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Leukaemia Section

Review

der(21)t(1;21)(q11-12;p11-13) and der(21)t(1;21)(q21-32;p11-13)

Adriana Zamecnikova

Kuwait Cancer Control Center, Kuwait annaadria@yahoo.com

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Abstract

Unbalanced chromosome translocations involving all or part of the whole long arm of chromosome 1 and the short arms of acrocentric chromosomes are widely reported in human neoplasia. Among them, chromosome translocations between the long arm of chromosome 1 and chromosome 21 have been reported in patients with various conditions, including myeloid malignancies, acute lymphoblastic leukemia, multiple myeloma and lymphomas.

KEYWORDS
Gain of 1q; unbalanced translocations; gene overexpression; acrocentric chromosome.

Clinics and pathology

Disease

Chronic and acute myeloid malignancies, acute lymphoblastic leukemia (ALL), multiple myeloma (MM) and various lymphoid neoplasms.

Epidemiology

There were 13 males and 10 females (1 unknown) aged 8 to 90 years old (median 65 years) in a group of patients with 1q11-12 translocations (Table 1). Patients with 1q25-32 translocations tended to be younger and included 6 males and 5 females aged 0 to 72 years (median age 17 years), 2 of them were infants (Felix et al., 1998; Chessells et al., 2002) (Table 2).

	SEX/ AGE	DISEASE	KARYOTYPE
MYELOPROLIFERATIVE DISORDERS			
1	M/68	CMML	46,XY,der(21)t(1;21)(q11;p11)
2	F/76	PV	46,XX,der(4)t(1;4)(q12;p16)/46,XX,der(21)t(1;21)(q12;p12)

3	F	ET	46,XX,der(21)t(1;21)(q11;p13)
MYELODYSPLASTIC SYNDROME			
4	M/56	MDS APL-like	47,XY,+11 47,XY,t(4;11)(q10;p15),+11/48,idem,+8/48,idem,+11/48,idem,+13/48,idem,+17/48,idem,+19/47,idem,der(22)t(1;22)(q12;p13) 47,XY,t(4;11),+11,der(21)t(1;21)(q12;p13)
5	F/75	RARS	46,XX,del(20)(q11)/46,idem,der(21)t(1;21)(q12;p11)
6	F/80	RAEB	46,XX,der(21)t(1;21)(q10;p10)
ACUTE MYELOID LEUKEMIA			
7	M/36	AML	58,XY,-X,-1,-3,-4,-5,+6,-7,-9,-10,-12,der(15)t(1;15)(q12;p11),-16,-17,-18,-21/58,idem,-der(15),der(21)t(1;21)(q12;p11)/47,XY,+8
ACUTE LYMHOBLASTIC LEUKEMIA			
8	M	B-ALL	46,XY,der(19)t(1;19)(q23;p13)/46,idem,der(21)t(1;21)(q12;p13)
9	F	ALL	46,XX,der(19)t(1;19)(q23;p13)/46,idem,der(21)t(1;21)(q11;p11)
10	M	ALL	46,XY,del(13)(q1?2),der(21)t(1;21)(q12;p12)
11		B-ALL	46,X?,der(1)t(1;19)(q23;p13),i(7)(q10),der(21)t(1;21)(q12;p13)
12	M	B-ALL	46,XY,del(6)(q13q23),der(19)t(1;19)(q23;p13)/46,idem,der(21)t(1;21)(q12;p11)
MULTIPLE MYELOMA			
13	M	MM	43,X,-Y,+1,der(1;15)(q10;q10),der(4)t(1;4)(q11;q35),-13,-14,der(21)t(1;21)(q11;p11),-22 /td>
14	F	MM	44,X,-X,der(6)add(6)(p25)t(1;6)(q12;q12),?inv(7)(p14p22),del(8)(p11),-13,del(20)(q12),der(21)t(1;21)(q10;p11)
15	F	MM	44-45,XX,del(1)(p13p32),t(2;14)(p23;q32),t(4;14)(p16;q32),add(5)(q33),der(5)t(1;5)(q10;p15),der(7;7) t(7;7)(p22;?q33)add(7)(p22),-13,del(14)(q24),der(21)t(19;21)(?p13;p11),add(21)(p11)/45,XX,der(1) del(1)add(1)(q32),t(2;14),t(4;14)(p16;q32),add(5),der(5)t(1;5)(q11-12;p15),-13,del(14),der(19)t(1;19) (q11-12;q13),der(21)t(19;21),add(21)/45,XX,der(1)del(1)add(1),t(2;14),t(4;14)(p16;q32),add(5),der(5)t(1;5),-13,del(14),der(14)del(14)t(1;14)(q11-12;q24),der(21)t(19;21),add(21)/45,XX,der(1)del(1)add(1), t(2;14),t(4;14)(p16;q32),add(5),der(5)t(1;5),-13,del(14),der(21)t(1;21)(q11-12;p11),der(21)t(19;21), add(21)
16	F	MM	46,X,-X,add(1)(q21),ider(1)(q10)del(1)(q42),?del(5)(p15),+hsr(7)(p15),der(8)t(1;8)(p13;q24),+add(9)(p12),der(10)t(1;10)(q21;p13)add(10)(q26),del(11)(q21q23),del(13)(q12q22),i(13)(q10),-14,add(15)(q26),der(18)t(1;18)(q12;q23),add(20)(q13),der(21)t(1;21)(q12;p13)ins(21;?)(p13;?),add(22)(p11)
NON HODGKIN LYMHOMA			

17	M/8	MBN	46,XY,der(8)t(7;8)(q21;q24)dup(7)(q21q36),der(14)t(8;14)(q24;q32),der(21)t(1;21)(q11;p13)
18	M	MBN	42-47,XY,add(3)(q11),add(8)(q24),der(14)t(8;14)(q24;q32),t(14;18)(q32;q21),del(16)(q13),+20/42-47, idem,der(21)t(1;21)(q11;p11)/47-48,idem,+X/47-48, idem,+7/49,idem,+X,+7 **LN**
19	F	FL	49-50,X,del(X)(p21),dic(1;12)(?p21;q24),t(3;4)(q27;p13),+i(6)(p10),t(14;18)(q32;q21),i(17)(q10),+add(19)(q13),der(21)t(1;21)(q11;p11),+2mar **LN**
20	F	FL	42-54,XX,t(6;7)(p21;q22),+7,+der(7)t(6;7),t(8;14)(q24;q32),+11,+11,+12,+der(14)t(8;14),+21,der(21)t(1;21)(q12;p13)x2 **LN**
21	M	DLBCL	46,X,-Y,add(1)(p32),dup(1)(q21q31),t(3;14)(q27;q32),add(8)(p11),del(9)(p11),der(21)t(1;21)(q12;p13),+mar **LN** LN
22	M/90	BL	46,XY,t(8;14)(q24;32),der(21)t(1;21)(q14;p12) **LN**
OTHERS			
23	M/65	PCL	82-87,XXY,-Y,-1,-2,-3,-4,-5,del(6)(q21)x2,-8,del(8)(p21),-10,-10,add(11)(p15)x2,-13,-13,-14,-15,-15,-18, +19,der(20)t(1;20)(q11;q13)ins(20;?)(q13;?)x2,der(21)t(1;21)(q11;p13)ins(21;?)(p13;?),-22,inc
24	M/30	HD	46,X,-Y,del(4)(q28),+8,add(9)(p24),der(14)t(1;14)(q11;p11),der(21)t(1;21)(q11;p11) **LN**

Abbreviations: M, male; F, female; CMML, Chronic myelomonocytic leukemia; PV, Polycythemia vera; ET, Essential thrombocythemia; MDS, Myelodysplastic syndrome; APL, Acute promyelocytic leukemia; RARS, Refractory anemia with ringed sideroblasts; RAEB, Refractory anemia with excess of blasts; AML, Acute myeloid leukemia; ALL, Acute lymphoblastic leukemia/lymphoblastic lymphoma; MM, Multiple myeloma; MBN, Mature B-cell neoplasm; LN, lymph node; FL, Follicular lymphoma; DLBCL, Diffuse large B-cell lymphoma; BL, Burkitt lymphoma/leukemia; PCL, Plasma cell leukemia; HD, Hodgkin disease.

1. Amenomori et al., 1986; 2. Juneau et al., 1998; 3. Gangat et al., 2009; 4. Najfeld et al., 1994; 5. Huh et al., 2010; 6. Makishima et al., 2013; 7. Liu et al., 2007; 8. Raimondi et al., 1990; 9. Uckun et al., 1998; 10. Heerema et al., 2000; 11. Lu et al., 2002; 12. Bousquet et al., 2007; 13. Sawyer et al., 1998; 14. Sawyer et al., 1998; 15. Gabrea et al., 2008; 16. Sawyer et al., 2014; 17. Dayton et al., 1994; 18. Schmitz et al., 1997; 19. Roumier et al., 2000; 20. Katzenberger et al., 2004; 21. Ruminy et al., 2006; 22. Trcic et al., 2010; 23. Andreasson et al., 1998; 24. Stamatoullas et al., 2007

	SEX/AGE	**DISEASE**	**KARYOTYPE**
ACUTE MYELOID LEUKEMIA			
1	M/0	AML-M5	46,XY,der(1)t(1;1)(p36;q21)/45,idem,-Y/47,idem,+8/46,XY,der(21)t(1;21)(q21;p11)
B-CELL ACUTE LYMHOBLASTIC LEUKEMIA			
2	M	ALL	46,XY,der(21)t(1;21)(q21;p13)dup(1)(q21q32)
3	F/0	ALL	47,XX,+X,t(11;19)(q23;p13),der(21)t(1;21)(q25;p11)
4	M/11	ALL	46,XY,del(6)(q13q21),der(19)t(1;19)(q23;p13),der(21)t(1;21)(q21;p11)

5	M/50	ALL	46,XY,der(8)t(8;9)(p22;p24)t(8;22)(q24;q11),der(9)t(8;9)(p21;p24),der(21)t(1;21)(q21;p11),der(22)t(8;22) (q24;q11) 46,XY,t(8;9)(q22;q24) 46,XY,der(8),der(9)x2,der(21),der(22)/46,idem,der(16)t(16;22)(q24;q11)
T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA			
6	M/72	ALL	46,XY,der(21)t(1;21)(q25;p11)
MULTIPLE MYELOMA			
7	F	MM	39-41,-X,der(X)t(X;18)(q28;q11)ins(X;?)(q28;?),t(1;8)(p11-13;q24),add(2)(p25),dup(3)(q21q29), add(4)(q?31),t(4;14)(p16;q32),add(7)(p22),-8,der(9;17)(p10;q10),der(10)t(8;10)(q11;p13),-13,-14, add(15)(p11),der(15)t(9;15)(q12;p11),der(18)t(X;18),add(19)(q13),+20, der(21)t(1;21)(q23;p11) ins(21;?)(p11;?),+mar
8	F	MM	39-45,XX,der(1;21)(p10;q10),+r(?1)(p13q?31),der(2)t(1;2)(q12;q37),add(3)(q29),der(4;18)(p10;q10), add(5)(q34),+7,add(10)(q26),add(12)(p12),-13,add(15)(p11),der(15)t(?14;15)(q31;q24),add(17)(q25), der(19)t(?7;19)(p13;q13),add(20)(p12),der(21)t(1;21)(q?31;p13)
NON HODGKIN LYMHOMA			
9	F/17	BL	46,XX,del(7)(q22q32),t(8;14)(q24;q32)/46,idem,t(1;18)(q11;p11)/46,idem,t(1;21)(q11;p11) 48,X,der(X)t(X;8)(q11;q11),+del(3)(q21q29),t(3;16)(p12;q24),+del(7),t(8;14),?del(14)(q11q21), der(21)t(1;21)(q21;p13)
10	F/67	DLBCL	51-56,XX,+X,+del(1)(q21),+2,+5,+6,+7,+del(8)(q24),+9,+10,+11,+13,+14,+17,+20,-21,der(21t(1;21)(q21;p11),-22,-22,+2mar **exudate**
OTHERS			
11	M/65	MF/SS	45,XY,der(1)t(1;17)(p13;q21),t(2;5)(p14;q14),t(3;7)(p21;q35),t(4;9)(p?15;p?22),-5,-6,-9,-11,del(12)(q22),-17,-19,add(19)(q13),der(21)t(1;21)(q32;p13),+5mar

Abbreviations: M, male, f, female, BL, AML-M5, Acute monoblastic leukemia; ALL, Acute lymphoblastic leukemia; MM, Multiple myeloma; Burkitt lymphoma/leukemia; DLBCL, Diffuse large cell lymphoma; MF/SS, Mycosis fungoides/Sezary syndrome.

1. Chessells et al., 2002; 2. Raimondi et al., 1990; 3. Felix et al., 1998; 4. Andersen et al., 2011; 5. Patterer et al., 2013; 6. Safavi et al., 2015; 7. Gabrea et al., 2008; 8. Sawyer et al., 2014; 9. Fitzgerald et al., 1984; 10. Gladstone et al., 1994; 11. Schlegelberger et al., 1994.

Patients with centromeric 1q11-12 translocations were diagnosed mainly with myeloid malignancies and lymphomas

Myeloid malignancies in 7: 1 chronic myelomonocytic leukemia (CMML) (Amenomori et al., 1986), 1 myelodysplastic syndrome (MDS)/ acute promyelocytic leukemia (APL)-like leukemia (Najfeld et al 1994), 1 polycythemia vera (PV) (Juneau et al., 1998), 1 essential thrombocythemia (ET) (Gangat et al., 2009), 1 refractory anemia with ringed sideroblasts (RARS) (Huh et al., 2010), 1 refractory anemia with excess of blasts (RAEB) (Makishima et al., 2013) and 1 acute myeloid leukemia (AML) (Liu et al., 2007).

Acute lymphoblastic leukemia in 5 (Raimondi et al., 1990; Uckun et al., 1998; Heerema et al., 2000; Lu et al., 2002; Bousquet et al., 2007).

Multiple myeloma in 4 (Sawyer et al., 1998; Gabrea et al., 2008; Sawyer et al., 2014).

Various lymphoid malignancies in 7: 2 mature B-cell neoplasm (MBN) (Schmitz et al., 1997; Dayton et al., 1994), 1 Burkitt lymphoma/leukemia (BL) (Trcic et al., 2010), 1 Plasma cell leukemia (PCL) (Andreasson et al., 1998), 2 follicular lymphoma (FL) (Roumier et al., 2000; Katzenberger et al.,

2004), 1 diffuse large B-cell lymphoma (DLBCL) (Ruminy et al., 2006) and 1 HD (Hodgkin disease) (Stam atoullas et al., 2007).

der(21)t(1;21) with 1q21-32 breakpoints was less frequent and has been detected mainly in patients with ALL: 4 of them were diagnosed with B-cell ALL (Raimondi et al 1990; Felix et al., 1998; Andersen et al., 2011; Patterer et al., 2013) and 1 patient with T-ALL (Safavi et al., 2015). In addition, there were sporadic cases with other malignancies: 1 acute monoblastic leukemia (AML-M5) (Chessells et al., 2002), 1 diffuse large B-cell lymphoma (DLBCL), 1 Burkitt lymphoma/leukemia (BL) (Fitzgerald et al., 1984), 1 mycosis fungoides/Sezary syndrome (MF/SS) (Schlegelberger et al., 1994) and 2 multiple myeloma patients (Gabrea et al., 2008; Sawyer et al., 2014).

Prognosis

Associated with poor-risk genetic features and/or complex karyotypes in the majority of described patients, indicative of chromosomal instability related to disease progression and therapy resistance.

Cytogenetics

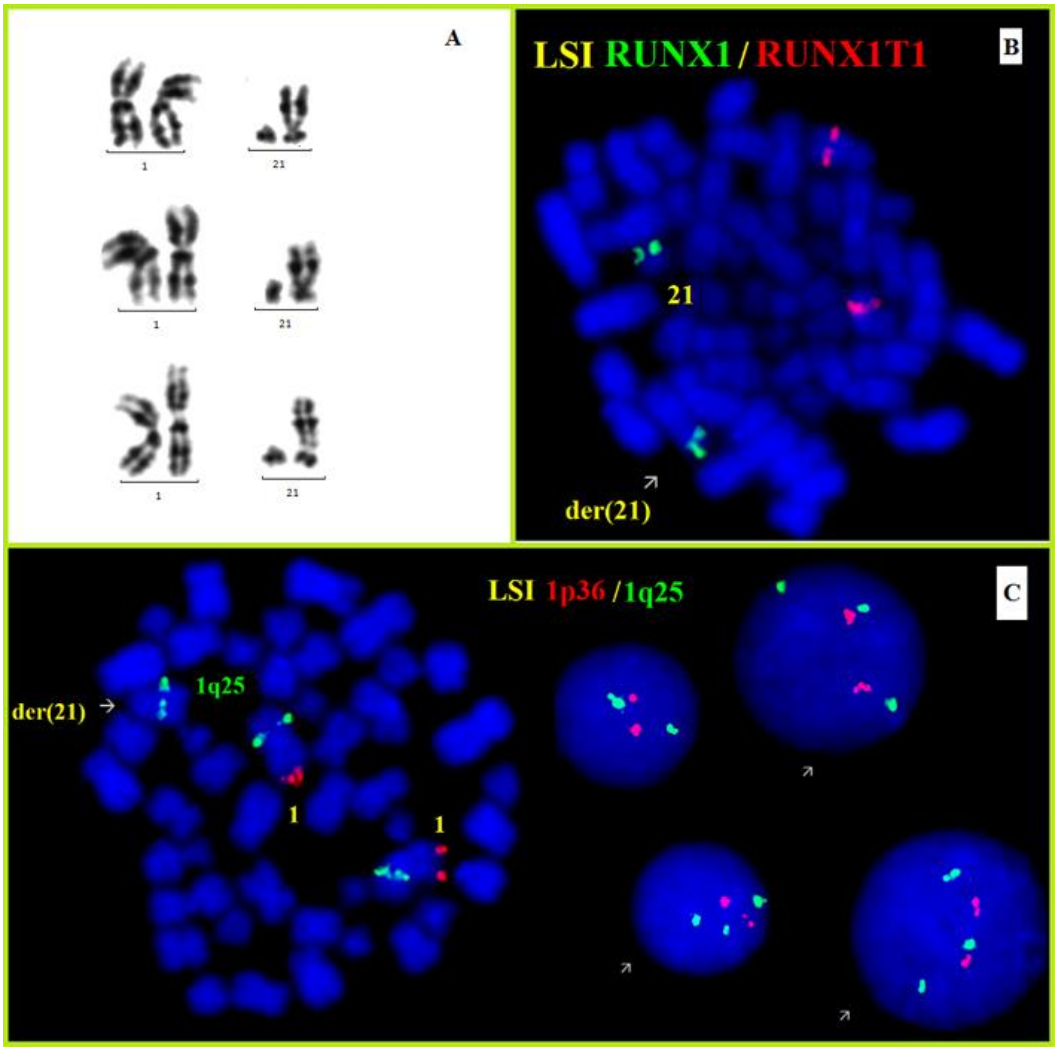

Figure 1. Partial karyotypes with der(21)t(1;21)(q11-12;p11-13) (A). Fluoresce in situ hybridization with LSI RUNX1/ RUNX1T1 probe (Vysis/Abott Molecular, US) revealing hybridization of RUNX1 probe to der(21) chromosome (green signal). (B). Hybridization with LSI 1p36/1q25 probe on metaphases and interphase cells showing the presence of extra green signal of 1q25 on der(21) chromosome and in interphase cells (green signal) (C).

Cytogenetics morphological

der(21)t(1;21)(q11-12;p11-13) has been detected as sole anomaly in 3 myeloproliferative disorders (Amenomori et al., 1986; Gangat et al., 2009; Makishima et al., 2013), found in association with trisomy 11 in MDS transforming to APL-like leukemia (Najfeld et al., 1994), del(20)(q11) in RARS (Huh et al., 2010) and additional 1q abnormalities in PV (Juneau et al., 1998) and AML patients (Liu et al., 2007). In patients diagnosed with ALL, there was a notable association with der(19)t(1;19)(q23;p13) as except 1 case with del(13q), in the remaining 4 ALL patients der(19)t(1;19)(q23;p13) was detected. Associated with t(8;14)(q24;q32) in 4 mature B-cell/Burkitt lymphoma/leukemia (Dayton et al., 1994; Schmitz et

al., 1997; Katzenberger et al 2004; Trcic et al 2010) and with highly complex karyotypes in the remaining patients.

In the group of **patients with 1q21-32 breakpoints** , sole anomaly was detected only in 1 T-ALL (Safavi et al., 2015); found in association with t(11;19)(q23;p13) in an infant with B-ALL (Felix et al., 1998), der(19)t(1;19)(q23;p13) in the pediatric B-ALL (Andersen et al., 2011), t(8;22)(q24;q11) in 1 B-ALL (Patterer et al., 2013) and (8;14)(q24;q32) in the BL patient (Fitzgerald et al., 1984). Found in the sideline with der(1)t(1;1)(p36;q21) and -Y/ +8 in infant with AML-M5 (Chessells et al., 2002) and as a part of complex karyotypes in the remaining patients.

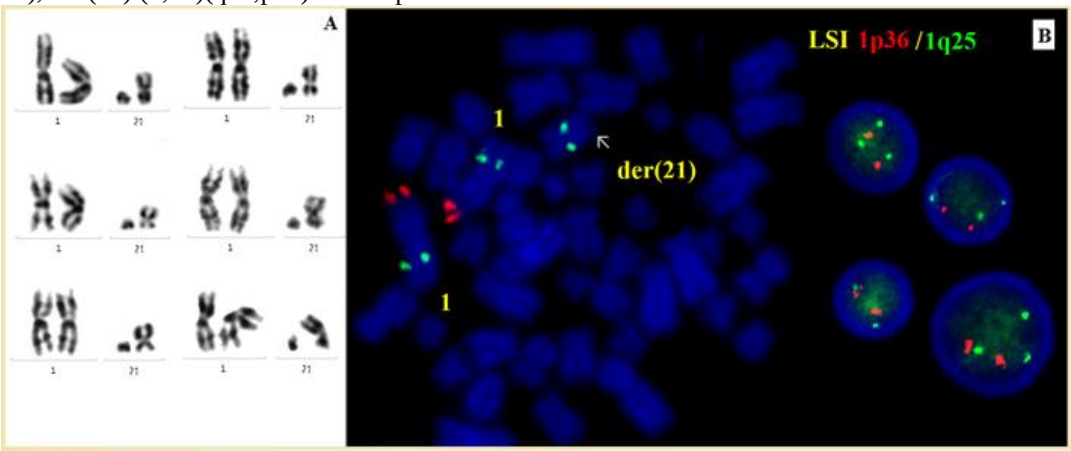

Figure 2. Partial karyotypes with der(21)t(1;21)(q21;p11-13) (A). Fluorescence in situ hybridization with LSI 1p36/1q25 probe (Vysis/Abott Molecular, US) on metaphase showing the extra 1q25 signal on der(21) chromosome and in interphase cells (B).

Result of the chromosomal anomaly

Fusion protein

Oncogenesis

Unbalanced 1q translocations to the short arms of acrocentric chromosomes are recurrent chromosome anomalies detectable in both hematologic neoplasms and lymphomas. Their main consequence is an extra copy of part of the long arm of chromosome 1 resulting in gene dosage abnormalities. Unbalanced translocations involving 1q and an acrocentric chromosome typically do not involve key genes, but they have as main consequence gain of the long arm of chromosome 1. 1q gains typically involve large chromosome regions, therefore simultaneous overexpression of multiple genes that might cooperate in an additive or synergistic way is likely implicated in neoplastic processes. der(21)t(1;21) was apparently a late event in the majority of reported patients- occurring together with the well-known primary abnormalities or as part of complex karyotypes, therefore representing clonal evolution change preceding or accompanying disease evolution.

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