Ring chromosomes in human neoplasias

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Accepted in revised form for publication by M. Schmid, 25 January 2008.

Abstract. Though reported from a wide variety of human neoplasias, ring chromosomes, in general, are a rare finding in these diseases. The majority were detected by chance when tumors were screened for chromosomal aberrations. In most cases they are a part of highly complex karyotypic alterations and therefore part of unfavourable prognostic factors. However, in some tumor entities (e.g. tumors of mesenchymal origin) they are of such high prevalence (up to 70% of these tumors) and of such extraordinary specificity that they can even serve as cytogenetic hallmarks for differential diagnosis and for prognostic purposes. The well-known technical problems in malignant cells of achieving high banding quality to define all single chromosomal alterations have severely hampered clear identification of the chromosomes involved in rings until recently. Substan-

tial progress of ring identification could only be achieved when molecular cytogenetic techniques became available. By these techniques it could not only be shown that certain breakpoint regions nonrandomly contribute to ring rearrangements which – at least in certain malignancies – are of basic importance, but also the molecular consequences of these changes could be defined in some cases. The present review summarizes a great number of reports on a total of 760 ring chromosomes in human neoplasias at different sites, but includes only cases with clearly identified rings. In addition, the molecular consequences of ring formation are addressed wherever pertinent information has recently been presented in the literature.

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Ring chromosomes have been observed in a wide variety of human neoplasias. As reviewed by Sandberg (1980), first well-documented reports date back to 1959 (solid tumor: Makino et al., 1959) and 1962 (leukemia: Sandberg et al., 1962). Although not being a very frequent finding in general (e.g. about 10% at maximum in epithelial cancers, and less than 10% in hematopoietic neoplasias), they apparently are of some impact on the tumors in which they are present. In leukemias, for instance, the presence of ring chromosomes seems to be associated with poor prognosis in most but not all cases. In some tumor subentities, however, they are so frequent and typical that they can even serve as cyto-

genetic hallmarks (Gisselsson et al., 1999) for differential diagnosis (see below). For instance, 63% of the atypical lipomatous tumors (ALT) studied in 1996 by the CHAMP group contained ring chromosomes (Rosai et al., 1996).

Before the advent of fluorescence in situ hybridization techniques several problems have considerably hampered the characterization of chromosomal rings by banding and the correct interpretation of their meaning for a given neoplasia. Their effect may mainly be caused by two basic genetic changes in consequence of their formation: loss of distal genetic material of the involved chromosomal segments (harbouring e.g. tumor suppressor genes), and rearrangement of two breakpoint regions (thus possibly forming fusion genes). Both processes are of well known basic importance for malignant transformation. In addition, general chromosomal instability may be introduced into the karyotype by the presence of ring chromosomes, particularly by dicentric ones, because of the so-called break-fusion-bridge mechanisms (see below). It may be a source of tumor heterogeneity. In consequence, as will be shown in the follow-

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ing, amplification of involved genes must be considered as an additional (secondary) effect of ring chromosome formation.

For the present review papers on ring chromosomes were recruited from the 'Mitelman catalogue' (Mitelman et al., 2004) using a searching system developed by Hiller et al. (2004). In addition, other sources were screened under this aspect (e.g. Pubmed). The tables will only present reports on rings whose chromosomal derivation was identified. A plethora of nonidentified rings, in addition, has been mentioned in many papers, which, however, will only be considered for the estimation of the prevalence of ring chromosomes in certain entities of human neoplasias.

Methodology of identification

Just from the beginning of tumor cytogenetics, ring chromosomes have been mentioned from various neoplasias, but identification of the involved chromosomes was not possible at that time. Therefore, results of those early reports will only marginally be considered in this review.

Classical banding technology was for a long time, up to the 90's of the last century, the only way to identify and characterize ring chromosomes in clinical cytogenetics and also in cancer cytogenetics (Heim and Mitleman, 1995). For this reason, many of these attempts failed because of the small size or the low banding quality, but also because of the complexity of rearrangements of some of the rings. Very often the well-known low banding quality of tumor chromosomes does not allow detailed definition of the involved chromosomes or chromosomal segments. FISH techniques, however, have greatly improved the possibilities of identification of the latter and have also paved the way to understand the molecular changes caused by ring formation.

Fluorescence in situ hybridization techniques using various DNA probes efficiently helped to overcome the problems outlined above (Gisselsson et al., 1998a). Chromosome-specific alphoid DNA repeat probes readily detect centromeric areas (Koch et al., 1989; Hopman et al., 1991; Nietzel et al., 2002), breakpoint spanning cosmid and YAC-probes can be used for defining the involved breakpoint regions and relevant genes (Kievits et al., 1990; Rowley et al., 1990) and telomeric probes document the lack of telomeres on the rings (Yan et al., 2003). Chromosome libraries are suitable for identifying the affected chromosome(s) by multicolour-FISH (Zitzelsberger et al., 2002) or spectral karyotyping (Mrozek et al., 2002) and 'reverse painting' detects the chromosome of origin, particularly if very small rings have to be identified (Carter et al., 1992; Chudoba and Senger, 2002). Comparative genomic hybridisation (CGH) (Kim et al., 2001; Feuerstein et al., 2002) allows detection of genomic losses and amplifications caused by ring formation (Szymanska et al., 1996; Nishio et al., 2001a, b; Micci et al., 2002).

In many examinations a combination of several of these techniques brought the most convincing results (Fadl-

Elmula et al., 2001; Micci et al., 2002; Schoch et al., 2002). In addition, these technological advances eventually allowed understanding the role ring chromosomes play in the process of tumor formation and progression (see below).

Phenomenology

A high variety of size, number, and shape characterize ring chromosomes of human neoplasias. Tiny additional chromosomal elements with ring structure up to very large rings composed of more than one chromosome mark the spectrum of rings in malignant diseases. In several cases the ring chromosome is the only visible change in the karyotype but more often it is accompanied by a varying number of additional chromosomal abnormalities. While in the former case the ring chromosome may causatively be involved in the development of the neoplasia, the latter phenomenon rather points to an addition of the ring in the process of karyotype evolution as a secondary change.

Gisselsson et al. (1999) conclude from their findings in eight cases of acute myeloid leukemia, 17 solid tumors, and five cases of constitutional rings that 'human ring chromosomes can be broadly divided into two different categories based on structure as well as on behaviour: the first category consists of rings not containing amplified sequences. These can be identified by chromosome banding techniques and they frequently occur together with gain, loss, or structural rearrangement of the chromosome of origin. They show C-bands and α -satellite arrays similar to the corresponding normal chromosome. In more than half of the cases, such rings contain subtelomeric sequences, whereas telomeric repeat sequences are rare... The second category consists of rings that contain amplified chromosomal material. Chromosome banding produces an unspecific band pattern and the rings often occur without concurrent karyotypic changes of the chromosome of origin. C-bands and α -satellite sequences frequently have an abnormal distribution or are completely absent from the rings. In rings devoid of alphoid DNA, formation of a neocentromere may occur. Subtelomeric sequences are rarely present. Intercellular variation in ring size and number is great, owing to frequent recombination, most probably through BFB (break-fusion-bridge, – annotation of the author) events' (end of citation).

As will be shown in the following these phenomenological predictions will be found fulfilled in only those cases that can be subjected to all molecular cytogenetic techniques presently available. This, however, is the exception rather than the rule in the performed analyses, as in most cases ring chromosomes are detected by chance in the frame of screening neoplasias for karyotypic changes. This will be reflected in the Tables 1 to 4 which present only those cases where at least the chromosome affected by ring formation was identified. The large number of non-identified rings found in many malignancies will, therefore, not be considered here in detail.

Ring chromosomes in human leukemias and lymphomas

After the first report of a ring chromosome in a human leukemia (Sandberg et al., 1962), rings of various chromosomal origins were detected in a number of more or less sporadic cases. Sandberg (1990) summed up 85 cases – the majority were acute non-lymphoblastic leukemias – and a series of further reports followed until recently. In the majority of the cases examined by classical banding analysis the chromosome(s) forming the corresponding ring could not be clearly defined.

The incidence of cases with ring chromosomes is generally rather low in human hematopoietic neoplasias, but apparently varies slightly between the different entities. If only those studies are considered in which ring chromosomes are mentioned at all, 7.4% of the evaluated 1464 cases of acute nonlymphocytic leukemia (ANLL) contained ring chromosomes, 6.8% of chronic lymphocytic leukemia (CLLs), 5.9% of myelodysplastic syndromes (MDS) and 5.1% of the lymphomas, while their incidence in acute lymphoblastic leukemia (ALL, 3.4%) and multiple myeloma (1.9%) was even distinctly lower. Several examinations of larger populations of patients merit being mentioned. A study on 125 AML cases with complex karyotypic aberrations detected rings in 15 cases (Schoch et al., 2002). Of 112 cases of untreated myelodysplastic syndromes three showed a ring chromosome in addition to other anomalies (Solè et al., 1992). Among a consecutive series of 152 childhood ALLs, however, only one case with a ring chromosome was found (Andreasson et al., 2000), as was found among 200 multiple myelomas (Sawyer et al., 1995). In a series of 23 Chinese patients with chronic myeloid leukemia (CML) in transformation, one showed a r(4) (Tien et al., 1989).

The use of FISH techniques not only helped to identify the affected chromosomes (Table 1) but also detected non-randomness of the involvement of individual chromosomes. If all 371 rings of hematopoietic neoplasias, presented in Table 1, are summarized, chromosome 11 was most often involved (about 15% of all reported ring chromosomes in leukemia), followed by chromosome 7 (14%), 21 (~ 9%), and 5 (~ 6%). All other chromosomes were much less often (5% or less) affected by ring formation in hematopoietic neoplasias.

If, however, single entities are evaluated, these percentages differ considerably in some cases. For instance, in chronic myeloproliferative diseases (CML + MDS) chromosome 7 was involved in 23% of all rings, 11 in 10.5%, 5 in 9%, and chromosomes 18 and 20 in 8%, each. In contrast, in acute myeloid leukemias chromosome 11 was clearly dominating (23%), while chromosome r(7) was clearly less frequent (11%), followed by r(21) (10%). The latter chromosome was most frequently affected by ring formation in ALL, i.e. chromosome 21 was involved in 25.5% of all rings, chromosome 9 in 16%, 7 in 14%, and 1 in 11.5%. Chromosome 1 was the dominating ring-forming chromosome in non-Hodgkin's lymphomas (18%). These differing involvements may well reflect genetic differences of karyotypic evolution in the various entities.

In most cases the ring chromosomes were part of a more or less complex karyotype. This means that the ring chromosomes seemed to be secondary changes in the course of disease development. In spite of their generally low incidence, just in the early studies rings were reported to be associated with a poor prognosis when present (Alimena et al., 1975; Sadamori et al., 1983; Whang-Peng et al., 1987; Lewis et al., 1988; Hiorns et al., 1997). No influence of the presence of a ring chromosome on prognosis, however, was found in the few cases of non-Hodgkin's lymphoma reported by Juneja et al. (1997).

In about 13% of the cases, the ring was the only aberration present in the karyotype (Table 1, case numbers in italics). If the solitary rings were causal in these cases, the pattern of chromosomal involvement could point to chromosomal segments critical for neoplasia development. Chromosome 7 was the chromosome most often involved also in the formation of solitary rings (in about 33% of the cases), and its involvement was nearly exclusively restricted to the myeloid line (with the exception of one single large B-cell lymphoma). All other chromosomes were more or less randomly affected. Several cases exhibited a ring chromosome in addition to one basic leukemia-specific chromosomal change. While in those cases chromosome 7 also was the chromosome most frequently involved in the rings, no distinct association with a certain basic alteration was observed. In contrast, there were three independent cases of AML M3 reported, where the t(15;17) was accompanied exclusively by r(6) (Swansbury et al., 1985; Xue et al., 1992; Hiorns et al., 1997). A Philadelphia positive (Ph⁺) CML case must be mentioned, which 34 months after successful contrastex bone marrow transplantation developed a relapse characterized by a subclone with a r(18) accompanying the Ph chromosome (Calabrese et al., 1989).

The non-randomness of chromosomal involvement and their prognostic value rather early initiated examinations of the molecular changes caused by ring formation. With respect to ring chromosomes 11, signals of the *MLL* gene were found on the ring (Michaux et al., 2000; Yan et al., 2003), and *MLL* amplification in the form of size-variable ring chromosomes was observed in two patients (Streubel et al., 2000). In addition, chromosome 13 was shown to be involved in the rings and rRNA genes were amplified in these cases (Fonatsch et al., 2001). On the other hand, among 31 leukemias with *MLL* amplification, besides seven cases with r(11), other rings were also detected, e.g. r(5), r(5;17), and r(7) (Poppe et al., 2004). In an AML case with *MLL* rearrangements, in which chromosomes 10 and 11 were involved in the rings, an r(10) was detected including the 5' part of the *MLL* gene from chromosome 11q23 (Klaus et al., 2003). The 3' end of *ETV6* and the *MLL* gene were present on an r(11;12) in an AML case with a complex karyotype (Andreasson et al., 1998). Several other reports also point to oncogene amplifications caused by the instability of rings. Of particular interest is the case of a phenotypically normal patient with a constitutional ring chromosome 21 who developed AML. The leukemic cells revealed size-variable ring chromosomes 21 with amplification of the proto-onco-

Table 1. Identified ring chromosomes in human leukemias and lymphomas

Identified ring (breakpoints) ^a	No. of cases ^b	Leukemia type (FAB class) ^c	References
r(4)	1	1 CML	Tien et al., 1989
r(7)	(1)(1) ^d	1 CML (myeloid BP), 1 CML (AP)	Sandberg, 1990 (review); Terre et al., 2004
r(9)t(9q;16p;22q)	1	1 CML	Morel et al., 2003
r(11)(:p11.2;q13.1::q14:) ^e	(2) ^a	2 CML (1 Ph-, 1 Ph+)	Starke et al., 2001
r(15)	1	1 CML	Lai et al., 1987
r(17)	4 (2) ^d	2 CML (myeloid BP), 1 CML (before BP), 1 CML (erythroblastic BP)	Sandberg, 1990 (review)
r(18)	3(1) ^d	1 CML (myeloid BP); 1 CML after BMT	Da Silva et al., 1988; Calabrese et al., 1989; Sandberg, 1990 (review)
r(19)	1	1 CML	Carbonell et al., 1982
r(20)	1	1 CML after BMT	Calabrese et al., 1989
r(1)(p35;q31)	1	RAEBT	Duell et al., 2006
r(2)(p21;q31) ^e	2	1 RA, 1 RAEB	Harbott et al., 1998; van Limbergen et al., 2002
r(3)	2	1 RAS, 1 RAEB	Jenkins et al., 1989a; Gibbons et al., 1994
r(5)(p13;q13) ^e	7 (1)	1 RAEBT, 3 RAEB,+1 CMMoL, 2 MDS	Musilova and Michalova, 1988; Lai et al., 1995; GFCH, 1996; Engel et al., 1997; Streubel et al., 1998; Yan et al., 2001, 2003; van Limbergen et al., 2002
r(6)	4 (1)	3 MDS; 1 CMMoL	Pedersen-Bjergaard et al., 1990; Tien et al., 1994; Passmore et al., 1995; GFCH, 1996
r(7)(p22→p12;q11.2→q36)	14 (5)	6 RAEB; 1 MDS with dysplastic eosinophilia, 2 CMMoL, 3 RAEB, 1 sMDS, 1 PMMM	Slee et al., 1981; Emilia et al., 1989; Gibbons et al., 1994; Viguie et al., 1995; Wang et al., 1997; Sessarego et al., 1998; Soenen et al., 1998; Streubel et al., 1998; Bakotic et al., 1999; Hasle et al., 1999; Mauritzson et al., 2001; Gonzalez et al., 2004; Poppe et al., 2004
r(7;12)	2	2 RAEBT	Veldman et al., 1997; Sessarego et al., 1998
r(8)(p23;q24.1) ^e	3	2 MDS, 1 RAEBT	Fugazza et al., 1996; Keung et al., 1997 ^a ; Harrison et al., 2001
r(9;21)	1	1 RAEBT	Kim et al., 2001
r(11)(p15→p11;q23→q25)	6 (2)	1 RAEB, 3 RAEBT, 1 ET, 1 MDS	GFCH, 1984; Liozon et al., 1997; Kim et al., 2001; Mauritzson et al., 2001; Yan et al., 2001, 2003; Poppe et al., 2004
r(11;19)	1	1 RAEB	Kim et al., 2001
r(12)(p13→p12;q11)	2	2 RAEBT	Andreasson et al., 1998; Mauritzson et al., 2001
r(14)	1	1 RAEB	Park et al., 2002
r(15)	1	1 RAEBT	Kim et al., 2001
r(18)	3	2 RAEB, 1 RAEBT	GFCH, 1984; Smadja et al., 1989; Geddes et al., 1990; Michalova et al., 1999;
r(20)	5	4 RAEB, 1 MDS	Prieto et al., 1985; Sole et al., 1992; Sessarego et al., 1998; Streubel et al., 1998; Ma et al., 2002
r(21)(p?;q22) ^e	1	1 MDS	Streubel et al., 1998 ^a
r(21;22)	1	1 RAEBT	Kakazu et al., 1999
r(X)	(1)	1 RAEBT	Sole et al., 1992
r(Y)	1	1 NOS	Dewald et al., 1985
r(1)(p35→p11;q12→q41)	4 (1)	AML: 1 M1, 1 M3, 2 M5	Shi et al., 1993; Hda et al., 1996; Dolan et al., 2002; Frenny et al., 2003
r(2)(p15;q36) ^e	6	AML: 1 M0, 2 M4, 1 M5, 1 Mx	Pui et al., 1992; Shi et al., 1993; Cuneo et al., 1995; Tanaka et al., 2001; Charrin et al., 2002; Barjesteh van Waalwijk et al., 2003
r(2;11)(:p25::p15;q23::q37:) ^e	1	AML: 1 M4	Wang-Peng et al., 1987
r(3)(p26→p25;q27→q29)	9 (1)	AML: 1 M1, 2 M2, 1 M4, 3 M6, 2 NOS	Shiraishi et al., 1982; Huret et al., 1991; Gibbons et al., 1994; Vicari et al., 1994; Harrison et al., 2001; Odero et al., 2001; Reddy et al., 2001; Mrozek et al., 2002; Sait et al., 2002; Cigudosa et al., 2003
r(3;6)	1	AML: 1 NOS	van Limbergen et al., 2002
r(3;12)	1	AML: 1 M	Streubel et al., 1998
r(4)	2	AML: 1 M6, 1 NOS	Trent et al., 1983; Schoch et al., 2002
r(5)	12 (2)	AML: 1 M0, 1 M2, 2 M4, 3 M6, 5 NOS	Conjalka et al., 1983; Trent et al., 1983; Brandwein et al., 1990; Bower et al., 1994; Olopade et al., 1996; Sessler et al., 1997; Streubel et al., 1998, 2000; Fonatsch et al., 2001; Kim et al., 2001; Schoch et al., 2002; Poppe et al., 2004
r(5;12)	1	AML: 1 NOS	Willem and Mendelow, 1997
r(5;17)	2	AML: 1 M2, 1 NOS	van Limbergen et al., 2002; Poppe et al., 2004
r(5;21)	1	AML: 1 NOS	Schoch et al., 2002
r(6)(p25;q21→q27)	10 (2)	AML: 1 M0, 5 M2, 3 M3, 1 M4, t-ANLL	Swansbury et al., 1985; GFCH, 1988; Russell et al., 1988; Soekarman et al., 1992; Xue et al., 1992; Gebhart et al., 1993; Roman-Unfer et al., 1995; Hiorns et al., 1997; Raimondi et al., 1999; Strehl et al., 2001; Schoch et al., 2002
r(7)(p15→p12;q35→q36)	23 (5)	AML: 5 M2, 1 M3, 1 M4, 1 M5, 2 M6, 2 M7, 11 NOS	Kaneko et al., 1982; Arthur and Bloomfield, 1984; Fourth International Workshop on Chromosomes in Leukemia, 1984; GFCH, 1988; Hayashi et al., 1988; Pettenati et al., 1989; Heim et al., 1990; Lampert et al., 1991; Olopade et al., 1992; Zhao et al., 1993; Gibbons et al., 1994; Sato et al., 1995; Forrest et al., 1998; Raimondi et al., 1999; Wieser et al., 2000; van den Heuvel-Eibrink et al., 2001; Chessels et al., 2002; Schoch et al., 2002; Barjesteh van Waalwijk et al., 2003; Kobayashi et al., 2005
r(8)	9	AML: 3 M2, 2 M4, 2 M6, 2 NOS	Kerkhofs et al., 1982; Morgan and Hecht, 1985; Stamberg, 1987; Gisselsson et al., 1999; Salomon-Nguyen et al., 2000; Harrison et al., 2001; Lindvall et al., 2001; Berger and Busson, 2002

Table 1 (continued)

Identified ring (breakpoints) ^a	No. of cases ^b	Leukemia type (FAB class) ^c	References
r(9)	4	AML: 1 M4, 3 NOS	Mauritzson et al., 2002; Mrozek et al., 2002; Schoch et al., 2002; van Limbergen et al., 2002
r(9;11)	1	AML: 1 NOS	Schoch et al., 2002
r(10)	1	AML: 1 NOS	Klaus et al., 2003
r(11)(p15→p11; q14→q25)	39	AML: 1 M0, 4 M1, 7 M2, 6 M4, 4 M5, 7 M6, 1 M7, 9 NOS	Garson, 1980; GFCH, 1984; Johnson et al., 1985; Mamuris et al., 1989; Nakamura, 1989; El-Rifai et al., 1997; Fischer et al., 1997; Johansson et al., 1997; Liozon et al., 1997; Avet-Loiseau et al., 1999; Michaux et al., 2000; Streubel et al., 2000; Fonatsch et al., 2001; Lindvall et al., 2001; Tanaka et al., 2001; Chessels et al., 2002; Dastugue et al., 2002; Mrozek et al., 2002; Schoch et al., 2002; Cigudosa et al., 2003; Poppe et al., 2004; Zatkova et al., 2004
r(11;11)(p15q25::q?)	3	AML: 2 M2, 1 NOS	Mrozek et al., 2002; Poppe et al., 2004; Zatkova et al., 2004
r(11;12)	1	AML: 1 NOS	Andreasson et al., 1998
r(11;16)	1	AML: 1 NOS	Zatkova et al., 2004
r(12)	6	AML: 1 M1, 1 M2, 2 M7, 2 NOS	De Oliveira et al., 1992; Ribeiro et al., 1993; Huang et al., 1997; La Starza et al., 1999; Yan et al., 2001; Schoch et al., 2002
r(12;16)	1	AML: 1 M5	Stamberg, 1987
r(13)	3	AML: 1 M4, 2 NOS	Stamberg, 1987; Fonatsch et al., 2001; Leroux et al., 2002
r(13;15)	2	AML: 2 NOS	Mrozek et al., 2002; Welborn, 2004
r(14)	2	AML: 2 NOS	Conjalka et al., 1983; Berger and Busson, 2002
r(15)	3	AML: 3 NOS	GFCH, 1990; Teixeira et al., 1999; Leroux et al., 2002
r(16)	5	AML: 3 M6, 2 NOS	Trent et al., 1983; Stamberg, 1987; Raimondi et al., 1999; Schoch et al., 2002
r(16;18)	1	AML: 1 NOS	Mrozek et al., 2002
r(17)	1	AML: 1 M6	van Limbergen et al., 2002
r(18)	8 (3)	AML: 1 M0, 3 M4, 1 M6, 3 NOS	Fitzgerald et al., 1983; Testa et al., 1985; Lee et al., 1987; GFCH, 1988; Gibbons et al., 1994; Sawyer et al., 1995; Michalova et al., 1999; Schoch et al., 2002
r(18;20)	1	AML: 1 M6	Gisselsson et al., 1999
r(19)	3	AML: 3 M6	Kovacs et al., 1986; Cigudosa et al., 2003
r(20)	3	AML: 3 NOS	Geraedts et al., 1980; Archimbaud et al., 1998; Mrozek et al., 2002
r(21)	14 (3)	AML: 1 M0, 5 M1, 5 M4, 1 M5, 1 M7, 1 NOS	Olinici et al., 1978; Testa et al., 1979; Najfeld et al., 1989; Pui et al., 1992; Marlton et al., 1995; Falzetti et al., 2000; Fonatsch et al., 2001; Schoch et al., 2002; Harewood et al., 2003
r(21;21)	1	AML: 1 NOS	Heller et al., 2004
r(21;21;21;21)	1	AML: 1 M4	Mrozek et al., 2002
r(21;22)	1	AML: 1 M4	Sole et al., 1992
r(22)	2	AML: 2 NOS	Yunis, 1982; Velloso et al., 1996
r(X)(p22;q13) ^e	4	AML: 1 M4, 3 NOS	Garson, 1980; Chen et al., 1992; Marosi et al., 1992; Lindquist et al., 2000
r(1)(p36.1;q42) ^e	4 (1)	ALL: 1 B-, 1 pre-B-, 2 NOS	Waghay et al., 1986; Chervinsky et al., 1995; Elghezel et al., 2001
r(1;9)(q44;p12::p11;q24)	1	ALL: 1 NOS	Heerema et al., 1994
r(2)(p25→p23;q33→q37) ^e	2 (1)	ALL: 1 pre-B-, 1 NOS	Martineau et al., 1996; Kovacs et al., 2004
r(4)	(1)	ALL: 1 NOS	Chessels et al., 2002
r(7)(p22→p21;q11→q31)	6	ALL: 1 B-, 1 pre-B-, 2 T-, 2 NOS	Kristofferson et al., 1985; Gibbons et al., 1994; Cuneo et al., 1994; Sato et al., 1995; Dascalescu et al., 1999; Jarosova et al., 2003; Barber et al., 2004
r(8)(p23;q22→q24) ^e	1	ALL: 1 C-	Edelhäuser et al., 2000
r(9)	5 (2)	ALL: 1 early pre-B-, 4 NOS	Ludwig et al., 1989; Cuneo et al., 1995; Chessels et al., 2002
r(9;13)	1	ALL: 1 NOS	GFCH, 1993
r(10)	1	ALL: 1 L1	Heerema et al., 1999
r(11)	1	ALL: 1 pre-B-	Rosbach et al., 1998
r(12)	2	ALL: 1 'special type', 1 NOS	Latham et al., 1994; Leroux et al., 2002
r(13)	1	ALL: 1 'special type', 1 pre-B-	Jonveaux et al., 1990; Leroux et al., 2002
r(15)	(1)	ALL: 1 'special type', 1 NOS	Abdi et al., 1990; Leroux et al., 2002
r(16)(p13;q24) ^e	2	ALL: 2 T-	Mecucci et al., 1988; Schneider et al., 2000
r(19)	1	ALL: 1 NOS	Martin et al., 1996
r(21)	11 (2)	ALL: 1 L1, 1 pre-B-, 9 NOS	Stern et al., 1979; Werner-Favre et al., 1986; Kaneko et al., 1989; Heim et al., 1990; Uckun et al., 1998; Andreasson et al., 2000; Harewood et al., 2003
r(4)	1	CLL: 1 NOS	Jonveaux et al., 1990
r(7)(p11;q36) ^e /(p22;q11) ^e	3 (1)	CLL: 2 NOS, 1 B-	Yunis, 1982; Oscier et al., 1996; Wang et al., 1997
r(15)	3 (1)	CLL: 2 B-, 1 NOS	Lewin et al., 1988; Amiel et al., 1994; Lishner et al., 1995
r(17)	1	CLL: 1 NOS	Rimokh et al., 1993
r(X)	2 (1)	CLL: 2 NOS	Huret et al., 1989
r(9)	1	TPL	Taylor and Butterworth, 1986
r(16)	2	2 PCL	Yip et al., 1990; Nordgren et al., 2000
r(17)(p13;q21) ^e	2	2 TPL	Mecucci et al., 1988; Zver et al., 2004 ^a
r(19)	(1)	1 HCL	Haglund et al., 1994

Table 1 (continued)

Identified ring (breakpoints) ^a	No. of cases ^b	Leukemia type (FAB class) ^c	References
r(3)(p26;q29) ^e	2	2 multiple myeloma	Calasanz et al., 1997 ^a ; Smadja et al., 2001
r(5)	1	1 multiple myeloma	Smadja and Grange, 1998
r(6)	1	1 multiple myeloma	Kaufmann et al., 2003
r(8;12)(:q24.3q21.1::q24.1p13:) ^e	1	1 multiple myeloma	Sawyer et al., 1998
r(X)	1	1 multiple myeloma	Lai et al., 1998
r(1)(p36;q43) ^e	6	NHL: 3 NMZB, 1 LB, 1 FL, 1 mixed TCL	Lakkala-Paranko et al., 1987; Dierlamm et al., 1996; Horsmann et al., 2001; Itoyama et al., 2002; Ferti et al., 2004 ^d
r(1;7)	1	NHL: 1LL	Dascalescu et al., 1999
r(2)(p?;q?)	1	NHL: 1FL	Lestou et al., 2003
r(3)(q25;q27) ^e	1	NHL: 1 FL	Koduru et al., 1997
r(4)(p16;q31) ^e	1	NHL: 1 DSI	Speaks et al., 1992
r(6)(p25;q27) ^e	1	NHL: 1 SMZB	Ott et al., 2000
r(7)(p22;q22) ^e	5 (1)	NHL: 1 LL, 1 MCL, 1 LB, 1 TCL, 1 SMZB	Oscier et al., 1996; Dascalescu et al., 1999; Mohren et al., 2003; Viaggi et al., 2004 ^a ; Tamaska et al., 2006
r(8)(p23;q24) ^e	3 (1)	NHL: 1 FL, 1 LB, 1 matB	Reeves and Pickup 1980; Arcaroli et al., 1999; Wlodarska et al., 2004
r(12)	2	NHL: 1 LB, 1 matB	Mark et al., 1978; Lambrechts et al., 1995
r(13)	2	NHL: 1FL, 1 MCL	San Roman et al., 1982; Dave et al., 1999
r(14;18)	1	NHL: 1 matB	Juneja et al., 1997
r(17)	2	NHL: 2 FL	Juneja et al., 1997; Fan and Rizkalla, 2003
r(18)	1	NHL: 1 FL	Lestou et al., 2003
r(19)(p13;q13)	2	NHL: 1 LB, 1 FL	Cabanillas et al., 1988; Bosga-Bower et al., 2003
r(22)	3	NHL: 1 MCL, 1 MFS, 1 PTCL	Schlegelberger et al., 1994; Mohr et al., 1996; Nowotny et al., 1996
r(X)	3	NHL: 1 LB, 1 FL, 1 MCL	Goyns et al., 1993; Dave et al., 2002; Lestou et al., 2003
r(Y)(p11;q12) ^e	2	NHL: 1 LB, 1 matB	Whang-Peng et al., 1995; Dave et al., 2004 ^a

^a As far as determined.

^b Numbers in italics represent cases with ring as sole aberration.

^c CML: chronic myeloid leukemia; BP: blastic phase; AP: accelerated phase; BMT: bone marrow transplantation; RAEB: refractory anemia with excess of blasts (T: in transformation); RA: refractory anemia; RAS: refractory anemia with sideroblasts; CMMoL: chronic myelomonocytic leukaemia; ET: essential thrombocythemia; MDS: myelodysplastic syndrome; sMDS: secondary MDS; AML: acute myeloid leukemia; NOS: no other specification; ANLL: acute nonlymphocytic leukaemia; ALL: acute lymphocytic leukaemia (B-cell, T-cell Common), CLL: chronic lymphocytic leukemia; TPL: T-cell prolymphocytic leukemia; HCL: hairy cell leukemia; PCL: plasma cell leukemia; NHL: non-Hodgkin lymphomas; NMZB: nodal marginal zone B-cell lymphoma; LB: large B-cell l., FL: follicular l., DSI: diffuse small irregular lymphocytic l., TCL: T-cell l., PTCL: peripheral T-cell l., LL: lymphocytic l., SMZB: splenic marginal zone B-cell l.; MCL: mantle cell lymphoma; MFS: Mycosis fungoides (Sezary syndrome).

^d In addition to Ph chromosome.

gene *AML1* (21q22) within the rings (Streubel et al., 2001). Once more, rRNA genes were shown to be amplified in this case. *AML1* amplification was also detected in an MDS where the *AML1* gene signal was found on three to six copies of chromosome 21 material in a ring chromosome also containing chromosome 22 material (Kakazu et al., 1999). Four to seven *AML1* signals were reported from five cases with r(21) and a duplication of chromosome 21 in ALL (Harewood et al., 2003). These entire findings document that it is an instability of ring size which apparently is the cause of onco-gene amplification, the latter occasionally being associated with amplification of rRNA genes in some of these cases.

Ring chromosomes in human solid tumors

In many solid tumors ring chromosomes have been observed more or less sporadically, i.e. in the course of screening tumors for cytogenetic alterations. Clonal and non-clonal rings were described, but most often as a sign of a progressed tumor stage. Because of the well-known technical difficulties of cytogenetic analyses in solid tumors, in a

majority of cases the nature and structure of the observed ring chromosomes could not be defined in detail. About 390 ring chromosomes could be described at least with respect to the involved chromosome(s). Whenever the breakpoints contributing to the ring formation could be clearly analysed, the information obtained led to valuable insights into the meaning of ring formation in the process of malignancy.

Ring chromosomes in mesenchymal tumors

Ring chromosomes reach their highest incidence and also biological significance in mesenchymal tumors. In certain subentities up to approximately more than 70% of all examined tumors show ring chromosomes which in some cases are highly specific for the respective tumor entity (Nilbert, 1997) and often represent primary chromosome aberrations (Mandahl, 1996). Therefore, these subentities will be addressed first. On the other hand, there are also benign mesenchymal tumors which apparently are lacking ring chromosomes, as, for instance, shown for 191 pulmo-

Table 2. Identified ring chromosomes in mesenchymal tumors

Ring chromosome (breakpoints) ^a	No. of cases ^b	Type of tumor, remarks ^c	Reference(s)
Dermatofibrosarcoma protuberans			
r(1)	1	DFSP	Mandahl et al., 1990
r(4;17;22)(?::q22::q13.1;?) ^d	1	DFSP (+ trisomy 5)	Navarro et al., 1998
r(5)(p15;q35) ^d	1	DFSP [+ t(12;17;22)]	Gisselsson et al., 1998b
r(8;17)(:qter→q11.2::q21→qter:) ^d	1	DFSP	Nishio et al., 2001a
r(17)	12 (2)	DFSP	Pedeutour et al., 1994, 1995a; Minoletti et al., 1995; Stenman et al., 1995; Mandahl et al., 1996a; Vanni et al., 2000
r(17;22)(?:q21→q25::q13;?)	13 (1)	DFSP	Pedeutour et al., 1994; Minoletti et al., 1995; Naeem et al., 1995; Mandahl et al., 1996a; Vanni et al., 2000; Nishio et al., 2001b; Sirvent et al., 2003
Lipomatous tumors (including liposarcomas)			
r(1)	2	2 ALT	Becher et al., 1984; Mandahl et al., 1994
r(1;4;19;12;15)	1	1 LP	Sirvent et al., 2000
r(1;12)	18 (2)	10 ALT, 8 LPS	Pedeutour et al., 1999; Sirvent et al., 2000; Micci et al., 2002; Nilsson et al., 2004
r(3)	3	3 ALT	Heim et al., 1987
r(6;11;12;15)	1	1 LPS	Sirvent et al., 2000
r(8)(p23.3;q11.2) ^d	1	1 LP	Chen et al., 2000
r(11)+r(12)	1	1 LPS	Sirvent et al., 2000
r(11;12)	1	1 LPS	Pedeutour et al., 1999
r(12)(p13;q14→q24) = various	60 (6)	25 ALT, 1 LP, 34 LPS	Dal Cin et al., 1993b; Pedeutour et al., 1993, 1994, 1995b; Iwasaki et al., 1998; Mandahl et al., 1998; Gisselsson et al., 1999; Pilotti et al., 2000; Sirvent et al., 2000; Meis-Kindblom et al., 2001; Micci et al., 2002; Dahlen et al., 2003; Storlazzi et al., 2003
r(12;13)	1	1 LPS	Pedeutour et al., 1999
r(12;16)	1	1 LPS	Pedeutour et al., 1999
r(X;12)	1	1 ALT	Sirvent et al., 2000
Leiomyoma/Leiomyosarcoma/Rhabdomyosarc.			
r(1)(p32→p36;q21→q44) = various	26 (4)	25 ULM, 1 LMS	Becher et al., 1984; Nilbert et al., 1988; Fan et al., 1990; Nilbert and Heim, 1990; Kiechle-Schwarz et al., 1991; Pandis et al., 1991; Meloni et al., 1992; Rein et al., 1998; Polito et al., 1999; Quade et al., 2003; Gross et al., 2004
r(1;12)	1	1 ULM	Pandis et al., 1991
r(3)	1	1 MFT	Mansoor et al., 2004
r(4;12)	1	1 ULM	Vanni et al., 1989
r(5)	1	1 ULM	Vanni et al., 1991
r(6)	1	1 MS	Gollin and Janecka, 1994
r(7)(p22;q36) ^d	1	1 ULM	Fan et al., 1990
r(8)	3	2 LMS, 1 MFT	Sankary et al., 1993; Su et al., 1998; Griffin et al., 1999
r(8;10)	1	1 lipoleiomyoma	Pedeutour et al., 2000
r(9)	2	1 LMS, 1 MFT	Limon et al., 1986; Lestou et al., 2002
r(13)(p11;q34)	2 (1)	1 LMS, 1 RMS	Sreekantaiah and Sandberg, 1991; Voullaire et al., 1991
Bone and cartilaginous tumors			
r(1)	1	1 OS	Werner et al., 1998
r(4)(p16.3;q35) ^d	(1)	1 CHBL	van Zelderen-Bhola et al., 1998
r(6)	2	1 CHS, 1 FSB	Gunawan et al., 2000; Hallor et al., 2007
r(7)	1	1 GCT	Bridge et al., 1992
r(9)(p24;q34) ^d	1	1 CHS	Sawyer et al., 1998
r(10)(p15;q26) ^d	1	1 GCT	Bridge et al., 1992
r(11)(p15;q25) ^d /(p15;q13) ^d	2	2 GCT	Bridge et al., 1992; Sawyer et al., 2005
r(12)(q13;q15) ^d	19 (2)	17 OS, 1 GCT, 1 CTS	Bridge et al., 1992; Szymanska et al., 1996; Gisselsson et al., 1998a, 2002 ^a ; Zambrano et al., 2004
r(13)	1	1 PCD	Limon et al., 1998
r(15)	2	1 GCT, 1 CMF	Gisselsson et al., 1998a, 2002; Sawyer et al., 1998
r(17)	1	1 GCT	Schwartz et al., 1991
r(22)	4	1 OS, 3 EWS	Davison et al., 1989; Bown et al., 1994; Lopez-Gines et al., 1996; Szuhai et al., 2007
Other mesenchymal tumors			
r(1)	3	1 SS, 1 MT, 1 CCS	Limon et al., 1991; Ribotta et al., 1998
dic r(1;7)(:p36;q44::p22;q32:) ^d	1	1 MFH	Mohamed et al., 1997
t(1;12)	(1)	1 ME	Fletcher et al., 1991, 1994; Geurts van Kessel et al., 1999
r(3)	1	1 SS	Fletcher et al., 1991, 1994
r(6)(p25;q13) ^d	7 (2)	1 SS, 1 MT, 1 SCH, 4 THY	Fletcher et al., 1991; Dal Cin et al., 1993a; Fletcher et al., 1994; Mirza et al., 2000; Van den Berghe et al., 2002; Buddingh et al., 2003 ^a
r(7;16)(p14q31 of #7)	1	MFS	Mezzelani et al., 2000
r(9)(p24;q34)	3	1 SS, 1 SCS	Mohamed et al., 1997; Lestou et al., 2002
r(10)	4	1 MFS, 1 MFH, 1 ES, 1 NOS	Aspberg et al., 1995; Gisselsson et al., 1999; Storlazzi et al., 2003; Lualdi et al., 2004
r(12)	8	2 MT, 1 STCH, 5 MFH	Gibas et al., 1986; Nilbert et al., 1994; Gisselsson et al., 1999; Shadan et al., 2000
r(12;18)	1	1 SCS	Lestou et al., 2002
r(13)	1	1 GIST	Sreekantaiah and Sandberg, 1991

Table 2 (continued)

Ring chromosome (breakpoints) ^a	No. of cases ^b	Type of tumor, remarks ^c	Reference(s)
r(18)	2	SCS, RTS	Fleischman and Prigogina, 1977; Lestou et al., 2002
r(19)(p13;q13)	5	5 MFH	Mandahl et al., 1988a, b, 1989; Rydholm et al., 1990; Szymanska et al., 1995
r(20)(q10;q13) ^d	(1)	MFS	Meloni-Ehrig et al., 1999
r(21)(p13;q22) ^d	3	? MT, 1 MFH, 1 CMN	Tiainen et al., 1988; Mandahl et al., 1988a, b, 1989 ^a ; Varsa et al., 1989
r(22)(p13;q13) ^d	1	1 MFH	Mandahl et al., 1988a, b, 1989

^a As far as determined.

^b Numbers in italics represent cases with ring as sole aberration.

^c DFSP: dermatofibrosarcoma protuberans; ALT: atypical lipomatous tumor; LP: lipoma; LPS: liposarcoma (in most cases 'well-differentiated'); ULM: uterine leiomyoma; LMS: leiomyosarcoma; MS: myosarcoma; MFT: inflammatory myofibroblastic tumor; RMS: rhabdomyosarcoma; CHBL: chondroblastoma; FSB: fibrosarcoma of bone; GCT: giant cell tumors of bone; NOS: no other specifications; OS: osteosarcoma; CHS: chondrosarcoma; SCH: synovial chondromatosis; THY: thymoma; CMF: chondromyxoid fibroma; SCS: spindle cell sarcoma; EWS: Ewing sarcoma; CTS: cartilage tumor (special type); PCD: parachordoma; SS: synovial sarcoma; MT: mesothelioma; MFH: malignant fibrous histiocytoma; ME: mesenchymoma; CCS: clear cell sarcoma; MFS: myxofibrosarcoma; ES: epitheloid sarcoma; STCH: soft tissue chondroma; CMN: congenital mesoblastic nephroma; GIST: gastrointestinal stromal tumor; RTS: Reticulosarcoma.

^d Only from one case.

nary chondroid hamartomas (Kazmierczak et al., 1999). In the 242 identified ring chromosomes (Table 2) at least 299 chromosomes were involved, and this involvement was highly nonrandom. For instance, of the chromosomes forming the ring or part of the ring, 71% were derived from chromosome 12 in lipomatous tumors, and 49% in bone and cartilage tumors. In leiomyomas and leiomyosarcomas chromosome 1 was the chromosome most often involved (64%), and in dermatofibrosarcoma protuberans it was chromosome 17 (60%), followed by 21 (31%). As will be shown below, this nonrandomness markedly reflects the molecular changes in these malignancies.

Dermatofibrosarcoma protuberans (DFSP), though being a rare entity among sarcomatous tumors, is an exemplary tumor with respect to the meaning of ring chromosomes. The addition of the data of recent reviews on cytogenetics of DFSP (Sandberg and Bridge, 2003a; Sirvent et al., 2003) reveals 51 karyotyped tumors since the first attempts in 1990 (Bridge et al., 1990; Mandahl et al., 1990). Thirty-six of them (i.e. more than 70%) exhibit a ring chromosome, the rest shows other rearrangements. As shown in Table 2, the majority of the identified rings include parts of chromosomes 17 and 22 resulting in a genomic gain of the bands 17q23→q24 and 22q11→q12 (Pedeutour et al., 1994, 1995a). Other authors concluded from their investigations that amplification of chromosome 17 and 22 sequences in ring form is a characteristic aberration in DFSP (Naeem et al., 1995). In a few cases these rings involving chromosome 17 are added as the sole karyotypic anomaly to the normal karyotype (Minoletti et al., 1995; Naeem et al., 1995; Vanni et al., 2000; Table 2, case numbers in italics). This finding and the observation that in non-ring cases the same chromosomes often are involved in translocations led to molecular breakpoint analyses, as reviewed by Mandahl (1996). Both the rings and the linear der(22) contain a specific fusion of *COL1A1* with *PDGFB* (Simon et al., 1997; Sirvent et al., 2003). The breakpoint in the *PDGFB* gene proved to be remarkably constant placing exon 2 under the control of the *COL1A1* promoter (O'Brien et al., 1998). In contrast, the

COL1A1 breakpoint was found to be variably located within the exons of the α -helical coding region (O'Brien et al., 1998). This rearrangement results in production of a chimeric *COL1A1*-*PDGFB* RNA (Sandberg and Bridge, 2003a) increasing the production of PDGF locally and promoting autocrine and paracrine tumor growth. As Imatinib mesylate was developed as an inhibitor of the PDGF receptor tyrosine kinase, the rearrangement could promise new therapeutic approaches at least in the rare cases of metastatic DFSP (Maki et al., 2002; Sirvent et al., 2003; Bianchini et al., 2007).

It should, however, be noted that a few DFSP cases show other rings as e.g. a r(8;17) (Nishio et al., 2001a) or r(5)(p15q35) (Gisselsson et al., 1998b), the latter, however, aside multiple copies of *COL1A1* and *PDGFB*, included in a large marker chromosome. A complex involvement of sequences from chromosomes 17 and 22 in a ring chromosome 4, also resulting in *COL1A1*-*PDGFB* fusion, was also reported (Navarro et al., 1998). It should be noted that childhood DFSP, but also the closely related giant cell fibroblastomas, though containing the same rearrangement of chromosome 17 and 22 sequences, do not present with ring chromosomes (Sirvent et al., 2003). However, the ring 17/22 was also found in a Bednar tumor which also belongs to the DFSP family (Nishio et al., 2001b).

Large studies on lipomatous tumors have revealed a correlation between clonopathological features and karyotypes (Fletcher et al., 1996). Just in 1991 Cooper and Stratton (1991) stated that ring chromosomes have been detected in about 15% of the analyzed **lipomas**, but at that time most of these rings could not be identified. Some of them were suspected 'to arise through end-to-end joining of the 3q+ chromosome that is found as a result of the specific translocation involving chromosomes 3 and 12'. More recent examinations using various techniques of molecular cytogenetics could show that the overwhelming majority of the observed rings was constituted by chromosome 12 or parts of it (at least 85 cases reported so far: Table 2), particularly in **atypical lipomas and well-differentiated liposarcomas**. They

invariably contain amplified sequences from 12q, with a few exceptions including the *MDM2* gene (Nilsson et al., 2004). A more detailed FISH analysis using the ML12q1315 probe confirmed extensive painting of the ring chromosomes found in ten adipose tissue tumors, but painting was discontinuous, i.e., the ring chromosomes were never completely painted (Dal Cin et al., 1993a). Mertens et al. (2004) studied polymorphic loci on chromosome 12 in 14 cases of atypical lipomatous tumors showing one or more supernumerary ring chromosomes in order to shed light on the mechanisms behind the formation of those rings. Their molecular genetic analyses revealed that the tumor cells always retained both parental copies of chromosome 12 thus refuting the hypotheses of trisomy or duplication of chromosome 12 preceding the ring formation.

24 other reported rings contained other chromosomal material in addition to chromosome 12 (Table 2). It cannot definitely be excluded that also some of the reported rings involving chromosomes 1, 3, and 8 might also contain chromosome 12 material. Among 22 well-differentiated lipomatous tumors, for instance, five tumors showed rings including chromosome 1 segments in addition to chromosome 12 (Micci et al., 2002). The frequent co-amplification and colocalization of sequences from chromosomes 1 and 12 in rings, according to Nilsson et al. (2004) raises the question whether this is related to the mechanism of formation of these supernumerary rings or to the pathogenetic process. However, in the material examined by these authors absence or presence of extra copies of *COAS* genes could not be correlated with any clinical or histopathologic parameter. Ring chromosome 12 as the sole karyotypic anomaly (in addition to the 46 chromosomes) was found in four lipomas (Gisselsson et al., 1998a, 1999; Pilotti et al., 1998).

Liposarcomas (LPS) account for approximately 20% of mesenchymal tumors. At present they are subdivided into three major categories, 1) well-differentiated, 2) myxoid and round cell, and 3) pleomorphic LPS. As shown by a recent review of cytogenetics of LPS (Sandberg, 2004), this categorization in some way is associated with the presence or absence of ring chromosomes in the karyotype. Among the collected 107 tumors of the well-differentiated type, 81 had rings (i.e. 75%) while only two rings (i.e. 3%) were found in 66 tumors of the myxoid and round-cell type. One of five pleomorphic, 11 of 14 dedifferentiated, and one of three mixed LPS were also characterized by ring chromosomes. In the majority of the ring-positive cases (67.7%) the ring chromosome(s) accompanied several other chromosomal abnormalities, and in a considerable number of LPS (59%), more than one ring chromosome was found. In only one case, so far, r(12) in two samples has been added to the 2n karyotype as the sole karyotypic alteration (Gisselsson et al., 1999).

Considering the relatively rare cases (about 13–14%) with cytogenetically well-defined rings (Table 2), chromosome 12 is affected in the great majority of all cases, and chromosome 1 is additionally involved in about 30% of these rings (Table 2). In several cases an additional chromosome could be defined participating in the chromosome 12 rings. The critical meaning of ring chromosomes 12 or rings contain-

ing segments of chromosome 12 is supported by the finding of several cases of lipomas/liposarcomas presenting this anomaly as the sole karyotypic change (Pedeutour et al., 1993; Gisselsson et al., 1998a, 1999; Pilotti et al., 2000; Micci et al., 2002; Table 2: case numbers in italics). An extensive investigation of the structure and composition of rings in a series of 17 well-differentiated liposarcomas and atypical lipomas by comparative genomic hybridisation (CGH) combined with FISH (Micci et al., 2002) revealed that the ring formation leads to amplifications of sequences of chromosome 12q14→q15 including the *MDM2* gene, and to a co-amplification of variable segments from other chromosomes (Mandahl, 1996; Pedeutour et al., 1999). In addition, the rings, though displaying in vitro and in vivo stability, did not show signals of α -satellite DNA (Pedeutour et al., 1999). Nevertheless, these rings have a functional centromere as has been shown by the positive labeling with CREST sera and a specific anti-CENPC antibody (Sirvent et al., 2000). Nilsson et al. (2004) particularly studied amplifications of 1q21→q23 showing that among the sequences included in this amplicon three novel oncogenes could be found (*COAS1–3*). The most common localization of extra *COAS* signals in the studied lipomatous tumors was in supernumerary ring and giant marker chromosomes.

Also among the well-analysed **tumors of the bone and cartilage** (Bardi et al., 1991) a non-random involvement of chromosome 12 in the rings was reported (Table 2). While rings apparently are a rare finding in cartilaginous tumors (21/180 – Sandberg and Bridge, 2003b), they are more frequent in **osteosarcomas**. 22% of the 146 cases collected by Sandberg and Bridge (2003c) presented with rings, most of which, however, remained unidentified. Rings containing amplified material of chromosome 12q13→q15 are characteristic in parosteal osteosarcomas, 17 of 19 ring-containing cases showing an r(12). In this rare tumor entity these rings are present as the sole anomaly or accompanied by only a few other changes (Table 2, case numbers in italics). By this finding these tumors can be distinguished from conventional osteosarcomas (Sandberg and Bridge, 2003c), in which the rings always are embedded in numerous other chromosomal abnormalities. In addition, parosteal osteosarcomas are a prognostically favorable osteosarcoma subtype (Bridge et al., 1997); this fact pointing to a different prognostic value of rings as a sole anomaly vs. an anomaly embedded in a complex aberrant karyotype. Sequences from the long arm of chromosome 12 including the *SAS*, *CDK4*, and *MDM2* genes have been found to be amplified in these rings (Szymanska et al., 1996; Wunder et al., 1999). However, amplifications of these genes have also been found in a number of high-grade, metastatic osteosarcomas. By interphase FISH with probes for *CCND2*, *ETV6*, *KRAS2*, *D12S85* (on 12p), *cen12*, and *MDM2* (on 12q) Gisselsson et al. (2002) could show an amplification pattern of chromosome 12p specific genes by which grade III–IV tumors could be differentiated from grade I–II tumors.

In 15 out of 106 chondrosarcomas collected by Sandberg and Bridge (2003b), ring chromosomes were reported mostly as part of complex karyotypic alterations. In one chon-

droblastoma r(4) (Van Zelderen-Bhola et al., 1998) and in another 'cartilage tumor' r(12) (Zambrano et al., 2004) were reported as the sole karyotypic anomalies (Table 2, case numbers in italics).

In a recent review by Sandberg (2005) among 220 cytogenetically analyzed **leiomyomas** 13 cases with ring chromosomes were reported. As shown in Table 2, in a great majority of cases chromosome 1 was non-randomly involved in the rings which could be identified by cytogenetic and molecular cytogenetic techniques. Applying FISH with PAC-clones for the *HMGI7* gene which is located on 1p35, Polito et al. (1999) could not detect a signal on the r(1): 'This could suggest that *HMGI7* does not play a mechanistic role in leiomyoma similar to that observed with other high-mobility proteins'. In particular, r(1) or r(1;?) were found as the sole karyotypic anomaly in six of the examined uterine leiomyomas as part of a $2n = 46$ karyotype (Nilbert and Heim, 1990; Kiechle-Schwarz et al., 1991; Polito et al., 1999). This is not really in contrast to Sandberg's (2005) view that rings containing chromosome 1 may be secondary changes in these tumors, as the cases with r(1) as the sole karyotypic abnormality still are the minority. Just several years before Pandis et al. (1991) had suggested that r(1) formation is a preferred pathway in clonal evolution of uterine leiomyomas.

Ring chromosomes 12 and 19 are the most frequent rings found in **malignant fibrous histiocytomas (MFH)** (Table 2) as a part of a complex karyotype. In two myxoid MFH, two DFSP (see above) and one parosteal osteosarcoma (out of a series of 60 karyotypically abnormal non-lipogenic bone and soft tissue tumors), the ring chromosome was the sole cytogenetic anomaly or the only structural rearrangement (Örndal et al., 1992): 'All five tumors were borderline or low malignancy'. The authors concluded from these findings that supernumerary ring chromosomes alone are not associated with any particular histopathologic diagnosis, but may characterize a group of bone and soft tissue tumors of borderline or low malignancy. Complex supernumerary ring chromosomes composed of chromosome 3 segments were recently reported from a myxoinflammatory fibroblastic sarcoma (Mansoor et al., 2004).

In **synovial sarcoma** only three of 92 cases collected by Sandberg and Bridge (2002a) showed ring chromosomes. r(6) was found in one of those tumors as the sole karyotypic alteration included in a $2n = 46$ karyotype (Buddingh et al., 2003). In congenital fibrosarcoma no ring was reported among 27 cases (Sandberg and Bridge, 2002b). In four of 43 gastrointestinal stromal tumors rings were found (Sandberg and Bridge, 2002c), one of them, r(13), being the sole abnormality of this tumor.

A ring chromosome 6 was reported from two **thymomas** (Table 2); in one of these cases it was the only karyotypic abnormality (Dal Cin et al., 1993b). This points to some importance of genes on chromosome 6 for the development of tumors of this site.

Ring chromosomes in epithelial tumors

Ring chromosomes in epithelial cancer evidently are rare and, in addition, are very difficult to define because of the well-known extremely low quality of chromosome preparations obtained from those tumors. Nevertheless, a number of data have been collected also in this group of tumors (Table 3). It can, however, not be excluded with certainty that some non-identified rings are hiding among the numerous marker chromosomes reported in several publications (e.g. Kovacs, 1981). The chromosomes forming the 104 identified rings, with a few exceptions, seem to be rather randomly affected. Chromosomes 1 (16%) and 8 (13%) are slightly more often involved than other chromosomes (all below 10%).

The first report on ring chromosomes as a rare phenomenon in **breast cancer** dates back to 1968 (Katayama and Masukawa, 1968). Most later reports, as well, confirm the rarity of ring chromosomes in those tumors, and most of them, in addition, were not able to define the chromosomes involved. A large series of cytogenetically examined breast tumors (e.g. Gebhart et al., 1986) did not reveal any ring chromosomes, but in a number of other tumors ring chromosomes were found. If only the latter studies are considered, about 8.5–9% of the analysed tumors exhibited rings. Their incidence, however, would be considerably lower if it was based on all tumors cytogenetically examined. In only a few reports the chromosomes constituting the rings could definitely be determined (Table 3), but in most cases the found rings remained unidentified. Chromosome 11 was involved in five of the 24 breast cancer cases with identified rings, chromosomes 1 and 8 in four, chromosomes 3, 6, 7, 9, and 17 in two cases, and chromosomes X, 15 and 16 in one case, each. As all the reported studies aimed at screening for chromosomal abnormalities, only a few detailed examinations of the breakpoints involved in the constitution of the observed rings are available and in most cases no recurrent breakpoints could be identified. In one case chromosome painting revealed, for instance, that sequences from chromosomes 8 and 11 were interspersed in two large homogeneously staining ring chromosomes (Bernardino et al., 1998). No other attempts of a molecular analysis of the ring formation have been reported. This applies also to the cases where the ring chromosome was the sole karyotypic anomaly: r(6) in an adenocarcinoma, and r(9)(p24q34) in a subclone, each, of an adenoma and a hyperplasia of the breast (Dietrich et al., 1995).

Ring chromosomes were found to be even rarer in **ovarian cancer** than in breast carcinomas. In only nine cases the chromosome constituting the ring could be identified (Table 3). In five cases (three of them 'borderline' tumors) chromosome 1, in two chromosome 5, and in one case, each, chromosomes 16 and 19 were involved. In none of the cases a more detailed molecular analysis of the breakpoints or the biological meaning of the ring was performed. In addition, eleven non-identified rings were reported.

Table 3. Identified ring chromosomes in human epithelial tumors

Ring chromosome (breakpoints) ^a	No. of cases ^b	Type of tumor, remarks ^c	Reference(s)
Gynecologic tumors			
r(1)(p36;q23→q42)	10	4 BRC, 5 OVC, 1 UC	Bertrand et al., 1979; Gerbault-Seureau et al., 1987; Couturier et al., 1988; Yang-Feng et al., 1991; Thompson et al., 1994; Pejovic et al., 1996a, b; Deger et al., 1997; Flagiello et al., 1998; Adeyinka et al., 2000
r(3)	3	2 BRC, 1 UC	Gerbault-Seureau et al., 1987; Hainsworth et al., 1991; Brink et al., 2002
r(5)	1	1 OVC	Thompson et al., 1994
r(5;18)(p15.3;p13::p11.3;q12) ^d	1	1 STC	Truss et al., 2004
r(6)	2 (1)	2 BRC	Pandis et al., 1995a, b
r(7)(p22;q36) ^d	2	2 BRC	Fletcher et al., 1991; Parada et al., 1999
r(8)	2	2 BRC	Pandis et al., 1995a, b
r(8;11)(p23;q22::q13;q25) ^d	2	2 BRC	Bernardino et al., 1998; Adeyinka et al., 2000 ^a
r(9)(p24;q34)	(2)	2 BRC (benign hyperprolif. disorders)	Dietrich et al., 1995, 1997
r(11)	3	3 BRC	Leuschner et al., 1994; Rohen et al., 1996; Tsarouha et al., 1999
r(15)	1	1 BRC	Rodgers et al., 1984
r(16)	2	1 BRC, 1 OVC	Jenkins et al., 1993; Flagiello et al., 1998
r(17)	2	2 BRC	Pandis et al., 1995a, b; Flagiello et al., 1998
r(19)(p13;q13) ^d	1	1 OVC	Pejovic et al., 1992
r(X)	1	1 BRC	Petersson-Lundin et al., 1998
Head and neck cancer			
r(1)	2	1 PT, 1 PSGA	Hrynchak et al., 1994; Persson et al., 2007
r(2)	2 (1)	2 PT	Mark et al., 1992, 1997
r(4)(p16;q35) ^d	4 (1)	1 OHPC, 3 PT	Mark et al., 1988; van Dyke et al., 1994 ^a ; Wanschura et al., 1996; Mark et al., 1997
r(5)	7 (1)	4 PT, 3 PSGA	Mark et al., 1983, 1997; Persson et al., 2007
r(6)	2	1 PT, 1 PSGA	Mark et al., 1997; Persson et al., 2007
r(8)	16	4 PT, 1 NPC, 11 PSGA	Mark et al., 1997; Sankary et al., 1993; Persson et al., 2007
r(9)	2	1 PT, 1 PSGA	Mark et al., 1988; Persson et al., 2007
r(22)	1	1 NPC	Lopez-Gines et al., 1994
Cancer of the digestive and endocrine system			
r(1)(p34;q32)	2	1 PANC, 1 ACLI	Bardi et al., 1997; Gorunova et al., 1998
r(6)(p25;q21) ^d	1	1 PANC	Gorunova et al., 1998
r(7)	1	1 ACLI	Bomme et al., 1994
r(11)	1	1 PANC	Gorunova et al., 1998
r(12)	2 (1)	1 ACLI, 1 THC	Bardi et al., 1993; Belge et al., 1998
r(17;17)(p11;q25::q11;q23) ^d	1	1 PANC	Gorunova et al., 1998
r(18)	2 (1)	1 PANC, 1 ACLI	Bomme et al., 1996; Gorunova et al., 1998
Cancer of the respiratory tract			
r(3)	1	PCH	Fletcher et al., 1991
r(19)(p13;q13) ^d	1	ACL	Johansson et al., 1994
Cancer of the urogenital tract			
r(1)	3	3 WT	Bown et al., 2002
r(1;11)(p3?:q3?:p?:q25) ^d	1	1 WT	Nakadate et al., 1999
r(3)(p25;q27) ^d	4 (3)	3 RC, 1 BDT	Kovacs et al., 1987; Gregori-Romero et al., 1996; Gunawan et al., 2001
r(7;7)(p22;q21::q21.2;q22) ^d	1	1 WT	Ehrlich et al., 2003
r(8)(p23;q24.3) ^d	1	1 RCC	Alimov et al., 2004
r(12)(p13;q10) ^d	1	1 TEC	Smolarek et al., 1999
r(15)	1	1 RC	Kovacs et al., 1991
r(17)	1	1 BDT	Gregori-Romero et al., 1996
r(18)	1	1 UBC	Fadl-Elmula et al., 2001
r(20)	(1)	1 ROC	Kovacs et al., 1989
r(21)	1	1 RC	Varsa et al., 1989
Skin cancer			
r(2)(p25;q37) ^d	2	1 MM, 1 PA	Chen and Shaw, 1973; Mark et al., 1997 ^a
r(3)	1	1 CMM	Atkin and Baker, 1981
r(4)(p16→q12;q31→q35)	2	2 PA	Mark et al., 1997
r(5)(p15;q12) ^d	3	1 UMM, 2 PA	Mark et al., 1997 ^a ; Naus et al., 2002
r(6)(p25→p23;p21.1→?)	2	1 CMM, 1 UMM	Cowan et al., 1988; Prescher et al., 1995
r(7) const.	2	2 CMM	DeLozier-Blanchet et al., 1992; Vollenweider Roten et al., 1993
r(8)(p23→p10;q12)	4	4 PA	Mark et al., 1997
r(9)(p24;q34)	3	2 CMM, 1 UMM	Pedersen et al., 1986 ^a ; Singh et al., 1994
r(12)	1	1 MM	Atkin and Baker, 1981
r(14)(p11;q32) ^d	(1)	1 BCC	Jin et al., 1998
r(17)	1	1 BET	Gorunova et al., 1994

^a As far as determined.^b Numbers in italics represent cases with ring as sole aberration.^c BRC: breast cancer; LM: liver metastasis; OVC: ovarian cancer; UC: uterine cancer; OHPC: oro/hypopharynx carcinomas; NPC: nasopharynx carcinomas; PT: parotis tumors; PSGA: pleomorphic salivary gland adenoma; PANC: pancreas cancer; PCH: pulmonary chondroid hamartoma; ACL: adenocarcinoma of the lung; ACLI: adenocarcinoma of the large intestine; THC: thyroid carcinoma; UBC: urinary bladder cancer; WT: Wilms tumor; RC: renal cancer; RCC: renal cell carcinoma; ROC: renal oncocytoma; BDT: Bellini duct tumor; TEC: testicular cancer; STC: Sertoli-Leydig cell tumor; PA: pleomorphic adenoma; CMM: cutaneous malignant melanoma; UMM: uveal malignant melanoma; MM: malignant melanoma; BCC: basal cell carcinoma; BET: benign epithelial tumor; const.: constitutional ring.^d Only from one case.

Although the first report on ring chromosomes in carcinoma of the cervix was published some time ago (Spriggs and Cowdell, 1972), only very scarce information is available on **epithelial tumors of the uterus** (Table 3). Three identified rings involving chromosomes 1, 3 and 8/10 were reported. The latter r(8;10), however, was found in a leiomyoma of the uterus, which is rather a mesenchymal tumor (Pedeutour et al., 2000). Non-identified rings were found in not more than five tumors (Micci et al., 2004). The mesenchymal leiomyomas of the uterus have just been considered separately above (see Table 2).

Among the **head and neck tumors** a large series of pleomorphic adenomas contributed to the data collected in Table 3. For instance, in 97 new cases of these benign tumors eight ring chromosomes could be defined (Mark et al., 1997), four of which affected chromosome 8. One of the latter included only the short arm of chromosome 8. In three of these tumors rings were also found constituting the sole karyotypic anomaly: r(4) (Mark et al., 1988), r(2) and r(5) (Mark et al., 1997).

With the exception of *FGFR1* in 8p12 and *PLG1* in 8q12.2 in 10 of 11 pleomorphic salivary gland adenomas with r(8) (Persson et al., 2007) no data on the molecular structure of the ring or on the genes rearranged by the ring formation have been reported so far.

Although ring chromosomes apparently are present in more than 10% of **pancreatic carcinomas** (Griffin et al., 1995; Gorunova et al., 1998), most of the rings remained undefined with respect to the involved chromosomes. r(1), r(6), r(11), r(17;17), and r(18) were reported from one case, each (Table 3). No further attempt for molecular identification of affected genes has been made so far and also not for the only case with r(18) as the sole karyotypic anomaly (Gorunova et al., 1998). The authors also reported a non-random involvement of chromosome 1 in telomeric associations with other chromosomes.

Renal cancer and Wilms tumors differ with respect to the chromosomes involved in rings which have been described so far from tumors of this location. While chromosomes 1, 7, and 11 were involved in Wilms tumors, chromosomes 3, 8, 15, 20 and 21 were associated with other renal tumors. The six Wilms tumors with ring chromosomes (among 127 with abnormal karyotypes) belonged without exception to the group of tumors with complex karyotypic changes and poor prognosis (Bown et al., 2002). In three renal carcinomas and one oncocyoma the ring was the sole chromosomal alteration as part of a $2n = 46$ karyotype. All three renal cancers exhibited an r(3) at least in one subclone (Kovacs et al., 1987; Gunawan et al., 2001), the oncocyoma an r(20) (Kovacs et al., 1989). In addition, another case of Wilms tumor had previously been described as a carrier of a ring chromosome as the sole anomaly (Wang-Wuu et al., 1990). As far as an identification of the chromosomal bands involved in the ring rearrangement was attempted, this only refers to single tumors. Therefore, no recurrent involvement could be found, nor could recurrently involved genes be identified.

Apparently more than 15% of **urinary bladder** tumors harbor ring chromosomes (Milasin et al., 1989; Fadl-Elmula et al., 2001), but in all but one case a definition of the involved chromosome(s) apparently was impossible. There was, however, an association found between the presence of rings and histologic grade of the tumors. G1 and G2 tumors contained ring chromosomes more frequently than G3 tumors, although the difference (22% and 20% in the former vs. 10% in the latter) was not statistically significant (Milasin et al., 1989). In addition, these authors report another common feature of ring-containing cases, i.e., numerous and frequent (2–3 months) relapses.

In a series of 67 **adenocarcinomas of the lung** ten cases with ring chromosomes were found, but only one ring could be defined as an r(19) in a solid cancer of T1N0M0 classification (Johansson et al., 1994). Eight of these ten tumors did not metastasize (N0).

Among the skin cancers **malignant melanoma** clearly dominates the small number of cancers of this location from which ring chromosomes have been described at all. No preference for one specific chromosome could be clearly defined, although r(9) was found in three of the ten corresponding cases. As discussed below, some association may exist between ring chromosomes 7 and melanotic skin lesion which eventually can become malignant.

Ring chromosomes in tumors of the nervous system and adjacent tissues

Similar to the situation in epithelial tumors, ring chromosomes are also a rare phenomenon in tumors of the nervous system and its adjacent tissues (Jenkins et al., 1989a; Table 4). As most of the observed rings could not be definitely assigned to certain chromosomes, our knowledge about a possible meaning of rings in tumors of these tissues is even scarcer. For instance, ring chromosomes which could be finally identified were found in only nine astrocytomas, in three rhabdoid tumors of the brain and neuroglial tumors, each, in two ependymomas and neuroblastomas, and in one glioblastoma and one ganglioglioma. Chromosome 22 was involved in ring formation in six, chromosomes 1, 12, 14, and 20, in two tumors, each.

In some of the mentioned tumors, the ring chromosome was the sole karyotypic anomaly, e.g. r(22) in an ependymoma (Wernicke et al., 1995) and an astrocytoma (Orr et al., 2002), r(1) in a neuroglial neoplasm (Neumann et al., 1993), and r(12) in another astrocytoma (Sawyer et al., 1993). In none of these cases, however, a molecular analysis of the involved genes was performed. Rather as far as the involved chromosomal bands were determined, terminal breakpoints were the basis of the ring rearrangement in most cases. Nevertheless, speculations on the meaning of genes affected by the ring rearrangements remain premature.

Among the tumors of 'adjacent' tissue, meningiomas show ring chromosome in about 2.5% (Sawyer et al., 2005). Nevertheless, in 22 meningiomas a ring chromosome could

Table 4. Identified ring chromosomes of human nervous system and adjacent tissues

Ring chromosome (breakpoints) ^a	No. of cases ^b	Type of tumor, remarks ^c	Reference(s)
Adjacent tissue			
r(1)(p34;q43) ^d	4	4 MN	Rey et al., 1988 ² ; Chio et al., 1991; Bhattacharjee et al., 1997
r(3)	1	1 NF	Molenaar et al., 1997
r(6)	1	1 MN	Biegel et al., 1994
r(7)	2	2 MN	Biegel et al., 1994; Sawyer et al., 2003
r(8)(p23;q24) ^d	2	1 MN, 1 NST	Bello et al., 1993 ³ ; Sawyer et al., 2000
r(11)(p15;q25)	2 (1) ^e	2 MN	Yamada et al., 1994; Sawyer et al., 2003
r(12)	2 (1) ^e	2 MN	Debiec-Rychter et al., 1999; Sawyer et al., 2000
r(16)	1	1 MN	Sawyer et al., 2000
r(17)	2 (1) ^e	2 MN	Rey et al., 1988; Lekanne-Deprez et al., 1995
r(19)	(2) ^e	2 MN	Rey et al., 1988; Doco-Fenzy et al., 1993
r(21)	1	1 MN	Griffin et al., 1994
r(22)	3	3 MN (1 constitutional, 1 radiation-induced)	Arinami et al., 1986; Perry et al., 1996; Chauveinc et al., 1999
r(X)	2 (1) ^e	1 MN, 1 NST	Mertens et al., 1995; Sawyer et al., 2003
r(X;20)(p22.2;q26::p13;q13:)	1	1 NST	Decker et al., 1990
CNS tumors and other neurogenic tumors			
r(1)(p36;q42)	3 (1)	1 ASC, 1 GGL, 1 NGL	Neumann et al., 1993
r(2)	1	1 NBL	Bown et al., 1994
r(3)(p25;q29) ^d	1	1 DNF	Molenaar et al., 1997
r(6;11)(p25;p22::p15;q25) ^d	1	1 RTB	Lopez-Gines et al., 2000
r(9;10)(p24;q34::p14;q11:)	1	1 ASC	Bigner et al., 1988
r(11)(p15;q25) ^d	1	1 ASC	Sawyer et al., 1996
r(12)(p13;q24)	2 (1)	2 ASC	Jenkins et al., 1989b; Sawyer et al., 1993
r(13)	1	1 NBL	Bown et al., 1994
r(14)(p11;q23) ^d	2	1 ASC, 1 EPM	Lindström et al., 1991; Mazewski et al., 1999 ^a
r(17)	1	1 GBM	Orr et al., 2002
r(20)(p13;q13) ^d	2	1 ASC, 1 NGL	Sawyer et al., 1992
r(22)(p11;q13) ^d	6 (2)	2 ASC, 1 EPM, 2 RTB, 1 NGL	Sawyer et al., 1992 ² ; Wernicke et al., 1995; Klopfenstein et al., 1997; Orr et al., 2002

^a As far as determined.^b Numbers in italics represent cases with ring as sole aberration.^c MN: meningioma; NST: nerve sheet tumor; NF: neurofibroma; ASC: astrocytoma; GBM: glioblastoma multiforme; GGL: ganglioglioma; EPM: ependymoma; NBL: neuroblastoma; DNF: diffuse neurofibroma; RTB: rhabdoid tumor of the brain; NGL: neuroglial tumor.^d Only from one case.^e In addition to -22.

be identified; chromosome 1 was involved in 20% and chromosome 22 in 15% of these cases. In six meningiomas the characteristic monosomy 22 was accompanied by ring chromosomes as a sole additional karyotypic change. In two cases it was an r(19) (Rey et al., 1988; Doco-Fenzy et al., 1993), and in one case, each, an r(11) (Yamada et al., 1994), r(12) (Debiec-Rychter et al., 1999), r(17) (Lekanne-Deprez et al., 1995), and r(X) (Sawyer et al., 2003). The latter group, based on the findings in CNS tumors and meningiomas, proposed a hypothesis of ring formation as a consequence of telomeric instability as reflected by frequent telomere associations. Among eight 'aggressive meningiomas', four cases had dicentric or ring chromosomes (Perry et al., 1996). Comparative analyses in 200 histologically benign and 47 additional previously reported atypical and malignant meningiomas underscored the conclusion of the latter authors that cytogenetic changes – including the presence of ring chromosomes – may determine the prognosis of these tumors.

Constitutional rings and neoplasia

'A ring chromosome is a relatively rare condition, with a frequency of 1 in 50,000 newborns' (Welborn, 2004). Constitutional chromosome aberrations can also act as pathogenetic events in hematologic malignancies. In a series of cases with constitutional rings aside their well described clinical effects, the development of neoplastic diseases was observed. Rings of chromosome 21, in particular, could be associated with neoplasias of the hematopoietic system (AML: Pui et al., 1992; Palmer et al., 1995; Streubel et al., 2001; ALL: Stern et al., 1979; Cabrol et al., 1983; Falchi et al., 1987). Although the breakpoints forming these rings varied, molecular analyses rendered it probable that genes were duplicated which are candidate genes for leukemia, like *AML1*, *ETS*, and *ERG* (Palmer et al., 1995). In the AML case examined by Streubel et al. (2001) the *AML1* gene even proved to be amplified. In addition, singular cases of a constitutional ring of chromosome 1 (Bobrow et al., 1973) and of chromosome 18 (Welborn, 2004) were reported – among other symptoms – to result in AML.

As reviewed by Tommerup and Lothe (1992), constitutional rings associated with solid tumors apparently are also limited to a few certain chromosomes. Among 356 patients with constitutional rings collected by these authors, only ten developed a solid tumor.

Constitutional r(7) seems to be associated with hyperpigmented skin lesions which occasionally could develop into malignant melanoma as shown in a 17-year old girl (Delozier-Blanchet et al., 1992; Vollenweider-Roten et al., 1993). Similarly, a highly proliferating melanocytic congenital naevus with somatic mosaicism of chromosome 7 was found in a male child with a constitutional ring chromosome 7 (Mehraein et al., 2004). A close association between constitutional rings of chromosome 22 and meningiomas (Arinami et al., 1986; Petrella et al., 1993) or neurofibromatosis 1 or 2 (Duncan et al., 1987; Tommerup et al., 1992; Kehrer-Sawatzki et al., 1997; Tsilchorozidou et al., 2004) is well documented. In addition, an atypical teratoid/rhabdoid brain tumor was found in a girl with r(22) (Rubio, 1997). Retinoblastomas, but also a rhabdomyosarcoma and an embryonic sarcoma were reported from patients with constitutional rings of chromosome 13 (as reviewed by Tommerup and Lothe, 1992; Morrisette et al., 2001). A follicular adenocarcinoma of the thyroid arose in a patient with r(10) and a Wilms tumor (Romain et al., 1983) in another one with r(11). Constitutional rings of varying size which, however, apparently were not derived from chromosome 11 were also reported from the latter tumor type (Kakati et al., 1991). Two reports point to a relation of constitutional r(17) and neurofibromatosis (NF1) (Andersen et al., 1990; Wiktor et al., 1993). In a patient with ring chromosome 12 a leiomyoma of the uterus has been found (Hajianpour et al., 1996). In a low percentage of normal somatic cells ring chromosomes in a varying number may be indicative of sensitivity to structural alterations of some chromosome regions in MEN IIA S (multiple endocrine neoplasia of type IIA) (Temperani et al., 1989). In their review, Tommerup and Lothe (1992) clearly point to the high probability of an affection of tumor suppressor genes by the ring formation in most or even all of these cases.

In contrast, no ring was found in abnormal constitutional karyotypes in more than 50 patients with neuroblastoma (Satge et al., 2003).

Conclusion

The formation of a ring chromosome can have three basic genetic consequences, each of which may be more or less involved in cancer development, and/or tumor progression. Those are: 1) loss of acentric chromosomal segments created by the ring rearrangement and loss of the genes located on them. A presumptive role of this phenomenon, so far, has only exceptionally been observed (e.g. losses of *HMG17* by chromosome 1 ring formation in leiomyomas). 2) Fusion of genes or of genetic areas which, in consequence are coding for new proteins or at least contribute new protein functions. This mechanism is convincingly documented by the

demonstration of highly specific rearrangements in tumors of mesenchymal origin which have attained a sort of pilot function. In particular, the highly specific rearrangements of chromosomes 17 and 22 in DFSP resulting in *COL1A1/PDGFB* fusion, and the occasional rearrangement of segments of chromosomes 1 and 12 in lipomatous tumors are impressive documents of the role of this mechanism. 3) Amplification of chromosomal segments in consequence of ring formation has not only been shown in certain cases of leukemia but is particularly verified for chromosome 12 segments, for instance those including the *MDM2* gene in lipomatous tumors and tumors of the bone and cartilage, but also for chromosome 1 rings including *COAS* genes. A more intense molecular analysis of other more or less sporadic ring chromosomes present in other tumor entities can open new views of their functional and clinical meaning. 4) Last but not least, ring chromosomes can contribute to a general genomic instability of the cells they are present in. Particularly, dicentric rings may cause formation of anaphase bridges which by their breakage create new fusions at the breakpoints ('break-fusion-bridge cycle') and thus new chromosomal rearrangements.

As reported above, ring chromosomes are often embedded in highly complex aberrant karyotypes. Their specific role in those neoplasias remains rather enigmatic, as it cannot be decided whether the complex karyotype or the presence of a ring chromosome influences the prognosis in these cases. Therefore, a general statement that ring chromosomes, e.g. in leukemias, act as a poor prognostic factor, must be considered with great caution. On the other hand, exceptional cases of leukemias were observed where the presence of ring chromosomes improved the prognosis. Nevertheless, molecular analyses of rings could also contribute to a better understanding of their role in the complex karyotype. Most interesting are cases with ring chromosomes as the sole karyotypic change which have been separately documented above. These cases, however, are too rare to base a solid statistical evaluation of outcome upon. Nevertheless, cases with rings as a sole alteration should come into the focus of future examinations, also under the aspect of molecular consequences and clinical impact of ring formation in human neoplasia.

The present – sometimes still rather sporadic – examinations of ring chromosomes in human neoplasias must be further extended and intensified for an eventual achievement of deeper insights into the mechanisms governing ring formation and into the role rings actually play in malignancy.

Acknowledgement

Particular gratitude of the author is due to Dr. B. Hiller, Marburg, who screened the 'Mitelman catalogue' for ring chromosome cases using the screening software developed by him.

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