

Significance of Chromosome 14 Anomaly at Band 14q11 in Japanese Patients With Adult T-Cell Leukemia

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The chromosomes of leukemic blood cells in eight Japanese patients with acute adult T-cell leukemia (ATL) were examined by a direct method or short-term culture method without any mitogens. Six patients showed a chromosome 14 anomaly with a break at band q11-13: inv(14)(q11q32) in two patients, t(11;14)(p13;q13) in one patient, t(14;14)(q11;q32) in addition to del(14)(q11q13) in another, and only del(14)(q11q13) in two patients. Thus, a proximal 14q rearrangement exists in ATL as in other types of T-cell malignancies. Based on these facts, the pathogenesis of ATL is discussed in reference to the literature.

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THE NUMEROUS DATA ON SPECIFIC CHROMOSOME CHANGES in various hematologic disorders were collected and reviewed by Sandberg.¹ Nevertheless, cytogenetic studies on adult T-cell leukemia (ATL) have been scarce.²⁻⁹ Various chromosome anomalies such as trisomy 3, partial deletion of the long arm of chromosome 6 (i.e., 6q-) and trisomy 7, and elongation of the long arm of chromosome 14 with a break at band 14q32, have been reported by investigators.²⁻⁹ These observations suggest that there may not be a specific chromosome anomaly in ATL.

We preliminarily reported a chromosome 14 anomaly with a break at band 14q11-13 in 10 of 11 patients with ATL.¹⁰ However, most of the patients reported¹⁰ showed complicated karyotypes. To objectively determine the karyotypes in ATL and related disorders, an *ad hoc* committee was established in Japan. In this report, the cytogenetic data of eight previously reported patients are presented with revised karyotypes, confirmed by the committee.

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Materials and Methods

The current study is based on observations in eight typical ATL patients who were natives of Nagasaki Prefecture, one of the clustering areas of ATL incidence in Japan. The clinical, hematologic, and serologic data are shown in Table 1.

Leukemic cells for cytogenetic study were obtained from the peripheral blood of all patients at the time of diagnosis. Mononuclear cells separated by centrifugation over Ficoll-Hypaque gradients were cultured in RPMI 1640 medium supplemented with 10% fetal calf serum (without any mitogens). The cells were harvested after 1 to 20 hours. The culture time was shortened to avoid possible *in vitro* artifacts and to clarify the karyotypes that are closely associated with the clinical features, although the number of cases with adequate metaphases might have been a limiting factor and only cases with aggressive leukemic cells might have been selected. Colcemid was added 1 or 2 hours before harvesting. In each specimen, at least 15 metaphases were analyzed using G- and Q-banded techniques.¹

More than two karyotypes with an abnormal clone of each patient were submitted to the ATL Karyotype Workshop 1985 in Japan (organized by the ATL Karyotype Review Committee 1985, supported by a Grant from the Japanese Welfare Ministry, and arranged by Drs. Ken-ichi Suemasu and Masanori Shimoyama of the National Cancer Center). One rule of the Committee was that the final karyotypes were determined upon unanimous

(Age/sex)	Stages
(52/M)	-
(62/F)	-
(56/M)	-
(68/M)	-
(68/F)	-
(48/F)	-
(57/F)	-
(55/M)	-

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48,X,-X,+2,-4
48,XY,-15,-22
48,XY,-4,-9,-
48,X,-X,-1,-3
+del(12)(p12)
+mar1,+mar2
48,X,-X,+3,-4
48,X,-X,-10,-
48,X,-Y,-2,-3
+del(6)(q21),
+mar1,+mar2

TABLE 1. The Clinical, Hematologic, and Serologic Data in Eight Patients With Adult T-Cell Leukemia

(Age, sex)	Skin lesion	Hepato-megaly	Spleno-megaly	Lymphad-enopathy	Leukocyte Count (/ μ l)	Leukemic cells (%)	Anti-HTLV antibody	Elevation of LDH	Elevation of calcium	Survival (mo)
1 (M)	+	+	+	+	14,950	30	+	+	+	2.5
2 (M)	+	+	+	+	51,600	35	+	+	+	0.6
3 (F)	+	+	+	+	65,250	47	+	+	+	6.6
4 (M)	+	+	+	+	65,500	51	+	+	+	5.1
5 (M)	+	+	+	+	97,250	53	+	+	+	30.0
6 (F)	+	+	+	+	203,700	89	+	+	+	15.2
7 (F)	+	+	+	+	183,500	91	+	+	+	5.2
8 (M)	+	+	+	+	91,000	94	ND	+	+	2.9

LDH, lactic dehydrogenase; ND, not done.

ment of the ten Committee members who are cytogeneticists (Nanao Kamada, Hiroshima University; Shun-ichi Abe, Hokkaido University; Masaharu Sakurai and Shun-ichi Kaneko, Saitama Cancer Center; Tatsuo Abe, Nagasaki Prefectural University of Medicine; Naoki Sadamori, Nagasaki University; Yukimasa Shiraishi, Kochi Medical School; Kanji Miyamoto, Okayama Red Cross Hospital; Isao Sanada, Kumamoto University; and Tetsuo Fukuhara, Kyoto University).

Chromosomes and karyotypes have been designated according to the ISCN system.¹¹ An abnormal clone was detected as two cells with the same extra chromosome or reciprocal rearrangement. All karyotypes demonstrated in this report were confirmed by the committee.

Results

As shown in Table 2, the number of chromosomes ranged from 44 to 48. All patients had complicated abnormal chromosomes such as derivatives and markers of unknown origin. Trisomy 3, 6q- chromosome and trisomy 7, which have been reported by other investigators,^{2,3} were detected in Case 1, and 6q- anomaly was

detected in Case 8 in this series. Interestingly, five (Cases 2, 3, 5, 6, and 8) of eight patients with ATL showed a chromosome 14 anomaly with a break at band 14q11, although some patients showed the coexistence of a distal rearrangement at band 14q32. One patient (Case 1) was judged to have a der(11)t(11;14)(p13;q13), although it is difficult to determine exactly whether the breakpoint of chromosome 14 was at band 14q11 or 14q13, as shown in Figure 1. Two patients (Cases 6 and 8) had inv(14)(q11q32) as shown in Figure 2, and three patients (Cases 2, 3, and 5) had del(14)(q11q13) as shown in Figure 3. The t(14;14)(q11;q32) in three of four patients who were reported in the previous short study¹⁰ could not be confirmed by the Committee. Only one patient (Case 3) was confirmed to have t(14;14)(q11;q32) as shown in Figure 4. Partial karyotypes of two other patients (Cases 2 and 8) with chromosome 14 anomalies with a break at band 14q11 are shown in Figure 5. Thus, a total of six of eight patients with ATL in this series showed a break in the upper segment of chromosome 14. Two other patients (Cases 4 and 7) could not be recognized to have a chromosome #14 anomaly with a break at band 14q11, although the proximal 14q rearrangement might be masked

TABLE 2. The Cytogenetic Data in Eight Patients With Adult T-Cell Leukemia

Modal karyotype	Case no. in the previous report ¹⁰
47,XY,-2,+3,-6,+7,-14,-15,+der(2)t(2;?)q37;?,+der(6)t(6;?)p25;?,+der(11)t(11;14)(p13;q13)	5
48,X,-X,+2,-4,-14,+der(4)t(4;?)p16;?,del(5)(q13),+der(14)t(14;?)q32;?,del(14)(q11q13),+mar,+min	2
48,XY,+15,-22,t(14;14)(q11;q32),+der(14)(q11q13),+mar	3
46,XY,-4,-9,-10,-12,del(1)(p32),+der(4)t(4;?)p16;?,+mar1,+mar2,+mar3	7
44,X,-X,-1,-3,-5,-8,-10,-12,-13,-14,-17,-17,-18,+der(1)t(1;?)p36;?,+der(3)t(3;?)q29;?,+der(12)t(12;?)p13;?,+der(14)t(14;?)q32;?,del(14)(q11q13),+der(17)t(17;?)q25;?,+mar1,+mar2,+mar3,+mar4,+min	11
47,X,-X,+3,-4,+15,+der(4)t(4;?)q35;?,inv(14)(q11q32)	6
46,X,-X,-10,-12,-14,-17,+der(14)t(14;?)q32;?,+mar1,+mar2,+mar3,+min	10
45,X,-Y,-2,-3,-3,-5,-8,-9,-11,-15,-16,-17,del(1)(q42),+der(2)t(2;?)p25;?,+der(3)t(3;?)p21;?,+der(6)(q21),+der(11)t(11;?)q25;?,inv(14)(q11q32),+der(15)t(15;?)p11;?,+mar1,+mar2,+mar3,+mar4,+mar5	9

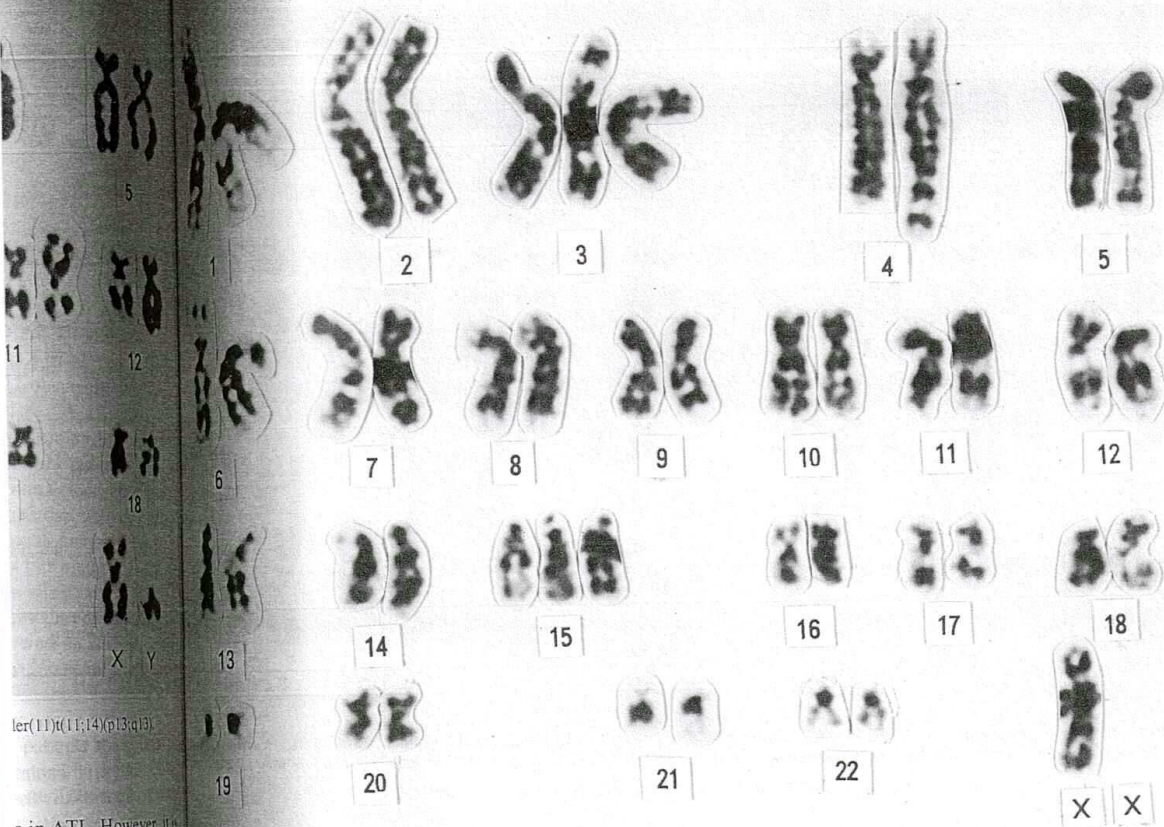


FIG. 2. Clonal karyotype in Case 6: 47,X,-X,+3,-4,+15,+der(4)t(4;?)(q35;?),inv(14)(q11q32).

s in ATL. However, it is a type of chromosome abnormality, trisomy 7, which is reported in various B-cell lymphomas. Trisomy 7 is demonstrated in patients with leukemia (B-CLL),^{12,13} (NHL),^{14,15} and multiple myeloma.¹⁶ Trisomy 7 in B-cell NHL,¹⁷ B-cell NHL,^{14,18} MM,¹⁹ and myeloid leukemia (B-ALL),²⁰ and Trisomy 7 was described in B-ALL,²¹ and MM.²² Specific translocations of chromosome 7, such as t(4;7)(q32;q32) in various B-cell lymphomas, reported, such as t(8;14)(p11;p11) in B-CLL,²³ and t(14;18)(q32;q21) in B-CLL,²⁴ and t(14;18)(q32;q21) in B-CLL,²⁵ and t(14;18)(q32;q21) in B-CLL,²⁶ and t(14;18)(q32;q21) in B-CLL,²⁷ and t(14;18)(q32;q21) in B-CLL,²⁸ and t(14;18)(q32;q21) in B-CLL,²⁹ and t(14;18)(q32;q21) in B-CLL,³⁰ and t(14;18)(q32;q21) in B-CLL,³¹ and t(14;18)(q32;q21) in B-CLL,³² and t(14;18)(q32;q21) in B-CLL,³³ and t(14;18)(q32;q21) in B-CLL,³⁴ and t(14;18)(q32;q21) in B-CLL,³⁵ and t(14;18)(q32;q21) in B-CLL,³⁶ and t(14;18)(q32;q21) in B-CLL,³⁷ and t(14;18)(q32;q21) in B-CLL,³⁸ and t(14;18)(q32;q21) in B-CLL,³⁹ and t(14;18)(q32;q21) in B-CLL,⁴⁰ and t(14;18)(q32;q21) in B-CLL,⁴¹ and t(14;18)(q32;q21) in B-CLL,⁴² and t(14;18)(q32;q21) in B-CLL,⁴³ and t(14;18)(q32;q21) in B-CLL,⁴⁴ and t(14;18)(q32;q21) in B-CLL,⁴⁵ and t(14;18)(q32;q21) in B-CLL,⁴⁶ and t(14;18)(q32;q21) in B-CLL,⁴⁷ and t(14;18)(q32;q21) in B-CLL,⁴⁸ and t(14;18)(q32;q21) in B-CLL,⁴⁹ and t(14;18)(q32;q21) in B-CLL,⁵⁰ and t(14;18)(q32;q21) in B-CLL,⁵¹ and t(14;18)(q32;q21) in B-CLL,⁵² and t(14;18)(q32;q21) in B-CLL,⁵³ and t(14;18)(q32;q21) in B-CLL,⁵⁴ and t(14;18)(q32;q21) in B-CLL,⁵⁵ and t(14;18)(q32;q21) in B-CLL,⁵⁶ and t(14;18)(q32;q21) in B-CLL,⁵⁷ and t(14;18)(q32;q21) in B-CLL,⁵⁸ and t(14;18)(q32;q21) in B-CLL,⁵⁹ and t(14;18)(q32;q21) in B-CLL,⁶⁰ and t(14;18)(q32;q21) in B-CLL,⁶¹ and t(14;18)(q32;q21) in B-CLL,⁶² and t(14;18)(q32;q21) in B-CLL,⁶³ and t(14;18)(q32;q21) in B-CLL,⁶⁴ and t(14;18)(q32;q21) in B-CLL,⁶⁵ and t(14;18)(q32;q21) in B-CLL,⁶⁶ and t(14;18)(q32;q21) in B-CLL,⁶⁷ and t(14;18)(q32;q21) in B-CLL,⁶⁸ and t(14;18)(q32;q21) in B-CLL,⁶⁹ and t(14;18)(q32;q21) in B-CLL,⁷⁰ and t(14;18)(q32;q21) in B-CLL,⁷¹ and t(14;18)(q32;q21) in B-CLL,⁷² and t(14;18)(q32;q21) in B-CLL,⁷³ and t(14;18)(q32;q21) in B-CLL,⁷⁴ and t(14;18)(q32;q21) in B-CLL,⁷⁵ and t(14;18)(q32;q21) in B-CLL,⁷⁶ and t(14;18)(q32;q21) in B-CLL,⁷⁷ and t(14;18)(q32;q21) in B-CLL,⁷⁸ and t(14;18)(q32;q21) in B-CLL,⁷⁹ and t(14;18)(q32;q21) in B-CLL,⁸⁰ and t(14;18)(q32;q21) in B-CLL,⁸¹ and t(14;18)(q32;q21) in B-CLL,⁸² and t(14;18)(q32;q21) in B-CLL,⁸³ and t(14;18)(q32;q21) in B-CLL,⁸⁴ and t(14;18)(q32;q21) in B-CLL,⁸⁵ and t(14;18)(q32;q21) in B-CLL,⁸⁶ and t(14;18)(q32;q21) in B-CLL,⁸⁷ and t(14;18)(q32;q21) in B-CLL,⁸⁸ and t(14;18)(q32;q21) in B-CLL,⁸⁹ and t(14;18)(q32;q21) in B-CLL,⁹⁰ and t(14;18)(q32;q21) in B-CLL,⁹¹ and t(14;18)(q32;q21) in B-CLL,⁹² and t(14;18)(q32;q21) in B-CLL,⁹³ and t(14;18)(q32;q21) in B-CLL,⁹⁴ and t(14;18)(q32;q21) in B-CLL,⁹⁵ and t(14;18)(q32;q21) in B-CLL,⁹⁶ and t(14;18)(q32;q21) in B-CLL,⁹⁷ and t(14;18)(q32;q21) in B-CLL,⁹⁸ and t(14;18)(q32;q21) in B-CLL,⁹⁹ and t(14;18)(q32;q21) in B-CLL,¹⁰⁰ and t(14;18)(q32;q21) in B-CLL,¹⁰¹ and t(14;18)(q32;q21) in B-CLL,¹⁰² and t(14;18)(q32;q21) in B-CLL,¹⁰³ and t(14;18)(q32;q21) in B-CLL,¹⁰⁴ and t(14;18)(q32;q21) in B-CLL,¹⁰⁵ and t(14;18)(q32;q21) in B-CLL,¹⁰⁶ and t(14;18)(q32;q21) in B-CLL,¹⁰⁷ and t(14;18)(q32;q21) in B-CLL,¹⁰⁸ and t(14;18)(q32;q21) in B-CLL,¹⁰⁹ and t(14;18)(q32;q21) in B-CLL,¹¹⁰ and t(14;18)(q32;q21) in B-CLL,¹¹¹ and t(14;18)(q32;q21) in B-CLL,¹¹² and t(14;18)(q32;q21) in B-CLL,¹¹³ and t(14;18)(q32;q21) in B-CLL,¹¹⁴ and t(14;18)(q32;q21) in B-CLL,¹¹⁵ and t(14;18)(q32;q21) in B-CLL,¹¹⁶ and t(14;18)(q32;q21) in B-CLL,¹¹⁷ and t(14;18)(q32;q21) in B-CLL,¹¹⁸ and t(14;18)(q32;q21) in B-CLL,¹¹⁹ and t(14;18)(q32;q21) in B-CLL,¹²⁰ and t(14;18)(q32;q21) in B-CLL,¹²¹ and t(14;18)(q32;q21) in B-CLL,¹²² and t(14;18)(q32;q21) in B-CLL,¹²³ and t(14;18)(q32;q21) in B-CLL,¹²⁴ and t(14;18)(q32;q21) in B-CLL,¹²⁵ and t(14;18)(q32;q21) in B-CLL,¹²⁶ and t(14;18)(q32;q21) in B-CLL,¹²⁷ and t(14;18)(q32;q21) in B-CLL,¹²⁸ and t(14;18)(q32;q21) in B-CLL,¹²⁹ and t(14;18)(q32;q21) in B-CLL,¹³⁰ and t(14;18)(q32;q21) in B-CLL,¹³¹ and t(14;18)(q32;q21) in B-CLL,¹³² and t(14;18)(q32;q21) in B-CLL,¹³³ and t(14;18)(q32;q21) in B-CLL,¹³⁴ and t(14;18)(q32;q21) in B-CLL,¹³⁵ and t(14;18)(q32;q21) in B-CLL,¹³⁶ and t(14;18)(q32;q21) in B-CLL,¹³⁷ and t(14;18)(q32;q21) in B-CLL,¹³⁸ and t(14;18)(q32;q21) in B-CLL,¹³⁹ and t(14;18)(q32;q21) in B-CLL,¹⁴⁰ and t(14;18)(q32;q21) in B-CLL,¹⁴¹ and t(14;18)(q32;q21) in B-CLL,¹⁴² and t(14;18)(q32;q21) in B-CLL,¹⁴³ and t(14;18)(q32;q21) in B-CLL,¹⁴⁴ and t(14;18)(q32;q21) in B-CLL,¹⁴⁵ and t(14;18)(q32;q21) in B-CLL,¹⁴⁶ and t(14;18)(q32;q21) in B-CLL,¹⁴⁷ and t(14;18)(q32;q21) in B-CLL,¹⁴⁸ and t(14;18)(q32;q21) in B-CLL,¹⁴⁹ and t(14;18)(q32;q21) in B-CLL,¹⁵⁰ and t(14;18)(q32;q21) in B-CLL,¹⁵¹ and t(14;18)(q32;q21) in B-CLL,¹⁵² and t(14;18)(q32;q21) in B-CLL,¹⁵³ and t(14;18)(q32;q21) in B-CLL,¹⁵⁴ and t(14

and 14q32 reported in ATL have also been demonstrated in various B-cell malignancies, which may indicate that these chromosome abnormalities might not be specific for ATL but are also common to lymphoproliferative disorders including T- and B-cell malignancies. Recently, Ueshima *et al.*²⁶ indicated that most reported patients with T-cell malignancies, such as Sézary syndrome, mycosis fungoides, cutaneous T-cell lymphoma, and T-cell chronic lymphocytic leukemia (T-CLL), had a rearrangement of the long arm of chromosome 14 with a break at band 14q11-13. Based on these facts, they suggested that the break at 14q11-13 probably constitutes the most common nonrandom abnormality in T-cell malignancies. However, no other investigators noticed the

proximal 14q rearrangement in ATL, as reviewed by Ueshima *et al.*²⁶

In our study, six of eight ATL patients showed a chromosome 14 anomaly with a break at band 14q11-13, although some of them showed the coexistence of a distal rearrangement at band 14q32 such as t(14;14)(q11;q32). Two patients in our ATL series showed inv(14)(q11q32). Zech *et al.*²⁷ also reported an inv(14)(q11q32) in four of five patients with T-CLL. These facts may indicate that inv(14)(q11q32) is one of the cytogenetic subtypes in various T-cell malignancies, like t(14;14)(q11;q32).²⁶ Interestingly, two patients in this series had a del(14)(q11q13) that was newly found in ATL and seems more likely to be specific.

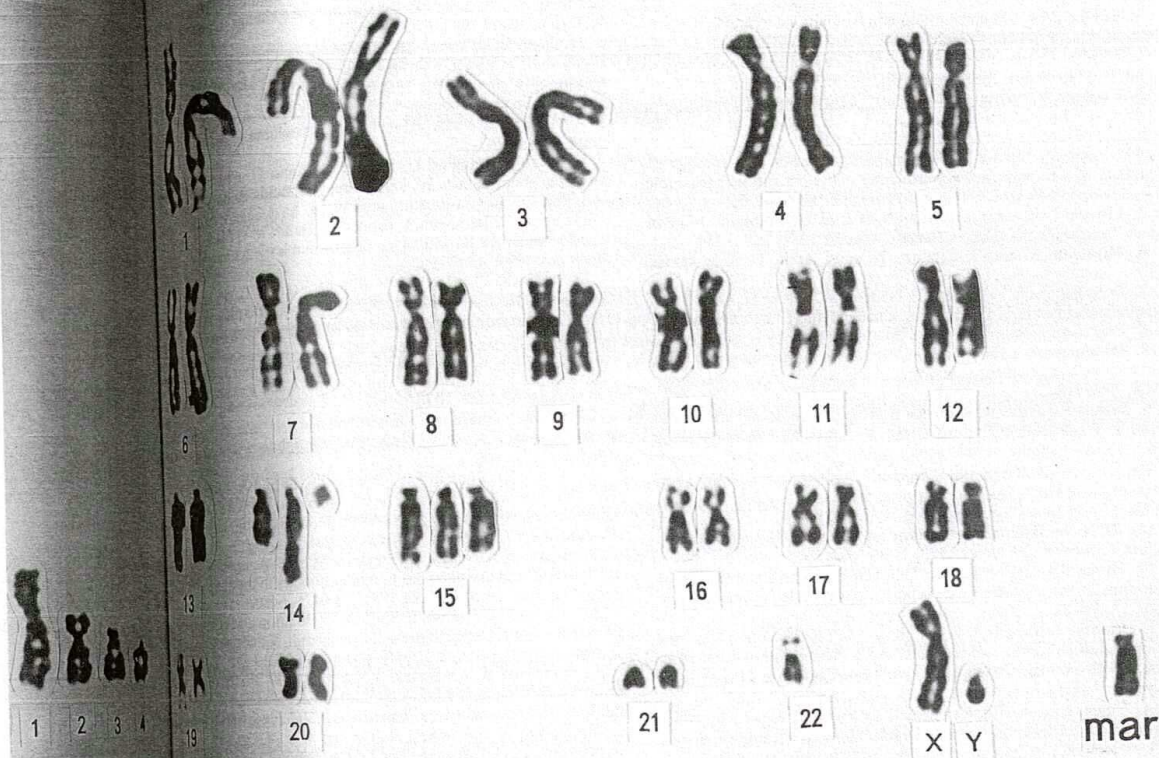
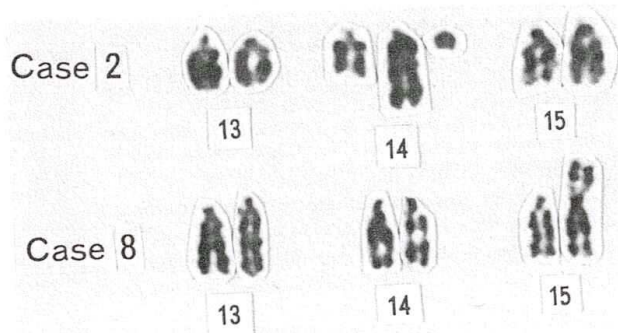


FIG. 4. Clonal karyotype in Case 3: 48,XY,+15,-22,t(14;14)(q11;q32),+del(14)(q11q13),+mar.

13), + der(1)t(1;7)(p36;p36), + mar4, + min.

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FIG. 5. Partial karyotypes of Case 2 with del(14)(q11;q32),der(14)t(14;7)(q32;q?) and a minute chromosome, and partial karyotypes of Case 8 with inv(14)(q11q32) and del(15)(p11;p2).



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