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Cytogenetic findings in adult secondary acute myeloid leukemia (AML): frequency of favorable and adverse chromosomal aberrations do not differ from adult de novo AML

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Abstract During a 15-year period, 161 adult patients were diagnosed with secondary acute myeloid leukemia (s-AML) in the region of Southern Denmark. In 73 patients, the AML diagnosis was preceded by myelodysplastic syndrome (MDS-AML), in 31 patients by an antecedent hematologic disease, and in 57 patients by treatment with chemotherapy and/or irradiation (t-AML). Cytogenetic analysis was carried out in 93%, of which 61% had clonal chromosome aberrations. MDS-AML correlated to a normal karyotype ($P < 0.001$). t-AML correlated to abnormal clones with numerical and structural aberrations ($P = 0.03$), five or more unrelated aberrations ($P = 0.03$), marker chromosomes ($P = 0.006$), abnormal mitoses only ($P = 0.01$), female sex ($P < 0.001$), and −7 ($P = 0.006$). Centromeric breakage correlated to a complex karyotype ($P = 0.01$). The frequencies of aberrations in s-AML patients were compared with an age-matched group of de novo AML patients diagnosed in the same area and period. In this comparison, s-AML only correlated to −7 ($P = 0.02$). In 42 patients, we found that MDS patients with an abnormal karyotype were more likely to show cytogenetic evolution during progression to AML than MDS patients with a normal karyotype ($P = 0.01$). We conclude that population-based cytogenetic studies of adult s-AML and age- and sex-matched de novo AML show comparable distributions of chromosome abnormalities.

1. Introduction

Acute myeloid leukemia (AML) can be divided in de novo AML and secondary AML (s-AML). The latter category may be subdivided into three groups: (1) patients with a previous myelodysplastic syndrome (MDS) of >3 months duration (MDS-AML); (2) patients with a previous myeloproliferative neoplasm, except chronic myeloid leukemia, also called antecedent hematologic disease AML (AHD-AML); and (3) patients with a preceding hematologic neoplasm not included in groups 1 or 2, with a preceding nonhematologic neoplasm, or with a preceding nonneoplastic disease treated with chemotherapy, irradiation, or both (t-AML).

During later years, the incidence of secondary acute myeloid leukemia (s-AML) has been increasing, accounting for 10–30% of AML cases [1]. The incidence of s-AML is age dependent, with s-AML constituting a larger part of AML in the elderly than in the young [1–3].

In de novo AML, various cytogenetic aberrations are found. The same aberrations may be seen in s-AML. The frequencies of some of the aberrations is reported to be different, however, with fewer favorable aberrations

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(t(8;21), t(15;17), and inv(16)) and more adverse aberrations (−5, del(5q), −7, and −17) among patients with s-AML. Only few comparisons have been made between de novo AML and s-AML patients from the same area, and none of these comparisons have been population based [4].

Several cytogenetic aberrations do not only differ in frequency between de novo AML and s-AML. The frequencies also differ with age, as we have previously shown in a population-based group of patients with de novo AML [5] and has been shown by others [2,3]. To our knowledge, comparisons of the cytogenetic aberrations in a larger group of s-AML patients with age-matched de novo AML patients have not previously been published.

The aim of this study was to describe the cytogenetic aberrations in a population-based cohort of patients with s-AML and compare these aberrations to the cytogenetic aberrations in an age-matched group of patients with de novo AML. Further, we also investigated the evolution in cytogenetic aberrations in patients who were primarily diagnosed with MDS and later developed AML.

2. Materials and methods

2.1. Background population and health care system

The patients resided in the four counties of Funen, Ribe, Southern Jutland, and Vejle, which by January 1, 2001, had 472,064, 224,446, 253,249, and 349,186 inhabitants, respectively, totaling 1,298,945 people and comprising 24.3% of the total Danish population.

The Danish health care system was county based at the time of data acquisition, with each county taking care of virtually all patients living in its area. In each of the three counties, the diagnosis of leukemia is centralized, resting on initial evaluation at the counties' specialized departments of hematology and associated departments of pathology. In suspected cases of acute leukemia, peripheral blood (PB) and bone marrow (BM) specimens were sent for immediate evaluation or reviewing at the Department of Pathology at Odense University Hospital (OUH).

The completeness of follow-up data was facilitated by the Danish Central Personal Registration System.

2.2. Patient and data acquisition

We included all patients at least 15 years old, diagnosed with s-AML in the period January 1, 1992, to December 31, 2006, residing in the region at the time of diagnosis. Patients from the county of Southern Jutland and the county of Vejle were enrolled from January 1, 1995, and January 1, 1999, respectively.

To secure completeness of the AML population, the computer databases of the departments of hematology and pathology in the counties of Funen and Ribe, and the files of the corresponding departments in the county of Southern Jutland were supplemented by data extracted from the Danish Cancer Registry for the period 1992–1997 for which valid data were available. In addition, we performed a cross-check against data in the National Hospital Discharge Registry, corresponding to the county of Funen, from January 1, 1996, to November 17, 1998. Detailed data relating to AML demographics, patient characteristics, French–American–British (FAB) subtypes, and cytogenetics were entered consecutively in a computer database located at OUH.

In the county of Vejle, the completeness was secured by examination of the files of the Department of Hematology and the computer database of the Department of Pathology.

The patients were divided into three groups, as follows: (1) MDS-AML, patients with a previous MDS of >3 months' duration; (2) AHD-AML, patients with a previous myeloproliferative neoplasm, also called antecedent hematological disease AML; and (3) t-AML, patients treated with chemotherapy or irradiation or both for a preceding hematological neoplasm not included in group 1 and 2, or a preceding nonhematological neoplasm. This group also included three patients with a previous nonneoplastic disease treated with chemotherapy. In the MDS-AML group, 19 patients had been treated with chemotherapy during the MDS phase, 3 patients had been treated with thalidomide, and 1 patient had been treated with Glivec. In the AHD-AML group, 19 patients had been treated with chemotherapy before the AML diagnosis. Twenty-eight of the t-AML patients had been treated with chemotherapy only, 16 patients with irradiation only, and 13 patients with both.

During the same 15-year period, 579 patients were diagnosed with de novo AML in the region. For each patient with s-AML or de novo AML, the age at diagnosis was calculated in days. Starting with the youngest s-AML patient, the de novo AML patient with the same sex and the closest match in age at diagnosis was found.

2.3. AML classification

The AML diagnosis was based on PB and BM smears and biopsy samples stained with May–Grünwald–Giemsa in the 161 patients. In five patients, only PB samples were available (these patients all had >20% blasts in the PB). In the period January 1, 1992, to December 31, 2001, all patients had either >30% blasts in the BM or >30% blasts in PB, according to the FAB classification [6]. Since January 1, 2002, the World Health Organization (WHO) criteria were used, and all patients had either >20% blasts in the BM or >20% blasts in PB [7]. The diagnosis was confirmed in most cases (n = 141) by appropriate cytochemical staining and by immunophenotyping by dual-color flow cytometry. All patients except the five with only PB smears available were also subtyped according to FAB criteria [6,8,9].

2.4. Chromosome analysis

Of the 161 patients, 150 (93%) had a cytogenetic analysis performed at the time of the AML diagnosis. All

cytogenetic investigations were carried out in a standardized fashion at the Chromosome Laboratory, Department of Pathology, OUH. Briefly, G-band karyotyping was carried out after direct collection or short-term unstimulated culture of BM cells as described earlier [10,11]. Clonal chromosome abnormalities were described in accordance with the International System for Human Cytogenetic Nomenclature (ISCN 2005) [12]. Karyotype grouping was carried out according to the presence of normal mitoses only, normal and abnormal mitoses, or abnormal mitoses only, and according to the classification by Grimwade et al. [2].

2.5. Statistical analysis

Chi-square tests were used to compare categorical data. All *P* values were two-sided.

3. Results

3.1. Incidence rate and age distribution

The 161 patients constituted 28% of all AML patients diagnosed in the period: 73 MDS-AML, 31 AHD-AML, and 57 t-AML. The crude incidence rate was 1.28/100,000 per year. This corresponds to 1.22 after age and sex adjustment to the Danish population and to 0.98 and 0.78 after age adjustment to the European and world standard populations, respectively. The median age was 70 years (MDS-AML 71 years, AHD-AML 75 years, t-AML 69 years), ranging 27–88 years (Fig. 1).

Among the 161 patients were 77 men and 84 women. In the three subgroups, the sex ratios (M:F) were as follows: MDS-AML 2.0, AHD-AML 0.7, and t-AML 0.4. There were significantly more women in the t-AML group compared to the two other groups; 24 of 57 patients in this group were treated for cancers of the female genital tract or for breast cancer.

3.2. Diagnoses before AML

Among the MDS-AML patients, the primary diagnosis was refractory anemia (RA) in 17, RA with ringed sideroblasts (RARS) in 6, RA with excess blasts (RAEB) in 31, RA with excess blasts in transformation (RAEB-T) in 7, chronic myelomonocytic leukemia (CMML) in 10, and MDS not otherwise specified in 2 patients. The AHD-AML group included patients diagnosed with polycythemia vera ($n = 12$), myelofibrosis ($n = 7$), essential thrombocythemia ($n = 4$), and myeloproliferative syndrome not otherwise specified ($n = 8$). The t-AML group included patients diagnosed with non-Hodgkin lymphoma ($n = 10$), multiple myeloma ($n = 5$), chronic lymphocytic leukanemia ($n = 4$), Hodgkin lymphoma ($n = 2$), carcinoma of the breast ($n = 16$), carcinoma of the endometrium ($n = 5$), prostate carcinoma ($n = 2$), carcinoma of the rectum ($n = 1$), carcinoma of the ovary ($n = 1$), carcinoma of the cervix ($n = 1$), vesical carcinoma ($n = 1$), choriocarcinoma ($n = 1$), testicular neoplasm ($n = 1$), carcinoma of the thyroid ($n = 1$), carcinoma of the lung ($n = 1$), polyarteritis nodosa ($n = 1$), rheumatoid arthritis ($n = 1$), and Crohn disease ($n = 1$). This category also included two patients who had been treated for AML for >15 years before the current AML diagnosis. Because of this long time interval, these patients were included in the t-AML group.

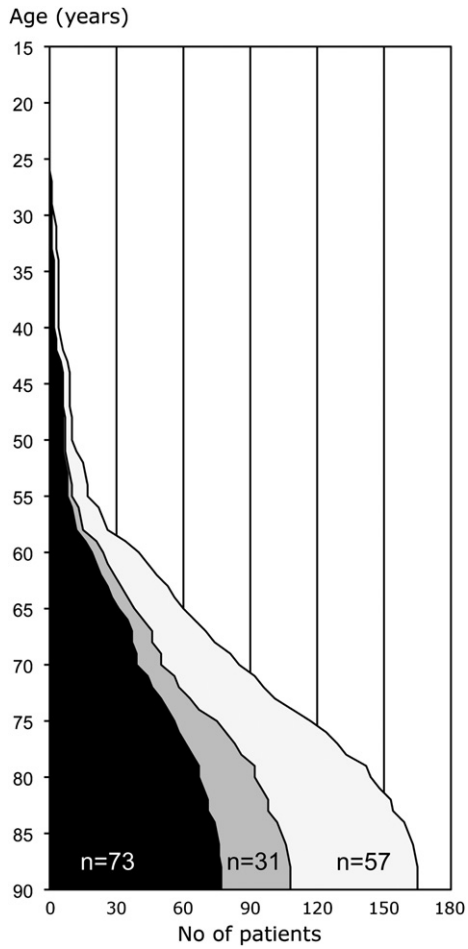

Fig. 1. Age distribution at diagnosis of 161 patients with secondary acute myeloid leukemia.

3.3. Cytogenetic findings

Material for chromosome analysis at diagnosis was available in 150 patients (93%) (Table 1). Mitoses were obtained in all cases. Twenty or more mitoses were analyzed to exclude clonal abnormalities except in one case where only 14 mitoses, all of which were abnormal, could be analyzed (median 25, range 14–30). An abnormal karyotype was found in 61%: 30 (44%) MDS-AML, 22 (79%) AHD-AML, and 39 (72%) t-AML. Karyotypes from the 91 patients with clonal aberrations are listed in Table 1. Twenty-eight abnormal karyotypes showed one or more

Table 1
Karyotypes, sex, and age of 91 patients with s-AML and cytogenetic aberrations

Sex/age (y)	FAB subtype	Diagnosis prior to AML	Karyotype
M/41	M6	RAEB	66,XY,add(1)(p12),add(2)(p13),+3,add(3)(p13),t(3;8)(p21;p23),der(3)t(3;8)(p21;p23),−4,−5,+6,add(6)(q27),−7,−10,−10,−11,−12,−13,−16,add(16)(q24),+20,+21,−22,+3mar[cp3]/46,XX[22]
M/43	M5	CMML	46,XY,del(9)(q13q31)[12]/47,XY,+13[9]/46,XY[4]
F/52	M2	RAEB	46,XX,t(5;16)(q31;q24),del(17)(q21)[3]/46,XX[22]
M/56	M4	RARS	47,XY,+19[2]/48,idem,+8[23]
F/57	M1	RAEB	46,XX,add(1)(p35),del(7)(q32),add(8)(p11),del(10)(q24)[15]/46,XX,idem,+8,+10,+del(11)(q22),+13,+19,+20,+21[15]
F/59	M2	RAEB	45,XX,t(3;3)(q21;q26),−7[25]
F/60	M2	RA	46,XX,der(7)t(1;7)(q11;q11)[9]/47,idem,+8,del(12)(p11p12)[16]
F/60	M2	RARS	47,XX,+19,del(20)(q11)[10]/48,idem,+11[15]
F/62	M6	RA	44,XX,−3,del(5),−7,add(11)(p15)[22]/46,XX[3]
M/62	M5	CMML	46,XY,del(9)(q21q32)[6]/46,XY[19]
M/63	M5	CMML	47,XY,+8[10]/46,XY[15]
F/63	M1	RAEB	45,XX,add(1)(p36),del(5)(q13q33),r(7),del(12)(q15q22),−13[23]/46,idem,−r(7),add(11)(p15),+2mar[2]
M/63	M2	RAEB-T	47,XY,+11[18]/46,XY[7]
F/65	M7	MDS	46,XX,del(5)(q13q33)[2]/44,idem,−7,−20,−21,+mar[5]/43,idem,−3,−7,add(9)(p13),−20,−21,+mar[4]/46,XX[3]
M/65	M2	RA	47,XY,del(7)(q32q36),+19[24]
F/67	M1	RAEB	45,XX,−7,t(14;21)(q22;q22)[15]/46,XX[10]
M/69	M4	RAEB	46,XY,dup(2)(q21q33)[3]/46,XY[22]
M/71	M2	RA	46,XY,del(7)(q22),del(12)(p12)[3]/45,XY,−7[16]/46,XY,der(16)del(16)(q22)add(16)(p13)[2]/46,XY[4]
M/72	M6	RAEB	47,XY,−5,del(7)(q21q35),+8,del(15)(q12),−18,del(20)(q12),+2r[3]/47,XY,−5,del(7)(q21q35),+8,−18,−18,+der(18)t(11;18;22)(q14;q11;q12)x2,del(20)(q12),−22,+2r[24]
F/73	M2	RAEB	47,XX,+8[25]
M/74	M7	RARS	45,XY,der(5)t(5;15)(q11;q11),−7,del(15)(q11)[4]/43,XY,idem,t(10;13)(q21;q33),t(12;22)(p12;q13),add(13)(p11),−18[2]/62,XY,−3,der(5)t(5;15)(q11;q11),+6,−7,−9,−11,−12,add(13)(p11),−14,del(15)(q11)x2,−17,−18,der(19)add(19)(p13)add(19)(q13),−20,+21,−22[15]/99,XXYY,+X,+1,+3,der(5)t(5;15)(q11;q11)x3,+6,+6,−7,del(15)(q11)x2,−16,der(19)add(19)(p13)add(19)(q13)x2,+21,+21[4]
M/75	M2	RAEB	47,XY,+i(1)(q10)[6]/46,XY[19]
M/76	M1	CMML	48,XY,+8,+21[13]/46,XY[12]
M/77	M2	RA	46,XY,del(5)(q13q31)[13]/47,XY,del(5)(q13q31),+8[13]
F/77	M2	RAEB	47,XX,+21[10]/45,XX,−7[4]/46,XX[15]
M/78	M0	RA	47,XY,+8[6]/46,XY[17]
F/79	M2	RAEB-T	46,XX,del(3)(p11),−5,+r[2]/45,idem,del(6)(p23),−7,der(12)t(3;12)(p11;p10)[14]/45,idem,del(6)(p23),−7,der(12)t(3;12)(p11;p10),add(18)(p11)[5]
F/81	M2	RAEB	47,XX,+8[25]
M/84	M2	RAEB	47,XY,+8[17]/46,XY[8]
F/86	M2	RA	47,XX,+8[9]/46,XX[16]
F/48	M7	MF	46,XX,t(6;17)(p23;q12)[21]/46,XX[4]
M/54	M2	MPS	46,XY,t(6;12)(p21;p12),der(18)t(1;18)(q21;q25)[18]/46,XY[2]
F/56	M6	ET	45,XX,der(1)t(1;5)(q21.2;q33),del(3)(p11q26),der(5)t(1;5)(q31;q33),−7,del(10)(p11),−17,+mar[25]
F/59	M7	MPS	46,XX,del(11)(p13p15)[18]/46,XX[7]
M/62	M1	PV	47,XY,+der(1)t(1;7)(q10;p10),−7,+8[26]
M/64	M2	PV	43,XY,−3,−5,del(9)(q21q34),−13,add(14)(q32),add(16)(q12),−17,−19,+3−4mar[cp7]/43,idem,add(1)(p35),del(8)(q22)[cp9]/46,XY[9]
F/67	M2	PV	59,XX,+1,+2,+4,+6,+8,+8,+9,+11,+13,+18,+19,+20,+mar[21]
F/67	M7	ET	47,XX,+8[15]/46,XX[10]
F/69	M2	ET	46,XX,add(3)(q27),−7,add(9)(p24),+r[15]/46,XX,t(4;21)(q27;q22)[8]/46,XX[6]
M/69	M2	MPS	47,XY,+21[11]/46,XY[14]
M/71	M0	MF	46,XY,i(17)(q10)[3]/46,XY[23]
F/75	M6	PV	46,XX,ins(15;13)(p12;q14q12)[24]
F/75	M1	PV	47,XX,+8[17]/46,X,del(X)(q13q24)[3]/46,XX[5]
F/75	M2	ET	46,XX,t(9;21)(q22;q22)[25]
F/76	M2	MPS	47,XY,+11[25]
F/76	M1	PV	47,XX,+11[10]/46,XX[15]
M/79	M7	PV	48,XY,+8,+9[23]/46,XY[2]
F/79	NOS	MF	46,XX,del(1)(p13p36),del(9)(q21q32),−18[24]
M/82	M0	MF	47,XY,+13[24]
F/84	M1	MPS	46,XX,del(7)(q31.2q32),del(20)(q11q12)[14]/46,XX[11]
F/85	NOS	MPS	46,X,del(X)(q23q27)[8]/47,idem,+mar[8]/48,idem,+22,+mar[8]/46,XX[1]

(*Continued*)

Table 1
Continued

Sex/age (y)	FAB subtype	Diagnosis prior to AML	Karyotype
M/87	M2	PV	47,XY,+8[22]/46,XY[2]
F/51	M5	Breast cancer	46,XX,t(9;11)(p22;q23)[25]
F/31	M2	HL	46,X,t(X;2;5)(q27;q11;q13),add(1)(p36),del(6)(q13q26),+8,add(12)(p12),−17,der(17)t(17;20)(p13;p11),+19,−20,add(21)(q22)[cp25]
F/42	M7	Cervix cancer	44,XX,inv(3)(p23q24),del(4)(q26q31),−5,−7,−10,−12,+mar1,+mar2[14]/43,XX,−3,del(4)(q26q31),−5,−7,der(12)t(12;14)(p13;q11),−14,+mar1[9]/46,XX[2]
F/52	M1	Breast cancer	46,XX,t(10;11)(p14;q21),der(10)t(10;11)(p14;q21)[25]
M/52	M6	NHL	45,XY,−7[21]
F/56	M3	ET, Breast cancer	46,XX,t(15;17)(q22;q11)[10]/46,XX[15]
F/56	M2	NHL	46,XX,t(12;22)(p12;q12)[23]/46,XX[2]
M/58	M2	NHL	44,XY,−5,del(7)(q22q32),i(11)(q10),add(15)(p11),−16,del(17)(p11),−21,−22,+mar1,+mar2[10]/44∼45,idem,−i(11)(q10),+add(11)(p10),add(11)(p10),+mar3,+mar4[cp15]
F/59	M1	NHL	47,XX,−4,−4,del(5)(q13q31),−7,+11,add(15)(q26),add(16)(q24),+3mar[19]/46,XX[6]
F/60	M2	Breast cancer	46,XX,t(6;9)(q21;p23)[3]/46,idem,t(8;21)(q22;q22)[22]
F/60	M6	NHL	47,XX,add(19)(q13),+mar1,+mar2[cp4]/46,XX,add(2)(q37),−4,−5,−6,−7,add(9)(p24),add(10)(q22),add(19)(q13),+mar1−4[13]/51,XX,−5,+6,+8,+8,+11,add(19)(q13),−21,+mar1−3[8]
F/61	M2	Breast cancer	45,XX,−7[23]/46,XX[2]
F/62	M1	CLL	46,XX,t(11;19)(q23;p13)[17]/46,idem,i(21)(q11)[5]/47,idem,+mar[2]
M/61	M4	Lung cancer	46,XY,inv(16)(p13q22)[14]/47,idem,+8[2]/46,XY[7]
F/63	M1	Endometrial cancer	46,XX,t(3;3)(q21;q26)[4]/45,idem,−7[4]/46,idem,ins(15;15)(q15q24;q21)[11]/46,idem,−7,ins(15;15)(q15q24;q21)[6]
F/63	M2	Endometrial cancer	45,XX,del(5)(q31q33),−7[25]
M/65	M1	NHL	46,XY,del(7)(q21)[9]/46,XY[20]
M/67	M1	Prostate carcinoma	45,XY,−7[21]/46,XY[4]
M/68	M2	Prostate carcinoma	47,XY,+8[25]
F/68	M3	Endometrial cancer	46,XX,del(3)(p21p22),del(9)(p21p24),der(10)del(10)(q22q24)t(1;10)(q11;q11),t(15;17)(q22;q11)[13]/46,XX[13]
M/68	M2	Polyarteritis nodosa	47,XY,+der(1)t(1;7)(q10;p10),−7,+mar[23]
F/68	M1	Breast cancer	46,XX,del(20)(q11)[5]/45,X,i(x)(p10),−7,del(20)(q11)[20]
F/69	M1	CLL	46,XX,del(5)(q33),−7,+del(8)(q13),del(9)(p13),−11,add(11)(p13),del(12)(p11.2p12.2),del(17)(q21q24),add(22)(q13),+mar[cp25]
F/69	M1	NHL	45,XX,t(3;7)(p23;p21),−5,−7,+mar[6]/46,XX,del(3)(q24q26),−5,−7,add(13)(p11),+2mar[11]/46,XX,inc[7]
F/70	M4	Breast cancer	45,XX,t(3;3)(q29;p13),−7[24]
F/70	M2	NHL	46,XX,inv(3)(q23q27),−7,+mar[27]
M/72	M2	HL	43,XY,−3,del(5)(q13q33),+8,del(9)(q22q34),−10,add(11)(p15),−13,−18,−21,−22,+2mar[18]/46,XY[7]
F/72	5b	Crohn disease	51,XX,+4,+8,+12,+15,+mar[18]/54,XX,+4,+8,+11,+12,+13,+16,+18,+mar[3]/46,XX[3]
F/74	M6	Ovarian cancer	44,XX,−5,−7,−9,−10,der(10)del(10)(q24)add(10)(q24),−20,−21,+4mar[5]/45,XX,der(1)del(1)(p11)add(1)(p11),−5,−7,−10,der(10)del(10)(q24)add(10)(q24),−21,+3mar[20]
F/74	M2	Thyroid cancer	45,XX,−5,−7,der(17)(t(5;17)(p11;p10),+mar[cp23]/46,XX[3]
F/76	M2	Endometrial cancer	46,XX,der(5)del(5)(q13q33)t(5;11)(q35;q12),del(7)(q21q31),del(8)(q21),−11,der(12)del(12)(p11)t(12;17)(p11;q11),−16,−17,+3mar[21]/46,XX[4]
M/76	M3	Rectal cancer	46,XY,t(15;17)(q22;q11),del(20)(q11)[13]/47,XY,+8[5]/47,XY,+8,del(20)(q11)[4]
F/76	M2	Multiple myeloma	44∼45,XX,−5,dic(5;17)(p10;q10),−7,−9,−1?,+r,+2mar[cp12]/44,idem,8∼10dmin[2]/48,XX,−X,+1,−5,+6,−7,+8,−11,−12,−13,−15,−17,−20,+5mar[cp8]/46,XX[2]
F/79	M2	Multiple myeloma	46,XX,del(5)(q13q33),del(6)(q21q23),del(7)(q22q32)[7]/46,idem,i(11)(q10)[17]
F/79	M2	Endometrial cancer	47,XX,+8[3]/46,XX[22]
F/80	M2	Ovarian cancer, Breast cancer, AML	44,XX,add(3)(q13),−4,−7,+8,add(8)(p21),i(8)(q10),+del(9)(p13p22),del(9)(q13q22)x2,−10,der(11)t(3;11)(q25;p14),del(16)(p11p13),−17,add(18)(p11),−20,−20,+2mar[cp23]/46,XX[2]
F/82	M2	Multiple myeloma	54,XX,+X,+X,+8,+11,+12,+14,+19,−21,+2mar[5]
F/83	M2	Multiple myeloma	46,XX,+1,der(1;7)(q10;p10)[25]
F/84	M1	NHL	46,XX,−6,add(7)(q31),+8,−11,−17,−17,+3mar[23]/46,XX[2]

Abbreviations: s-AML, secondary acute myeloid leukemia; FAB, French–American–British.

marker chromosomes. Marker chromosomes were significantly more often found in t-AML ($P = 0.006$). In four cases, one or two ring chromosomes were found.

3.3.1. Numerical and structural aberrations

Numerical aberrations only were found in 23 patients, and structural aberrations only were found in 19 patients. Forty-nine patients had both numerical and structural aberrations, most frequently in t-AML ($P = 0.03$) (Table 2).

3.3.2. Ploidy levels

Of the 91 patients with clonal aberrations, 26 showed only pseudodiploid clones, 40 showed one or more hyperdiploid clones, and 25 showed one or more hypodiploid clones (Table 2; Fig. 2). Among the hyperdiploid and hypodiploid cases, 47 and 45 chromosomes, respectively, were the most common finding. Massive hyperdiploidy (>52 chromosomes) was seen in five cases. Hypodiploidy as defined for acute lymphatic leukemia (<44 chromosomes) was found in seven cases. Hyperdiploidy was less frequently found in t-AML ($P = 0.002$) (Table 2).

3.3.3. Numbers of aberrations

A total of 33 of the 91 patients with an abnormal karyotype (MDS-AML 11, AHD-AML 11, t-AML 11) had only one aberration, 17 patients (MDS-AML 9, AHD-AML 4, t-AML 4) had two unrelated aberrations, 14 patients (MDS-AML 3, AHD-AML 3, t-AML 8) had three or four, and 27 patients (MDS-AML 7, AHD-AML 4, t-AML 16) had five or more unrelated aberrations (Table 2). A complex karyotype defined as five or more unrelated aberrations was most frequent in t-AML ($P = 0.03$).

In 59 patients (MDS-AML 38, AHD-AML 6, t-AML 15), only normal mitoses were found. A mixture of normal and abnormal mitoses was found in 48 patients (MDS-AML 17, AHD-AML 14, t-AML 17) and only abnormal mitoses were found in 43 patients (MDS-AML 13, AHD-AML 8, t-AML 22) (Table 2). Normal mitoses only were found more often in MDS-AML ($P < 0.001$), whereas abnormal mitoses only were found more often in patients with t-AML ($P = 0.01$).

3.3.4. Favorable aberrations

t(8;21) was found together with t(6;9) in one patient. t(15;17) was found in three patients—as the only aberration in one patient; in a second patient together with three unrelated aberrations, including del(9q); and together with del (20q) and +8 in a third patient. inv(16) was found together with +8 in one patient (Tables 2 and 3).

3.3.5. Intermediate aberrations

del(7q) was found in nine patients. In one patient, del (7q) was the only aberration, whereas in five patients, it was part of a complex karyotype. The aberration most often accompanying del(7q) was +8 ($n = 3$). Trisomy 8 was found in 30 patients. Trisomy 8 was the only aberration in 10 patients. In 6 patients, +8 was found together with other numerical aberrations only, and in 10 patients, +8 was involved in a complex karyotype. Trisomy 8 occurred most often together with −7 ($n = 4$) and −17 ($n = 4$) (Table 3). del(9q) was found in six patients, in one patient as the only aberration. 11q23 aberrations were found in two patients (t(9;11) and t(11;19)). del(20q) was found in four patients, +21 in six patients, and +22 in one patient (Tables 2 and 3).

3.3.6. Adverse aberrations

3q aberrations were found in eight patients. t(3;3) was found in three patients and inv(3) was found in two patients. In all eight patients, the 3q aberration was accompanied by −7. Monosomy 5 was found in 11 patients, of whom 10 had a complex karyotype. In six patients, −5 was accompanied by −7 and in two patients by del(7q). Among t-AML patients, 13% had −5. del(5q) was found in 10 patients. In five patients, del(5q) was part of a complex karyotype, and it was found together with −7 in four patients. Monosomy 7 was the most common aberration found in 31 patients (MDS-AML 13%, AHD-AML 11%, t-AML 35%; $P = 0.006$) (Tables 2 and 3).

In three patients, −7 was the only aberration, and in 13 patients −7 was part of a complex karyotype. Monosomy 7 was most often found together with 3q aberrations ($n = 8$), and −5 ($n = 6$). Monosomy 17 was found in eight patients (Tables 2 and 3). Monosomy 17 was always part of a complex karyotype.

Other nonrandom MDS/AML related aberrations were also found. der(1)t(1;7)(q10;p10) was found in four patients. The breakpoints in translocations and genomic gains and losses are shown in Figures 3 to 5. Pericentromeric breakages are located in the chromosome bands p11 or q11. They most often result in unbalanced translocations, but may also result in deletions or balanced translocations. Fifty-one pericentromeric breakages and 154 nonpericentromeric breakages were found in the s-AML patients (MDS-AML 12 of 47, AHD-AML 7 of 32, t-AML 32 of 75). Pericentromeric breakage was found significantly more frequent in complex karyotypes ($P = 0.01$). Breakage in the pericentromeric region was most often found in chromosome 1 ($n = 7$), 13 ($n = 5$), 3 ($n = 4$), 5 ($n = 4$), 7 ($n = 4$), and 17 ($n = 4$).

3.4. Cytogenetic aberrations in s-AML patients compared to age- and sex-matched de novo AML patients

There were no differences in type of abnormality, ploidy levels, number of abnormalities, type of mitoses (normal mitoses, normal and abnormal mitoses, and abnormal mitoses), or number of pericentromeric breakages between the s-AML patients and the matched de novo AML

Table 2
Clinical and cytogenetic characteristics of 161 adult patients with secondary acute myeloid leukemia

Characteristic	All cases		Sex ratio (M/F)	MDS		AHD		Therapy		De novo	
	n	(%)		*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Total no. of cases	161			73	(45%)	31	(19%)	57	(36%)	161	
Sex											
Male	77	(48%)		49	(67%)	13	(42%)	15	(26%)	77	(48%)
Female	84	(52%)		24	(33%)	18	(58%)	42	(74%)	84	(52%)
Age											
Median age (y)	70			71		75		69		70	
Range (y)	27–88			27–88		48–87		30–86		27–88	
Age groups (y)											
15–34	2	(1%)	2F	0	(0%)	0	(0%)	2	(4%)	2	(1%)
35–54	12	(7%)	0.63	5	(7%)	2	(6%)	5	(9%)	12	(7%)
55–64	39	(24%)	0.86	20	(27%)	5	(16%)	14	(24%)	39	(24%)
65–69	25	(16%)	0.92	11	(15%)	4	(13%)	10	(18%)	25	(16%)
70+	83	(52%)	1.00	37	(51%)	20	(65%)	26	(45%)	83	(52%)
No. of cases analyzed	150	(93%)	0.91	68	(93%)	28	(90%)	54	(95%)	149	(93%)
Normal karyotype	59	(39%)	1.82	38	(56%)	6	(21%)	15	(28%)	72	(48%)
Abnormal karyotype	91	(61%)	0.58	30	(44%)	22	(79%)	39	(72%)	77	(52%)
Type of abnormalities[a]											
Numerical	23	(25%)	1.30	10	(33%)	8	(36%)	5	(13%)	16	(21%)
Structural	19	(21%)	0.40	4	(13%)	7	(32%)	8	(21%)	23	(30%)
Numerical and structural	49	(54%)	0.46	16	(54%)	7	(32%)	26	(66%)	38	(49%)
Ploidy levels[a]											
Pseudodiploidy	26	(29%)	0.23	3	(10%)	8	(36%)	15	(38%)	30	(39%)
Hyperdiploidy	40	(44%)	1.10	19	(63%)	11	(50%)	10	(26%)	31	(40%)
Hypodiploidy	25	(27%)	0.37	8	(27%)	3	(14%)	14	(36%)	16	(21%)
No. of abnormalities[a]											
1	33	(36%)	0.79	11	(37%)	11	(50%)	11	(28%)	29	(38%)
2	17	(19%)	1.00	9	(30%)	4	(18%)	4	(10%)	14	(18%)
3–4	14	(15%)	0.36	3	(10%)	3	(14%)	8	(21%)	5	(6%)
5+	27	(30%)	0.35	7	(23%)	4	(18%)	16	(41%)	29	(38%)
Type of mitoses[b]											
NN	59	(39%)	1.82	38	(56%)	6	(21%)	15	(28%)	72	(48%)
NA	48	(32%)	0.82	17	(25%)	14	(50%)	17	(31%)	42	(28%)
AA	43	(29%)	0.38	13	(19%)	8	(29%)	22	(41%)	35	(24%)
Specific abnormalities[b]											
t(8;21)	1	(0.7%)	1F					1	(1.9%)	2	(1.3%)
t(15;17)	3	(2.0%)	0.50					3	(5.6%)	2	(1.3%)
inv(16)/del(16q)	1	(0.7%)	1M					1	(1.9%)	2	(1.3%)
del(7q)	9	(6.0%)	1.50	3	(4.4%)	2	(7.1%)	4	(7.4%)	7	(4.7%)
+8[c]	14	(9.3%)	1.14	7	(10.3%)	3	(10.7%)	4	(7.4%)	12	(8.1%)
+8[d]	16	(10.7%)	0.60	5	(7.4%)	3	(10.7%)	8	(14.8%)	6	(4.0%)
del(9q)	6	(4.0%)	2.00	2	(2.9%)	2	(7.1%)	2	(3.7%)	3	(2.0%)
11q23	2	(1.3%)	2F					2	(3.7%)	2	(1.3%)
del(20q)	4	(2.7%)	1.00	1	(1.5%)	1	(3.6%)	2	(3.7%)	3	(2.0%)
+21	6	(4.0%)	2.00	5	(7.4%)	1	(3.6%)				
+22	1	(0.7%)	1F			1	(3.6%)			5	(3.4%)
3q	8	(5.3%)	0.14	1	(1.5%)	2	(7.1%)	5	(9.3%)	3	(2.0%)
−5	11	(7.3%)	0.57	3	(4.4%)	1	(3.6%)	7	(13.0%)	5	(3.4%)
del(5q)	10	(6.7%)	0.25	4	(5.9%)			6	(11.1%)	13	(8.7%)
−7	31	(20.7%)	0.29	9	(13.2%)	3	(10.7%)	19	(35.2%)	16	(10.7%)
−17	8	(5.3%)	0.33	1	(1.5%)	2	(7.1%)	5	(9.3%)	12	(8.1%)
Chromosome breakage											
Pericentromeric	51	(25%)	0.42	12	(20%)	7	(18%)	32	(30%)	29	(18%)
Nonpericentromeric	154	(75%)	0.44	47	(80%)	32	(82%)	75	(70%)	135	(82%)
FAB subtypes[e]											
M0	7	(4%)	7.00	4	(5%)	2	(6%)	1	(2%)	9	(6%)
M1	35	(22%)	0.70	13	(18%)	4	(13%)	17	(30%)	44	(27%)
M2	78	(48%)	0.98	40	(56%)	14	(45%)	24	(41%)	57	(35%)
M3	3	(2%)	0.50	0	(0%)	0	(0%)	3	(5%)	3[f]	(2%)
M4	7	(4%)	1.33	4	(5%)	0	(0%)	3	(5%)	11	(7%)
M5	7	(4%)	2.50	5	(7%)	0	(0%)	2	(4%)	16	(10%)

(*Continued*)

Table 2
Continued

Characteristic	All cases		Sex ratio	MDS		AHD		Therapy		De novo	
	n	(%)	(M/F)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
M6	11	(7%)	0.83	3	(4%)	4	(13%)	4	(7%)	10	(6%)
M7	9	(6%)	0.50	3	(4%)	4	(13%)	2	(4%)	9	(6%)
NOS	5	(3%)	5F	1	(1%)	3	(10%)	1	(2%)	2	(1%)

Abbreviations: MDS, myelodysplastic syndrome; AHD, antecedent hematologic disease; FAB, French–American–British; PCR, polymerase chain reaction.

[a] The frequencies refer to cytogenetically abnormal cases.

[b] The frequencies refer to cytogenetically analyzed cases.

[c] +8 alone or together with other aberrations belonging to the intermediate risk group.

[d] +8 together with aberrations belonging to the adverse risk group.

[e] The frequencies refer to all cases.

[f] One patient had a normal karyotype, and the PML/RARA fusion was found by polymerase chain reaction.

patients. Among the specific abnormalities, the only differences were a significantly higher number of s-AML patients with −7 ($P = 0.03$) and a tendency toward more patients with +8 in the s-AML group ($P = 0.06$).

There were no statistical differences in the chromosomal aberrations among the 161 sex- and age-matched de novo AML patients and the 418 de novo AML patients who did not match in age or sex.

3.5. Cytogenetic evolution from diagnosis of MDS to AML transformation

In 42 of 73 patients with MDS-AML, cytogenetic analysis had been performed both at diagnosis of MDS and at diagnosis of AML.

At diagnosis of MDS, 23 patients had a normal karyotype, and 15 of these patients also had a normal karyotype at diagnosis of MDS-AML, whereas in 8 patients, an abnormal karyotype was found at diagnosis of MDS-AML. Three of these eight patients had been treated with chemotherapy during the MDS phase. The cytogenetic evolution (defined as gain of aberrations) consisted of numerical aberrations in four patients and of structural aberrations in three patients, and the last patient had both numerical and structural aberrations at diagnosis of MDS-AML (Table 4).

Nineteen patients had an abnormal karyotype at diagnosis of MDS. In five patients, one of whom had been treated with chemotherapy, the karyotype remained unchanged. Karyotypic evolution was found in 10 patients, 3 of whom had been treated with chemotherapy. The most frequent additional aberration was −7 ($n = 3$), followed by +8 ($n = 2$). In these patients, no new and unrelated clones were found at diagnosis of MDS-AML (Table 4).

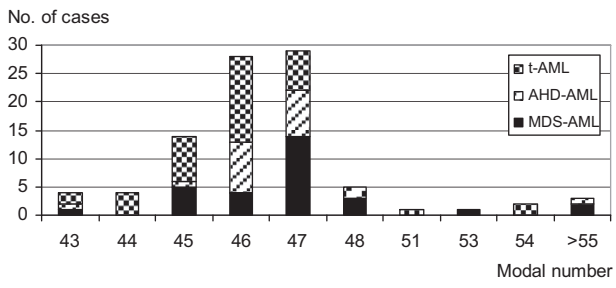

Fig. 2. Distribution of modal numbers in 91 patients with secondary acute myeloid leukemia with abnormal karyotype.

Karyotypic regression (defined as loss of aberrations) was found in two patients, and a combination of karyotypic evolution and regression (defined as both gain of new and loss of preexisting aberrations) was found in two patients. Significantly more patients in the group with a normal karyotype at diagnosis of MDS had an unchanged karyotype at progression to AML compared to the group of patients with aberrations at diagnosis of MDS ($P = 0.01$).

3.6. Rare recurrent aberrations

One unbalanced translocation, der(1)t(1;5)(q21.2;q33), was detected. So far, only two cases have been described [13].

3.6.1. New recurrent aberrations

Two aberrations t(3;7)(p23;p21) and t(6;17)(p23;q12) have now been described in two patients according to Mitelman's database of chromosome aberrations in cancer [13].

3.6.2. New aberrations

We found 8 balanced and 10 unbalanced translocations (Table 5), which, according to Mitelman's Database on Chromosomal Aberrations in Cancer, are new aberrations. One of the balanced and four of the unbalanced translocations are mentioned as partner chromosomes in translocations in Mitelman's Database [13], but the breakpoints were either not specified or the breakpoints differed from those found in our patients. Except for one patient, normal metaphases were observed in the same samples or in other samples at various disease status, indicating that these novel chromosome aberrations are acquired.

3.7. FAB subtypes

Approximately half of the s-AML patients belonged to FAB subtype M2. In the AHD-AML group, M6 and M7 were significantly more frequent than in the other two groups

Table 3
Characterization of additional cytogenetic aberrations in 91 adult patients with secondary acute myeloid leukemia and abnormal karyotype

Cytogenetic aberration	Total	t(8;21)	t(15;17)	inv(16)/ del(16)	7q−	+8	9q−	11q23	20q−	+21	+22	Other numerical	Other structural	3q−	−5	5q−	−7	−17	Complex	Mar
Total		1	3	1	9	30	6	2	4	6	1	41	51	8	11	10	31	8	27	28
Alone			2		1	10	1	1		1		5	10				3			
With the following:																				
t(8;21)	1												1							
t(15;17)	3					1			1				1							
inv(16)/del(16)	1					1														
7q−	9					3	1		2	1		7	8		2	1	1	2	5	4
+8	30						2		2	2		14	13		3	2	4	4	10	9
9q−	6											4	3	1	1	1		1	2	2
11q23	2											2	1							1
20q−	4											3	1		1		1		1	1
+21	6											3	3	0	1		3	1	3	2
+22	1												1							1
Other numerical	41												23	3	11	5	18	6	26	23
Other structural	51													5	11	5	22	7	25	26
3q−	8														2		8	1	3	4
−5	11																6	1	10	8
5q−	10																4	1	5	5
−7	31																	4	13	14
−17	8																		8	6
Complex	27																			20
Mar	28																			

($P = 0.01$). However, there was no difference between the whole s-AML group and patients in the age-matched de novo AML group in the distribution of FAB subtypes.

4. Discussion

For several years, it has been known that the incidence of s-AML is increasing, but the true incidence remains unknown. We have found a crude incidence rate of s-AML in adults of 1.28/100,000 per year, and in our 15-year material of AML patients, s-AML constituted 28%. In a material from Sweden on adult AML patients with a yearly incidence and age distribution comparable to ours, 22% of the patients had s-AML [14].

In most other materials, only patients eligible for intensive chemotherapy trials were included, and in these materials, s-AML constituted 7–8% [2,15], which is comparable to 10% of the younger patients included in our material. Among our AML patients >55 years of age, 26% had s-AML, which is a higher percentage than others have found [3,16–18]. One explanation for the discrepancy is the inclusion of patients according to the WHO criteria in the present study (>20% blasts instead of >30% in older material). As the incidence of s-MDS increases with age, another explanation may be that some very old patients, in earlier materials, went undiagnosed as they would not be eligible for treatment.

In the present study, MDS-AML constituted a smaller part (45%) of the s-AML patients compared to that found by others [1,19–21] and t-AML constituted 35%, which is comparable to that found by others [1,19–21]. The differences in frequency of MDS-AML could be caused by variations in treatment strategies: because treatment of MDS may cause AML, the percentage of MDS patients treated with chemotherapy in a given population may influence the number of patients with MDS-AML. However, geographical, environmental, and ethnic factors cannot be excluded.

The M:F ratio in the t-AML group was significantly lower compared to the MDS-AML and AHD-AML group ($P < 0.001$), which is explained by the fact that 24 of the t-AML patients had a primary tumor in the breast, endometrium, cervix, or ovary or a choriocarcinoma. This is comparable to what was found in the GIMEMA material [22]. The higher incidence in women may be explained by therapeutic strategies for neoplasms limited to female patients, differing from those affecting both male and female patients. Indeed, in the materials of Block et al. and Fonatsch et al., this skewing was also found in t-MDS/t-AML [23,24].

Significantly fewer s-AML patients were <55 years old compared to de novo AML patients ($P < 0.0001$), which agrees with the findings by Grimwade et al. [2,3]. An obvious explanation for this is the increasing risk of MDS/myeloproliferative neoplasms and solid tumors with age, which increases the risk of contracting s-AML in the elderly, as opposed to the young.

In 93% of the s-AML patients, cytogenetic analysis was carried out, and 61% had an abnormal karyotype, which is

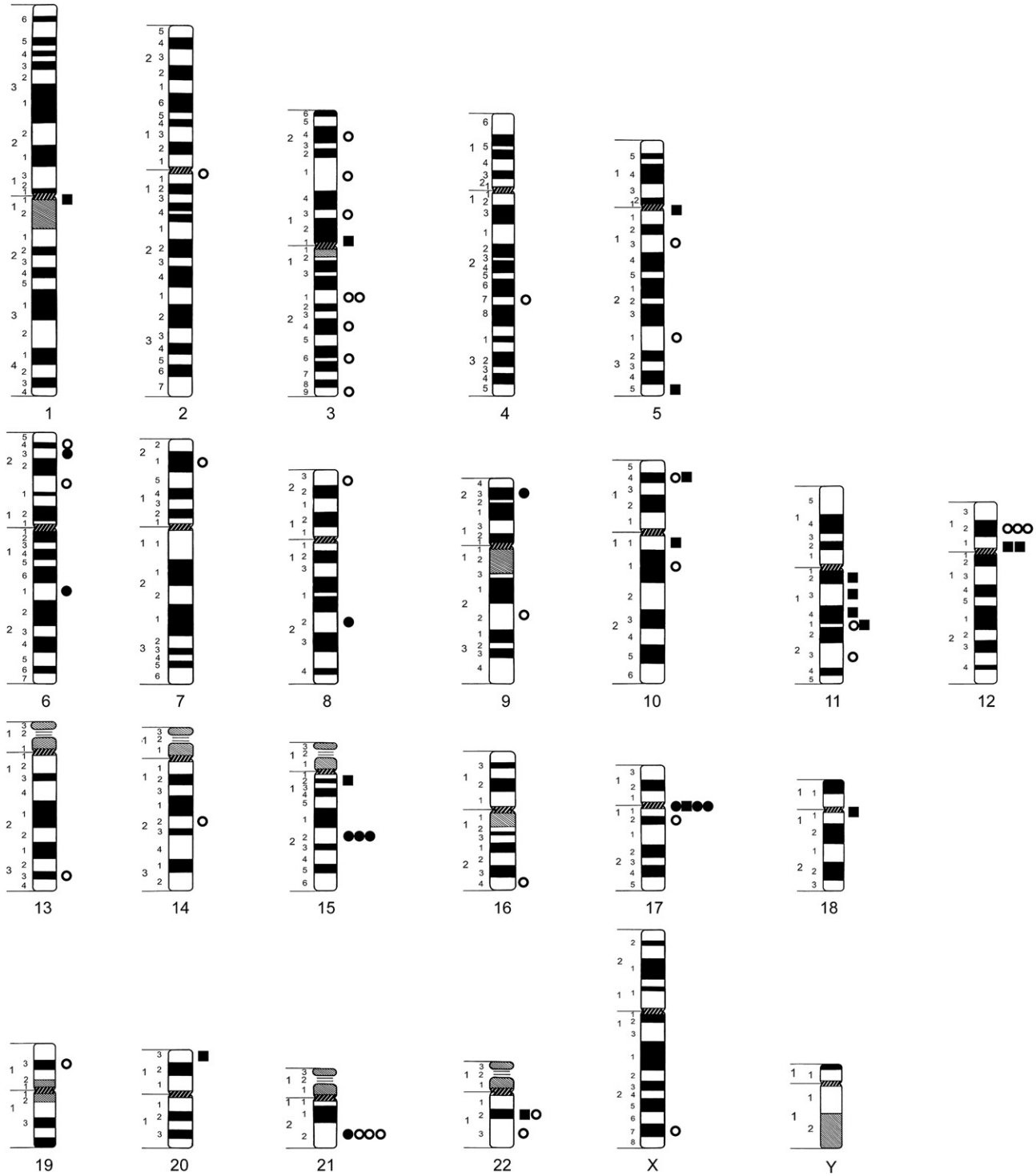

Fig. 3. Breakpoint map of translocations involving two or more chromosomes in 91 patients with secondary acute myeloid leukemia (AML) with abnormal karyotype. Closed circles represent breakpoints involved in the well-known and molecularly characterized AML-associated translocations t(6;9)(p23;q34), t(6;11)(q27;q23), t(8;21)(q22;q22), t(9;11)(p22;q23), t(9;22)(q34;q11), and t(15;17)(q24;q21). Open circles represent other balanced translocations; closed squares, unbalanced translocations.

comparable to that found by others [2–4,25]. We found that t-AML and AHD-AML patients, as compared to MDS-AML patients, significantly more often showed an abnormal karyotype. This could be attributed to the fact that a significantly lower number of MDS-AML patients had been treated with chemotherapy and/or irradiation ($P < 0.001$). Patients in the t-AML group were also more often found to have abnormal mitoses only, as well as a complex karyotype with

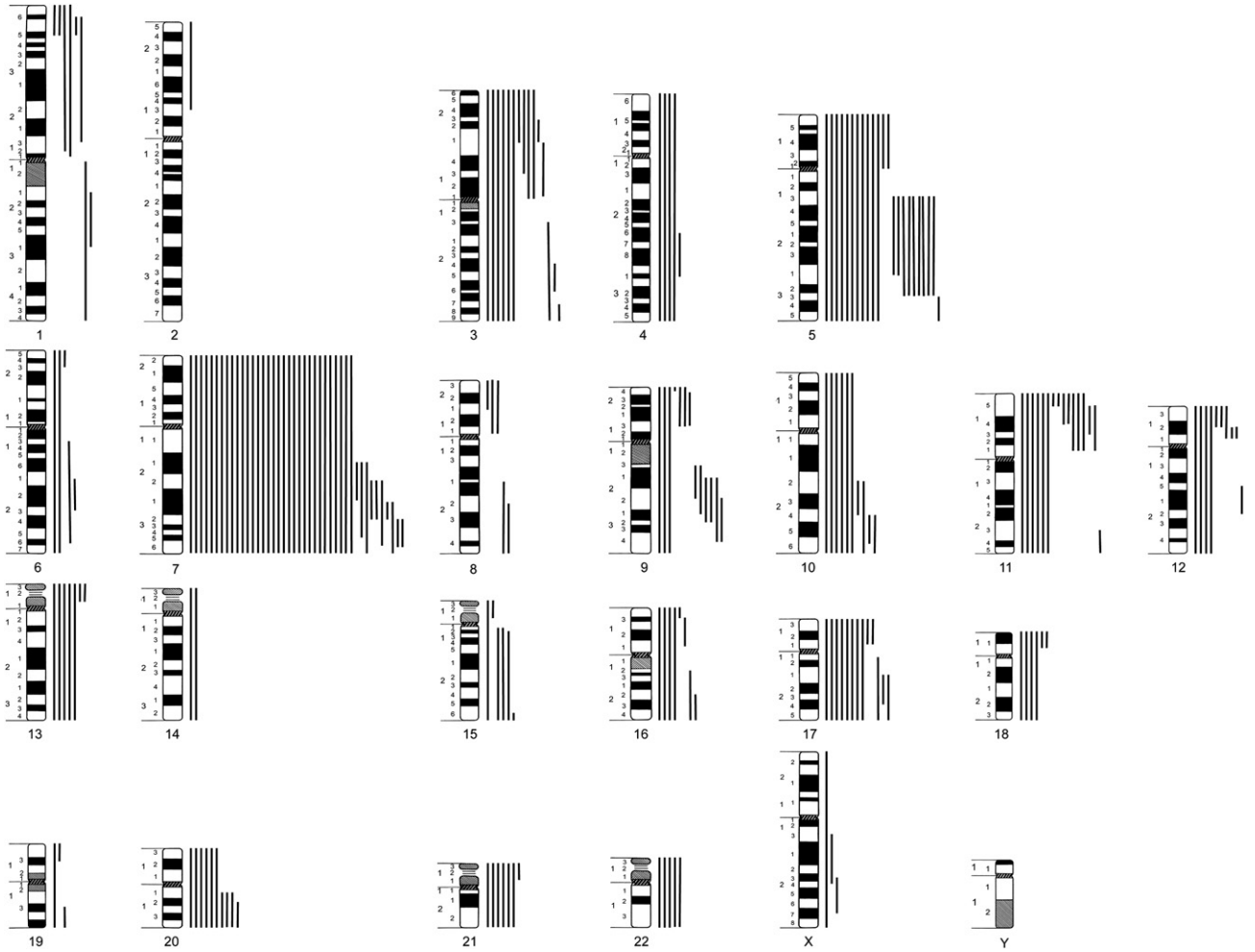

Fig. 4. Imbalance map of genomic losses in 91 patients with secondary acute myeloid leukemia with abnormal karyotype. Each bar represents one patient.

five or more unrelated aberrations, which might be explained by the previous treatment. Grimwade et al. and Mauritzson et al. also found a complex karyotype to be more common in t-AML than in de novo AML [2–4]. A reason why this was not confirmed in our material could be that our de novo AML patients were age matched, as we have previously shown that a complex karyotypes tend to be more common among old patients [5]. A mixture of numerical and structural aberrations was found more often in the t-AML group compared to the MDS-AML and AHD-AML groups and to the de novo AML group. Ben-Yehuda et al. and Horiike et al. found *TP53* to be mutated in 38% and 50% and microsatellite instability in 94% and 40%, respectively, of t-AML patients, which could explain the higher number of aberrations in these patients [26,27]. They also found this replication error phenotype to be correlated to −5/5q− and −7/7q−. This correlates with our findings of monosomy 5, del (5q) and monosomy 7 being more common in t-AML patients, although the difference was only significant for monosomy 7. Smith et al. found frequencies of chromosome 5 and 7 abnormalities comparable to those in our t-AML patients [28].

Comparing the maps of genomic gains and losses between de novo AML patients [5] and the s-AML patients, there were no differences in location or number of gained or lost genomic material. However, translocations were much more common among de novo AML patients, and in particular, unbalanced translocations were seen with higher frequency ($P = 0.01$). This is in contrast to the findings by Mauritzson et al. [4].

We found t(8;21), t(15;17), and inv(16) in one, three, and one patient, constituting 1.9%, 5.6%, and 1.9%, respectively, of t-AML patients. These aberrations were not found in the other two groups of patients with s-AML. In the literature, the frequency ranges 0–5% of t-AML [28–31]. Grimwade et al. found t(8;21) and inv(16) with a frequency of 2% and 1%, respectively, in s-AML [2,3]. This is comparable to our frequencies of 0.7% for each of these aberrations in the whole group of s-AML. All three patients with t(15;17) had previously been treated with irradiation only, and it could be argued that irradiation is not leukemogenic enough to cause s-AML, and that these patients might have de novo AML. At the International Workshop on the Relationship of Prior Therapy to Balanced Chromosome Aberrations in

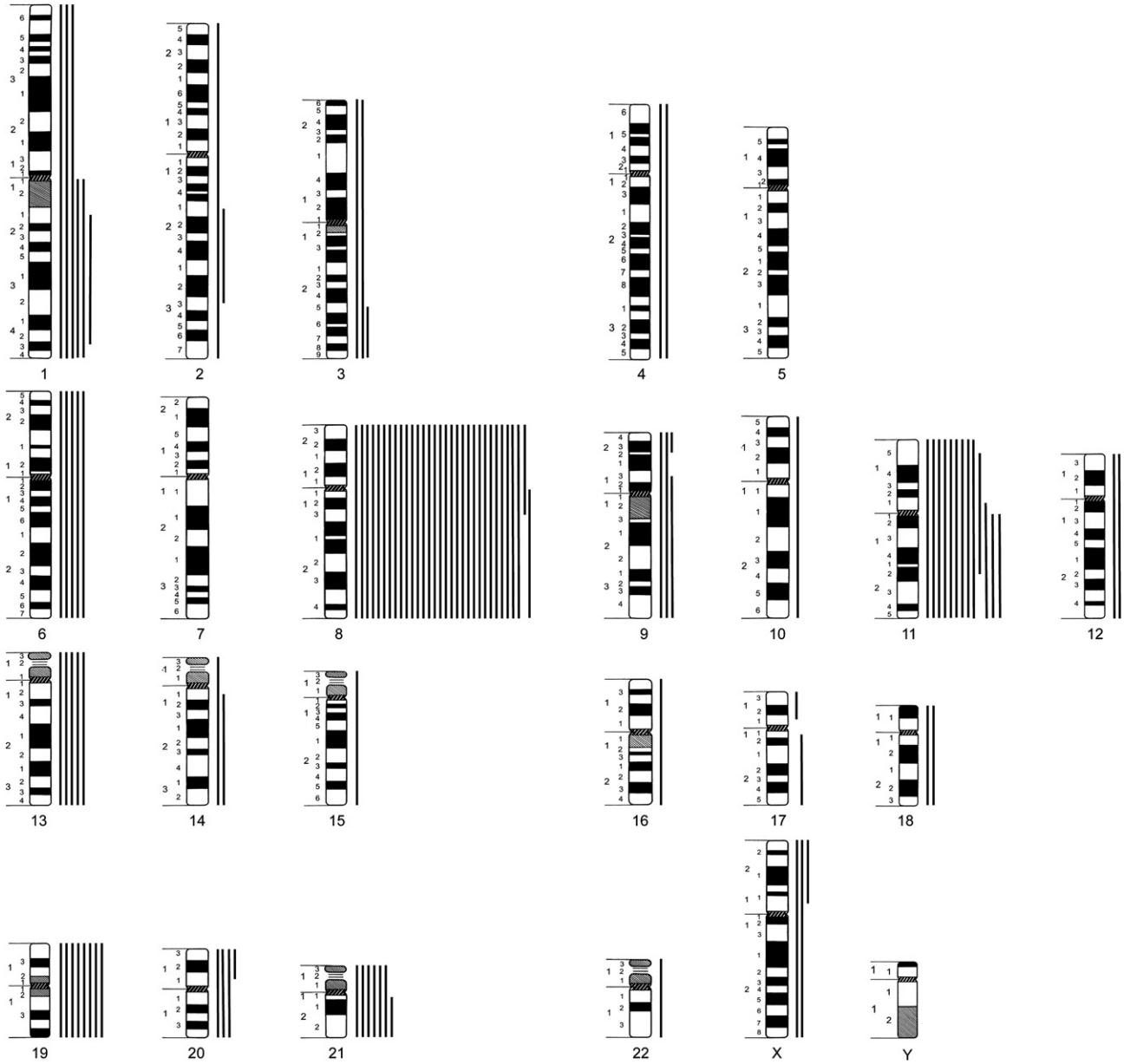

Fig. 5. Imbalance map of genomic gains in 91 patients with secondary acute myeloid leukemia with abnormal karyotype. Each bar represents one patient.

Therapy-Related Myelodysplastic Syndromes and Acute Leukemia, however, 12 of 41 patients with t-AML and t(15;17) were reported to have been treated with irradiation alone [32]. This supports the theory that radiotherapy may induce s-AML, even though the connection is not as well established as it is with topoisomerase II inhibitor treatment and s-AML with t(15;17) or inv(16) [32].

Favorable aberrations were more common in younger patients, whereas some of the adverse cytogenetic aberrations (−5/del(5q), −7/del(7q), and −17) were more often found in older patients—those older than 55 years. We therefore extracted a group of de novo AML patients matched for age and sex to the s-AML group. In the de novo AML group, the frequencies of t(8;21), t(15;17), and inv(16) were almost comparable to those of the whole s-AML group. Among the adverse aberrations, only monosomy 7 was significantly more common in the s-AML group compared to the age-matched de novo AML group ($P = 0.03$). Almost 20% of the s-AML patients had −7, and in the t-AML group every third patient had −7. This is in accordance with monosomy 7 being associated not only with age but also with previous treatment with chemotherapy and/or irradiation. Monosomy 5 and del(5q) was also found most frequently in the t-AML group, but because of the small number of patients, this was not statistically significant.

The frequency of −7 that we found is comparable to that of Iurlo et al., Mauritzson et al., and Smith et al. [4,28,29]. Grimwade et al. found a lower frequency of −7, but comparable frequencies of −5, del(5q), and del(7q) [2,3]. Le Beau et al. reported −7 in 70% of their patients, but they also

Table 4
Cytogenetic features of 42 adult patients with MDS-AML and cytogenetic analysis both at diagnosis of MDS and at diagnosis of AML

Karyotype	No. of patients
Normal at diagnosis of MDS	23
Normal → normal	15
Normal → abnormal	8
Additional numeric aberrations	4
Additional structural aberrations	3
Additional num. and struc. aberrations	1
Abnormal at diagnosis of MDS	19
Unchanged	5
Aberrant → evolution	10
Aberrant → regression + evolution	2
Aberrant → regression	2
New clone	0
Additional numeric aberrations	4
Additional structural aberrations	4
Additional num. and struc. aberrations	4
Fewer numeric aberrations	2
Fewer structural aberrations	2
Fewer numeric and strucural aberrations	0

Abbreviations: MDS, myelodysplastic syndrome; AML, acute myeloid leukemia.

Table 5
Abnormalities, previously never reported in acute myeloid leukemia, found in the present study

Abnormality	Sex/age (y)	FAB subtype	Sole change
t(X;2;5)(q27;q11;q13)	F/31	M2	No
t(3;3)(q29;p13)	F/70	M4	No
t(4;21)(q27;q22)	F/69	M2	No
der(5)t(1;5)(q31;q33)	F/56	M6	No
der(5)t(5;11)(q35;q12)	F/76	M2	No
der(5)t(5;15)(q11;q11)	M/74	M7	No
t(5;16)(q31;q24)	F/52	M2	No
t(6;12)(p21;p12)	M/54	M2	No
t(9;21)(q22;q22)	F/75	M2	Yes
der(10)t(1;10)(q11;q11)	F/68	M3	No
t(10;13)(q21;q33)	M/74	M7	No
der(11)t(3;11)(q25;p14)	F/80	M2	No
der(12)t(12;14)(p13;q11)	F/42	M7	No
t(14;21)(q22;q22)	F/67	M1	No
der(17)t(5;17)(p11;p10)	F/74	M2	No
der(17)t(17;20)(p13;p11)	F/31	M2	No
der(18)t(1;18)(q21;q25)	M/54	M2	No
der(18)t(11;18;22)(q14;q11;q12)	M/72	M6	No

Abbreviation: FAB, French–American–British.

found an abnormal karyotype in 98% of the patients, indicating patient selection [30].

Aberrations involving 11q23 (*MLL* gene) was found in only three patients, giving a frequency of 1.9%, which is low compared to some studies [4,25,28] but comparable to others [2,3]. An explanation for this discrepancy could be a difference in the number of patients treated with topoisomerase II inhibitors, which predispose for *MLL* rearrangements [33].

We found that all eight patients with 3q abnormalities also had monosomy 7. This is in accordance with earlier published studies. In a material of 77 t-MDS and t-AML patients with rare recurrent aberrations, Block et al. identified der (3q21∼q26) in 17 patients [23]. The most common secondary abnormality was −7/del(7q), which was found in 14 patients (82%). The association between der (3q21∼q26) and monosomy 7 was also described by Fonatsch et al. [24]. The strong association between −7/7q- was unique for der(3q21∼q26) in the material of Block et al. As mentioned earlier, in these studies a skewing of the M:F ratio was noted, and indeed, all patients with der (3q21∼q26) and −7/del(7q) in the material of Block et al. had been treated with alkylating agents for their primary neoplasm [23,24].

Twenty-five percent of the chromosome breakages in s-AML were localized in pericentromeric regions. Corresponding to the findings by Andersen et al., we found pericentromeric breakage more often in complex karyotypes as compared to karyotypes with one to four aberrations, which might indicate a correlation between genetic instability and pericentromeric breakage. We also found chromosomes 1, 5, 7, and 13 to have the highest number of centromeric breakage [34].

Investigating the cytogenetic changes during the progression from MDS to AML was possible in 42 of the 73 MDS-AML patients. We found that most patients with normal karyotypes at diagnosis of MDS also had a normal karyotype at progression to AML, whereas patients with aberrations at diagnosis of MDS more often showed cytogenetic evolution ($P = 0.01$). This might indicate a higher degree of genetic instability in the latter patients. Half of the patients with an abnormal karyotype at diagnosis of MDS showed genetic evolution during progression to AML, but no patient acquired a new, unrelated clone. Categorizing MDS-AML as one entity, regardless of whether the patients had been treated with chemotherapy during the MDS phase, is supported by the absence of relation between chemo therapy treatment during MDS phase and evolution in karyotype at progression to AML in the present material.

There was no difference in distribution among FAB subtypes in the s-AML groups, except for M6 and M7 being more frequent in the AHD-AML group, which could be attributed to seven of the AHD-AML patients having a diagnosis of primary myelofibrosis before the AML diagnosis, as M7 is the most common subtype in primary myelofibrosis evolving to AML.

In conclusion, t-AML is characterized by a higher degree of genetic instability than MDS-AML and AHD-AML, as a combination of numerical and structural aberrations, a complex karyotype, abnormal mitoses only, and hypodiploidy are more frequent in t-AML. Further, MDS patients with an abnormal karyotype are more likely to demonstrate cytogenetic evolution during progression to AML than MDS patients with a normal karyotype. Last, when we compared s-AML to an age- and sex-matched de novo AML group in this population-based material, we found

few differences, with only monosomy 7 being significantly more frequent in s-AML. Thus, s-AML and de novo AML, on the genetic level, are very similar diseases, a finding that points to accumulated genetic hits that give rise to de novo AML, lead to the same genetic outcomes as in s-AML.

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