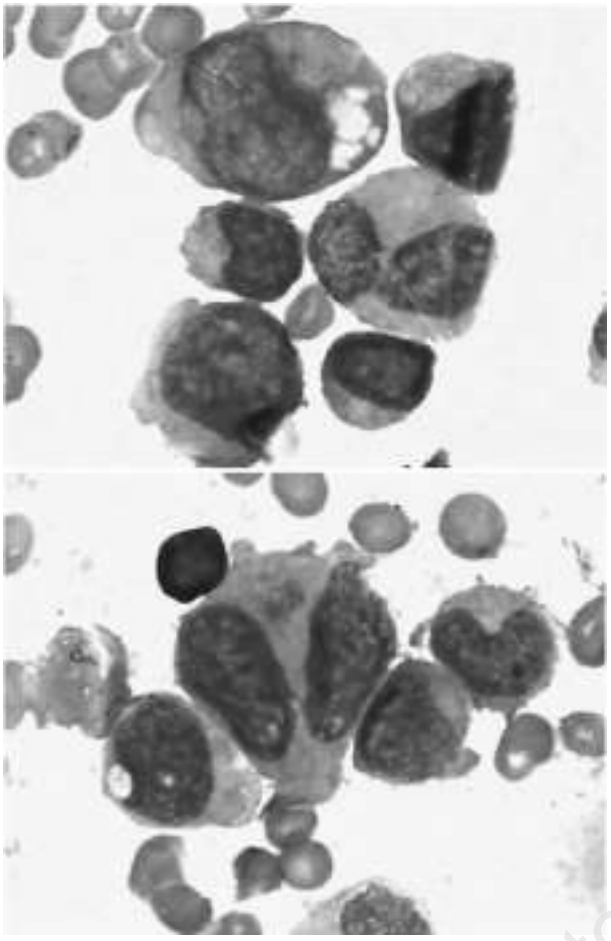

Figure 1. Leukemic cells in bone marrow smears are large (A) and bizarre (B) (Wright-Giemsa stain, ×1,000).

t(1;6)(p32;p10), t(1;7)(q10;p10), t(1;11)(q23;p15), t(3;11)(q23;p15), t(3;21)(q21;q21), t(4;22)(q10;q10), t(11;17)(p10;q10), inv(16)(p12p21) and t(18;20)(p11;q12), each in one case.

Six cases (2.85%) of near-tetraploidy or tetraploidy with double t(8;21) (q22;q22) AML were found in this series. There have been seven other t(8;21) AML with the same chromosome abnormality reported in the literature.[2-6] An analysis of all 13 cases (Table 1) was made to reveal any clinical and genetic features in common. The patients were aged from 6 to 61 years with a median of 12 years, six cases were male and 7 female. There were some common features, as follows: (i) the patients were mainly East-Asians (11/13 cases); (ii) there were giant and bizarre myeloblasts in the bone marrow smear (Figure 1); (iii) the immunophenotypes of the tetraploidy or near-tetraploidy cells were different from those in typical t(8;21)-AML despite a secondary genetic change originating from a diploid clone with t(8;21), the expression of CD2 or CD7 may be associated with clonal evolution to near-tetraploidy; and (iv) the prognosis was poor, the survival from diagnosis being less than one year. Cell fusion, endoreduplication and successive non-disjunction of the whole complement of chromosomes have been suggested as the possible mechanisms for the generation of leukemic tetraploidy cells.[7] Clonal karyotypic evolution has been followed in some tetraploidy or near-tetraploidy AML patients with double t(8;21) (q22;q22). In these patients the initial chromosome changes were only t(8;21) cells without double t(8;21) (q22;q22); the latter emerged during the course of the disease, suggesting that the tetraploidy or near-tetraploidy clone was the consequence of a clonal evolution.

In conclusion, a tetraploidy or near-tetraploidy clone with double 8;21 translocation is a non-random additional anomaly in some cases of t(8;21)(q22;q22) AML and predicts a poor prognosis.

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Reference

1. Lemez P, Michalova K, Zemanova Z, Marinov I, Trpakova A, Moravcova J, et al. Three cases of near-tetraploid acute myeloid leukemias originating in pluripotent myeloid progenitors. Leuk Res 1998;22:581-8.
2. Testa JR, Oguma N, Pollak A, Wiernik PH. Near-tetraploid clones in acute leukemia. Blood 1983;61:71-8.
3. Abe R, Raza A, Preisler HD, Tebbi CK, Sandberg AA. Chromosomes and causation of human cancer and leukemia. LIV. Near-tetraploidy in acute leukemia. Cancer Genet Cytogenet 1985;14:45-59.
4. Xue Y, Pan Y, Liu Z, Li J, Guo Y, Xie X. Tetraploid or near-tetraploid clones characterized by two 8;21 translocations and other chromosomal abnormalities in two patients with acute myeloblastic leukemia. Cancer Genet Cytogenet 1996;92:18-23.
5. Xue Y, Pan Y, Liu Z, Li J, Guo Y, Xie X. Secondary near-pentaploidy and/or near-tetraploidy characterized by the duplication of 8;21 translocation in the M2 subtype of acute myeloid leukemia. Int J Hematol 2000;71:359-65.
6. Yamamoto K, Nagata K, Kida A, Tsurukubo Y, Hamaguchi H. CD7+ near-tetraploid acute myeloblastic leukemia M2 with double t(8;21)(q22;q22) translocations and AML1/ETO rearrangements detected by fluorescence in situ hybridization analysis. Int J Hematol 2001;74:316-21
7. Au WY, Ma SK, Chan AC, Liang R, Lam CC, Kwong YL. Near tetraploidy in three cases of acute myeloid leukemia associated with mediastinal granulocytic sarcoma. Cancer Genet Cytogenet 1998;102:50-3.

Acute Lymphoblastic Leukemia

The t(12:21) is underrepresented in childhood B-lineage acute lymphoblastic leukemia in Kerala, Southern India

t(12;21) (*TEL/AML1*) is the most common genetic event in childhood B-cell acute lymphoblastic leukemia (B-ALL) in Western countries. Samples from 42 children with ALL in Kerala were tested by reverse transcription polymerase chain reaction for *TEL/AML1*, t(1;19) and t(4;11). Only 2 out of 42 (4.8%) cases were positive for the *TEL/AML1*, and t(1;19) and t(4;11) were not detected. We conclude that the incidence of *TEL/AML1* is lower in the Indian population.

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Recurrent chromosomal abnormalities can be used to classify pediatric cases of acute lymphoblastic leukemia (ALL). The overall frequency of t(1;19) is 5-6% in childhood ALL. *MLL* gene rearrangements have an incidence of 2% and are specifically associated with ALL in infants. The most frequent cytogenetic abnormality in childhood B-lineage ALL in Western countries is t(12;21) with frequencies ranging from 16% to 44%. This translocation results in the fusion of the oncogene *TEL1(ETV6)* from 12p13 with *AML1 (RUNX1)* at 21q22. Reverse transcription polymerase chain reaction (RT-PCR) has demonstrated the presence of the *TEL/AML1* transcript in all patients with t(12;21). The translocation t(12;21) is not detectable by routine cytogenetics, and fluorescent *in situ* hybridization (FISH) analysis or RT-PCR is required for detection of the *TEL/AML1* fusion.

Most studies on t(12;21) have been performed on Caucasian populations and only a few studies have been carried out on other populations.[1-5] The pediatric peak of ALL in the West may be due to an excess of t(12;21) cases. The frequency of the translocation and its variable geographic distribution raise the possibility that it is associated with the emergent pediatric peak of ALL in developing countries. In this study we collected a representative sample of B-lineage pediatric ALL from Kerala in India with the aim of defining the frequency of the *TEL/AML1* fusion. From November 1996 to June 2000, 308 pediatric cases of ALL (age 0-14 years) were identified. Informed consent was obtained from parents. RNA extracted from 74 samples was transcribed into cDNA; 42 yielded usable cDNA. All were tested by RT-PCR for *TEL/AML1* and the translocations (1;19) and (4;11).

The median age of the patients was 5 (range 0–14) years and 48% of the cases were in the 2-5 year age group. Morphologically the cases were typical, and immunophenotyping performed on 53 cases showed 49 cases to be of B-lineage ($CD19^+$, $CD7^-$); 1 case was T-lineage ($CD7^+$, $CD19^-$); and 3 were $CD19^-$ and $CD7^-$. Of the 42 cases with cDNA, B lineage was implied in 31 by the presence of immature TCRδ rearrangements. Using a sensitive RT-PCR method, we were able to show that only 2 out of the 42 cases (4.8%) were positive for *TEL/AML1*, and also that no cases carried t(1;19) or t(4;11). Of the B lineage ALL defined by T-cell rearrangement analysis, 6.5 % were positive for the *TEL/AML1*.

The main finding of this study is the low frequency of the *TEL/AML1* fusion in pediatric B-lineage ALL in Kerala. Geographic variations have been reported in the frequency of this fusion. García-Sanz *et al*. in Spain[6] used RT-PCR and FISH on samples from 38 children with ALL. All were negative for the *TEL/AML1* fusion transcript. However, a study by Magalhaes[7] reported a frequency of the *TEL/AML1* fusion gene in 67 Brazilian children with ALL which is similar to that found in predominantly white Caucasian populations, suggesting that Spanish populations are not at a separate risk of this translocation. There are few other studies looking at the frequency of the t(12;21) in populations other than Caucasian (Table 1). Only two other studies from India have looked at this question. Inamdar *et al*. studied 46 cases of childhood ALL from Bombay; 8.7% (4/46) were found to have *TEL/AML1*.[2] Siraj *et al*. studied 259 children with precursor B-cell ALL,[4] and found 7% with *TEL/AML1* by RT-PCR. They concluded that the frequencies of the subgroups of ALL may differ from those in western countries. In contrast, studies in Chinese populations have found higher frequencies. Liang *et al*. studied 41 children with ALL in a Chinese population[3] and demonstrated a 17% frequency of this translocation in the overall ALL population overall and a 19% frequency in patients with B-lineage ALL. Tsang *et al*. studied 75 Chinese children with ALL[5] and detected the translocation in 17.9% of the B-lineage ALL. In another population, the translocation was detected in 6 (22.2%) of 41 Egyptian children.[8]

Table 1. Geographic distribution of t(12;21) in childhood ALL.

Study location	*n.*	*Frequency (%) of t(12;21)*	*Reference*
India	42	4.8	Current paper
England	56	39	Codrington *et al.*
Australia	66	33	Amor *et al.*
Germany/ Italy	334	18.9	Borkhardt *et al.*
Taiwan	165	18	Liang *et al.*
Brazil	67	17.9	Magalhães *et al.*
U.S.A.	86	17	Jamil *et al.*
Taiwan	41	17	Liang *et al.*
Hong Kong	75	16	Tsang *et al.*
Sweden	72	15	Andreasson *et al.*
Japan	108	13	Nakao *et al.*
Scotland	36	11.1	Spathas *et al.*
Japan	74	9.5	Eguchi-Ishimae *et al.*
India	46	9	Inamdar *et al.*
India	259	7	Siraj *et al.*
Spain	41	2	García-Sanz *et al.*

The frequency of the *TEL/AML1* fusion found in our study is similar to that in the other 2 Indian studies[2,4] and supports the theory that the etiology of ALL is dependent on gene-environment interactions.[4] It remains important to explain the higher frequencies in the Chinese and Egyptian studies.

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Key words: t(12;21), TEL-AML1 fusion gene, acute lymphoblastic leukemia, childhood ALL, India.

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References

1. Eguchi-Ishimae M, Eguchi M, Tanaka K, Hamamoto K, Ohki M, Ueda K, et al. Fluorescence in situ hybridization analysis of 12;21 translocation in Japanese childhood acute lymphoblastic leukemia. Jpn J Cancer Res 1998;89:783-8.
2. Inamdar N, Kumar SA, Banavali SD, Advani S, Magrath I, Bhatia K. Comparative incidence of the rearrangements of TEL/AML1 and ALL1 genes in pediatric precursor B acute lymphoblastic leukemias in India. Int J Oncol 1998;13:1319-22.
3. Liang DC, Chou TB, Chen JS, Shurtleff SA, Rubnitz JE,

Downing JR, et al. High incidence of TEL/AML1 fusion resulting from a cryptic t(12;21) in childhood B-lineage acute lymphoblastic leukemia in Taiwan. Leukemia 1996;10:991-3.
4. Siraj AK, Kamat S, Gutierrez MI, Banavali S, Timpson G, Sazawal S, et al. Frequencies of the major subgroups of precursor B-cell acute lymphoblastic leukemia in Indian children differ from the West. Leukemia 2003;17:1192-3.
5. Tsang KS, Li CK, Chik KW, Shing MM, Tsoi WC, Ng MH, et al. TEL/AML1 rearrangement and the prognostic significance in childhood acute lymphoblastic leukemia in Hong Kong. Am J Hematol 2001;68:91-8.
6. Garcia-Sanz R, Alaejos I, Orfao A, Rasillo A, Chillon MC, Tabernero MD, et al. Low frequency of the TEL/AML1 fusion gene in acute lymphoblastic leukaemia in Spain. Br J Haematol 1999;107:667-9.
7. Magalhaes IQ, Pombo-de-Oliveira MS, Bennett CA, Cordoba JC, Dobbin J, Ford AM, et al. TEL-AML1 fusion gene frequency in paediatric acute lymphoblastic leukaemia in Brazil. Br J Haematol 2000;111:204-7.
8. Mikhail FM, Serry KA, Hatem N, Mourad ZI, Farawela HM, El Kaffash DM, et al. AML1 gene over-expression in childhood acute lymphoblastic leukemia. Leukemia 2002;16:658-68.

Malignant Lymphomas

Family clustering of blood cancers as a risk factor for lymphoid neoplasms

Family aggregation of cancer was significantly more common among 588 incident cases with lymphoid neoplasms than among 631 controls (OR: 1.4; 95%CI= 1.1-1.8, *p* value=0.004). This association was of particular relevance among cases of multiple myeloma and chronic lymphocytic leukemia, with a 2-fold increased risk, the latter also showing an almost 4-fold increased risk of family aggregation of hematologic cancers.

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A 2- to 4-fold increased risk of lymphoma has been identified in patients with a family history of hematologic disease or lymphoma in first-degree relatives,[1-3] with chronic lymphocytic leukaemia (CLL),[4,5] multiple myeloma (MM)[6] and Hodgkin's lymphoma (HL)[7-9] being the three entities more consistently reported. The purpose of this study was to evaluate the risk of lymphoid neoplasms and its association with a family history of cancer.

The study was conducted in four Spanish hospitals during the period from 1998 to 2002.[10] Cases were 588 consecutive patients newly diagnosed with a lymphoid neoplasm according to the WHO classification. Simultaneously, 631 controls were randomly selected from hospitalized patients and frequency-matched to cases by age (±5 years), gender and study center. Personal interviews were conducted in order to collect data on demographics, environmental exposure to risk factors, medical and family history, including cancer. The site of cancer age at diagnosis, and status of any affected relatives with cancer were requested. Informed consent was obtained from all subjects prior to enrollment, and the Institutional Review Boards from each of the participating centers approved the study. Odds ratio and 95% confidence intervals were calculated from logistic regression analysis (OR, 95%CI) in order to estimate the degree of association between lymphoid neoplasms and family history. Table 1 shows that cases and controls were comparable for age, sex, recruitment area and educational level. The probability of having a first-degree relative with cancer was significantly higher among the patients with lymphoid neoplasm (252/588) than among the control subjects (218/631) (43% vs.35%, $p<0.05$). The cases also tended to have a higher number of affected relatives than did the controls (more than 1 affected relative: 23.8% vs. 19.3%, respectively; $p>0.05$) (*data not shown*) but this difference was not statistically significant. All-lymphoma patients, B-cell lymphoma, CLL and MM patients were significantly more likely to report a first-degree relative with any cancer, with a risk increase ranging from 1.4 up to 2.1 among CLL patients (Table 2). A family history of hematologic cancer was statistically associated only with CLL patients, based on the fact that 10 out of 125 cases with CLL reported at least 1 relative with a hematologic cancer. Of these, 4 affected relatives had been diagnosed as having acute leukemia, 3 with CLL (2 out of 3 confirmed by medical records), 2 with lymphoma and 1 with MM. The average age at diagnosis was 54 years for CLL patients and 52 for the affected relatives ($p>0.05$). Only one CLL case had an affected relative who was diagnosed with cancer at a younger age. One patient reported more than 1 affected relative with a hematologic cancer: the father, at the age of 85 years, and a sister at the age of 56 years. In one family of a case patient with HL, the father and a brother were diagnosed with the same histology as the index case. The data presented shows a significant familial aggregation of cancer cases among subjects with CLL and MM. Cases were at least 40% more likely than controls to report a first degree relative with cancer. This proportion reached over 200% among CLL patients. Furthermore, 8% of CLL patients show a significant familial aggregation of hematologic cancers. These results are in agreement with the existing literature on the magnitude of the association and with the identification of CLL and MM as the most likely histologies to show fam-

Table 1. Characteristics of the study population.

	Cases (n=588)	*Controls (n=631)*	*p*
Median age (range)	64 (17-89)	63 (17-96)	0.12
Gender			
Male	330 (56%)	328 (52%)	0.15
Female	258 (44%)	303 (48%)	
Recruitment area			
Barcelona	465 (79%)	527 (83%)	0.12
Madrid	70 (12%)	55 (9%)	
Tarragona	53 (9%)	49 (8%)	
Educational level attained			
Never attended school	76 (13%)	68 (11%)	
No degree reached	124 (21%)	150 (24%)	0.51
Primary school	240 (41%)	243 (38%)	
Secondary school and higher	109 (18%)	120 (19%)	
Other	39 (7%)	50 (8%)	
First-degree relatives with cancer			
No	336 (57%)	413 (65%)	0.004
Yes	252 (43%)	218 (35%)	
Number of relatives			
1	192 (33%)	176 (28%)	0.5
2	47 (8%)	33 (5%)	
3	11 (2%)	6 (1%)	
4	2 (0%)	3 (1%)	