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NONRANDOM CHROMOSOMAL CHANGES IN HUMAN MALIGNANT CELLS

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ABSTRACT. The role of chromosomal changes in human malignant cells has been the subject of much debate. The observation of nonrandom chromosomal changes has become well recognized in CML, and more recently in AML. In the present report, data are presented on the sites of duplication of chromosome No. 1 in hematologic disorders. Trisomy for region 1q25 to 1q32 was observed in every one of 34 patients whose cells showed duplication of some part of chromosome No. 1. Adjacent regions 1q21 to 1q25, and 1q32 to 1qter, also were trisomic in the majority of patients. Two patients had deletions, one of 1q32 to qter, and the other, of 1p32 to pter. The sites of chromosomal breaks leading to trisomy differ from those involved in balanced reciprocal translocations. Some of these sites are sometimes, but not always, vulnerable in constitutional chromosomal abnormalities. The nature of the proliferative advantage conferred on myeloid cells by these chromosomal changes is unknown.

MASTER

INTRODUCTION

The role of chromosomal changes in human malignant cells has been debated for more than 60 years. The observation of a consistent chromosomal abnormality in chronic myelogenous leukemia (17), and more recently in meningioma (11), provides support for the concept, proposed by Boveri (5) in 1912, that chromosomal changes are among the fundamental alterations occurring in malignant cells. The majority of human tumors, however, appeared to have widely disparate karyotypes; therefore most investigators accepted the view that these abnormalities were merely epiphenomena (6). The presence of a normal karyotype in highly malignant cells further complicates our understanding of the significance of chromosomal changes (15, 29). Most of the evidence bearing on this question was obtained prior to the use of the new chromosomal banding techniques, which now permit the identification not only of individual chromosomes, but also of parts of chromosomes.

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These techniques have been used in the analysis of the karyotypes of a wide variety of human malignant and potentially malignant cells. Analysis of cells from patients with various hematologic disorders, including leukemia, polycythemia vera, refractory anemia, and other chronic myeloproliferative states, provides the most abundant data on the frequency and types of chromosomal changes. These data have recently been reviewed (25, 26) and only a summary table (Table 1) is included here.

Some nonrandom rearrangements, such as the 9;22 translocation (22) in chronic myelogenous leukemia (CML) and the 8;21 translocation (23) in acute myelogenous leukemia (AML), are well recognized. Chromosomal banding techniques permit us to identify karyotypic aberrations with precision and to determine whether others, previously unrecognized, occur.

In this paper, I intend to focus on abnormalities affecting chromosome No. 1. The available information will be used in answers to the following questions: (1) Are there specific regions of chromosome No. 1 that frequently or invariably show the same abnormality? (2) Do breaks affect specific sites on the chromosome? (3) If such specific sites exist, can they be related to specific gene loci? (4) Can information regarding these chromosomal abnormalities be related to the problem of malignancy?

MATERIALS

Patients with hematologic diseases, whose cells have been studied with chromosome banding techniques in my laboratory between January, 1970 and January, 1976, provide the basis for this report. From this group, I selected all patients who showed any abnormality involving chromosome No. 1. There were three patients who had an additional No. 1, six patients who had structural rearrangements leading to a duplication of a part of No. 1, and six patients who had an apparently balanced translocation affecting chromosome No. 1, one of whom also had a deletion of part of No. 1.

To these patients I have added all those with hematologic disorders and abnormalities affecting No. 1 of whom I am aware. In a few instances, I have altered the sites of breakage listed in the published data. Finally, constitutional chromosomal abnormalities affecting chromosome No. 1, particularly with reference to break points, have been summarized from Borgaonkar's Catalog (2) and from his Repository of Chromosomal Variants and Anomalies in Man (3, 4).

The identification of chromosomes and band numbers used in this report is based on the nomenclature adopted at the Paris Conference (21), and the karyotypes are expressed as

TABLE 1

CHROMOSOME ABNORMALITIES ASSOCIATED WITH HEMATOLOGIC DISORDERS*

<u>Disorder</u>	<u>% of Patients Abnormal</u>	<u>Trisomy for all or long arm of No.1</u>	<u>5q-</u>	<u>-7</u>	<u>+8</u>	<u>8q[†] transl.</u>	<u>+9</u>	<u>9q+</u>	<u>15/17 transl.</u>	<u>17q+</u>	<u>20q-</u>	<u>Ph[‡] (22q-)</u>	<u>Double Ph[‡]</u>
Chronic myelogenous leukemia	85							+				+	
Acute phase	70 [¶]				+			+		+		+	+
Acute non- lymphocytic leukemia	50	+		+	+	+	+			+			
Acute pro- myelocytic leukemia	100								+				
Polycythemia vera	25	+			+		+				+		
Refractory anemia	15 [§]		+		+						+		
Myelosclerosis with or with- out myeloid metaplasia	15 [§]	+		+			+						

*Adapted from table published in reference (25).

[†]Usually to No. 21; frequently associated with loss of an X or Y chromosome.[‡]Translocation to No. 9 in more than 90% of Ph[‡] positive patients.[¶]Other chromosome abnormalities superimposed on Ph[‡] positive cell line.

recommended under this system. The total chromosome number is indicated first, followed by the sex chromosome constitution, and then by the gains, losses, or rearrangements of the autosomes. A + or - sign before a number indicates a gain or loss, respectively, of a whole chromosome; a + or - after a number indicates a gain or loss of part of a chromosome. The letters "p" and "q" refer to the short and long arms of the chromosome, respectively; "i" and "r" stand for "isochromosome" and "ring chromosome." "Mar" is marker, "del" is deletion, "ins" is insertion, and "inv" is inversion. Translocations are identified by "t", followed by the chromosomes involved in the first set of brackets; the chromosome bands in which the breaks occurred are indicated in the second brackets. Uncertainty of the chromosome or band involved is signified by "?."

RESULTS

The study included 36 patients who had abnormalities of No. 1 that altered the amount of genetic material of this chromosome in the cell; in 34 patients, the aberration led to duplication of part or all of No. 1. The data including karyotype, portion trisomic for No. 1, hematologic diagnosis, and reference are presented in Table 2 and Figure 1. The data from the two patients with deletions will be considered later. As can be seen from an analysis of the table, every patient is trisomic for the region from 1q25 to 1q32. Five patients are trisomic for all of No. 1, and 16 have part of No. 1 translocated to another chromosome, usually with two other normal No. 1's as well (exceptions are cases 1 and 4) (20). Five patients have an additional chromosome composed only of part of No. 1, as well as two normal No. 1's. Finally, 8 patients have complex structural rearrangements involving only chromosome No. 1 and leading to a duplication of part of the chromosome. These rearrangements usually produce a very large marker chromosome.

Except for the five patients who have an extra intact chromosome, 29 patients are trisomic for no more than the proximal one-third of the short arm and for the long arm. In addition to the trisomy for region 1q25 to 1q32 present in every patient, trisomy for 1q32 to qter or for 1q25 to 1q21 is present in 28 and 30 patients, respectively.

The 16 translocation trisomies involve No. 1 with chromosome Nos. 4, 6, 9, 11, 13, 15, 17, 22, and Y (Table 3). All breaks in No. 1 are in the centromere, or in q21 or q25. With three exceptions, all breaks in the centromere region involve translocations with acrocentric chromosomes (Nos. 13, 15, 22) which are also broken at the centromere. The

TABLE 2

ABNORMALITIES OF CHROMOSOME NO. 1

<u>Karyotype</u>	<u>Portion Trisomic for No. 1</u>	<u>Disease</u>	<u>Reference</u>
46,XX,dup(1) (pter→q32::q21→qter)	q21→q32	MMM	Case 1 (27)
50,XY,dup(1) (pter→q21::q32→q11::q21→qter t(4;?) (p16;?) + t(4;?) (p16;?) , t(14;?) (q32;?) , t(17;?) (p13;?) , t(18;?) (q23;?) , +20,+mar	q11→q32	HL	Case 2 (27)
47,XY,t(1*;10) (p22;p15) , dup(1*) (p22→q32:: q11→qter) , inv(6) , del(11) (q23) , 14q+, 21p+, +ring	q11→q32	PCL	Case 3 (27)
48,XX,+1,del(5) (q13-15) , +11	whole chromosome	ANLL	Case 1 (24)
55,XX,+1,+1,+3,-4,-5,+6,+6,-8,-10,10q-,-11, +18,19q+,+4mar,+4min	whole chromosome	ANLL	Case 4 (27)
50,XX,+1,del(5) (q13-15) , +6,-7,+8,+10,t(13q;14q) , +21,+mar	whole chromosome	MM→AML	Case 5 (27)
46,XX,-6,+t(1;6) (q25;p25)	q25→qter	MMM	Case 6 (24)
46,XX,-15,+t(1;15) (cen;cen)	centromere→qter	PV→AML	Case 2 (24)
46,XY,t(12;17) (q13;p11) / 47,X,t(1;Y) (q21;q12) , +9	q21→qter	PV	Case 3 (24)

TABLE 2 (Continued)

<u>Karyotype</u>	<u>Portion Trisomic for No. 1</u>	<u>Disease</u>	<u>Reference</u>
46,XX,-4,+t(1;4) (q21;q35)	q21→qter	ANLL	(8)
47,X,del(Yq),+1	whole	RA	(33)
46,XX,-15,+t(1;15) (cen;cen)	centromere→qter	PV	Case 32 (36)
47,XX,+del(1) (p13-21)	p13-21→qter	PV	Case 274 (36)
47,XY,+del(1) (p22)	p22→qter	MM	Case E.I. (32)
47,XY,+del(1) (p22)	p22→qter	PV	Case J.W. (32)
47,XY,+del(1) (p13)	p13→qter	PV	Case E.K. (32)
47,XY,+del(1) (p21?)	p21?→qter	PV	Case E.D. (35)
47,XX,+t(1;9) (q21;q13)	q21→qter	PV	Case B.M. (35)
47,XX,-4,+t(1;4) (q25;p14-15),+13	q25→qter	ANLL	Case 3 (20)
43,X-Y,t(1;8) (p22;q24)-1,-22,+t(1q;22q), +t(1q;22q) and other complex abnormalities	centromere→qter	ANLL	Case 1 (20)
46,XX,del(7) (q22),-9,+t(1;9) (q21-22;p24) and other patterns	q21-22→qter	LS→ANLL	Case 2 (20)

TABLE 2 (Continued)

<u>Karyotype</u>	<u>Portion Trisomic for No. 1</u>	<u>Disease</u>	<u>Reference</u>
46,X?,t(9*;22)(q34;11),-1,+t(1;9*)(cen;p11-13)	centromere→qter	CML- blast	Case 4 (20)
46,XX,dup(1)(pter→q32?:q21?→qter)	q21?→q32?	MMM	Case 418 (18)
47,XX,t(1*;9)(cen?;cen?),+del(1q)(cen?), del(7)(q22),20q-	centromere?→qter	PV→MMM	Case 422 (18)
46,XX,-6,+t(1;6)(q25;p21)	q25→qter	MMM	(9)
46,XY,-13,+t(1;13)(cen;cen)	centromere→qter	PV	(9)
46,XX,dup(1)(pter→q32::21→qter)	q21→q32	MM	(30)
44,X,-21/45,XY,-21/46,XY,dup(1)(pter→q44:: q12→qter)	q12→q44	RA	Case 12 (37)
46,XY,dup(1)(pter→q32::q12 or 21→qter)	q12 or 21→q32	ALL	Case 10 (37)
48,XXX,-15,-17,+t(1;i(17q))(q21;q25?),+2ring (17qter→17cen→17q25?:1q21→1qter)	q21→qter	LS	(7)
51,XX,+1,del(2)(q33),+6,+9,-19,+20q-,+mar1	whole chromosome	MMM	(16)

TABLE 2 (Continued)

<u>Karyotype</u>	<u>Portion Trisomic for No. 1</u>	<u>Disease</u>	<u>Reference</u>
46,XY,-11,+t(1;11) (q11 or 12;q23)	q11 or 12→qter	RA	Case 2 (16)
47,XY,dup(1) (qter→q11:p36→qter),+ring	q11→qter	PV	Case 2 (16)
46,XX,-6,+t(1;6) (q25?;p23 or 25?)	q25→qter	PV	Case 5 (16)

*Same chromosome affected in both rearrangements.

ABBREVIATIONS:

MMM = Myelosclerosis with or without
myeloid metaplasia

HL = Histiocytic lymphoma

PCL = Plasma cell leukemia

ANLL= Acute nonlymphocytic leukemia

MM = Multiple myeloma

PV = Polycythemia vera

RA = Refractory anemia

LS = Lymphosarcoma

CML = Chronic myelogenous leukemia

ALL = Acute lymphoblastic leukemia

Region Trisomic for Chromosome No. 1 in 34 Patients

Fig. 1. The part of chromosome No. 1 that is trisomic in each patient listed in Table 2 is represented by a vertical line. The lines occur in the same order as the patients are listed in the table. Dashed vertical lines indicate uncertain break points. A short horizontal bar indicates the end(s) of the chromosome. The dashed horizontal lines enclose the segment that is trisomic in every one of the 34 patients.

exceptions involve (1) a translocation with 9p, a chromosome whose centromeric region contains repetitive DNA, in two patients, and (2) the end of the short arm of No. 1. Six of the eight tandem duplications of 1q have the distal break point in band 1q32; half of the proximal break points are in q21, and the other half are in bands q11 or q12.

Two patients had deletions of No. 1. In one, there was a 1;11 reciprocal translocation and a deletion of the same No. 1 distal to 1q32 (Table 4, case 42) (29); the other

TABLE 3

TRANSLOCATIONS OF 1q LEADING DIRECTLY TO TRISOMY*

<u>Abnormality</u>	<u>Reference</u>
t(1;Y) (q21;q12)	Case 3 (24)
t(1;4) (q25;p14-15)	Case 3 (20)
t(1;4) (q21;q35)	(8)
t(1;6) (q25;p25)	Case 6 (27)
t(1;6) (q25;p23-25)	Case 5 (16)
t(1;6) (q25;p21)	Case 1 (9)
t(1;9) (q21;q13)	Case B.M. (35)
t(1;9) (q21-22;p24)	Case 2 (20)
t(1;9) (cen-q11;p11-13)	Case 4 (20)
t(1;11) (q21;q23)	Case 1 (16)
t(1;13) (cen;cen)	Case 2 (9)
t(1;15) (cen;cen)	Case 2 (24)
t(1;15) (cen;cen)	Case 32 (36)
t(1;i(17q)) (q21;q25)	(7)
t(1;22) (cen;cen)	Case 1 (20)

*Data taken from Table 2.

patient had a complex 3-way translocation that resulted in the loss of part of No. 1 from lp32 to pter (12).

In addition to these 36 patients, nine patients with hematologic disorders have been reported who have reciprocal translocations involving chromosome 1 which do not lead to either gain or loss of No. 1. Four of the 36 patients considered earlier (cases 3 [27], 42 [29], 1 [20], 422 [18]) also have balanced rearrangements of No. 1 as well as trisomy

TABLE 4

OTHER REARRANGEMENTS OF NO. 1

<u>Abnormality</u>	<u>Disease</u>	<u>Reference</u>
<u>Deletions</u>		
45,XY,t(1;4;7) (p32;q31;q11 and q32) [†]	MMM	(12)
46,XX,t(8;17),t(1;*11); del(1)*(q32) [§]	ANLL	Case 42 (29)
<u>Reciprocal Translocations</u>		
t(1;5) (p36;q31)	PV [¶]	Case A.O. (34)
t(1;9?) (p36;q13?)	ANLL	Case 49 (29)
t(1*;11) (p36;q13),del(1*) (q32)	ANLL	Case 42 (29)
t(1;13) (p34-36;q14)	ANLL	Case M.S. (19)
t(1;17) (p36;q21)	ML→ANLL	Case 3 (28)
t(1;?) (p36?;?)	ML→ANLL	Case 8 (28)
t(1;?) (p36;?)	ALL	(1)
t(1;?) (p36;?)	PV	Case 8 (16)
t(1;9) (p34?;q34)	ANLL	Case 31 (29)
t(1;8) (p22;q24)	ANLL	Case 1 [#] (20)
t(1;9) (cen;cen),+t(1q;9p)	PV→MMM	Case 422 [#] (18)
t(1*;10) (p22;p15)	PCL	Case 3 [#] (27)
t(1;6;11) (q12;q23;p15)	ANLL	Case 14 (37)

*Same chromosome involved in rearrangement.

[†]Deletion of No. 1 p32 pter.

[§]Deletion of No. 1 q32 qter.

[¶]Following treatment with chloramphenicol.

[#]Also listed in Table 2.

or deletion. In two cases, the reciprocal rearrangement involves the affected No. 1. The findings for these 13 cases are summarized in Table 4. Except in case 14 (37), the break points are located in the short arm of No. 1, specifically in bands p22, p34, and p36.

In marked contrast, the break points found in constitutional abnormalities (e.g., translocations, inversions, deletions) are distributed along the length of the chromosome, although there is some evidence of clustering. The data on 80 break points in Borgaonkar's registries (2-4) show 10 in band lq32, 8 in band lp32, 7 each in bands lp36 and lq21, 6 in lql2, and 5 each in lql1, lq42, and lq44. The rest of the 27 breaks are distributed in 13 bands.

DISCUSSION

The first two questions raised in the introduction can be answered affirmatively. There is one specific region of chromosome No. 1 that is *invariably* present in the trisomic state, and the two regions bounding this invariant region are trisomic in the majority (28 or 30/34) of patients. Except in patients who have an extra whole chromosome, trisomy for the short arm, bands p22 to pter, was never seen. Chromosomal studies of the malignant cells have been reported in only a few patients with cancer. Abnormalities of No. 1, often leading to partial trisomy, such as an isochromosome for the long arm of No. 1 or an extra lq chromosome, have been observed (10, 31).

The sites of breakage show a very curious distribution. Breakage which leads directly to the trisomic state, through tandem duplication, translocation to another chromosome, or the production of an extra lq chromosome, is confined to bands p22, cen, ql2, q21, q25, and q32 (Fig. 2). All breaks in the short arm of No. 1 (p13 and p22) lead to an extra, separate chromosome that results in trisomy for the entire long arm. Breaks at the centromere usually involve a translocation with the long arm of an acrocentric chromosome. Of the other translocations which lead directly to trisomy for part of lq, all have breaks in q21 or q25. All of the six breaks seen in band lq32 were identified in patients with tandem duplications of No. 1.

A different pattern emerges if one scores for sites of breakage in reciprocal translocations that do not directly lead to trisomy. In this situation, the breaks are primarily in lp36, with a smaller number occurring in lp34 and lp22; not a single break near the centromere or in the long arm was observed in these patients. These two sets of data, namely, breaks involved in trisomy and those involved in

CHROMOSOME NO.1

*Less than 4 breaks

Fig. 2. A diagrammatic representation of chromosome No. 1, showing the number of breaks in a particular band related to (a) sites of breaks in adenovirus 12-infected cells, first vertical column of numbers. No. 1 is the site of the highest and No. 4 the lowest frequency of breaks. (b) break points leading to partial trisomy, second vertical column; data summarized from Table 2 and Fig. 1. (c) break points in balanced reciprocal translocations, third column; data summarized from Table 4. (d) break points for structural rearrangements noted in inborn chromosomal abnormalities, abstracted from refs. 2-4. (e) portion of No. 1 trisomic in hematologic disorders; solid line - trisomic in all patients, dashed line - trisomic in most patients. (f) location of selected gene loci on No. 1 (14).

reciprocal translocations, provide strong support for the notion of a specific association between the regions affected and the type and result of the structural rearrangement.

A comparison of the sites of breakage in the somatic mutations surveyed here and the break points seen in individuals with constitutional chromosomal abnormalities reveals a general similarity, as well as some major discrepancies. Thus, a high incidence of breaks is found in both types of patients in bands lp36, the centromere, lq12, lq21, and lq32. Bands lp32 and lq42-44 are frequently broken in constitutional rearrangements, whereas bands lp22 and lq25 are affected in somatic mutations and rarely in inborn abnormalities.

The mechanisms that produce these breaks and rearrangements are unclear. It may be significant that all of the four sites of breakage along chromosome No. 1 in adenovirus-type 12 (AD-12)-infected cells, namely, bands p36, p32, q12, and q42-44, are frequently involved in constitutional rearrangements (13, and McDougall, in preparation). Exceptions to this are the centromere and bands q21 and q32, which are often affected in constitutional rearrangements, but not in virus-induced breaks. In somatic mutations, lp36 is affected in reciprocal translocations, and lq12 in translocation trisomy; no breaks are seen in lq42 or 43, or in lp32, which are, respectively, the sites of the greatest (20%) and lowest (3%) frequency of AD-12-induced breaks.

Finally, I come to the last two questions concerning specific gene loci affected and their possible relationship to malignancy. The locations of selected gene loci are indicated in Figure 2. Guanylate kinase 1 and 2 (GUK 1 and 2) are located from lq31 to qter, uridyl diphosphate glucose pyrophosphorylase (UGPP) and peptidase C (pep C) are located on bands lq21 to lq23, and the genes for 5 S RNA are on bands lq41-42 (14). Fumerase hydratase 1 and 2 and possibly uridine-cytidine kinase (UCK) are on bands lq42 to qter (14). It may be significant that some of these genes are involved in nucleic acid metabolism. At present we have no evidence to link abnormalities of any of these genes with malignancy.

In my view, the question no longer is, "Are there non-random chromosomal changes?" The significant question for the future is, "What is the role of nonrandom changes in malignant transformation?"

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