To the editor:

No evidence for preferential maternal origin of duplicated chromosome 14 in hyperdiploid ALL

Hyperdiploid childhood acute lymphoblastic leukemia (ALL) is associated with the nonrandom gain of chromosomes, most commonly X, 4, 6, 10, 14, 17, 18, and 21, and is thought to arise as a consequence of a single aberrant mitosis that then becomes clonal.[1] Paulsson et al[1] investigated the parental origin of trisomies in ALL hyperdiploid cases and found that in 7 of 8 cases with trisomy 14 (+14) the duplicated chromosome was of maternal origin.

Previous research by our group[2] has shown a preferential maternal loss of 9p21 alleles in 9 of 10 ALL cases, suggesting a possible role for epigenetic factors in the onset of ALL. Given that imprinting has been found in a number of genes on chromosome 14[3] and both maternal and paternal uniparental disomy of chromosome 14 have clinical phenotypes,[4] Paulsson et al's[1] observations warranted further investigation.

We determined the parental origin of +14 in ALL cases held in our laboratory. Children with ALL were recruited at pediatric oncology clinics in New Zealand. DNA was extracted from presentation and remission bone marrow slides as published.[2] Parental DNA was extracted from peripheral blood. Using diagnostic cytogenetic reports, 7 probable +14 ALL cases from children aged 23 months to 8 years were selected. In 5 cases +14 was specifically reported, while in 2 cases +14 was likely from the reported karyotype.

Microsatellite markers D14S306 (14q21.1), D14S587 (14q22.2), and D14S617 (14q32.12) were examined. Samples were initially analyzed with D14S587, and then with other markers if the initial results were uninformative or ambiguous. The α-P^{32} deoxycytidine triphosphate (dCTP)–labeled polymerase chain reaction (PCR) products were electrophoresed on 6% polyacrylamide sequencing gels, and the products visualized using a Fuji Bas-1500 phosphoimager (Fujifilm, Tokyo, Japan). Allele ratios were determined by dividing the size of the upper allele by the size of the lower allele. The leukemia DNA allele ratios were divided by remission ratios to standardize for bias due to preferential amplification of the shorter allele. A ratio of approximately 1 was interpreted as no trisomy, a ratio of 2 as duplication of the upper allele, while a ratio of 0.5 suggested duplication of the lower allele. The parental origin of the duplicated allele was determined visually.

Of the 7 cases, 4 had paternal and 3 maternal inheritance of +14 (Table 1). In 2 cases the ratios were not as expected, but these do not alter the overall conclusion. Case 1710 showed disconcordant ratios for the 2 markers tested. The cytogenetic information for this case included del(?13), and if the deletion actually affected chromosome 14 then there would be partial tetrasomy, which might explain our result. There was insufficient DNA to analyze this sample at other markers. Case 1744 showed a 3:1 ratio at 2 markers suggesting the presence of 4 copies of chromosome 14, but the karyotype showed partial trisomy to 14q32.

Our results do not show any parental bias with respect to the duplication of chromosome 14. Although the possibility that imprinted genes are involved in childhood ALL is appealing, our data do not support the possible bias reported by Paulsson et al.[1]

Table 1. Karyotype, allele ratios, and parental origin of duplicated chromosome 14

Case	Karyotype	Allele ratio*			Origin +14
		D14S587	D14S617	D14S306	
1728	53-57,XX,+X,+X,dic(1;6)(p13;q25),+10,+11,+13,+14,+17,+18,+21,+22[cp4]/46,XX[5]	1.72	—	—	Paternal
1730	46,XX,del(6)(q12q14),add(14)(q32)[4]/53-66,XX,+X,+X,+2,+3,+4,+5,del(6)(q12q14)×2,+6,+11,+12,+13,+18,+21,+22[cp5]/46,XX[3]	0.35	0.42	—	Maternal
1754	49-55,XY,+X,+14,+18,+21,+21,inc[15]	1.34	1.85	0.39	Paternal
1744	63-65,XX,+X,+1,t(2;14)(p11.2;q32),+del(2)(p11.2),+4,+5,+6,+6,+7,+8,+10,+10,+13,+add(14)(q32),+16,+18,+19,+20,+21,+21,+22,+mar1-4[cp6]/46,XX[4]	0.29	—	0.37	Maternal
1710	52-60,XXX,+1,+6,+11,del(?13)(q13q31)t(?13;17)(q14;q11),+14,+17,+21[cp4]/46,XX[6]	0.89	0.40	—	Paternal
1748	51-52,XX,+8,+16,+18,+20,+21,+21[cp4]/46,XX[6]	0.62	—	—	Maternal
1722	56-57,XY,+X,+4,+6,+10,+14,+17,+21,+21,+22[cp2]/46,XY[8]	—	—	0.55	Paternal

— indicates not done.

*The allele ratio is the ratio of upper to lower bands, divided by the same ratio for the patient's normal (remission) DNA.

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References

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Response:

The parental origin of trisomy 14 in hyperdiploid childhood ALL

In a recent study,[1] commented upon by Wilson and Morison, we investigated the formation of the hyperdiploid pattern in childhood acute lymphoblastic leukemia (ALL) and the possibility of imprinting effects related to the parental origin of the gained chromosomes,[2,3] using a large set of polymorphic microsatellite markers. The finding of equal allele dosage for tetrasomy 21 indicated that hyperdiploidy most likely originates through a simultaneous gain of chromosomes in a single abnormal mitosis. Furthermore, no preferential duplications of maternal or paternal copies of chromosomes X, 4, 6, 10, 17, 18, and 21 were seen, and we concluded that imprinted regions on the duplicated chromosomes are generally not of major pathogenetic importance in hyperdiploid childhood ALL.

However, 2 possible exceptions to the just-mentioned conclusion were noted. Trends toward significance were seen for trisomies 8 and 14: +8 was of paternal origin in 4 of 4 cases ($P = .125$) and +14 was of maternal origin in 7 of 8 cases ($P = .0703$)—findings that were noteworthy considering that imprinted regions have been shown to reside in at least the latter of these 2 chromosomes.[4] Unfortunately, our limited number of cases precluded definitive conclusions.[1] We now read with great interest the letter by Wilson and Morison, in which they report 7 cases of trisomy 14. Their results of 4 cases with paternal inheritance and 3 with maternal inheritance strongly indicate that the trend toward preferential maternal origin in our previous study does not represent a true skewness in the duplication process for chromosome 14. In fact, we have similar findings in an ongoing study of additional hyperdiploid childhood ALLs. Of 9 cases with trisomy 14, only 4 had maternal origin for the gained chromosome ($P = .50$; K.P. and B.J., unpublished data, December 15, 2004).

Taken together, our previous study,[1] the present results by Wilson and Morison, and our ongoing investigation strongly indicate that there is no preferential duplication of the maternal chromosome 14. Thus, imprinting effects related to the parental origin of trisomy 14 are most likely not of pathogenetic importance in hyperdiploid childhood ALL.

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