Constitutional ring chromosomes and tumour suppressor genes

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Abstract

The types of malignancy reported in carriers of constitutional ring chromosomes r(11), r(13), and r(22) are concordant with the chromosomal assignment of tumour suppressor loci associated with Wilms' tumour, retinoblastoma, and meningioma. It is suggested that the somatic instability of ring chromosomes may play a role in this association and that constitutional ring chromosomes may be a source for mapping of tumour suppressor loci with the potential for covering most or all of the human genome. The hypothesis predicts the presence of a locus on chromosome 10 associated with follicular carcinoma of the thyroid, in line with previous cytogenetic findings of rearrangements involving chromosome 10 in thyroid tumours, and a locus on chromosome 22 associated with testicular cancer. Development of neurofibromatosis (NF) that do not fulfil the clinical criteria of neurofibromatosis type 2 (NF2) in carriers with r(22) suggests either the presence of an additional NF locus on chromosome 22 or that ring chromosome mediated predisposition to somatic mutation of a specific tumour suppressor may be associated with atypical development of features usually associated with germline mutations.

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Homozygotic loss of function of specific growth suppression genes¹ may form the biological basis for a two mutation theory of tumour initiation.^{2,3} In carriers of a germline mutation affecting one allele of a tumour suppressor gene, a second somatic mutation involving the other allele may initiate the tumorigenic process in susceptible cell types. Since the number of potential target cells may be large, carriers of such germline mutations frequently develop multifocal or bilateral tumours or both.

In some cases the germline mutation may present as a cytogenetically visible constitutional chromosome rearrangement. In the prototype of inherited tumours, retinoblastoma (RB1), chromosome deletions and translocations involving the RB1 locus at 13q14 may be observed in up to 10% of cases.⁴ In some cases, somatic mosaicism for a visible chromosome deletion of 13q14 appears to be responsible for predisposition to RB1.⁵

In the present report we have focused on the pattern of tumour development in carriers of constitutional ring chromosomes. The loss/rearrangement of chromosomal material in

most ring carriers can be ascribed to two different mechanisms. During the initial ring formation, fusion of the distal part of the short arm with the distal part of the long arm may result in loss of material distal to the break-points on both chromosome arms.⁶ As a constitutional mutation, this primary loss would be expected to predispose to tumour formation as other germline deletions if a tumour suppressor locus happened to be involved.

A second mechanism for loss or rearrangement of chromosomal material in carriers of ring chromosomes is associated with a generalised mitotic instability of ring formed chromosomes.^{7,8} Sister chromatid exchange(s) within a monocentric ring chromosome results in the formation of dicentric or interlocked pairs of rings. As a result, a diversity of aneuploid conditions and rearrangements are frequent findings in cells from ring carriers, ranging from gain of chromosomal material to partial or complete loss of the specific chromosome.⁹ The frequency of aneuploid/rearranged cells may vary from chromosome to chromosome, from cell type to cell type, and from person to person, and ring carriers may thus be considered to be unpredictable, but continually evolving, mosaics (dynamic mosaics).¹⁰ In contrast to a germline deletion/rearrangement, which will only involve functional loss/alteration of tumour suppressor loci located within the deleted/rearranged area, dynamic mosaicism might have the potential for involving tumour suppressor loci anywhere on the ring chromosome. This type of instability would still be predicted to be associated with the development of chromosome specific types of tumours, but at a lower frequency than observed in germline mutations, since only a fraction of the somatic target cells would be expected to undergo loss/rearrangement of the ring during mitosis.

Methods

More than 350 cases of published and unpublished constitutional ring chromosomes were included in the search for associated malignancies (Medline 1984-1991)^{11,12} (table 1).

Results and discussion

Solid tumours were reported in 10, possibly 11, cases with constitutional ring chromosomes¹²⁻²² (table 2), and in all cases the chromosome involved was shown to harbour one or more tumour suppressor genes (table 1).

Furthermore, in those cases with tumours with a mapped predisposition locus (RB1,

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Table 1 Number of reviewed cases with constitutional autosomal ring chromosomes and reported numbers with associated solid tumours.

Ring chromosome	No of cases	No with solid tumour	Chromosome known to harbour tumour suppressor*
1	4		+
2	6		
3	4		+
4	25		
5	12		+
6	16		+
7	4		
8	3		
9	13		+
10	10	1	+
11	7	1	+
12	5		
13	40	4 (5)	+
14	32		
15	15		
16	4		
17	8	1†	+
18	48		+
19	3		
20	11		
21 + GI	41		
22 + GII	51	3	+
Total	358	10 (11)	

* Adapted from reference 1.

† Ring structure only inferred indirectly.

Wilms' tumour (WT), meningioma), ring formation involved the chromosome known to harbour the specific locus. Retinoblastoma, mapping to 13q14,²³ has been reported at least twice^{13,14} and possibly three times¹⁵ in ring carriers and only in association with r(13). Two Wilms' tumour loci have been mapped to chromosome 11, one at 11p13²⁴ and one to the distal 11p15 region²⁵ and WT was described in one of seven cases with r(11).¹⁶ A putative meningioma locus has been mapped to chromosome 22^{26,27} and multifocal meningioma occurred in a 25 year old adult male in whom a r(22) had been detected five years earlier.¹⁷

In addition, tumours with an unestablished or only tentative chromosomal localisation of predisposing loci have been reported.

CHROMOSOME 13 AND MESENCHYMAL TUMOURS

The retinoblastoma gene, which has been found to be involved in a variety of other tumours including osteosarcoma and soft tissue sarcoma,^{28,29} would be a potential candidate for being involved in the development of an embryonic sarcoma in association with a ring D chromosome, presumably a r(13).¹⁸

Patients with an inherited susceptibility to retinoblastoma also have a high incidence of rhabdomyosarcoma,²⁸ and a specific chromosome abnormality, t(2;13), involving the region 13q14 known to harbour the RB1 locus has been observed in rhabdomyosarcoma cells.³⁰ The development of rhabdomyosarcoma in a patient with constitutional mosaicism of ring 13 further supports the association between this tumour type and the retinoblastoma gene or a nearby locus.¹⁹

CHROMOSOME 10 AND FOLLICULAR ADENOCARCINOMA OF THE THYROID

The development of a well differentiated follicular adenocarcinoma of the thyroid in one of ten cases with r(10)²⁰ would make chromosome

10 a candidate for harbouring a locus associated with this type of thyroid tumour. A transforming oncogene has been isolated from several human papillary thyroid carcinomas³¹ and mapped by in situ hybridisation to chromosome region 10q11-q12.³² Translocations involving chromosome 10 have been described in both papillary carcinoma and follicular adenoma of the thyroid.^{33,34} Many well differentiated thyroid carcinomas may show admixtures of both papillary and follicular elements, which may suggest a common pathogenetic mechanism, and familial occurrence of papillary carcinoma of the thyroid have been reported,³⁵⁻³⁷ suggesting the involvement of a tumour suppressor gene. Interestingly, a candidate locus for another malignancy of the thyroid, medullary carcinoma of the thyroid, which is a feature of multiple endocrine neoplasia type IIA (MEN2A), has also been mapped to chromosome 10, within the pericentric region 10p11.2-q11.2.^{38,39}

GERMLINE MUTATIONS OR DYNAMIC SOMATIC MOSAICISM?

A much lower frequency of retinoblastoma has been observed in subjects with r(13) than in those with interstitial deletions of 13q.⁴⁰ Although this may be taken as evidence that primary germline deletions involving RB1 are rare in r(13), we cannot exclude that germline mutations may have occurred in the few cases with r(13) who developed retinoblastoma, since the breakpoints were not mentioned. However, breakpoints have been reported in some of the other rings associated with tumour development (table 2). One was the case with r(11) who developed Wilms' tumour.¹⁶ Since one of the Wilms' tumour loci maps to the distal part of 11p15,²⁵ it is possible that this locus might have been deleted during the initial ring formation. However, visible constitutional deletions within 11p15 have not been reported, providing some support for the involvement of dynamic mosaicism in this case. Also, if the WT1 locus at 11p13²⁴ was the decisive locus involved in the tumour formation, a secondary ring mediated rearrangement would be the likely mutational mechanism.

Constitutional mosaicism for two rings, one with breakpoint far from the 13q14 region and one with a breakpoint within the 13q14 region,¹⁹ suggests that one of the two mutational mechanisms might have been operative in the case with r(13) who developed rhabdomyosarcoma.

The candidate regions on chromosome 10 which have been implicated in rearrangements in thyroid tumours³²⁻³⁴ all appear to be far from the terminal breakpoints in the r(10) associated with development of a thyroid tumour.²⁰ Thus, ring mediated dynamic mosaicism seems to be the most plausible mutational mechanism in this case.

R(22), R(17), AND NEUROFIBROMATOSIS

In familial retinoblastoma the inherited mutation is a germline mutation of the retinoblas-

Table 2 Reported tumours or tumour predisposing disorders in cases with constitutional autosomal ring chromosomes.

Tumour type	Ring	Breakpoints	Possible mode of mutation	
			Germline	Dynamic mosaicism
Follicular adenocarcinoma of the thyroid ²⁰	10	p15-q26		+
Wilms' tumour ¹⁶	11	p15-q26	+	+
Retinoblastoma ¹³	13	—		
Retinoblastoma ¹⁴	13	—		
Retinoblastoma ²¹⁵	13	—		
Rhabdomyosarcoma ¹⁹	13	p11-q34/p11-q14	+	+
Embryonic sarcoma ¹⁸	D(13)	—		
Neurofibromatosis ²²	17*	cen-q11.2 or q12		+
Meningioma ¹⁷	22	—		
Neurofibromatosis ²¹	22	p11.2-q13.2		+
Neurofibromatosis, intracranial tumour, testicular seminoma ¹²	22	—		+

— Breakpoints not determined/mentioned.

* Ring structure only inferred indirectly.

toma gene. Similarly, germline mutations of specific tumour suppressor loci are the likely mutations in other dominantly inherited tumour predisposition disorders like von Recklinghausen neurofibromatosis (NF1)⁴¹ and neurofibromatosis type 2 (NF2).^{42,43} Two cases with r(22) have been reported in association with neurofibromatosis.^{12,21} Because of lack of a family history of NF and lack of other clinical features associated with either NF1 or NF2 (café au lait spots, axillary freckling, Lisch nodules, bilateral acoustic neurinoma), the type(s) of neurofibromatosis in these two cases could not be determined. A candidate locus would be the NF2 locus which is located on chromosome 22.^{42,43} However, support for constitutional retainment of the NF2 flanking markers *D22S1* and *D22S28*⁴⁴ in one case¹² and the very distal breakpoints (22p13;22q13.2) in the other r(22)²¹ do not support a ring chromosome associated germline mutation involving the NF2 locus. Thus, more than one NF locus may be associated with chromosome 22, or the dynamic somatic mosaicism associated with r(22) might be responsible for an aberrant clinical development of NF2 in these two cases.

Dynamic somatic mosaicism was also suggested as a possible mutational mechanism in a sporadic case with late onset (40 years) of NF1, who carried a small, presumably ring chromosome excised from the proximal part of 17q,²² where data so far indicate that the NF1 gene has not been disrupted (Andersen, personal communication).

Interestingly, multiple café au lait spots of about 10 mm in size were reported in the two oldest (10 and 6 years) of the seven cases described with r(17),^{45,46} conforming to one of the diagnostic criteria of NF1 (six café au lait macules over 5 mm in size) in prepubertal persons.⁴⁷ Continued monitoring of r(17) carriers may indicate whether additional signs of NF1 (principally neurofibromas) will develop.

CHROMOSOME 22 AND TESTICULAR CANCER

Apart from being associated with the development of meningioma and acoustic neurinomas, chromosome 22 is also the chromosome the most frequently lost in colonic tumours from patients with hereditary polyposis coli.⁴⁸ Thus, chromosome 22 may contain several tumour suppressor genes or the same locus (loci) may

be associated with the development of a variety of different tumours. In a previous study of testicular tumours which showed significant loss of heterozygosity for markers on chromosome regions 3p and 11p only, chromosome 22 markers were not included.⁴⁹ The development of seminoma in a r(22) carrier¹² indicates that molecular analysis of testicular tumours with chromosome 22 markers may be worthwhile.

Since the development of cancer is age related and most subjects with rings have been examined cytogenetically in early life because of the associated mental retardation/dysmorphism, it is likely that only a few and predominantly childhood tumours like RB1 and WT have been reported in association with ring chromosomes so far. The subsequent development in young adulthood of meningioma¹⁷ and testicular cancer¹² in r(22) carriers years after the initial cytogenetic diagnosis supports this.

It is conceivable that the figures in table 1 proposing a risk for development of tumours in carriers of ring chromosomes harbouring tumour suppressor genes as high as 10 to 14% is an overestimate owing to ascertainment bias. Still, continuous clinical monitoring of carriers of ring chromosomes, especially of those known to harbour tumour suppressors, seems warranted. An important spin off may be hints of new associations between individual chromosomes and specific types of malignancies, which may then aid in chromosome directed molecular analysis of sporadic tumours.

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