Variant Philadelphia translocations with different breakpoints in six chronic myeloid leukemia patients

Altı Kronik miyeloid lösemi olgusunda farklı kırık noktalı varyant Philadelphia translokasyonları

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Abstract

Objective: The Philadelphia (Ph) chromosome, consisting of the t(9;22)(q34;q11) translocation, is observed in ~90% of patients with chronic myeloid leukemia (CML). Variant Ph translocations are observed in 5%-10% of CML patients. In variant translocations 3 and possibly more chromosomes are involved. Herein we report 6 CML patients with variant Ph translocations.
Materials and Methods: Bone marrow samples were examined using conventional cytogenetic meth ods. Fluorescence in situ hybridization (FISH) with whole-chromosome paints and BCR-ABL 1D probes were used to confirm and/or complement the findings, and identify rearrangements beyond the resolution of conventional cytogenetic methods.
Results: Variant Ph translocations in the 6 patients were as follows: t(7;22)(p22;q11), t(9;22;15)(q34;q11;q22), t(15;22)(p11;q11), t(1;9;22;3)(q24;q34;q11;q21), t(12;22)(p13;q11), and t(4;8;9;22)(q11;q13;q34;q11).
Conclusion: Among the patients, 3 had simple and 3 had complex variant Ph translocations. Two of the presented cases had variant Ph chromosomes not previously described, 1 of which had a new complex Ph translocation involving chromosomes 1, 3, 9, 22, and t(1;9;22;3)(q24;q34;q11;q21) apart from a clone with a classical Ph, and the other case had variant Ph translocation with chromosomes 4, 8, 9, and 22, and t(4;8;9;22)(q11;q13;q34;q11) full complex translocation. Number of studies reported that some patients with variant Ph translocation were poor responders to imatinib. All of our patients with variant Ph translocations had suboptimal responses to imatinib, denoting a poor prognosis also. Variant Ph translocations may be important as they are associated with prognosis and therapy for CML patients. *(Turk J Hematol 2011; 28: 186-92)*

Key words: Chronic myeloid leukemia (CML), variant Ph chromosome, cytogenetics, fluorescence in situ hybridization (FISH)

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Özet

Amaç: t(9;22)(q34;q11) sonucu oluşan Philadelphia (Ph) kromozomu, kronik miyeloid lösemi (KML) olgularının %90' dan fazlasında gözlenir. KML hastalarının %5-10 unda varyant Ph translokasyonları bulunur. Varyant translokasyonlar üç ve daha fazla kromozom içerebilmektedir. Bu çalışmada varyant Ph translokasyonlu 6 KML olgusu sunulmaktadır.
Yöntemler ve Gereçler: Kemik iliği örnekleri konvansiyonel sitogenetik kullanılarak incelendi; BCR-ABL 1D problarının kullanıldığı Floresan İn Situ Hibridizasyon (FISH) yöntemi bulguların doğrulanması ve konvansiyonel sitogenetik yöntemlerinin tespit etmekte yetersiz kaldığı yeniden düzenlemelerin tanımlanması amacıyla uygulandı.
Bulgular: Çalışmada yer alan 6 hastanın varyant Ph translokasyonları: t(7;22)(p22;q11), t(9;22;15)(q34;q11;q22), t(15;22)(p11;q11), t(1;9;22;3)(q24;q34;q11;q21), t(12;22)(p13;q11) ve t(4;8;9;22)(q11;q13;q34;q11) dır.
Sonuç: Üç olguda basit, 3 olguda ise karmaşık (kompleks) varyant Ph translokasyonları saptamış bulunuyoruz. Olgularımızın ikisi daha önce bildirilmeyen varyant Ph kromozomları taşıyorlardı. Bu olgulardan biri klasik Ph'lı bir klonun yanısıra 1, 9, 22 ve 3 numaralı kromozomları içeren t(1;9;22;3)(q24;q34;q11;q21) formüllü yeni bir kompleks Ph translokasyonuna; diğeri ise 4, 8, 9 ve 22 numaralı kromozomları içeren t(4;8;9;22)(q11;q13;q34;q11) kompleks translokasyonlu varyant Ph'ya sahiptiler. Varyant Ph'lı 6 olgunun tümü kötü prognoza işaret eden yetersiz imatinib cevabı gösterdiler.
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Anahtar kelimeler: Kronik myeloid lösemi (KML), varyant Philadelphia kromozomu, sitogenetik, floresan in situ hibridizasyon (FISH)

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Introduction

Chronic myeloid leukemia (CML) is a clonal myeloproliferative neoplasm arising from neoplastic transformation of a pluripotent stem cell. The Philadelphia (Ph) chromosome, which is the result of t(9;22)(q34;q11), is observed in ~90% of CML patients. The translocation leads to fusion of the proto-oncogene Abelson (ABL) and a particular DNA sequence known as breakpoint cluster region (BCR), thereby giving rise to 2 new chimeric genes 5' ABL-3' BCR on the derivative chromosome 9 and 5' BCR-3' ABL on the derivative chromosome 22. Variant Ph translocations have been observed in 5%-10% of CML patients [1]. These variant translocations may be simple or complex. Simple variant translocations occur when the deleted segment of 22q is translocated onto a chromosome other than chromosome 9. In complex translocations, 3 and possibly more chromosomes are involved [2,3]. In a few cases of variant Ph translocations the BCR-ABL fusion gene is located on chromosomal sites other than 22q11 [4].

More than 1 mechanism plays a role in the evolution of variant Ph translocation; it can originate secondary to simple Ph translocation or can arise simultaneously in a 3-way rearrangement. Different mechanisms involved in the formation of a variant translocation may have different clinical implications: a 2-step evolution might resemble a clonal evolution, whereas variant translocations that evolve simultaneously in a 3-way rearrangement may be similar to simple Ph translocation [5]. The clinical significance of variant t(9;22) translocations is not clear [4].

In the present study bone marrow samples from 6 CML patients were examined using conventional cytogenetic methods, FISH with whole-chromosome paints, and BCR-ABL 1D probes to confirm and/or complement the findings, and identify rearrangements beyond the resolution of conventional cytogenetic methods. Additionally, 2 of the CML patients had new complex translocations; 1 between chromosomes 1, 3, 9, 22, and other between 4, 8, 9, and 22. Possible correlations between chromosome breakpoints other than 9 and 22 in these Ph variant tranlocations, and recent updates for the map locations of consistent cancer breakpoints, fragile sites, and oncogenes are discussed.

Materials and Methods

Patients

The study included 6 clinically diagnosed CML patients that were referred for cytogenetic analysis and had variant Ph translocations. Clinical features of the patients are shown in Table 1.

Table 1. Clinical features of the patients

Case	1	2	3	4	5	6
Age/Sex	39/F	23/M	52/M	33/F	60/F	32/M
Reason for referral	CML	CML	CML	CML	CML	CML
Splenomegaly (cm below the costal margin)	0	NA	0	15	0	25
Hemoglobin level (g/dL)	9.7	NA	13.9	9,7	11	8,4
Platelet count (mm^3)	360	NA	220	360	180	214
Leukocyte count (mm^3)	75.4	NA	67.7	160	69,7	123,7
Blasts in PB (%)	1	NA	0	1	0	3
Sokal score	Low	NA	Low	Intermediate	Low	High
Best cytogenetic response	PCR	NA	CCR	NCR	NCR	NCR
Treatment	HU, IFN, IM	NA	HU, IFN,I M	HU, IFN, ARA-C, IM, D	HU, GL	HU, IM, D

NA: Not Available; F: Female; M: Male; PB: Peripheral Blood; HU: Hydroxyurea; INF: Interferon; ARA-C: Cytosine arabinoside; IM: Imatinib mesylate; D: Dasatinib; PCR: Partial cytogenetic response; CCR: Complete cytogenetic response; NCR: No cytogenetic response

Cytogenetic and FISH analysis

Bone marrow (BM) samples were used for cytogenetic and FISH analysis.

Cytogenetics

Cytogenetic analysis was performed on overnight and 24-h unstimulated BM cultures using standard procedures. The GTL (G-bands via trypsin using Leishman) banding technique [6] was applied to the slides, karyotypes were described according to the International System for Human Cytogenetic Nomenclature (2005) [7], and 15-20 metaphases were analyzed for each sample.

FISH analysis

Fresh slides were used for FISH analysis. Before hybridization the slides were pre-treated with pepsin, followed by post-fixation and denaturation. FISH analysis was performed according to the manufacturer's protocols. BCR-ABL1 rearrangement was examined using a BCR-ABL1 D-FISH probe (BCR: 500 Kb in red; ABL1: 600 Kb in green; Oncor, Inc., Gaithersburg, MD, USA).

FISH analyses using whole chromosome paint (WCP) probes to characterize only complex variant translocations in patients 2, 4 and 6.: for patient 2 painting probes for chromosomes 15 and 22 were digoxigenin labeled (WCP 15 and WCP 22; Oncor, Gaithersburg, MD, USA); for patient 4 painting probes for chromosomes 1, 9, and 22 (WCP 1, 9, and 22; XCP-MetaSystems); for patient 6 painting probes for chromosomes 4, 8, 9, and 22 (WCP 4, 8, 9, and 22; XCP-MetaSystems and Cytocell). Fluorescence microscopy was performed with a Nikon E600 microscope with a triple-pass filter and a cooled monochrome CCD camera, using MacProbe FISH analysis software and a CytoVision Ultra system (Applied Imaging, Pittsburgh, PA).

Results

Variant Ph translocations were identified in all 6 patients using G-banding analysis, and were confirmed via FISH analysis. G-banding and FISH results are shown in Table 2.

Table 2. G-Banding and FISH results in the patients

Patient	Karyotype	Probe	Hybridization pattern
1	46,XX,t(7;22)(p22;q11)	BCR-ABL1 D-FISH	BCR-ABL (+)
2	46,XY,t(9;22;15) (q34;q11;q22)	WCP 15 and 22	confirmed
3	46,XY,t(13;15)(p11;q13), t(15;22)(p11;q11)	BCR-ABL1 D-FISH	BCR-ABL (+)
4	46,XX,t(9;22)(q34;q11)/ 46,XX,t(1;9;22;3) (q24;q34;q11;q21)	BCR-ABL1 D-FISH WCP 1, 9, 22	BCR-ABL (+), confirmed
5	46,XX,t(12;22)(p13;q11)	BCR-ABL1 D-FISH	BCR-ABL (+)
6	46,XY,t(4;8;9;22) (q11;q13;q34;q11)	BCR-ABL1 D-FISH WCP 4, 8, 9, and 22	BCR-ABL (+), confirmed

Cytogenetics

In all, 3 of the patients (1, 3, and 5) had simple variant Ph translocations and 3 (2, 4, and 6) had complex translocations. Among the complex variant Ph translocations, 3 chromosomes were involved in 1 patient (2) and 4 chromosomes were involved in 2 patients (4 and 6). Clonal evolution was observed only in patient 4; there were 2 clones 1 with a classical Ph and 1 with t(1;9;22;3)(q24;q34;q11;q21). The chromosomal breakpoints of the variant Ph translocations were 1q24, 3q21, 4q11, 7p22, 8q13, 12p13,15p11, and 15q22. In patient 3 additional clonal chromosomal changes along with variant Ph translocation were observed [t(13;15)(p11;q13)]. Partial G-banding karyotypes are presented in Figure 1.

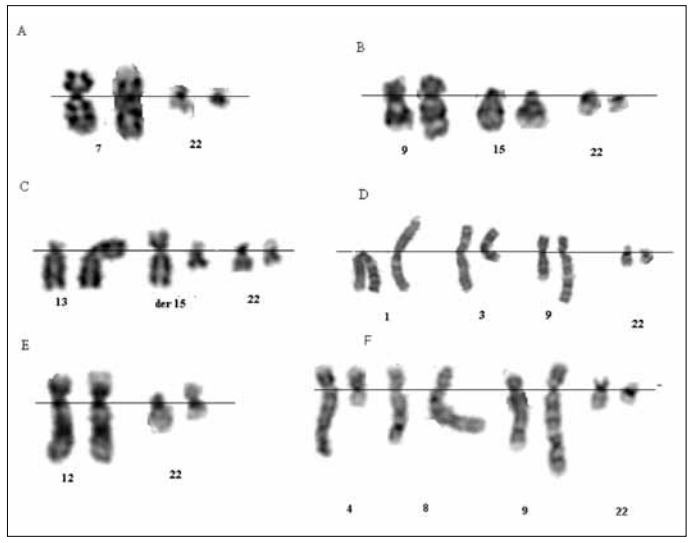

Figure 1. Partial G-banding karyotypes in the 6 patients. A. Patient 1: t(7;22)(p22;q11). B. Patient 2: t(9;22;15)(q34;q11;q22). C. Patient 3: t(15;22)(p11;q11) and clonal chromosomal changes t(13;15)(p11;q13). D. Patient 4: t(1;9;22;3)(q24;q34;q11;q21). E. Patient 5: t(12;22)(p13;q11). F. Patient 6: t(4;8;9;22)(q11;q13;q34;q11)

FISH analysis

In 5 patients (1, 3, 4, 5, and 6) dual-color FISH with the use of the BCR and ABL probes showed the BCR-ABL fusion gene on the Ph chromosome. In patient 2 BCR and ABL probes could not be used due to insufficient material. With the WCP probes involvement of chromosomes other than 9 and 22 in the complex variant translocations were confirmed in patients 2, 4, and 6. FISH images are shown in Figure 2.

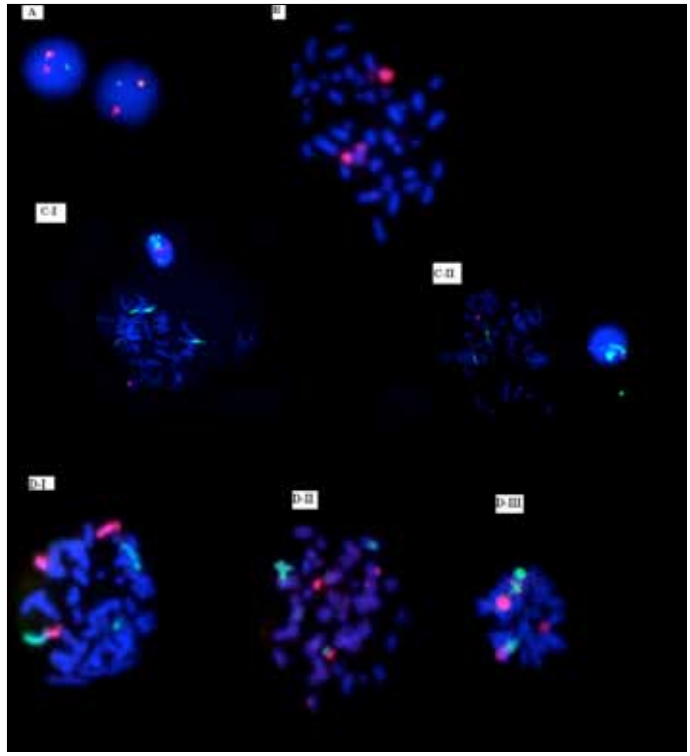

Figure 2. FISH analysis results. A. Signals of BCR-ABL fusion on interphase cells via the BCR-ABL1 D-FISH probe (ONCOR). Green signals on 1 of chromosome 9, red signals on 1 of chromosome 22, and yellow signals on the Ph chromosome showing BCR-ABL fusion. B. In patient 2 metaphase FISH showing t(9;22;15) via WCP 15 (ONCOR) red signals. C. In patient 4 metaphase FISH showing t(1;9;22;3) via WCP 1, 9, and 22 (MetaSystems). CI. Chromosome 1 is green and chromosome 22 is red. CII. and chhromosome 9 is green and chromosome 22 is red. D. In patient 6 metaphase FISH showing t(4;8;9;22) via WCP 4 and 8, (Cytocell), and WCP 9 and 22 (MetaSystems). DI. Chromosome 4 is green and chromosome 8 is red. DII. Chromosome 4 is green and chromosome 22 is red. DIII. Chromosome 8 is red and chromosome 9 is green

Discussion

In the present study chromosomal breakpoints of the variant Ph translocations other than classical 9 and 22 breakpoints were 1q24, 3q21, 4q11, 7p22, 8q13, 12p13,15p11, and 15q22. All 8 breakpoints observed in the 6 patients are listed as variant Ph translocations in the Mitelman database (http://www.cgap.nci.nih.gov/Chromosomes/Mitelman; updated 23 February 2009) [8]. Among the chromosomes that constituted variant Ph translocations in the presented patients, those that were previously described are shown in Table 3.

It was reported that breakpoints involved in variant Ph translocations are primarily located in light-staining bands [2]. Apart from 1q24, the breakpoints observed in the present study were also in light-staining bands. Most of the breakpoints observed in the present study harbor genes known to be associated with neoplasia. GPA33 in 1q24, DIRC2 and HSPBAP1 in 3q21, BTL in 4q11, ETV6 in 12p13, and PML in 15q22 genes are implicated in different leu-

kemias and solid tumors, but the gene in 8q13 is unknown [20]. Band 7p22 in patient 1 corresponded to the map location of common fragile sites [21].

Among the 6 presented patients, 3 had simple and 3 had complex variant Ph translocations. To the best of our knowledge only a few cases of variant Ph translocations involving >3 chromosomes have been reported [1,5,9,11-19,22,23]. In all, 2 of the presented patients (4 and 6) had 4-way rearrangement [t(1;9;22;3)(q24;q34;q11;q21) and t(4;8;9;22)(q11;q13;q34;q11)], including breakpoints that differed from those previously reported. CML studies reported 1q24 and 3q21 in simple and 3-way variant Ph translocations [8,20]. The literature does not contain any reports of 4-way complex translocations involving the chromosomal band 1q24 in CML patients. Similarly, simple and complex variant Ph translocations involving chromosomal bands 4q11 and 8q13 have not yet been reported in CML patients. In CML patients 8q13 has been reported in translocations other than Ph and 4q11 was reported in association with ANLL [8,18,20]. Specific chromosomal abnormalities involving band 3q21 have been observed in all FAB subtypes of acute myeloid leukemia (AML), in myelodysplastic syndrome, occasionally in the blastic phase of chronic myeloid leukemia, and rarely in chronic phase CML.

In some older studies variant Ph translocations involving 3q21 were considered a marker of poor prognosis in CML, and were used to justify the necessity of increasing the dose of imatinib, as commonly administered in the accelerated phase [24]. Patient 4 in the present study did not have a hematological or cytogenetic response to imatinib. Consequently, imatinib was replaced by dasatinib, which was administered for 1 year, but also did not result in a cytogenetic or hematological response. Excluding patient 3, all the presented patients with variant Ph translocations were poor responders to imatinib and were therefore treated with dasatinib.

Table 3. Chromosomes involved in variant Ph translocations in the 6 patients and previously reported breakpoints

Chromosomes seen in our cases	Type of translocations reported in the literature	Reference
4p14, 14q32	t(4;14;9;22)(p14;q32;q34;q11)	Aoun et al. 2004 [1]
6q25, 8q22	t(6;8;9;22)(q25;q22;q34;q11)	Acar et al. 1997 [9]
1p36	t(1;9;22)(p36;q34;q11)	
3p25	t(3;9;22)(p25;q34;q11)	Yehuda et al. 1999 [5]
4p14	t(4;9;22)(p14;q34;q11)	
12q22	t(9;22;12)(q34;q11;q22)	
7q22	**t(7;9;22)(q22;q34;q11)**	Zagariaa et al. 2004 [4]
8q12	t(8;9;22)(q12;q34;q11)	
3q26	t(3;9;22)(q26;q34;q11)	
4p14	t(4;9;22)(p14;q34;q11)	Morel et al. 2003 [10]
4p16	t(4;9;22)(p16;q34;q11)	
6p22, 12q13	t(6,9;12;22)(p22;q34;q13;q11)	Zagariaa et al. 2006 [11]
1q36	t(1;22)(q36;q11)	
4q31	t(4;9;22)(q31;q34;q11)	
7q12	t(7;9;22)(q31;q34;q12)	Zang et al. 1993 [12]
12q24.1	t(9;22;12)(q34;q11;q24.1)	
3q26.2, 17q21	t(3;17;9;22)(q26.2;q21;q34;q11)	
1p36	der(1)t(1;9;22)(p36.1;q34;q11.2)	
1q42	t(1;9;22)(q42; q34;q11.2)	
7q11.2	der(9;22;7)ins(7;22)(q11.2;q11q.12)	Reddy et al. 2000 [13]
	t(9;22;7)(q34;q11.2;q11.2)	
12p13	**t(9;22;12)(q34;11.2;p13)**	
15q15, 21q11.2	t(9;22;15;21)(q34;q11.2;q15;q11.2)	
1q25, 20q13, 1p35	t(1;20;9;22;1)(q25;q13;q34;q11.2; p35)	

Table 3. Continued

Chromosomes seen in our cases	Type of translocations reported in the literature	Reference
1p36	t(1;9;22)(p36.1;q34;q11.2)	
1q21	t(1;9;22)(q21;q34;q11.2)	
12p13	**t(9;22;12)(q34;q11.2;p13)**	Costa et al. 2006 [14]
12q13	t(9;22;12)(q34;q11.2;q13)	
12p13, 20q12	**t(9;22;20;12)(q34;q11.2;q12;p13)**	
1p36	t(1;9;22)(p36;q34;q11)	
3p11	t(3;9;22)(p11;q34;q11)	Markovic et al. 2000 [15]
3q12	t(3;9;22)(q12;q34;q11)	
4q12	t(4;9;22)(q12;q34;q11)	
1p36,11p15q23	t(1;11;22)(p36.2;p15q13;q12),	Babicka et al. 2006 [16]
4q34	t(4;9;22)(q34;q34;q11)	
1p36	t(1;9;22)(p36;q34;q11)	
1q32	t(1;9;22)(q32;q34;q11)	
1q42	t(1;9;22)(q42;q34;q11)	
3p21	t(3;9;22)(p21;q34;q11)	
3q21	**t(3;22)(q21;q11)**	
4p14	t(4;9;22)(p14;q34;q11)	
4p16	t(4;22)(p16;q11)	
4q31	t(4;9;22)(q31;q34;q11)	
7q11	t(7;9;22)(q11;q34;q11)	
7q32	t(7,9,22)(q32;q34;q11)	Reid et al. 2003 [17]
12p12	t(12;22)(p12;q11)	
12q13	t(9;22;12)(q34;q11;q13)	
12q14	t(9;22;12)(q34;q11;q14)	
15q15	t(9;22;15)(q34;q11;q15)	
15q15	t(15;22)(q15;q11)	
15q24	t(9;22;15)(q34;q11;q24)	
5q13,7q11	t(5;7;9;22)(q13;q11;q34;q11)	
6q24, 8q24	t(6;9;22;8)(q24;q34;q11;q24)	
7q22,15q14	t(7;9;22;15)(q22;q34;q11;q14)	
4q12	t(4;22)(q12;q11)	Baxter et al. 2002 [18]
4q25	t(4;9;22)(q25;q34;q11)	Sheth et al. 2005 [19]

Note. The same breakpoints with ours that involved in variant Ph translocations in literature were marked by bold character

The strongest evidence for serial stepwise rearrangements resulting in variant Ph translocation comes from the rare observation of patients with a standard Ph in 1 clone and a complex variant Ph in another clone, as in patient 4 in the present study, who had 1 clone with t(9;22)(q34;q11) and 1 clone with a complex variant Ph translocation t(1;9;22;3)(q24;q34;q11;q21). Cytogenetic evidence suggests that complex Ph translocation is derived from simple Ph translocation [17,25].

The breakpoints of variant Ph translocations in CML patients may be important, as they are associated with carcinogenesis. Above all, monitorization of chromosomes and localization of precise breakpoints involved in the complex rearrangements in CML patients will improve our understanding of the genetic mechanisms that play a role in the progression of malignant disease. We trust that the present study's results will contribute to the scientific com-

munity's knowledge of CML cytogenetics. Written informed consent was obtained from all the patients.

Conflict of interest statement

The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

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