Chromosome 1 Abnormalities in Multiple Myeloma

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Abstract. *Multiple myeloma (MM) is a malignancy of the terminally-differentiated B cells and accounts for 10% of all hematological malignancies. Chromosome 1 aberrations are frequently described, the short arm being preferentially involved in deletions and the long arm in gains. The abnormalities were identified in the bone marrow of 37 MM patients by conventional cytogenetics. Fluorescence in situ hybridization (FISH) was used to confirm the presence of the abnormalities and to better characterize them. Chromosome 1 abnormalities were grouped into 4 categories: balanced translocations, deletions, amplifications and jumping translocations (JT). Breakpoints involved in balanced translocations were randomly distributed. The smallest region of overlap for deletions was 1p11→1p21 (present in 27% of the patients) and for gains 1q31→1qter (present in 54% of the patients). The whole long arm was found to be the donor segment for the majority of patients with JT, the most frequent recipients being chromosomes 16 and 19. Our results share some similarities with those obtained for 143 published patients studied by FISH. Band 1p21 was found to be frequently deleted, leading to the assumption that a 1p deletion could lead to hemizygosity of at least 1 tumor suppressor gene. Two regions of 1q showed preferential gains: q12 to q22 and q31 to q42; these amplifications could induce the overexpression of 1 or more oncogenes. In conclusion, our results confirm that chromosome 1 abnormalities play an important role in the pathogenesis of multiple myeloma.*

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Abnormalities of chromosome 1, in particular, rearrangements of the long arm, are common in hematopoietic disorders (1). They generally occur at an advanced stage of the disease and have been shown to be correlated with a poor prognosis.

Multiple myeloma (MM) is a malignancy of the terminally-differentiated B cells and accounts for 10% of all hematological malignancies. This disorder is characterized by complex karyotypes with numerous structural and numerical chromosomal aberrations. The most commonly detected abnormalities consist of rearrangements of the *IGH* gene located in band 14q32 and partial or total loss of chromosome 13 (2).

In MM, the most common structural aberrations involve chromosome 1 (3, 4). Taniwaki *et al.* showed that the short arm of chromosome 1 was preferentially involved in deletions, whereas the long arm tended to be amplified (5). More precisely, 1q trisomies were shown to be the most common genomic gain in MM, along with 9q and 11q trisomies (6). Jumping translocations involving 1q as the donor chromosome have also been described (7-9).

The results of 37 patients with MM, in whom banding cytogenetic analysis showed a chromosome 1 abnormality that was studied by fluorescent *in situ* hybridization, are reported.

Materials and Methods

Conventional cytogenetics. The MM patients included in this study were selected because of chromosome 1 abnormalities detected by conventional cytogenetics. Bone marrow of the MM patients was processed for chromosome studies as previously described (9). Briefly, the bone marrow cultures, unstimulated for 24 and 72 h, were synchronized with FudR (10^{-7} M) for 17 h followed by thymidine (10^{-5} M) for 6 h, before Colcemid exposure and standard harvesting. The chromosomes were R-banded and the karyotype described according to the ISCN (1995) (10). Twenty metaphases were studied per patient and culture.

Table I. *Karyotypes of patients with balanced translocations involving chromosome 1.*

Patient No.	Karyotype
1	46,XY,t(1;12)(p32;p12)/46,XY,t(1;18)(q31;p11)/46,XY,t(1;3)(q31;p11)/46,XY
6*	46,X,t(X;7)(q21;q22),t(1;2)(p33;q3?2),del(4),der(8)t(X ;8)(q21;q24),der(10)t(10;19), t(10;22)(q2;q12),der(11)t(2;11)(?;q22),der(14)t(4;14)(q?;q12)/46,X,t(X;7)(q21;q22),t(1;2) (p33;q3?2),der(1)t(1;8)(q4;?),del(4),der(6)t(X;6)(?;q2?6),der(8)t(X;8)(q21;q24),der(10)t(10;19), t(10;22)(q2;q12),der(11)t(11;12)(p15;q11),der(12)t(2;12)(?;q11),del(14q)
18	55,XY,der(1)t(1;4)(p34;p11),+3,t(3;15)(q21;q21),der(4)(1pter->1p33:4cen::4q26->4qter),+5,+6, t(7;19)(p15;q13),der(8),+9,+9,+11,del(12),der(16)t(12;16)(q21;q22),+19,+21
19	46,XY,del(1)(p11),der(10)t(10;15)(q2?5;?),der(12)t(2;12)(?;p13),der(20)t(1;20)(p1;q13)
25	49,XY,t(1;21)(q12;q22),der(3;18)(q10;q10),der(8)t(8;14)(q24;q32),del(14)(q32),der(14)t(11;14) (q13;q32),+15,+18
26	59,X,t(1;8)(p1;q24),+der(2)t(2;11)(q3;?),+3,+5,+6,+7,+9,+11,del(12p),+15,+15,der(16)t(9;16) (q11;q11),+17,+19,+19,+21,+22

*Patient also presented a deletion of chromosome 1.

Fluorescence in situ hybridization (FISH)

a) Whole chromosome 1 painting (wcp1). FISH was performed using whole chromosome painting probes specific to chromosome 1 (wcp1, labeled with spectrum red, Qbiogene, Illkirch, France), as previously described (11). The slides were counterstained with 4', 6-diamidino-2-phenyl-indole (DAPI). The purpose was to confirm the presence of chromosome 1 abnormalities and to identify them more precisely.

The slides were analyzed using a Zeiss Axioplan Microscope (Zeiss, Le Pecq, France). Subsequent image acquisition was performed using a CCD camera with Isis (Significant *In Situ* Imaging System) (MetaSystems, Altlussheim, Germany).

b) Twenty-four color FISH. Complex karyotypes were studied by 24 color FISH. The MetaSystems'24XCyte kit probe (MetaSystems, Altlussheim, Germany) contains 24 different chromosome painting probes specific to the 24 different human chromosomes. Each paint is labeled with 4 fluorochromes (FITC, SpecOra, TexasRed, DEAC) and biotin, respectively, or a unique combination of them. Detection of the biotin-labeled fraction is performed with streptavidin-Cy5 (B-tect). Slide denaturation, hybridization and post-hybridization washes were performed as previously described (9).

The slides were analyzed using a Zeiss AxioPlan Microscope (Zeiss, Le Pecq, France). Image capturing and processing was carried out with an Isis/mFISH imaging system (MetaSystems); a pseudocolor display of each of the 24 different chromosomes was obtained.

Results

Between January 2000 and December 2003, the cytogenetic laboratory received bone marrow samples of 55 MM patients, for whom the banding analysis showed chromosomal abnormalities. Thirty-seven patients were selected because chromosome 1 abnormalities were detected by conventional cytogenetics. There were 20 males and 17 females. The mean age at diagnosis was 59 years (range: 35-78 years) for men and 66 years (range: 59-71 years) for women. Nineteen MM (57%) were IgG and 8 (24%) were IgA. The light chain subtypes were equally represented: 15 κ and 16 λ.

Based on the banding and FISH analyses of the chromosome 1 abnormalities, the patients could be distributed into 4 groups, some being included in more than 1 group. The first group included 6 patients with balanced translocations involving chromosome 1 (Table I). Rearrangements were randomly distributed, although the pericentromeric region on the partner chromosomes was a privileged target.

Deletions of chromosome 1 were identified in 12 of the 37 patients (32.4%) (Table II). Ten patients had a deletion of the short arm, the smallest region of overlap (SRO) being included between bands 1p11 and 1p21 in 9 patients. Two patients had a deletion of the long arm and 1 deletions of both 1p and 1q (Figure 1).

Chromosome 1 amplification was identified in 59.5% of the patients (22/37 patients) (Table III) and consisted of unbalanced translocations, trisomy 1, duplication of part of chromosome 1 or jumping translocations (JT). JTs are an unusual form of amplification by which the same chromosomal segment is translocated onto various partner chromosomes. One patient showed a partial trisomy 1p31->1pter, whereas another patient had a partial trisomy of the short and long arms. Twenty-one patients had amplification of 1q, the SRO being 1q31→1qter present in 20 patients (Figure 2).

Table II. *Karyotypes of patients with deletions of chromosome 1.*

Patient No.	Karyotype
2	42,X,del(1)(p1?;p2?),der(3)t(X;3)(q24;p24),der(4)t(4;14)(p16;q32),der(5)t(5;17)(q34;q22),del(11p), der(11)t(11;12)(q13;q13),-13,der(14)t(14;17)(q23;q11), del(14)(q32),-17,-18
10	49,XX,der(1)t(1;12)(p1?;?),der(6)(1pter->1p31::6p11->6q1?::2?),der(2) (2::8:2p->2q?::5?), der(4;18)(q10;q10),+der(4;18)(q10;q10), der(5)t(4;5)(?;p15),+9,-13,der(14)t(4;14)(?;q2?3), der(17)t(13;17)(?;p13),-18,+19,+20
13*	42,X,i(1)(q10),t(4;18)(q2?3;p11),der(5)t(X;5)(?q25;p15),dup(12q),-13,-14,r(16),-22
14	46,XY,der(1)t(1;9)(p11;q12),t(3;14)(q22;q32),+7,del(10)(q25),-13,der(16)t(9;16)(p10;q10), del(17)(p11)
15*	48,XY,del(1)(q23),+der(1)(1pter->1q24::4?::14q32),t(1;16)(p31;q21),der(4)t(4;14)(p16;q32), der(5)t(5;12)(q31;q12),der(7)t(7;7)(p21;q22),+der(9)t(7;9)(q22;p21),-13,i(14)(q32->cen->q32), -14,+19/48,XY,del(1)(q23),+der(1)(1pter>1q24::4?::14q32),der(2)t(2;13)(p25;q11), der(4)t(4;14) (p16;q32),der(7)t(7;7)(p21;q22),+del(9)(p21),-13,-13, del(14)(q32), del(14)(q32),+19
16	46,XX,del(1)(p11;p31),der(1)t(1;9)(q44;q12),der(6)t(6;8)(q16;q21),-8,-13,der(13)t(8;13) (q11;p11),del(14)(q32),der(14)t(4;14)(q2?8;q2),+der(14)t(X;14)(?;q2), der(16)t(14;16)(q32;qter),-21,der(21)t(7;21)(q11;p11)
23*	46,XY,-1,der(6)t(1;6)(?q31;q23),del(7)(q?11q?21),der(8)t(1;8)(p21;p12), der(16)t(1;16)(q31;q11), der(17)t(1;17)(q31;p1?2),+der(19)t(3;19)(q12;p11)
27*	42,XX,i(1)(q10),-4,-13,-14,der(14)t(4;14)(q21;q32),-22
30*	52,XY,del(1)(p11p21),der(2)t(X;2)(q2?1;q25),+der(3)t(2;3)(q2?5;q28),der(4)t(4;14)(p16;q32), del(5)(q13q22),+der(5)t(5;8)(q13;q22),der(6)t(6;13)(p25;q3?3),+der(7)t(7;16)(p13;p11), der(8)t(4;8) (q28;q21),del(9)(q21q33),+del(9)(q21q33),+11,del(12p),-13,del(14)(q2?4),-13,+15, der(16)t(1;16) (q11;q11),+der(19)t(8;19)(q23;p12)/52,XY,del(1)(p11p21),der(2)t(X;2)(q2?1;q25), der(4)(4pter->4q3::4q2?1->4q3::11q23->11qter),der(4)t(4;14)(p16;q32),del(5)(q13q22), +der(5)t(5;8) (q13;q22),+der(7)t(7;8)(p13;?),del(9)(q21q33),+del(9)(q21q33), der(11)t(1;11)(q11;q2?1), del(12p),del(14)(q2?4),+15,+19/52,XY,del(1)(p11p21),der(2)t(2;4)(q24;q32), der(2)t(X;2)(q2?1; q25),+der(3)t(3;7)(p11;?),der(4)t(4;14)(p16;q32),del(5)(q13q22),+der(5)t(5;8)(q13;q22), der(7) t(7;8)(p13;?),del(9)(q21;q33),+del(9)(q21q33),+der(11)t(1;11)(q11;q2?1),del(12p),del(14)(q2?4),+15,+19
32*	44,XX,der(1)t(1;19)(p21;?),der(4)t(4;11)(q26;q23),-8,der(11)t(11;22),-13,-14,+der(19) (19::4::14::4),der(20)t(1;20)
34*	46,Xder(Y)t(Y;16)(q12;q11),dup(1q),der(1)t(1;2)(p11;q11),-2, der(5)t(5;8)(p1?5;q?22), +der(5)t(5;7)(q3?5;p1?3),t(6;15)(q21;q1?2),del(7)(p12),der(8)t(8;18)(q12;q21), +9,der(12)t(8;12) (q22;q24),-13,der(14)t(1;14)(p31;p11),+der(15)t(15;16)(p11;q11), -16,dic(16;21)(q24;p11), dic(16;17)(q11;q25),del(18)(q21),+19,-21

*Patients also presented chromosome 1 amplification.

JTs were observed in the following 6 (16.2%) patients: #7, 8, 20, 23, 30 and 35. JTs were identified by conventional cytogenetics for 4 patients (#7, 8, 30, 35), while 24 color FISH was necessary to reveal them in the remaining 2 patients. JTs were observed in different clones for patient #30, but in the same clone for the others. The 1q11->1qter region was the donor segment in 4 patients, the smallest region of overlap being 1q31→1qter. Fourteen recipient chromosomes were found, with telomeric breakpoints in 6 translocations and pericentromeric breakpoints in 7.

Discussion

A search on the web site of the Cancer Genome Anatomy Project (http://cgap.nci.nih.gov/Chromosomes/Mitelman) found 553 MM with chromosome 1 abnormalities (12). However, the aberrations involving chromosome 1 were not fully identified for the majority of the reported patients. Therefore, 143 MM patients, most of them studied by FISH techniques, were selected.

Balanced translocations were rare events, as observed in our cases. Chromosome 1 breakpoints were randomly

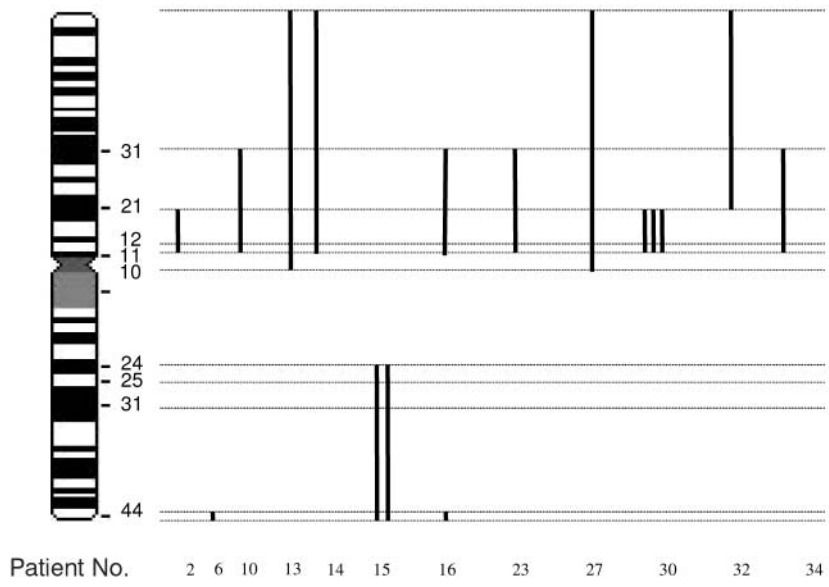

Figure 1. *Diagram of chromosome 1 showing the distribution of deletions.*

distributed, whereas the breaks occurred preferentially in the pericentromeric region of the chromosome partners.

Deletions of the short arm of chromosome 1 were reported in 32.2% of the patients taken from the literature. The smallest region of overlap found in the majority of the patients covered the region 1p21→1p22, which compared with the SRO found in our series (1p11→1p21). Band 1p21 is a hot-spot of genomic variation, described as large-scale copy-number variations (LCV), which exists in the genome of phenotypically and karyotypically normal individuals (13). These LCV could lead to chromosomal rearrangements that give rise to disease or more subtle phenotypic variations by influencing the expression of specific genes (13, 14). The deletion of 1p is a common feature in MM (15). It is hypothesized that the loss of chromosomal material leads to hemizygosity of at least 1 tumor suppressor gene (5, 6).

Polysomy 1q is the most frequent aberration of chromosome 1 observed in multiple myeloma, reported in 74.8% of the patients analyzed from the literature. Two SRO were identified, 1 including bands q12 to q22 and the second extending from band q31 to band q42. Although the SRO in our series covers the region 1q31→1qter, 17 patients were also polysomic for 1q12->1q22. This shows the high heterogeneity of candidate loci, as reported by Sawyer *et al.* (3). Le Baccon *et al.* showed that band 1q21 was the most frequently broken in multiple myeloma and non-Hodgkin lymphoma (16). The amplification of part or whole of chromosome 1q could induce an overexpression of 1 or several oncogenes. Indeed, recently, Corson *et al.* identified a candidate oncogene, *KIF14*, at 1q31.3-1q32.1 (17). This putative chromokinesin was overexpressed in different types of solid tumors, such as retinoblastoma, breast and lung cancers and medulloblastoma. Moreover, patients with lung cancer over-expressing *KIF14* had a decreased survival.

JTs are rare events in MM and have been identified in only 24 patients, including ours (7, 9, 16, 18, 19). Chromosomal arm 1q was the donor in each case. In 20 cases, the breakpoint on chromosome 1 was pericentromeric (located in 1q10-q11) and was situated in band 1q21 in 3 patients and in band 1q31 in 1 patient. All chromosomes were recipients, but chromosomes 14, 21 and Y, their distribution being non-random, together with chromosomes 16 and 19, were involved in 46% and 25% of the cases, respectively. Moreover, 46% of the breakpoints on the recipient chromosomes were pericentromeric and 40% telomeric (9). Sawyer *et al.* proposed that pericentromeric heterochromatic decondensation of chromosome 1q plays a role in the formation of JT. The highly decondensed heterochromatin permits the fusion of this chromosomal segment to other pericentromeric and telomeric heterochromatic regions (18).

Chromosome 1 abnormalities are globally associated with a poor prognosis (20). Although duplication of 1q is considered to be a minor cytogenetic cluster among MM cases (21), its high frequency suggests an important role in pathogenesis. The deletion of 1p is correlated with a bad prognosis and is considered to be one of the most important factors in predicting patient survival (22). Therefore, the results presented here reported 24 color FISH as an effective tool for the identification of abnormalities involving chromosome 1, their heterogeneity possibly revealing the existence of different subgroups of MM patients.

Table III. *Karyotypes of patients with amplification of chromosome 1.*

Patient No.	Karyotype
3	55,X,+der(2)t(2;5)(q1;?),+3,+5,+6,+7,+9,+15,+15,+17,der(18)t(1;18)(q11;p11),+19,der(21)t(2;21)(?;q22)
4	44,X,dup(1)(q12q4),der(7)t(7;7)(p1;q11),del(13q),-14,der(16)t(1;16)(q12;p13)
5	74,XXYY,+2,+3,+der(4)t(1;4)(?;q11),+der(4)t(1;4)(?;q11),+5,+6,+6,+7,+7,+8,+9,+9,+10,+der(11)t(7;11)(q22;pter), +der(11)t(7;11)(q22;pter),+der(12)t(3;12)(?;qter),der(14)t(?9;14)(?;q32),+der(16)t(1;16)(p31;?),+der(17) (16::15::17p11->17pter), +18,+18, +19,+19,+20,+20,+21,+22
7	49,XX,der(1;12)(q10;q10),+der(1;3)(q10;q10),+5,+7,-8,der(13)t(8;13)(q12;p11),-13,+15, der(16) t(9;16)(q11;q11),+der(19)t(1;19)(?q31;?q11),+21,-22
8	45,XY,der(8)t(1;8)(q11;p23),der(10)t(1;10)(q11;q2),-13,add(22q)
9	52,XYY,+der(1)t(1;19)(p10;q10),+der(1)t(1;19)(p10;q10),+9,+15,+18
11	51,X,+5,der(6)t(X;6)(q11;q22),+7,+11,+14,+15,der(16)t(1;16)(q11;q11),+19
12	48,X,der(Y)t(Y;1)(qter;?),+3,del(8)(q24),+11,+der(19)t(X;19)(?;qter)
17	48,X,t(1;12)(p21;q11),+5,-8,+9,der(11)(1qter->1q2?3::16::11p15->11qter),-13,+del(14)(q?), der(15)t(15;16)(p11;?),der(17)t(16;17)(?;q26),der(18)t(X;18)(p10;q10),+?r(19),+?r(19)
20	50,Xder(X)t(1;X)(q11;q11),del(1)(q2?),del(3)(q24),+der(3)t(3;4)(q28;q3),+del(5)(q32), del(6q), +der(7)t(7;15),+der(9)t(1;9)(q11;q11),der(11)t(2;11)(p15;p15),13,+19/51,Xder(X)t(1;X)(q11;q11), der(1)t(1;2)(q2?4;?),der(1)t(1;11)(q11;?),del(3)(q24),+der(3)t(3;4)(q28;q3),+del(5)(q32), del(6q), +der(7)t(7;15),+der(9)t(1;9)(q11;q11),der(11)t(2;11)(p15;p15),-13,+15,+19,der(21)t(5;21)(q?;p11)
21	47,XYY,inv(5)(p11q12),der(6)t(1;6)(p31;q1?4),+der(6)t(1;6)(p31;q1?4), del(8p),+der(8)(8p?->8q11::15::14),+9,der(10)t(10;20)(p11;p11),+der(11)t(X;11)(?;p11),-13, der(13)t(8;13)(q21;q35), der(14)t(14;15)(q24;q24), der(15)t(13;15)(q14;q26),-15,der(16)t(16;20)(q22;q11), der(19)t(10;19), -20.-20, der(22)t(20;22)(q?;q12)
22	53,X,+der(1)t(1;17)(p11;q11),+3,+5,+der(5)t(5;19)(p11;p11),del(7)(p11),dup(7), +del(7),der(8) t(7;8)(?;p?),+9,+10,-13,+15,del(16),del(17),+18
24	Trisomy 1q11->1qter
29	84-90,XX,der(Y)t(Y;9)(?;q11)x2,i(1)(q10)x2,+der(1)t(1;6)(q11;?),+del(1)(q11), der(2)t(2;9) (q37;q13)x2,del(4)(q2)x2,der(6)t(X;6)(q22;q22)x2,der(7)t(4;7)(q31;p21)x2, dup(8)(q22q24)x2, der(12)t(12;16)(p11;q11)x2,der(13)t(13;14)(q31;q11)x2,+r(13),-14,-14,-15,i(15)(q10), -16,-16, +der(17)t(6;17)(?;q24) avec variations
31	57,X,+der(2)t(1;2)(q11;p2?4),+3,+5,+der(6)t(6;15)(q21;q11),+7,i(8q), +i(8q),+9,+9,+11,+14, +der(15)t(15;17)(p13;?),+18
33	49,XY,t(1;20)(p3;q11),t(2;9)(q1;p21),t(3;10)(q1;q23),+7,der(8)t(8;17)(p11;q11),+9,+9, der(11) t(X;11)(q21;p15),-13,+15,+der(17)t(8;17)(q21;p13),der(19)t(1;19)(q11;cen),der(21)t(4;21)(?;p11), -22
35	48,X,dup(1)(q21q31),der(2)t(2;4)(q3 ?2 ;?),+der(3)t(3;9)(p11;q34), der(4)t(1;4)(q11;p16),-4, +del(5)(q14;q34),der(7)t(7;11)(q33;q11),der(9)t(3;9)(p14;q13), +der(9)t(9;13)(q31;q22), der(9)(9pter->9q11::16::1q11->1qter),+der(11)t(6;11), -13,der(15)t(15;18)(q10;q10),+der(15) t(15;18)(q10;q10),-16,der(17)t(1;17)(q?;q2?4),-18,+der(19)t(9;19)
36	Trisomy 1q25->1qter
37	83,XXY,+1,+2,+2,+3+3,+4,+4,+5,+5,+6,+6,+7,+7,+8,+8,+del(8)(?q11),+9,+9,+10, +11,+11,+11,+12,+13,t(14;20)(q32;q12),t(14;20)(q32;q12),+14,+15,+15,der(16)t(1;16)(q11;q11), +der(16)t(1;16)(q11;q11),+17,+18,+18,+19,+20,+21,+21,+22

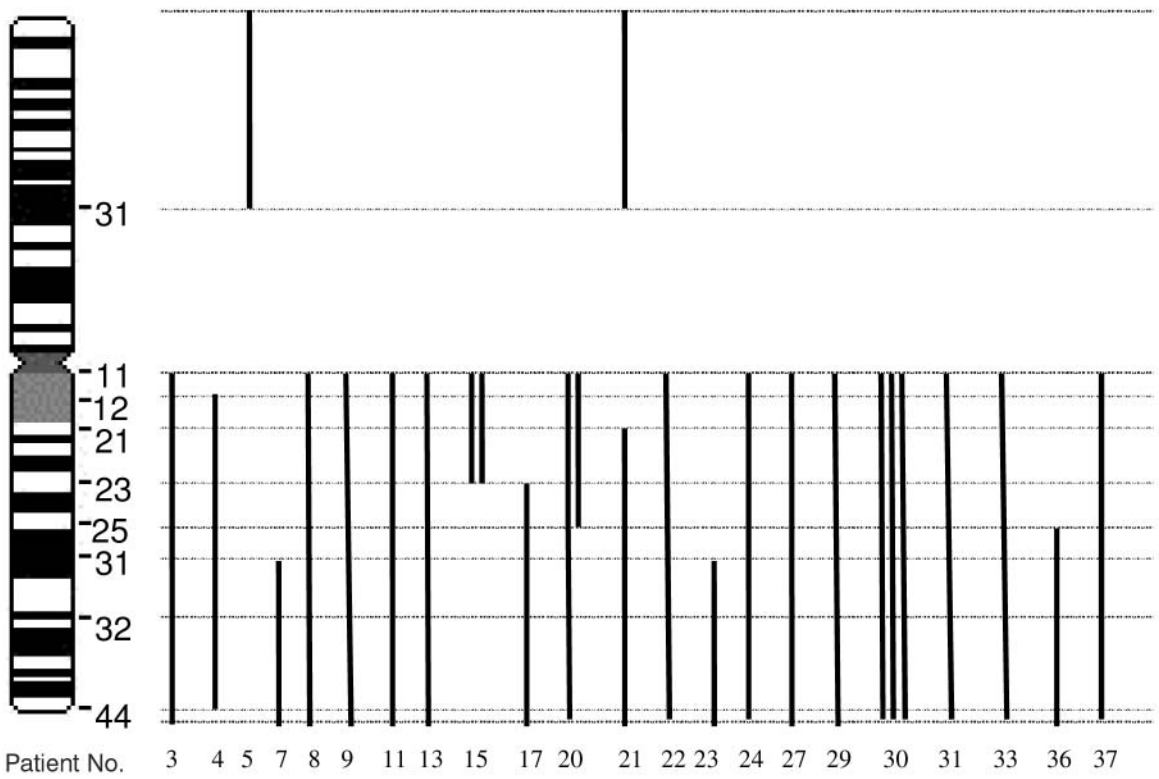

Figure 2. *Diagram of chromosome 1 showing the distribution of amplifications.*

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