AMCoR
Asahikawa Medical College Repository http://amcor.asahikawa-med.ac.jp/

Cancer Genetics and Cytogenetics (2008) 183(1):69-71.

A novel five-way chromosomal translocation observed in chronic myelogenous leukemia.

Ikuta K, Torimoto Y, Jimbo J, Inamura J, Hosoki T, Shindo M, Sato K, Takahashi H, Kohgo Y.

Short communication

A novel five-way chromosomal translocation observed in chronic myelogenous leukemia

Katsuya Ikuta[a], Yoshihiro Torimoto[a], Junko Jimbo[a], Junki Inamura[a], Takaaki Hosoki[a], Motohiro Shindo[a], Kazuya Sato[a], Hiroyuki Takahashi[b], Yutaka Kohgo[a]

[a]Division of Gastroenterology and Hematology/Oncology,
Department of Medicine, Asahikawa Medical College

[b]Department of Medical Laboratory and Blood Center,
Asahikawa Medical College

Corresponding author:
Katsuya Ikuta, M.D., Ph.D.
Division of Gastroenterology and Hematology/Oncology
Department of Medicine, Asahikawa Medical College
2-1-1-1, Midorigaoka-Higashi, Asahikawa, Hokkaido, Japan 078-8510
Tel: +81-166-68-2462
Fax: +81-166-68-2469

e-mail: ikuta@asahikawa-med.ac.jp

Abstract

Most patients with chronic myelogenous leukemia (CML) show a Philadelphia (Ph) chromosome with a characteristic translocation between chromosomes 9 and 22. However, there are variant complex translocations involving other chromosomes in addition to the standard translocation. We describe a case of CML who showed a complex and novel chromosomal translocation involving five chromosomes, t(9;22;12;4;7).

Introduction

Chronic myelogenous leukemia (CML) is a clonal myeloproliferative disorder of the primitive hematopoietic stem cell, and characterized by a marked overproduction of granulocytes. Most patients with CML show a Philadelphia (Ph) chromosome with a characteristic translocation between chromosomes 9 and 22. This rearrangement combines the *C-ABL* protooncogene on chromosome 9 with the breakpoint cluster region (*BCR* gene) on chromosome 22. However, there are variant complex Ph-translocations involving other chromosomes in addition to chromosomes 9

and 22. In such cases, three or four chromosomes are usually involved in the translocation; there are only a few reports on complex translocations involving five chromosomes.

We studied a patient with CML who showed a novel complex Ph translocation involving five chromosomes, 9, 22, 12, 4 and 7. We emphasize that spectral karyotyping (SKY) was valuable for the determination of the details of the complex translocation observed in this case.

Case Report

The patient was 32-year-old symptomless Japanese male. He was found to have a WBC of 9.94 x 10^9 /L, which was slightly higher than the normal range, at a medical checkup at his workplace on March 2004. He consulted a physician, who noticed that there were 4.5% basophils, and 1% myelocytes in his peripheral blood smear. Bone marrow aspiration was then performed, and it showed both nucleated cells and megakaryocytes were increased in number to 740,000/μl and 128/μl, respectively. He was referred to our department.

He has no remarkable past and family history. Physical examination on admission revealed no lymphadenopathy and hepatosplenomegaly. The laboratory data on admission showed that his WBC was 12.45 x 10^9 /L, with a differential of 67% neutrophils, 18% lymphocytes, 1% monocytes, 2% eosinophils, 10% basophils and 2% myelocytes. Hemoglobin concentration of 139 g/L and a platelet count of 289 x 10^9 /L, were both within the normal range. Biochemical data showed that an elevated γ-GTP 222 IU/L (normal range: 4-67 IU/L) and uric acid 7.8 mg/dL (2.4-7.0 mg/dL). Lactate dehydrogenase (LDH) was 168 IU/L (105-210 IU/L), which was in the normal range. Vitamin B12 was elevated to 1110 pg/ml, and NAP score was decreased to 79 (control score 230).

Bone marrow aspiration showed a marked increase of nucleated cell count of 490,000/μl and megakaryocytes of 266/μl. As shown in Figure 1A, G-banding analysis showed 46, XY, add(4)(q31), t(7;9;22)(p13;q34;q11), add(12)(q24), in 31 cells out of 37 analyzed cells. Although the findings in G-banding seemed to be complex compared to a typical Ph chromosome formation, *BCR-ABL* fusion signals were observed in

91 % of the cells analyzed by FISH, and polymerase chain reaction amplified major-*BCR/ABL* (p210) (b3a2 type).

Because of the complicated chromosomal translocation shown by the G-banding method, SKY was performed for more detailed information. As shown in Figure 1B, a portion of the long arm of a chromosome 9 was added to the long arm of chromosome 22, forming a Ph chromosome. However, the segment of chromosome 22 was translocated to a chromosome 4 instead of the chromosome 9. Therefore, the translocation between chromosomes 9 and 22 was not found in this case. The segment from the chromosome 4 was translocated to a chromosome 12, the segment from chromosome 12 was translocated to a chromosome 7, and the segment from the chromosome 7 was translocated to the chromosome 9. The karyotype of the five-way translocation observed by SKY method can be written as t(4;12;7;9;22)(q33?;q24;p13;q34;q11). As shown in Figure 1C, the nature of translocation among five chromosomes is presented schematically.

The patient was given imatinib mesylate at a dose of 400 mg/day. Although he experienced slight liver dysfunction and mild skin rash, those

improved gradually and he has been able to continue on imatinib mesylate. One month after starting on imatinib, he achieved complete hematologic response, as well as complete cytogenetic response two months later. Major *BCR-ABL* then disappeared by RT-PCR, and he has been in this condition for 41 months.

Discussion

We presented an unusual case of CML in whom a complicated Ph rearrangement was observed. It have been reported that 5-10% of CML cases have complicated Ph rearrangements that include more than three chromosomes. However, we found only seven other cases in whom five chromosomes were involved in five-way Ph translocations (Table 1) [1-8]. The involved chromosomes in our case were 9, 22, 12, 4 and 7. This combination has not been reported elsewhere.

At the diagnosis of this case, we did not found typical Ph, and we found that five chromosomes, such as 9, 22, 12, 4 and 7, seemed to be changed by G-banding. Then we performed SKY, and SKY revealed the

five-way translocation among those five chromosomes. Because the finding of SKY was consistent with that of G-banding, we believe that the possibility of false-positive in SKY should be quite low. In addition, the five-way translocation observed in this case seems to be well illustrated from SKY finding, therefore, we also believe that the possibility of involvements of other chromosomes, meaning the possibility of false-negative in SKY should be quite low.

In the present case, G-banding could not identify the nature of the Ph translocation occurred, whereas SKY showed its ability for determination of the details of the translocation. Thus, SKY should be performed in cases with complicated chromosomal rearrangements.

We believe that the translocations observed in our case was not formed by multi-steps, since we did not observe any other intermediate translocations before or during treatment. Some intermediate translocations would be expected to be seen if the five-way translocation is formed by multi-steps.

Apparently, prognoses are not remarkably different between cases with a typical Ph chromosome and those with complicated Ph translocations

involving more than three chromosomes. The present case has had a complete response at the molecular level following imatinib mesylate therapy, but careful follow-up in the future should be needed, because the translocations observed in this case has not been reported elsewhere and we cannot know the details of the clinical course now.

References

[1] Nakajima F, Takagi M, Tsuchiya K, Imashuku S, Arakawa S, Misawa S, Abe T. A five-way complex translocation in a patient with chronic myelocytic leukemia: t(4;18;13;9;22)(q12;q11.2;q14;q34;q11.2). Cancer Genet Cytogenet 1988;30:163-4.

[2] Misawa S, Nishida k, Taniwaki M, Nishigaki H, Takino T, Nakanishi S, Shimazaki C, Nakagawa M, Inazawa J, Abe T, Nakajima F, Nakai T. Clinical and cytogenetic features in six patients with chronic myelogenous leukemia and a complex Philadelphia translocation. Acta Haematol Jpn 1989;52:1013-21.

[3] Hayata I, Sasaki M. A case of Ph1-positive chronic myelocytic

leukemia associated with complex translocations. Proc Japan Acad 1976;52:29-32.

[4] Potter AM, Watmore AE, Cooke P, Lilleyman JS, Sokol RJ. Significance of non-standard Philadelphia chromosomes in chronic granulocytic leukaemia. Br J Cancer 1981;44:51-4.

[5] Abe R, Shiga Y, Ookoshi T, Tanaka T, Maruyama Y. A complicated translocation involving five chromosomes (Nos. 9, 11, 12, 21, and 22) in a patient with chronic myelocytic leukemia. Int J Hematol 1991;54:479-82.

[6] Lau L-C, Knight L, Tien S-L, Lim P, Yong M-H, Chong Y-Y. Highly complex chromosomal rearrangement of chromosome 9 in a case of chronic myeloid leukemia. Cancer Genet Cytogenet 1998;104:153-6.

[7] Young C, Benedetto JD Jr, Glasser L, Mark HFL. A Philadelphia chromosome positive CML patient with a unique translocation studied via GTG-banding and fluorescence in situ hybridization. Cancer Genet Cytogenet 1996;89:157-62.

[8] Morel F, Herry A, Le Bris M-J, Morice P, Bouquard P, Abgrall J-F,

Berthou C, De Braekeleer M. Contribution of fluorescence in situ hybridization analyses to the characterization of masked and complex Philadelphia chromosome translocations in chronic myelocytic leukemia. Cancer Genet Cytogenet 2003;147:115-20.

Table 1.
Previously reported CML cases with five-way translocations, and the present case.

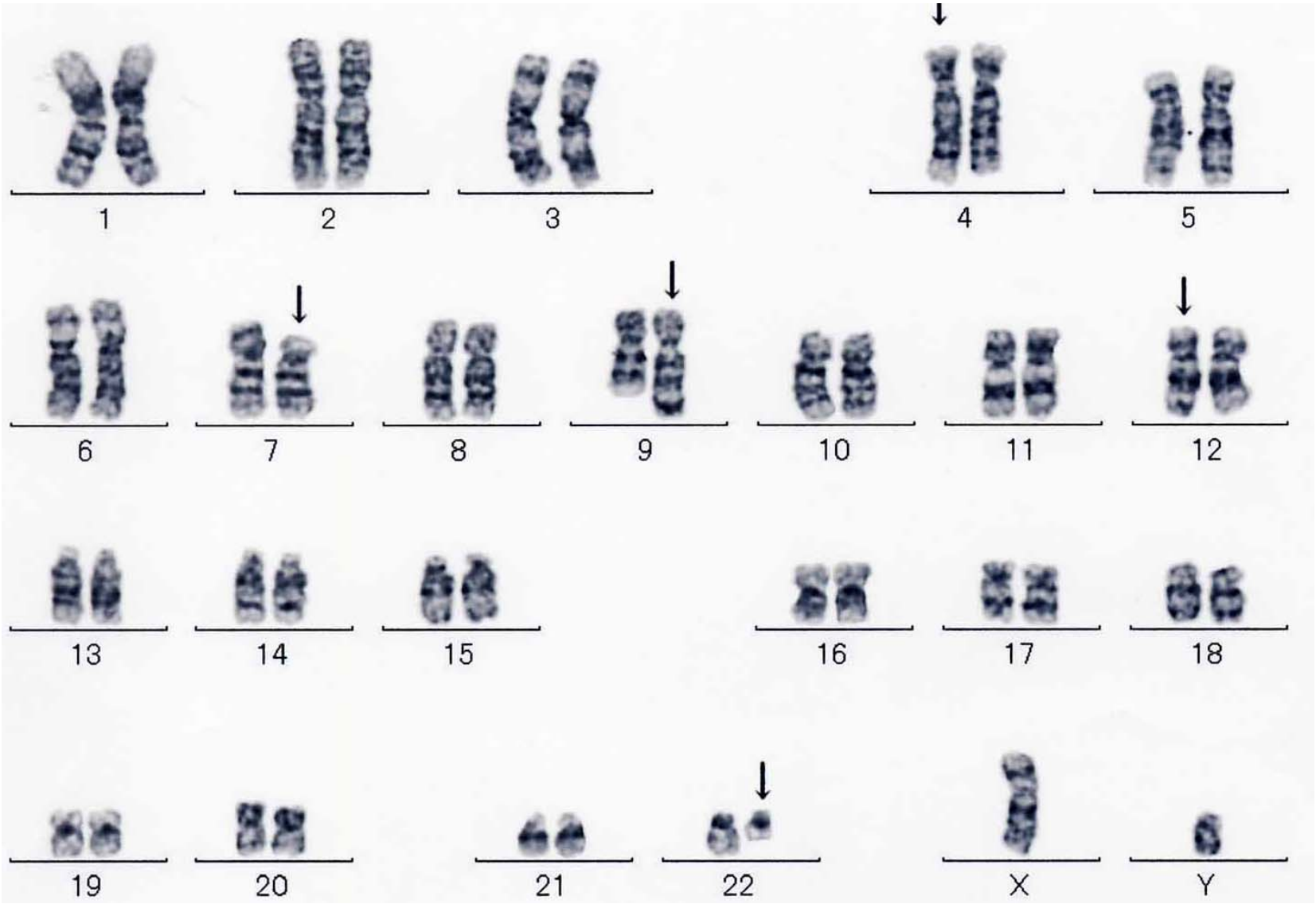
Case	Age / Sex	Karyotype of five-way translocation	reference
1	10/male	t(4;18;13;9;22)(q12;q11.2;q14;q34;q11.2)	[1]
2	23/male	t(9;22;15;19;10)	[3]
3	68/n.d.	t(3;4;9;11;22)	[4]
4	64/female	t(9;22;21;11;inv ins(12)(q15p12p13)) (q34;q11;q22;q13;q15)	[5]
5	63/male	t(9;22;10;12;1)(q34;q11.2;q22;p12;p36.1)	[6]
6	68/female	t(9;22;15;13;17)(q34;q11;q26;q14;q11)	[7]
7	n.d./n.d.	t(2;9;16;22;22)(q32;q34;q21;q11;q11)	[8]
8	32/male	t(4;12;7;9;22)(q33?;q24;p13;q34;q11)	The present case

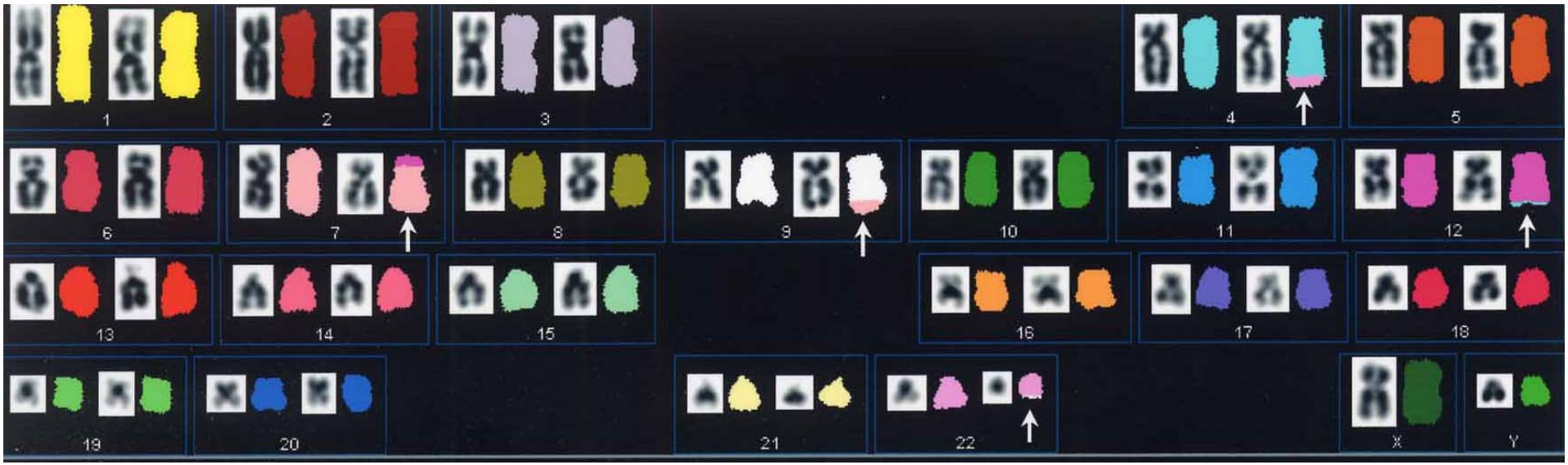
n.d.: not described

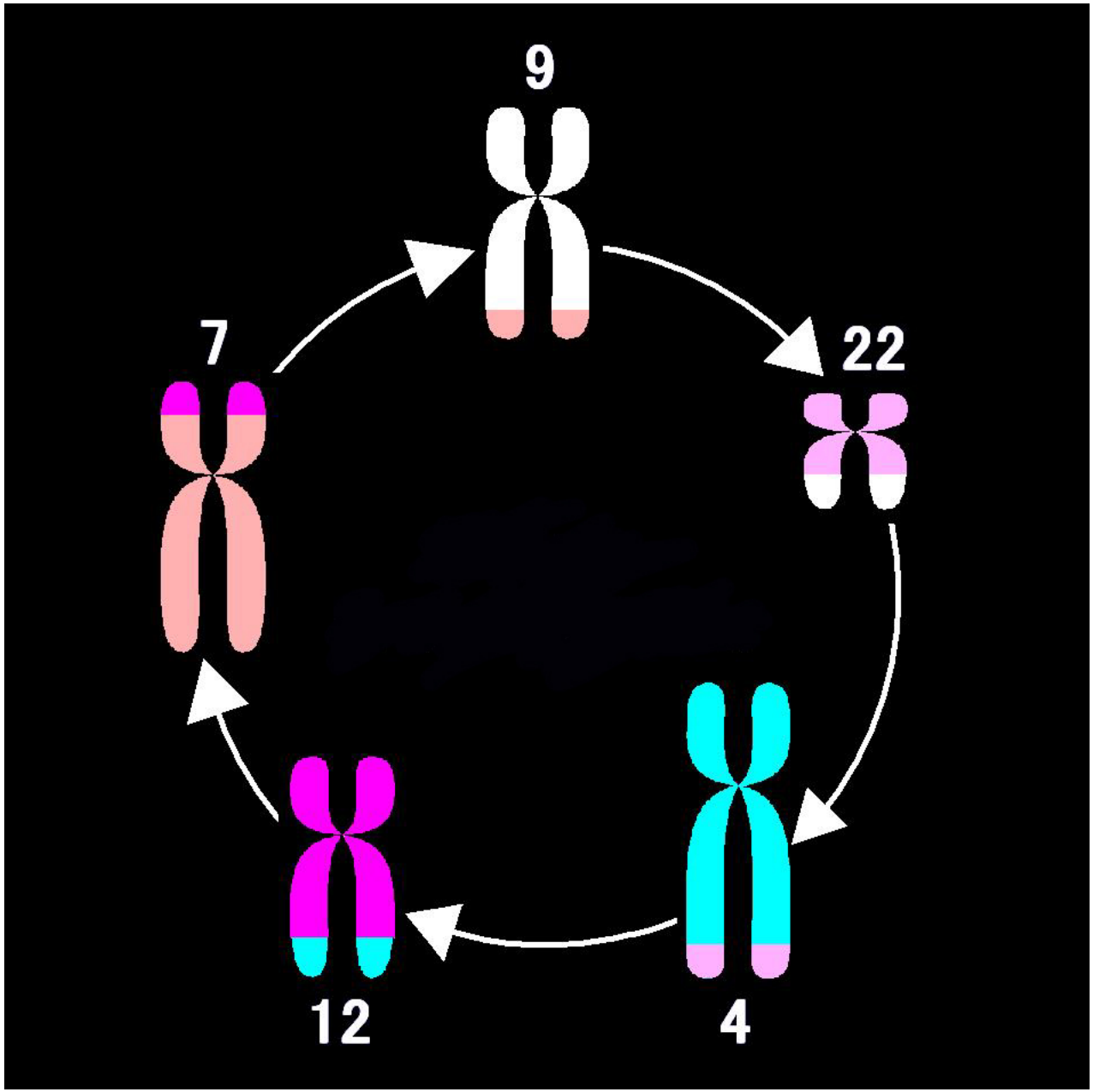
Figure legend

Figure 1.

(A) Karyotype of a bone marrow cell by a G-banding technique: 46, XY, add(4)(q31), t(7;9;22)(p13;q34;q11), add(12)(q24), in 31 cells out of 37 analyzed cells. (B) Karyotype of a bone marrow cell using SKY. Arrowheads indicate the five derivative chromosomes. (C) Schema of the five-way translocation observed in this case. The karyotype of the five-way translocation was considered to be t(4;12;7;9;22)(q33?;q24;p13;q34;q11).


1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
X
Y


1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
X
Y


9
22
4
12
7