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Unbalanced whole-arm translocation der(5;19)(p10;q10) is a novel and recurrent cytogenetic aberration in myelodysplastic syndrome

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Abstract

We describe here two cases of myelodysplastic syndrome (MDS) with a novel unbalanced translocation der(5;19)(p10;q10). Both patients had complex karyotypes including der(5;19) accompanied by an extra chromosome 19, resulting in deletion of the whole long arm of chromosome 5. Furthermore, these patients presented several common clinical and hematological characteristics: MDS subtypes as refractory anemia with excess of blasts (RAEB)-1 or RAEB-2, marked anemia and thrombocytopenia without neutropenia, leukoerythroblastosis, trilineage dysplasia with prominent dyserythropoiesis, CD7 expression in blasts, and association with abnormalities of chromosomes 6, 17 and 18. These findings indicate that der(5;19)(p10;q10) may play a crucial role in the pathogenesis of high-risk MDS as a rare but recurrent translocation.

Keywords: unbalanced whole-arm translocation; myelodysplastic syndrome; refractory anemia with excess of blasts; der(5;19)(p10;q10); deletion of the long arm of chromosome 5; CD7 expression.

1. Introduction

Myelodysplastic syndrome (MDS) is a clonal hematopoietic stem cell disorder characterized by ineffective hematopoiesis that leads to bone marrow failure and/or leukemic transformation. At diagnosis, clonal cytogenetic aberrations are present in 40-70% of patients with *de novo* MDS and in 65-95% of patients with therapy-related MDS (t-MDS) [1,2]. Cytogenetic findings are among the few independent variables correlated with clinical outcome in MDS, and they form the cornerstone of the International Prognostic Scoring System (IPSS) [1]. The recurring abnormalities found in MDS are usually unbalanced: total or partial chromosome losses, unbalanced translocations and chromosome gains, including del(5q)/-5, del(7q)/-7, +8, -Y, del(20q) and complex karyotypes, are commonly found [1,2].

Several unbalanced whole-arm translocations have been reported as a recurrent and primary anomaly in hematological malignancies [3,4]. For instance, the der(1;7)(q10;p10) has been clinically and molecularly characterized. It defines a discrete entity among myeloid neoplasms including MDS [5]. However, clinical significance of other unbalanced whole-arm translocations in MDS remains to be completely elucidated. We describe here MDS with a novel unbalanced whole-arm translocation der(5;19)(p10;q10).

2. Materials and methods

2.1. Cytogenetic analyses

Between January 2005 and December 2007, a total of 71 MDS patients were cytogenetically analyzed in the Hematological Division of the Kobe University Hospital. Chromosome analyses were performed by the G-banding technique on unstimulated short-term culture of the cells obtained from bone marrow. At least 10 metaphase spreads were successfully examined in all cases. According to the ISCN criteria, a clonal abnormality was defined by at least two cells with the same aberration. If the abnormality was a missing chromosome, the same change must have been present in at least three cells. Karyotypes were described in accordance with ISCN 2005. Spectral karyotyping (SKY) was carried out with SkyPaint kit (Applied Spectral Imaging, Migdal Ha'Emek, Israel) on five metaphase

spreads of cases 1 and 2. We also used CSF1R/D5S23, D5S721 Dual Color Probe (Abbott Molecular-Vysis, Des Plaines, IL, USA) for fluorescence *in situ* hybridization (FISH) on 20 metaphase spreads of cases 1 and 2. The nomenclature according to ISCN 2005 was used only for G-banding and SKY analyses.

2.2. Immunophenotypic analyses

Immunophenotypes of the bone marrow cells were analyzed by three-color flow cytometry with CD45/side scatter (SSC) gating. Expression of each antigen on the gated CD45 low/SSC low mononuclear cells was examined by monoclonal antibodies and defined as positive when at least 20% of cells showed fluorescence above the background staining.

3. Results

3.1. Case reports

3.1.1. Case 1

A 64-year-old man was referred to our department because of thrombocytopenia in December 2006. Six years prior, he had been diagnosed with transitional cell carcinoma of the bladder. He received two courses of systemic chemotherapy with methotrexate, vinblastine, doxorubicin, and cisplatin. Three months previously, he was diagnosed with squamous cell carcinoma of the lung. He was treated with two cycles of chemotherapy with cisplatin and gemcitabine, but the platelet count did not recover after the second course.

Peripheral blood showed hemoglobin 64 g/L, platelets 18 x 10^9/L and white blood cells (WBC) 3.9 x 10^9/L with 1% blasts, 51% segmented neutrophils, 9% monocytes, 3% eosinophils, 36% lymphocytes. One erythroblast was found among 100 WBC. Bone marrow was hypercellular with 14.3% myeloblasts, 59.0% myeloid cells and 21.2% erythroblasts. Trilineage dysplasia was observed in the bone marrow cells (Fig. 1A). A diagnosis of t-MDS, refractory anemia with excess of blasts (RAEB)-2, on the World Health Organization classification was made, because he had been exposed to cisplatin, a non-cell cycle specific, bifunctional, alkylating agent. As a result of the concomitant advanced lung cancer, he moved to the hospital closest to his home for best supportive therapies. He died of respiratory failure four months later.

3.1.2. Case 2

A 41-year-old man was admitted to our hospital because of general malaise in January 2005. Peripheral blood showed hemoglobin 49 g/L, platelets 62 x 10^9/L and WBC 4.6 x 10^9/L with 3% blasts, 9% myelocytes, 7% metamyelocytes, 2% band forms, 33% segmented neutrophils, 4% monocytes, 2% eosinophils, 2% basophils, 38% lymphocytes, and 9 erythroblasts. Bone marrow was hypercellular with moderate myelofibrosis: 4.2% myeloblasts, 65.7% myeloid cells and 24.3% erythroblasts. Trilineage dysplasia was observed (Fig. 1B). We diagnosed the disease as MDS, RAEB-1, because blasts in the peripheral blood were more than 1%. Five months later, he underwent myeloablative allogeneic bone marrow transplantation (BMT) from an HLA-matched unrelated male donor. He obtained complete chimerism and maintained hematological and cytogenetic complete remission (CR) after BMT. However, severe pancytopenia progressed again, indicating relapse of MDS after BMT. He died of severe infection on day 157 after BMT.

3.2. Cytogenetic analyses

Two patients were shown to have der(5;19)(p10;q10) (Table 1). Both patients had complex karyotypes including der(5;19) (Fig. 2). Furthermore, the der(5;19) was accompanied by an extra chromosome 19. Accordingly, this unbalanced translocation was described as der(5;19)(p10;q10),+19, which resulted in deletion of the whole 5q (monosomy 5q) and gain of the whole 19q (trisomy 19q). SKY analyses confirmed der(5;19),+19 (Fig. 3). Schematic presentation of der(5;19),+19 is shown in Fig. 4A. To verify the deletions of 5q, we next performed dual-color FISH analyses on metaphase spreads. In both cases, only *D5S23/D5S721* signals at 5p15.2 remained on the der(5;19), whereas *CSF1R* signals at 5q33 were lost in most cells analyzed (Figs. 4B to 4C, Table 1).

As additional aberrations besides der(5;19),+19, patient 1 had an abnormality of chromosome 18, idic(18)(p11.3), and an unbalanced complex translocation involving 17p11 and chromosome 6. In case 2, t(12;17)(q13;p11) and -18 were shown by G-banding, but SKY revealed that the former was a novel three-way translocation t(6;12;17)(p23;q13;p11).

3.3. Immunophenotypic analyses

The results of immunophenotypic analyses are shown in Table 2. Myeloblasts were positive for

CD7 as well as CD13, CD33, CD34 and HLA-DR in both cases. They also expressed CD4 in case 1, and CD41 and KOR-SA in case 2. CD56 was negative in both cases. In case 2, phenotypic conversion was observed at the relapse from the initial diagnosis. That is, the expression of CD7 considerably increased, whereas the expression of CD34 decreased at relapse.

4. Discussion

We have identified an unbalanced whole-arm translocation der(5;19)(p10;q10) in two cases of MDS. In the literature, only one case with adenocarcinoma of the large intestine has been reported to have der(5;19) as one of more than 30 cytogenetic abnormalities [3]. As a result, der(5;19) is shown to be a novel and recurrent cytogenetic aberration in MDS.

The der(5;19) was accompanied with an extra chromosome 19 in both cases. Duplication of a normal copy of one of the two chromosomes participating in the translocation occurs in more than half of the cases with unbalanced translocations, as +1,der(1;7)(q10;p10) [6]. In our cases, by an acquisition of a normal chromosome 19 but not a chromosome 5, the der(5;19) resulted in monosomy 5q and trisomy 19q. Together with monosomy 5q, del(5q)/-5 is the most frequent chromosome aberration in MDS [1,2], and is considered to be an initiating event responsible for clonal proliferation in MDS with many secondary cytogenetic abnormalities. Therefore, the der(5;19),+19 is proposed to play a crucial role in the pathogenesis of MDS by the total deletion of 5q, although we could not find this translocation as a sole abnormality.

Both patients presented several common clinical and hematological findings. That is, MDS subtypes were advanced stage, RAEB-1 or RAEB-2. IPSS subgroups were high-risk: High in case 1and Int-2 in case 2. Peripheral blood showed leukoerythroblastosis, and marked anemia and thrombocytopenia without neutropenia. Bone marrow demonstrated trilineage dysplasia with prominent dyserythropoiesis including megaloblastic changes and multinucleation. Besides der(5;19),+19, additional cytogenetic aberrations involving chromosomes 6, 17 and 18 were found. Abnormalities of 17p and partial or total monosomy 18 frequently occur as a part of complex changes, whereas the association with 6p rearrangements is remarkable since this abnormality rarely occurs in MDS [2]. These findings suggest that the der(5;19),+19 might constitute a distinct clinical entity in high-risk MDS.

With regard to surface marker analyses, myeloblasts were positive for CD13, CD33, CD34, and HLA-DR, indicating an immunophenotype of committed myeloid precursors. In addition, CD7, a marker for immaturity of myeloid cells, was also positive in both cases. Ogata et al. [7] reported that CD7-positive cases were more frequent in high-risk MDS than low-risk MDS, and that CD7 positivity of blasts was an independent variable for a poor prognosis in MDS. These results appear to be compatible with the poor prognoses of our two cases with complex karyotypes, although it is not clear whether der(5;19) itself could have an unfavorable impact on prognoses. In fact, the positive rate of CD7 in case 2 significantly increased at relapse after BMT.

The most functionally important consequence of unbalanced whole-arm translocations is the genomic imbalance. A recent study indicated that involvement of chromosome arms in the whole-arm translocations was non-random: a loss of 17p was most common, and losses of 7q, 13p, 14p, and 15p, and a gain of 1q were observed in more than 10% of cases in 131 hematological malignancies [4]. In contrast, loss of 5q was found in two cases, and there was no case with gain of 19q. According to the Mitelman database [3], only a total of 8 cases of MDS with unbalanced whole-arm translocations involving 5p10, which could result in loss of 5q, have been described. Six cases had der(5;17)(p10;q10), and others had der(5;17)(p10;p10) or der(5;21)(p10;q10). Therefore, the der(5;19) demonstrated here is the second most common translocation leading to monosomy 5q in MDS. In addition, loss of 5q and gain of 19q induced by whole-arm translocations seem to be a relatively rare aberration. Nevertheless, consistent appearance of trisomy 19q in the present cases suggests its particular role in the development of MDS. Unfortunately, the clinical significance of trisomy 19q remains to be elucidated, although trisomy 19 as a sole abnormality is often detected in myeloid malignancies and reported to be associated with the proliferative form of chronic myelomonocytic leukemia [8]. Accumulation of more cases and further molecular cytogenetic and clinical studies are needed to elucidate the pathological roles of der(5;19) in high-risk MDS.

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Figure legends

Fig. 1. Bone marrow smears at the diagnoses of MDS of (A) case 1 and (B) case 2 (x1000, May-Grünwald-Giemsa staining). Myeloblasts and trilineage dysplasia in the bone marrow cells are shown as follows: (A) myeloblasts, hypogranulation of neutrophils, nuclear abnormalities, multinucleation, and karyorrhexis of erythroblasts, and multi-separated nuclear megakaryocytes; (B) myeloblasts, megaloblastic changes and multinucleation of erythroblasts, hypogranulation of neutrophils and micromegakaryocytes.

Fig. 2. G-banded karyotypes of the bone marrow cells of (A) case 1 and (B) case 2. The karyotypes are as follows:
(A) 44,XY,der(5;19)(p10;q10),-6,add(17)(p11.2),-18,dic(18;?)(p11.3;?),+19, and (B) 45,XY,der(5;19)(p10;q10),t(12;17)(q13;p11),-18,+19. Arrows indicate rearranged chromosomes.

Fig. 3. Spectral karyotyping of the metaphase spreads after spectrum-based classification of (A) case 1 and (B) case 2 (left side, reverse DAPI; right side, SKY). Chromosomes were assigned a pseudocolor according to the measured spectrum. The karyotypes are revised as follows: (A) 44,XY,der(5;19)(p10;q10),-6,der(17)(17qter->17p11.2::6?::6q21->6qter),-18,idic(18)(p11.3),+19, and (B) 45,XY,der(5;19)(p10;q10),t(6;12;17)(p23;q13;p11),-18,+19. Arrows indicate rearranged chromosomes.

Fig. 4. (A) Ideograms of G-banding patterns for der(5;19)(p10;q10),+19 at 400-band levels. The locations of *D5S23/D5S721* signal at 5p15.2 and *CSF1R* signal at 5q33-34 are also shown. (B, C) Dual-color FISH analyses with CSF1R/D5S23, D5S721 probes on metaphase spreads of (B) case 1 and (C) case 2. Arrows indicate 1) *D5S23/D5S721* (green) and *CSF1R* (orange) signals on normal chromosome 5, and 2) *D5S23/D5S721* (green) signal on the der(5;19)(p10;q10).

Table 1. Results of G-banding, SKY and FISH analyses

Case No.	*Date*	*Disease Status*	*Methods*	*Karyotypes by G-banding and SKY, and signal patterns by FISH*
1	December 2006	diagnosis	G-banding	44,XY,**der(5;19)(p10;q10)**,-6,add(17)(p11.2),-18,dic(18;?)(p11.3;?),**+19**[13]/ 45,sl,+8[1]/46,XY[3]
			SKY	44,XY,**der(5;19)(p10;q10)**,-6,der(17)(17qter->17p11.2::6?::6q21->6qter),-18,idic(18)(p11.3),**+19**[4]/ 46,XY[1]
			FISH	1O2G[12]/2O2G[8]
2	January 2005	diagnosis	G-banding	45,XY,**der(5;19)(p10;q10)**,t(12;17)(q13;p11),-18,**+19**[17]/46,sl,+9[2]/46,XY[1]
	April 2005	progression	G-banding	45,XY,**der(5;19)(p10;q10)**,t(12;17)(q13;p11),-18,**+19**[14]/ 61,X,-X,-Y,-3,-5,+6,-7,+add(8)(q24),-10,-12,add(12)(p11),-13,-17,-18,-19,add(19)(p13),+20,+21,-22[3]/ 46,XY[1]
			FISH	1O2G[19]/2O3G[1]
	May 2005	progression	G-banding	45,XY,**der(5;19)(p10;q10)**,t(12;17)(q13;p11),-18,**+19**[18]
			SKY	45,XY,**der(5;19)(p10;q10)**,t(6;12;17)(p23;q13;p11),-18,**+19**[5]
			FISH	1O2G[18]/2O3G[1]/2O2G[1]

July 2005	CR, after BMT	G-banding	46,XY[20]
August 2005	CR, after BMT	G-banding	46,XY[20]
September 2005	relapse, after BMT	G-banding	59,X,-Y,+add(1)(p36),+5,**der(5;19)(p10;q10)**,t(6;12;17)(p23;q13;p11),+8,+8,-10,+add(11)(p11),+14,-16,+17, +20,+21,+21,+mar1,+mar2,+mar3,+mar4,+mar5,+mar6,+mar7[3]/46,XY[11]

Abbreviations: SKY, spectral karyotyping; FISH, fluorescence *in situ* hybridization; CR, complete remission; BMT, bone marrow transplantation. FISH analyses with CSF1R (orange, O) and D5S23/D5S721 (green, G) probes were performed on 20 metaphase spreads. Two orange and two green signals in a normal cell are shown as 2O2G. Numbers of metaphase cells are shown in brackets. The nomenclature according to ISCN 2005 is used only for G-banding and SKY analyses. The der(5;19)(p10;q10),+19 is described in bold letters.

Table 2. Results of immunophenotypic analyses

		Positive rate (%)																	
Case No.	*CD45 blast gating**	*CD2*	*CD3*	*CD4*	*CD5*	*CD7*	*CD8*	*CD10*	*CD13*	*CD14*	*CD16*	*CD19*	*CD20*	*CD33*	*CD34*	*CD41*	*CD56*	*HLA-DR*	*KOR-SA*
1	11.5	2.3	2.5	**51.8**	3.0	**53.3**	2.8	3.9	**61.8**	16.7	3.4	3.5	2.8	**86.9**	**42.0**	12.5	3.1	**92.0**	3.2
2D	13.0	0.8	1.5	1.0	2.0	**22.4**	0.6	0.2	**37.0**	1.1	5.1	1.6	1.0	**73.1**	**51.2**	**21.0**	0.9	**66.4**	**31.4**
2R	11.2	3.4	2.9	6.2	3.9	**68.9**	4.3	4.3	19.3	4.6	4.6	2.3	1.1	**98.1**	9.7	**27.8**	2.0	**60.1**	8.9

The positive rates of CD antigen expression on the cells surrounded by CD45 low/SSC low gating are shown. *Percentages of gated cells, which roughly correspond to those of myeloblasts, are also shown. Positive data (more than 20%) are described in bold letters. Abbreviations: D, at initial diagnosis; R, at relapse after bone marrow transplantation.

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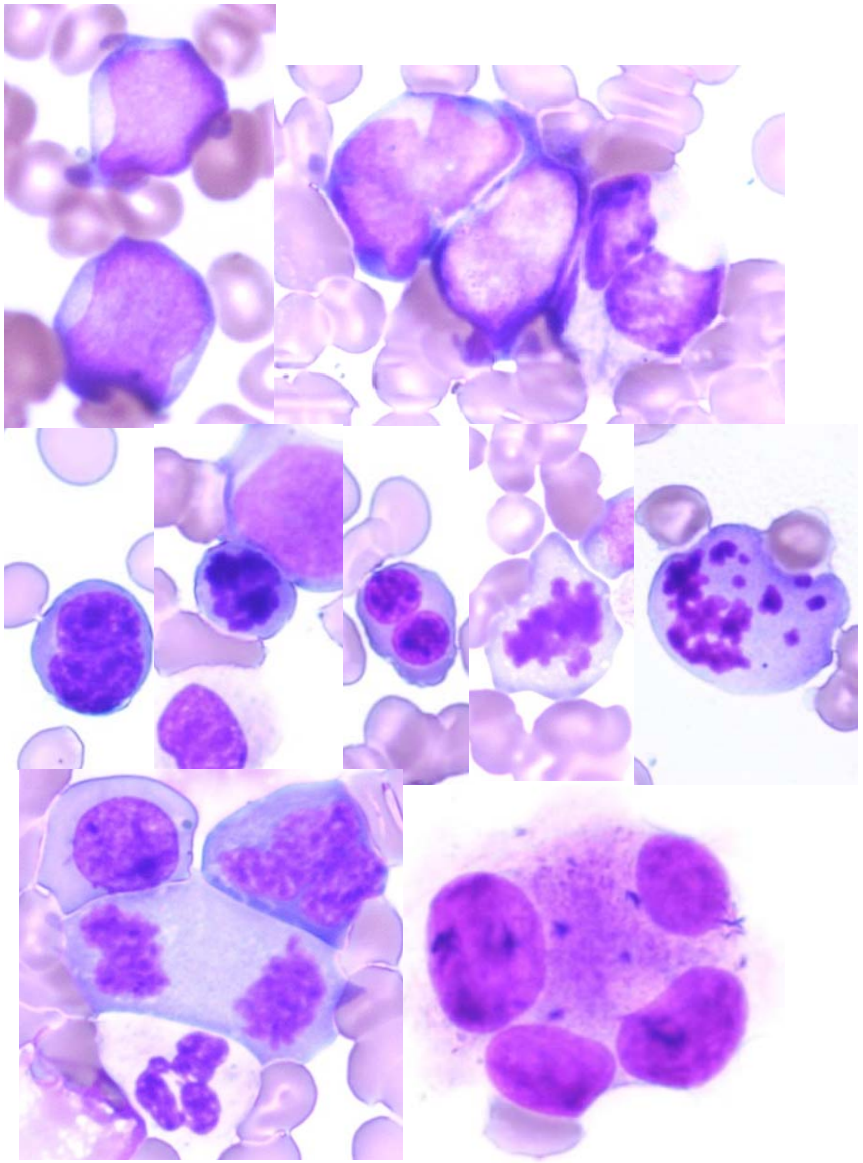

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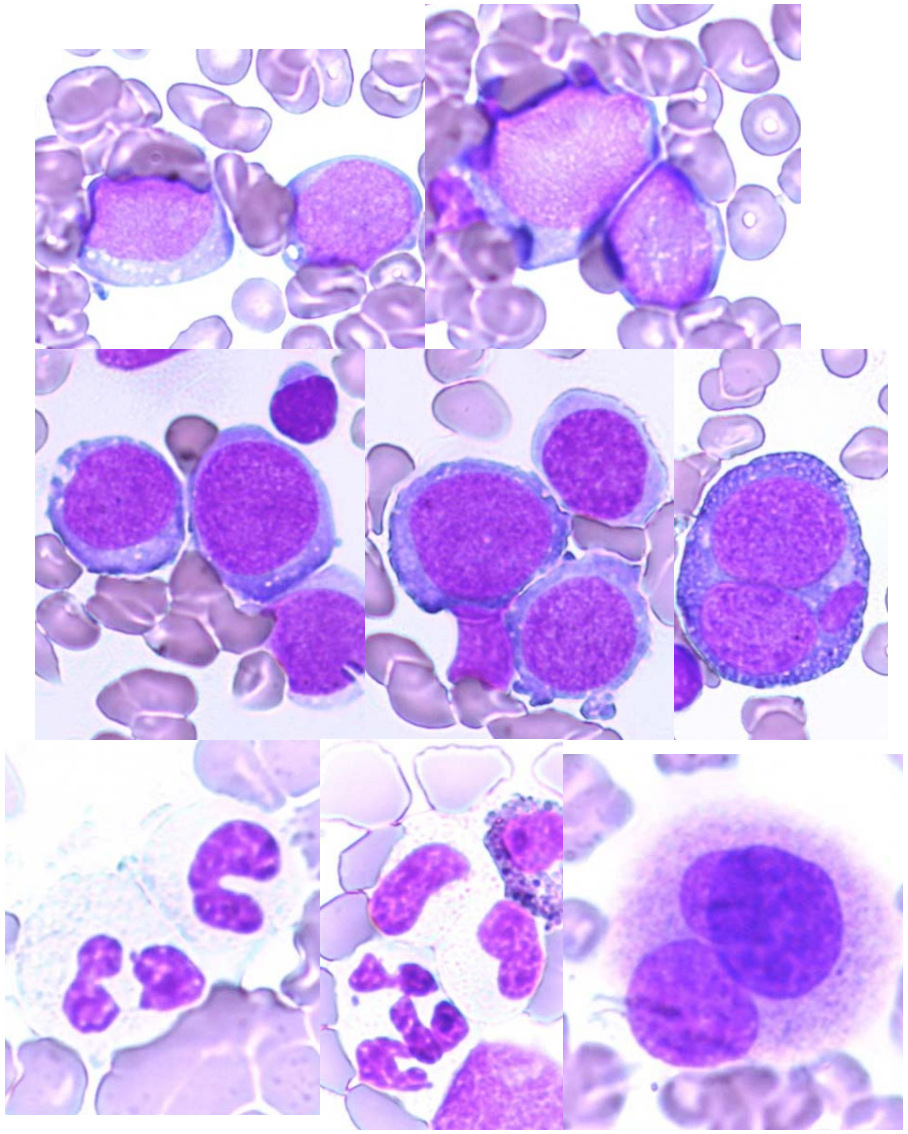

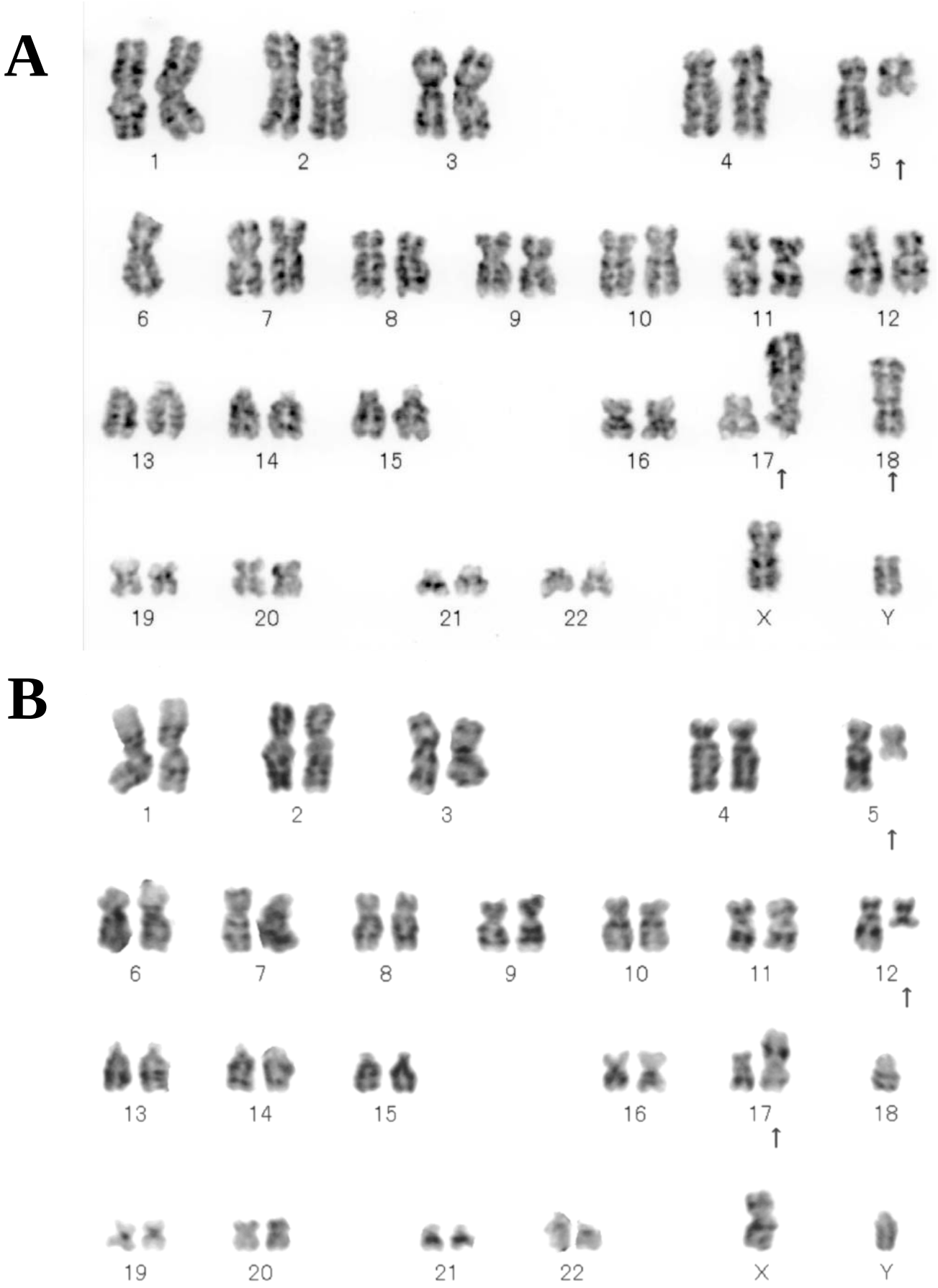
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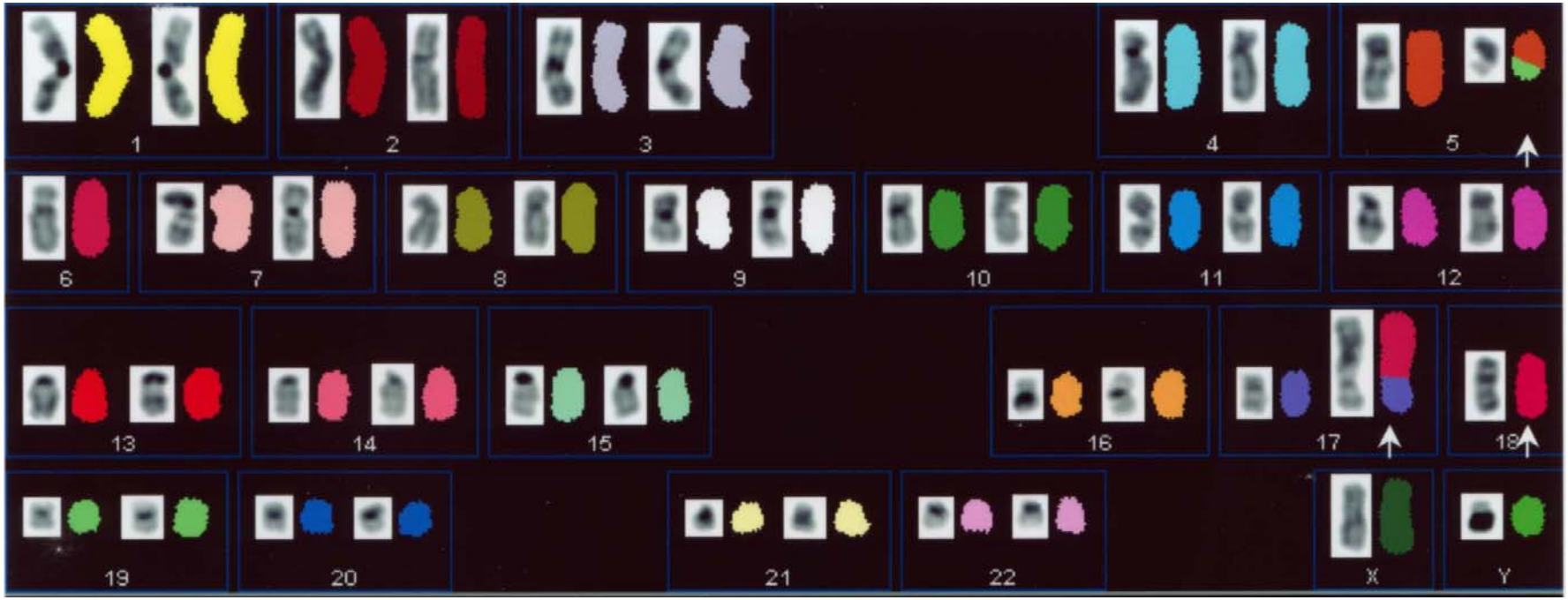
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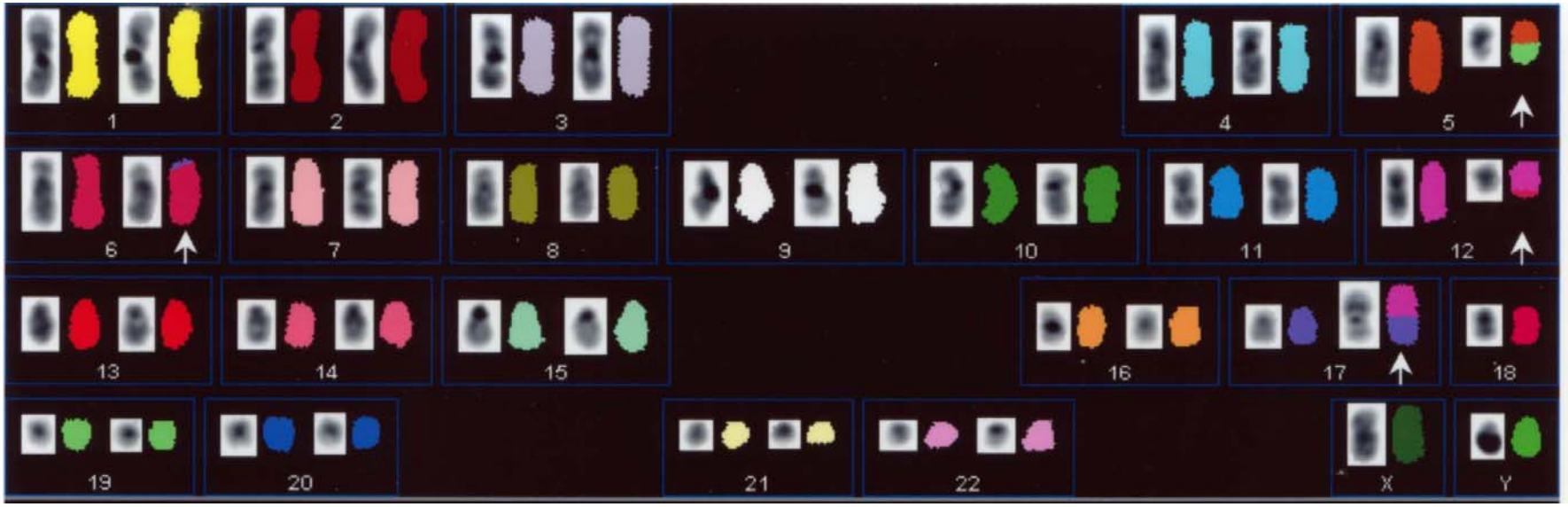
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chromosomes 19

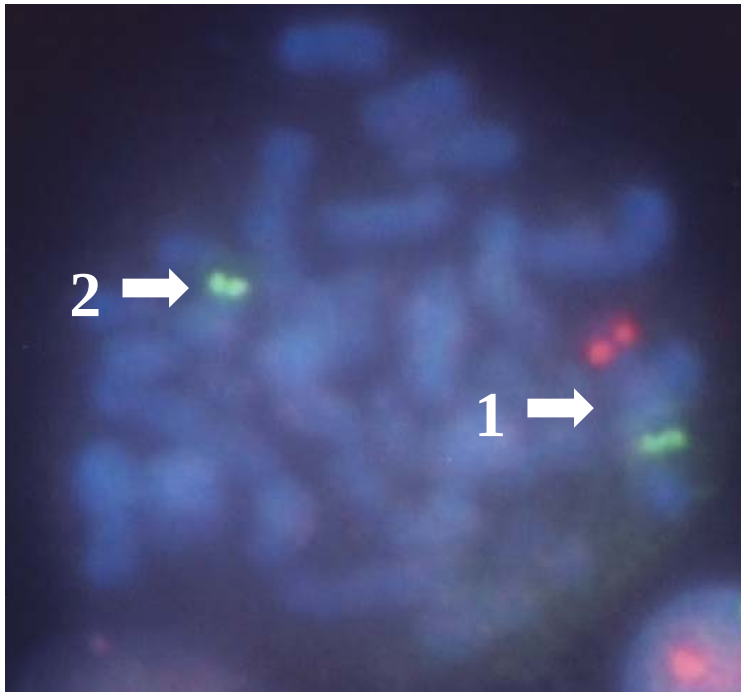
D5S23,
D5S721

der(5;19)(p10;q10)

CSF1R

chromosome 5

B



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