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Retrospective evaluation of chromosome 1 anomalies in hematologic malignancies: A single center study

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Chromosome 1, hematologic malignancies, translocations

Abstract

Various anomalies of chromosome 1 which is the largest chromosome of the human karyotype were found in various hematologic diseases. In this retrospective study, clinical features and cytogenetic anomalies of 35 hematological patients with various chromosome 1 anomalies were correlated. Also the effect of chromosome 1 anomalies to the disease prognosis of those patients was discussed. Conventional cytogenetic analysis of those patients was performed by investigating metaphases of 24 hours stimulated bone marrow samples. After cell culturing, the samples were treated with trypsin and stained with Giemsa (GTG Banding). Analyses were performed on image analysis system. Chromosome 1 anomalies were determined in 35 patients (0.5 %) among 6865 samples having done their conventional bone marrow cytogenetic analysis in our center between January 2008 and March 2016. The ratio of chromosome 1 anomalies of totally 701 anomalies among 6865 patients was 4.9%. Chromosome 1 anomalies were found mostly in patients with Multiple Myeloma (MM), Myelodysplastic syndrome (MDS) and Acute Myeloid Leukemia (AML) in our study group. The most common anomaly was deletion 1 which was seen in 16 (37%) patients. Second most common anomaly was derivation 1 which was seen in 13 (30%) patients. Also translocations between chromosome 1 and other chromosomes were observed. The genetic aberration formed as a result of chromosomal anomalies result in the formation of hematologic malignancies. The effect on disease pathogenesis and prognosis of some of those anomalies are unknown and have to be investigated and determined.

Introduction

Conventional cytogenetics is useful both diagnostically, such as for the diagnosis of chronic myelogenous leukemia (CML) and for the determination of subgroups of myelodysplastic syndromes (MDS) and acute myeloid leukemia

(AML). Besides, it is important for the determination of disease prognosis and response to treatment (Wan, 2014; Komanduri et al., 2016).

Chromosome 1 is the largest chromosome among all human chromosomes. Various anomalies of chromosome 1 were found in various hematologic diseases. These can be structural anomalies such as duplications, translocations, deletions and numerical anomalies such trisomy, monosomy (Caramazzaet al.,2010). Rearrangements of chromosome 1, especially the long arm, are frequently seen in hematologic malignancies. It usually occurs in advanced stages of malignancies and has been shown to correlate with poor prognosis. For example, multiple myeloma is one of the hematologic malignancies in which chromosome 1 anomalies are frequently seen. Deletions of short arm of chromosome 1 and amplification of long arm have been reported in MM (Marzin et al.,2006). It is stated that especially the long arm reorganizations provide the advantage of selection to cells during tumor development. (Sawyer, 2011).

In this study, retrospective analyses of 35 hematological patients with various chromosome 1 anomalies were done. Those were selected among the patients having cytogenetic analysis performed in our center between 2008 and 2016. The chromosomal anomalies and clinical features of those patients were correlated. Moreover, the effect of chromosome 1 anomalies to the prognosis of those patients was discussed.

Materials and methods

Thirty five adult hematology patients with various chromosome 1 anomalies were included in this study. Conventional cytogenetic analysis of those patients was performed by investigating metaphases of 24 hours stimulated bone marrow samples. In this method, firstly patients' bone marrow samples were incubated at 37^0C after adding uridine and 5-fluoro 2-deoxiuridine. After overnight incubation thymidine is added. Later, 30 minutes incubation in colsemide (0.05 g/mL) was done. Afterwards, the cells were put in hypotonic solution (0.075 M KCl) for 30 minutes and then they were fixed on slide with Carnoby solution (3 parts methanol/1 part iced acetic acid). After overnight incubation at 65^0C, the samples were treated with trypsin and stained with Giemsa (GTG Banding). Analyses were performed on image analysis system (Metasystem, Germany). For each patient, 20 metaphases were analyzed and karyotypes written according to "2013 International Human Nomenclature System-ISCN" (Hafferet al.,2013).

Results and Discussion

Chromosome 1 anomalies were determined in 35 patients (0.5 %) among 6865 patients having done their conventional bone marrow cytogenetic analysis in our center between January 2008 and March 2016. The ratio of chromosome 1 anomalies of totally 701 anomalies among 6865 patients was 4.9 %. Among total 35 patients with chromosome 1 anomaly, 22 (62.8 %) were men and 13 (37.1 %) were women. The average age of the patients was 57.5 and 60 years for men and women respectively.

Of the total of 35 patients with chromosome 1 anomaly, 11 were diagnosed with multiple myeloma (MM), 5 with acute myeloid leukemia, 7 with myelodysplastic syndrome (MDS), 2 with acute lymphoblastic leukemia, 3 with lymphoma (2 patients with B cell lymphoma and 1 patient with Burkitt lymphoma), 2 with chronic myelocytic leukemia (CML) and 1 patient with Polycytemiavera (PV), 1 with Aplastic anemia, 1 with Waldenstrom macroglobulinemia (WM), 1 with essential thrombocytosis and 1 with chronic myelomonocytic leukemia (CMML). In table 1, chromosome 1 anomalies according to the diagnosis are shown. Accordingly, del(1) was the most common anomaly in MM patients. MDS was the second most common diagnosis after MM in chromosome 1 anomaly patients, and in MDS patients derivative 1 anomaly was the most common. There were 5 AML patients, 2 patients had del(1) and others had rare translocations. In lymphoma patients again, del(1), derivation 1 and a very rare translocation were observed. In patients with PV, aplastic anemia and Waldenstrom macroglobunemia del(1) and derivative 1 anomalies were observed. The percentage distribution of chromosome 1 anomalies was shown in figure 1. Accordingly, the most common anomaly was deletion 1 which was seen in 16 (37%) of the patients. Second most common

Table 1: Chromosome 1 anomalies accordance to disease

Disease	del(1)	t(1;V)	monosomy(1)	trisomy(1)	dup(1)	der(1)	i(1)(q10)
AML	2	2	-	-	-	2	-
MM	9	1	1	-	-	3	1
MDS	1	1	-	-	1	4	-
PV	-	-	-	-	-	1	-
BHL	1	-	-	-	-	1	-
BL	-	1	-	-	-	-	-
ALL	-	1	-	-	-	1	-
CML	2	2	-	1	-	-	-
Aplastic Anemia	1	-	-	-	-	-	-
Waldenstrom	-	-	-	-	-	1	-
ET	-	1	-	1	-	-	-

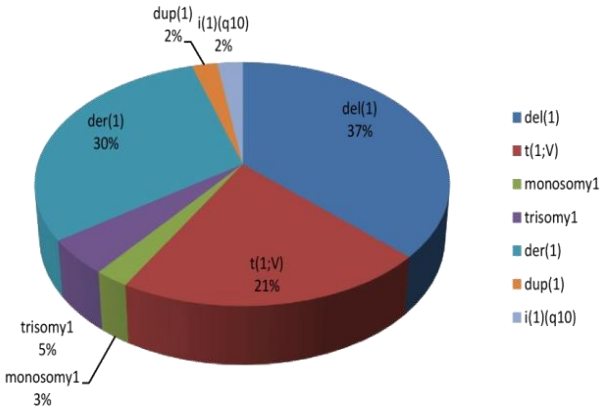
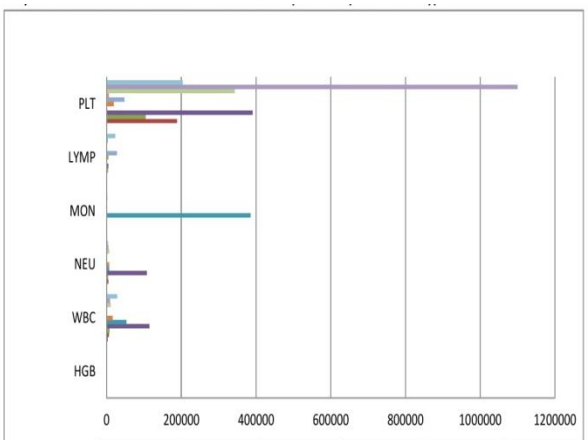


Figure 1. Distribution of chromosome 1 anomalies in 35 patients as a percentage

anomaly was derivation 1 which was seen in 13 (30%) of the patients. In our study group, we also detected translocations between chromosome 1 and other chromosomes, trisomy 1 (5%), monosomy 1 (3%), duplication 1 (2%) and isochromosome 1 (2%) were also detected. The age and sex distribution of the structural and numerical chromosome 1 anomalies is given in table 2. Accordingly, it can be said that all of the anomalies determined, the incidence in men was nearly two times higher than the incidence in women. The age interval of the patients with del(1), i(1)(q10) and t(1;V) was 48-55.The mean values of blood tests of the patients according to the disease groups is given in figure 2. Cytogenetic analysis is very important for hematologic patients. Besides being useful in diagnosis, it is also functional in determining subgroups of AML and MDS and in risk evaluation (Shumilovet al.,2018). In this retrospective study, chromosome 1 anomalies were determined most frequently in MM, MDS and AML patients. Karyotypes of the patients are listed in table 3. Overall, only in 3 (7%) patients numerical chromosome 1 anomalies were determined. Those patients with numeric anomalies also possessed some structural anomalies. The other 32 (93%) patients had only structural anomalies. When karyotypes of the patients are evaluated, among 35 patients with chromosome 1 anomalies, 25 (71.4%) patients had complex karyotypes and 10 patients (28.6 %) had non-complex karyotypes. Chromosome 1 anomalies are common in MM patients (Li et al., 2016), which was also observed in our study in 9 male and 2 female patients. All of those patients had complex karyotypes. In all but 3 MM patients with chromosome 1 anomalies, sex chromosome loss or excess was detected.

Table 2: Mean age and gender distributions of patients with structural and numerical chromosome 1 anomalies

Anomaly	Age	Gender, Male: Female
del(1)	48,2	11:5
t(1;V)	52,12	7:2
der(1)	55,4	8.5
dup(1)	23	1:0
i(1)(q10)	83	1:0
monosomy(1)	79	0:1
trisomy(1)		0:1



	HGB	WBC	NEU	MON	LYMP	PLT
PV	9,4	28500	3800	1000	23200	204000
ET	10	9100	4500	300	3400	1100000
Waldenstrom	10,7	10800	7200	2500	900	343000
Aplastik Anemia	9,9	1900	800		1100	6000
ALL	11,75	30,65	1350	1150	28050	47500
BL	14,2	16200	6900		4900	19000
BHL	9,3	52950	6900	385000	850	103,5
KML	9,65	114650	107950	1950	4400	390500
MDS	7,91	7833,3	3757,14	1428,57	3685,71	104857,14
MM	8,51	6388,8	4326,6	762,5	1162,5	188144
AML	8,62	3075	250	100	1033,3	112,25

Figure 2. Distribution of blood values in patient population by disease subtype

Among MM patients, del(1) was the most common chromosome 1 anomalies detected in 9 patients. In 7 of those patients, deletion was on p arm of chromosome 1 and in 2 patients the deletion was on q arm. del(1p) is one of the characteristic chromosomal anomalies seen in MM patients (Szalatet al., 2015; Oi et.al., 2016; Josephet al., 2017). For example, Jung et al. (2018) detected 52 cases of del(1p) among 120 patients diagnosed with MM having cytogenetic anomalies. In our patient group, del(1p) was detected on p21, p13p36 and p31 regions, as it is stated in the literature (Manier et al., 2017). In 3 MM patients with del(1p) other chromosomal anomalies such as derivative 1 and monosomy 1 were also detected. In MM patients, del(1p) is associated with bad prognosis such as quick progress of disease and short survival time (Ouyanget et al., 2014; Hebraud et al., 2014). In our patient group, among 7 MM patients with del(1p) only 1 is still alive and the others passed away. The average survival time for those patients was 7 months after the diagnosis. Short survival time of MM patients with del(1p) in our group was compatible with the literature (Carballo-Zarate et al., 2017). In our study, second most common disease with chromosome 1 anomalies was MDS that affected 7 patients, 3 women and 4 men. In 5 patients with MDS and chromosome 1 anomalies the karyotypes were complex. The most commonly found chromosome 1 anomaly in 4 MDS patients was derivative 1. In all karyotypes with der(1), monosomy 5, monosomy 7 and trisomy 8 anomalies were also detected. In one of those patients del (1p) and the other patients very rare dic (1;15)(p11;p11) and dup(1)(q31q44) anomalies were found (Table 3). All AML patients with chromosome 1 anomalies were men and among those 5 patients 3 had complex karyotypes and other 2 patients had non-complex karyotypes. In 2 AML patients del(1q), in one patient der(1), in 2 patients very rare t(1;11) and t(1;19) were determined. Again in 3 of those 5 patients, a monosomy 7 was found. One of the patients with derive 1 and the patient with del (1)(q32q43) are still alive.

Two of lymphoma patients with chromosome 1 anomalies had B-cell lymphoma, in those del(1)(p34p36) and der(21)t(1;21)(q21;q11.2) were determined respectively. The other patient with lymphoma was Burkitt's lymphoma and in this patient for the first time der(15)t(1;15)(q21;q11.2) and der(21)t(1;21)(q21;q11.2) translocations were determined. In the only patient in our study group diagnosed with Waldenstöm Macroglobunemia der(1) was determined. In the literature we can see that chromosome 1 anomalies are not present in Waldenstöm Macroglobunemia, instead 6q, 13q deletions and trisomy 18 chromosomal anomalies are seen (Kapoor et al., 2015; Hunter et al., 2017).

The last disease state and survivals of the patients with chromosome 1 anomalies is given on figure 3.

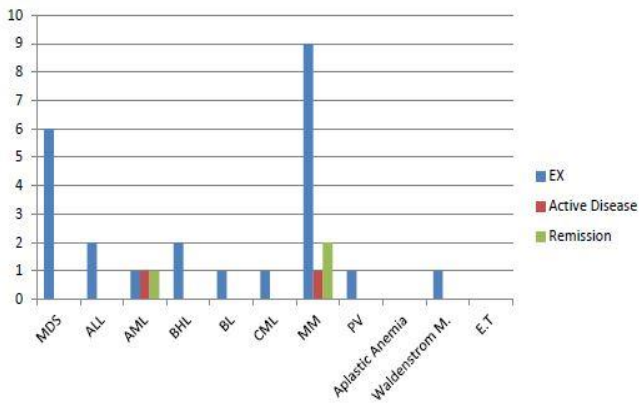


Figure 3. Last state disease by subtypes

Table 3: The karyotypes of the patients

Patient Number	Diagnosis	Karyotypes
1	MM	38-39,XY,+X,-Y,del(1)(p?),-4,-5,-5,-9,-13,-14,-16,-17,-18,-21,-22,+mar1,+mar2,+mar3[20]/70-76,XY[7]/46,XY[3]
2	MM	45,XY,i(1)(q10),-2,-13,-14,del(16)(q24),+mar1,+mar2 [15]/45,XY,i(1)(q10),-2,-13,-14,-14,del(16)(q24),+mar2,+mar3 [10]/84-98<4n>XY,q(1)q(10),-2,-13,-13,-14,-
3	MM	53,X,-Y,+del(1)(p35p21)x2,+der(2),+7,+der(14)x2,+15,-16,+18,+20,+21 [47]/46,XY [18]
4	MM	49-55,XX,+X,del(1)(p31),-1,-4,+5,-6,+7,+8,-11,+12,-12,-13,-14,+17,-17,+18,+19,+20,+21,+22,+ma1,+mar2,+mar3,+mar4,+mar5,+mar6,+mar7,+mar8 [52]/46,XX [38]
5	MM	50,X,-X,+del(1)(p35p21),+5,+5,-11,-16,+19,+mar1,+mar2,+mar3 [8]/46,XX[52]
6	MM	90,XY,+X,der(1)x2,del(1)(p13p16)x4,+2,+3,+3,+5,+6,+7,+8,+8,+8,+9,+10,+10,+10,+11,+12,+13,+13,+14,+15,+16,+16,+16,+16,+17,+18,+19,+19,+20,+20,+20,+21,+mar1,+mar2,+mar3,+mar4,+mar5,+mar6,+mar7[2],46,XY[18]
7	MM	46,XY,del(1)(q31q36),-12,-13,-17,+19,+mar1,+mar2 [9]/46,XY[11]
8	MM	44,X,-Y,del(1)(q32q43),-11,-14,-17,+mar1,+mar2[2]/46,XY[18]
9	MM	44,X,-Y,del(1)(p13p35),+der(1),t(3;16)(q21;q22),-4,-13,-14,+mar1[8]/46,XY[42]
10	MM	46,XY,dic(1;21)(p11p11),del(3)(q25q29),del(6)(q24q26),t(11;14)(q13;q32),del(13)(q14q21)[20]
11	MM	44,XY,der(1),+del(1)(p13p36),t(9;9)(p22;p24),-13,der(14),-15,-16,-22,+mar1[17]/46,XY[3]
12	CML	46,XY,t(1;2)(p36;p21)[20]
13	MDS	45,XX,der(1),-4,-7,-12,+mar1,+mar2,+mar3[19]/46,XX[1]
14	MDS	45,XY,+del(1)(p35;p21),-7,-16[47],46,XY [3]
15	MDS	46,XY,dic(1;15)(p11;p11)[1]/46,XY,del(13)(q14q22)[21]/46,XY[28]
16	MDS	46,XX,-5,-7,+8,del(12)(pter-p12),+mar1[21],43,XX,der(1),-2,-3,-5,-7,-9,-10,-12,-17,+mar1,+mar2,+mar3,+mar4,+mar5 [9]/46,XX[5]
17	MDS	46,XY,dup(1)(q31q44)[20]
18	MDS	44,XX,der(1),-5,-7,-9,der(17),+mar1[16]/46,XY[4]
19	MDS	48,XY,+der(1),+8,del(20)(q10)[20]
20	AML	46,X,-Y,del(1)(q32q43),del(2)(q33q37),-7,-8,-10,+17,+mar1,+mar2,+mar3,[13]/46,XY[7]
21	AML	46,XY,del(1)(q31)[8]/46,XY [12]
22	AML	45,XY,der(1),der(3),-7[16]/46,XY[4]
23	AML	46,XY,t(1;11)(p31;q23),-4,-7,-9,-12,-13,-14,-17,-20,-21,-22,+mar1,+mar2,+mar3,+mar4,+mar5,+mar6,+mar7,+mar8,+mar9,+mar10[20]
24	AML	46,XY,der(1),der(9)t(1;9)(q21;q34)[12]/47,sl,+6[8]
25	CML	46,XX,del(1)(q31q42),-7,t(9;22)(q34;q11.2),-16,+mar1,+mar2[20]
26	CML	47,XY,t(X;1)(q27-q28;p31-p32),+del(1)(p31-pter)[21]/46,+1,-6[25]
27	ALL	46,XY,der(1)[12]/47,XY,+22,der(1)[8]/46,XY[20]
28	ALL	46,XX,t(1;12)(p35;q24.1),t(9;22)(q34;q11.2)[27]/46,XX[13]
29	B-cell Lymphoma	46,XY,del(1)(p34p36)[4]/46,XY,del(1)(p34p36),-14,+mar3[6]/46,XY,del(1)(p34p36),-14,+mar4[6],46,XY,del(1)(p34p36)-6,-20,+mar1,+mar2 [43]
30	B-cell Lymphoma	47,XX,+X,der(1),der(3),-4,-7,-8,del(9)(p21),der(12),der(18),del(22)(q11.2),+mar1,+mar2,+mar3[22]/46,XX[48]
31	Waldenstrom	46,XX,der(1)[8]/46,XX[42]
32	Aplastic anemia	46,XX,del(1)(q42q43)[7]/46,XX[13]
33	ET	46,XX,+1,t(1;15)(p10;p10)[24]/46,XX[26]
34	P.V	46,XY,der(1),der(10),+15,-18[4] 47,XY,der(1),der(6)x2,-10,+18,+mar1[7]/46,XY [39]
35	Burkitt Lymphoma	46,XX,der(15),t(1;15)(q21;q11.2),der(21),t(1;21)(q21;q11.2),t(8;14)(q24;q32)[20]

The data about survival of 5 patients were not given because these patients were out of follow up. The other 30 patients, except 2 AML and 3 MM patients, have passed away.

In 9 out of 35 patients of our study group, the translocation of chromosome 1 to other chromosomes was detected. Among those, 5 were the translocation that are not reported in the databases for the associated breaking points (Atlas of Genetics and Cytogenetics in Oncology and Haematology, 2017; Mitelman et al., 2017). One of them was t(X;1)(q27-q28;p31-p32) translocation which was seen our 87 old male patient with CML. In the karyotype of the this patient, we also detected del(1)(p31-pter) and trisomy 1. The other translocation that is reported here for the first time is t(1;12)(p35;q24.1). This translocation was detected in one of the patient who diagnosed as Philadelphia chromosome positive ALL. In the databases searched (Atlas of Genetics and Cytogenetics in Oncology and Haematology, 2017; Mitelman et al., 2017) the translocations between 1p and 12q were reported but breaking points between p35 and q24.1 have not been reported before. Another anomaly that was described for the first time was dic (1;21)(p11;p11). There is no previous report for a translocation between chromosomes 1 and 21 at those breaking points. Therefore, we here describe this translocation in a MM patient for the first time. The patient with dic (1;21)(p11;p11) had also t(11;14)(q13;q32) which is common in MM patients and it is a good prognosis marker (Kumar et al.,2018), also del(13)(q14q21) was found in that patient and this translocation was linked with short survival time. Therefore it is not possible to directly link the effect on dic (1;21)(p11;p11) with the prognosis of the disease. In a female patient 2 new translocations were determined.

Those translocations were der(15)t(1;15)(q21;q11.2) and der(21)t(1;21)(q21;q11.2) and they were found together with t(8;14)(q24;q32) which is characteristic for Burkitt lymphoma.

As a result of having der(15)t(1;15)(q21;q11.2) and der(21)t(1;21)(q21;q11.2) in her karyotype, the patient had tetrasomy on (1q). Siddiki et al.(2018) stated that t(8;14)(q24;q32) seen together with tetrasomy (1q) could be a marker for very bad prognosis. Accordingly in our case, the patient with these anomalies died 8 months after the diagnosis.

The translocations found in some of our patients were very rare translocations. One of those was t(1;2)(p36;p21) which was determined in a male patient with chronic myelomonocytic leukemia (CMML). So far, there are only 9 hematology patients reported to have this translocation and all of them had some other disease besides CMML (Storlazzi et al., 2008; Mitelman et al., 2017). The patient died 4 years after the diagnosis and there is no definitive information about the effect of those anomalies on the disease prognosis. t(1;15)(p10p10) was detected in a 80 years old patient with essential thrombositopenia (ET).This translocation was reported only in one case so far with breast cancer in a complex karyotype (Adeyinka et al., 1999) and this is the first report of this anomaly in an ET patient. The genes related to this translocation are still unknown. t(1;11)(p22;q23) were determined in one adult patient with AML (Figure 4). MLL gene located on 11q23 codes for a methyl transferase active in epigenetic modification of histon proteins and 11q23 anomalies can be seen in patients with myeloid malignancies (Zhao et al., 2014).

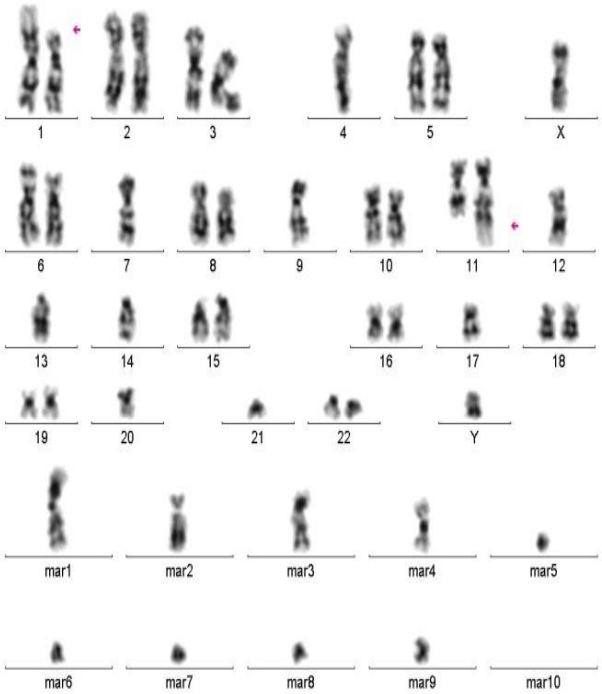


Figure 4. t(1;11)(p22;q23) in one adult patient with AML

Conclusion

Genetic aberrations in the form of chromosomal anomalies are frequent cause of hematologic malignancies. The effect on disease pathogenesis and prognosis of some of those anomalies is known and some needs to be investigated and determined. The results of our research indicate that the determination of effect on disease pathogenesis of newly defined and rare chromosomal anomalies could be helpful on increasing the treatment options of many hematologic malignant diseases.

Conflict of interest

Authors declare that there is no conflict of interest.

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