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Investigations in Probands with Rearrangements in the Acrocentric Chromosomes

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KEYWORDS Acrocentrics; structural aberrations; intra - and interchromosomal aberration distribution; heterochromatin rearrangement; origin of aberrations; Robertsonian translocations.

ABSTRACT Chromosome investigations in 25,571 cases revealed 432 patients with structural changes in the acrocentrics. These could be attributed to 8 cases of heterochromatin translocations with the Y-chromosome, 135 cases of rearrangements in heterochromatic regions of the short arms of the acrocentrics, and 289 cases with different types of exchanges and breakpoints in the euchromatin. Altogether, breakpoints in 547 acrocentrics were analysed. A specific intrachromosomal distribution of breakpoint maxima and minima was delineated for the 5 acrocentrics with individual characteristics regarding the 3 categories of rearrangements such as: Yq12 translocations, Robertsonian translocations as well as heterochromatic marker chromosomes, and rearrangements in the euchromatin. In addition, polymorphisms of the heterochromatin in the short regions of the acrocentrics were analysed. The origin of the 13 different aberration types documented showed a chromosome-specific pattern.

INTRODUCTION

Rearrangements of acrocentric chromosomes are rather frequent in humans. Theoretically, the break-points should be distributed equally along the chromosomes, but so-called "hot spots" of mutation with unequal inter- and intrachromosomal distribution can be demonstrated (Miller and Therman 2001).

There are balanced and unbalanced rearrangements, both of which can occur de novo or familial. Not all rearrangements that appear balanced will lead to a normal phenotype since cryptic deletions or duplications in break points may occur in a frequency of 3 - 7 %, concerning de novo cases as well as familial ones (Fryns et al. 1992).

Additionally, meiotic rescue of aberrant gametes and secondary selection against an unbalanced karyotype may lead to a partial or complete uniparental disomy (UPD) in patients with rearrangements that appear balanced (Gardner and Sutherland 2004).

The role of size variants in the heterochromatic short-arm regions of the acrocentrics, as far as origin and inheritance of rearrangements are concerned, has not been taken into account up till now but should be considered in the future (Kalz 2003).

Thus, more precise investigation of chromosome rearrangements is needed to enable a better characterization.

INVESTIGATION GROUP

Our investigation is based on 25,571 chromosome analyses after lymphocyte culture performed for diagnostic purposes, and extends to analyses of additional cell systems (amniocytes and fibroblasts) for family investigations. Of these, 432 cases showed various types of structural aberrations in the acrocentric chromosomes.

The investigation group was divided into 3 subunits: firstly, one with heterochromatin translocations involving the Y-chromosome (n = 8), secondly, one with rearrangements in heterochromatic regions (Robertsonian translocations and heterochromatic derivates) with a risk of malsegregation of euchromatin (n = 135), and thirdly, one with rearrangements involving euchromatic regions (n = 289). The investigation was extended by the comparison of polymorphisms of the constitutive heterochromatic regions in the acrocentrics 13 and 14 (p11.2 to p13) and their frequencies of size and staining variations in families with 13/14 translocations (7 pedigrees).

Chromosome analyses were performed following standard protocols after having applied different banding techniques (GTG, QFQ, RBA) (Wegner (Ed.) 1999). In cases of unclear localization of break points, several methods were combined and additional techniques (CBG, DA/DAPI, NOR) were used. For interphase analysis of marker chromosomes and specific break point

characterization, FISH-techniques were chosen (DNA-probes: wcp, cen, single copy; M-FISH).

Supplementary analyses of the heterochromatic short arms of the acrocentrics were performed concerning morphology, position, and staining conditions of the 3 different regions. The frequency of the 3 sizes very small (vs), small (s), and medium (m) was documented according to the definition of the ISCN (2005) and a previous investigation (Kalz et al. 2004). This investigation group consisted of 100 persons from Central European origin, including 7 families and 43 single probands with 13/14 translocation.

RESULTS

Structural aberrations of the acrocentric chromosomes were found in 432 out of 25,571 diagnostic cases (1.7 %). They fell into 3 units (s. investigation groups) with specific features in each of them. They consisted of very different numbers of probands and are described in detail as follows.

Subunit I: Translocations between Acrocentric Chromosomes and Yq12

This subunit consisted of 8 cases of heterochromatin translocations of Yq12 onto short-arm regions of the chromosomes 15 and 22. The carriers' phenotypes were normal. Indication for chromosome analysis was the increased maternal age at pregnancy followed by parental investigation in 6 cases, as well as infertility in 2 cases (patients of the ICSI-program). 6 cases (75 %) showed a translocation between the Y chromosome and 15, and 2 revealed a translocation between Y and 22 (25%). The origin of the translocation chromosomes was paternal in the majority of the known cases (83 %). The significance of this observation is reduced considerably by the relatively small size of the group (Table 1).

Table 1: Origins of translocation of Yq12 to short arm regions of acrocentric chromosomes in 8 patients (Subunit I).

	Translocation Chromosomes N = 8	
Yq12 to	**15**	**22**
	6	2
	Origins of aberration	
de novo		0
familial	total	6
	paternal	5
	maternal	1
unknown		2

Subunit II : Rearrangements in Heterochromatic Regions of the Acrocentric Chromosomes

This subunit included 135 cases of heterologous and homologous Robertsonian translocations as well as chromosome derivates that led to rearrangements in heterochromatic regions. In all, 244 chromosomes were characterized.

Robertsonian translocations (rob) dominated this unit in 218 incidents (89.3 %). Among these, heterologous rearrangements occurred significantly more often (184 or 84.4 %) than homologous ones (34 or 15.6 %). Heterochromatin derivates (heterochr. der) included 26 or 10.7 % of the aberrations. Of the 5 acrocentrics, chromosome 14 was involved most frequently in rearrangements with 36.9 %, followed by chromosome 13 with 25.8 %, chromosome 21 with 20.1 %, chromosome 15 with 11.9 %, and chromosome 22 with 5.3 % (Table 2).

Of the 3 analysed *aberration types* in this

Table 2: Rearrangements of acrocentrics and break points in the constitutive heterochromatin (N_c = number of aberrations in the specific chromosome) (subunit II).

		Types of aberrations and their frequencies $N_{chromosomes} = 244$											
		13		*14*		*15*		*21*		*22*		Σ	
		N_c	%	N_c	%	N_c	%	N_c	%	N_c	%	N_{total}	%
Robertsonian translocations (rob)	hetero-logous	56	88.9	82	91.2	12	41.4	27	55.1	7	53.8	184	89.3
	homo-logous	6	9.5	4	4.4	2	6.9	20	40.8	2	15.4	34	
heterochromatic derivates (heterochr. der)		1	1.6	4	4.4	15	51.7	2	4.1	4	30.8	26	10.7
Σ of N_c		63		90		29		49		13		244	
N_c/N			25.8		36.9		11.9		20.1		5.3		

group, heterologous Robertsonian translocations, with the exception of chromosome 15, represented most of these cases, with a maximum in chromosome 14. Considering the individual chromosome, they were dominant in the chromosomes 14 and 13, with 91.2 and 88.9 %, respectively, of the aberrations, followed by a nearly equal amount of rob (55.1 and 53.8 %) in the chromosomes 21 and 22, and 41.4 % in chromosome 15. Fusions of homologous chromosomes were frequent in chromosome 21 (40.8 %) and were represented in significantly smaller numbers in the chromosomes 22 (15.4 %), 13 (9.5 %), 15 (6.9 %), and 14 (4.4 %). Chromosome 15 showed the highest amount of heterochromatic derivates (51.7 %), followed by chromosome 22 with 30.8 %, and the chromosomes 14, 21, and 13 with 4.4, 4.1, and 1.6 %, respectively. The investigation demonstrated a significantly uneven interchromosomal distribution of the various aberration types in acrocentrics with break points in the constitutive heterochromatin (Table 2).

The *analyses of origin* showed significant differences in the distribution of de novo, familial and unknown origins, as far as heterologous and homologous translocations and derivates were concerned (Table 3). A closer look at the rearrangements of cases with de novo and familial origins and their frequencies regarding the chromosomes involved (Table 4) revealed that the chromosomes 13, 14, and 15 showed a preference for heterologous translocations with familial origin, with a maximum of 83 % occurring in chromosome 13, followed by 77 % in 14, 57 % in 15, the chromosomes 21 and 22 being half familial and half de novo. All homologous fusions were de novo (100 %). As far as heterochromatic derivates were concerned, chromosome 15 had 65 % cases of familial origin, chromosome 14 had 50 %, and chromosomes 13, 21, and 22 were 100 % familial.

Table 3: Types of aberration with break points in the constitutive heterochromatin and their parental origins in the different acrocentrics (subunit I)

Chromosome	*Frequencies of the different types of rearrangements (%) N=244 (without Y-translocations)*			
	Robertsonian translocations		*Heterochromatic derivates*	*Origin*
	heterologous	*homologous*		
13	13	100	-	de novo
	64	-	67	familial
	23	-	33	unknown
14	17	100	17	de novo
	57	-	17	familial
	26	-	66	unknown
15	27	100	26	de novo
	36	-	48	familial
	37	-	26	unknown
21	35	50	-	de novo
	35	-	25	familial
	30	50	75	unknown
22	29	100	-	de novo
	29	-	50	familial
	42	-	50	unknown

Subunit III: Rearrangements including Euchromatic Regions

This subunit consisted of 9 types of *rearrangements* in euchromatic regions and included interchromosomal abnormalities such as reciprocal translocations (rcp) between various acrocentrics, as well as between acrocentrics and other autosomes and the sex chromosomes, complex chromosome rearrangements (CCR), and intrachromosomal aberrations, such as deletions (del), duplications (dup), ring chromosomes (r), euchromatic derivates (euchr. der), isochromosomes (i), and inversions (inv). A total of 289 cases with 295 acrocentric chromosomes with rearrangements were analysed, 36.3 % of which were interchromosomal and 63.7 % intrachromosomal aberrations. Reciprocal translocations occurred most frequently (91.6 %) within the subunit of interchromosomal aberrations and 8.4 % belonged to CCRs. Rearrangements between acrocentrics and different other chromosomes appeared 7 times more often than between acrocentrics alone, with 87.8 % in comparison to 12.2 %. Of the 188 intrachromosomal aberrations with a total of 63.7 % of the above aberrations, 48.4 % were del, 30.3 % euchr. der, 11.3 % dup, 5.8 % r, 3.7 % i, and 0.5% inv (Table 5).

Table 6 shows *chromosome specific frequencies of euchromatic aberration types* for the 5 acrocentrics. Among the interchromosomal exchanges, in relation to the total number of chromosomes, the chromosomes 15 and 22 revealed the highest amount of reciprocal translocations with 26 and 25 out of 295 (8.8 and 8.5 %), whereas chromosome 14 had the lowest frequency with 15 or 5.1 %. Among the reciprocal translocations, the rearrangements with other chromosomes reached a peak in chromosome 22, with 8.2 %, followed by 15 (8.1 %), 21 (5.1 %), 13

Table 4: Rearrangements in constitutive heterochromatic regions and their origins regarding the different chromosomes involved (subunit II).

Chromosome	*Rearrangements of known origin and their frequencies (%)*			
	Robertsonian translocations		*Heterochromatic derivates*	*Origin*
	heterologous	*homologous*		
13	17	100	-	de novo
	83	-	100	familial
14	23	100	50	de novo
	77	-	50	familial
15	43	100	35	de novo
	57	-	65	familial
21	50	100	-	de novo
	50	-	100	familial
22	50	100	-	de novo
	50	-	100	familial

Table 5: Frequencies of inter- and intrachromosomal aberration distribution with break points of the acrocentric chromosomes localized in euchromatic regions (euchr. der = euchromatic derivate) (subunit III).

Types and frequencies of euchromatic chromosome aberrations
N=295

	% of N	*Type of aberration*	*% of N_{inter}*	*Exchange chromosome*	
Interchromosomal	36.3	rcp	91.6	acrocentric	12.2
N = 107				others	87.8
		CCR	8.4		
Intrachromosomal	63.7	del	48.4		
N = 188		dup	11.3		
		r	5.8		
		euchr. der	30.3		
		i	3.7		
		inv	0.5		

(4.0 %), and 14 (3.7). The CCRs varied between 0 and 1.4 %. As far as the intrachromosomal aberrations were concerned, aberrations peaked with deletions in chromosome 22, with 17.6 % of 295, followed by euchromatic derivates in 15 with 8.5 %, the lowest in frequencies being inversions and isochromosomes (between 0 and 1.4 %)

When comparing the *individual acrocentrics*, the distribution of interchro-mosomal rearrangements revealed a peak for reciprocal translocations in the chromosomes 21 and 13 (40.0 % each), closely followed by 14 (38.5 %), and 15 (34.2 %), but with a significantly lower percentage for chromosome 22 (25.0 %) (Table 6). Within the group of intrachromosomal aberrations, deletions proved to be the most frequent mode of aberration in the chromosomes 22, 14 and 13 (52.0, 41.0, 22.5 %), while euchromatic derivates showed the highest numbers in 15 and 21 (32.9 and 20.0 %). Ring chromosomes were found most frequently in chromosome 13 (12.5 %) being rare in the remaining chromosomes, isochromosomes were diagnosed in a smaller percentage only in 15, 21, and 22 (1.3, 10.0, 2.0 %) with a peak in chromosome 21, and inversions occurred only in 1 case in chromosome 14. Thus, our investigation group showed a very unequal distribution of inter- and intrachromosomal aberrations in acrocentrics with break points in euchromatic regions and of aberration tpes as well (Fig. 1).

The analysis of the origins of aberrations in these regions revealed that they were predominantly de novo for all acrocentrics in question except chromosome 15, thus fulfilling the expectation that deletions, duplications, ring chromosomes, and isochromosomes lead to phenotypical impair and prevent inheritance (Table 7).

IV. Polymorphisms

The polymorphic regions in p 11.2 and p13

Table 6: Types of euchromatic chromosome aberrations and their specific frequencies in the 5 acrocentrics (subunit III).

		Euchromatic chromosome aberrations and their frequencies in the 5 acrocentrics N=295														
chromosome		*13*			*14*			*15*			*21*			*22*		
		N_c	% of N_C	N_c/N_{total}	N_c	% of N_C	N_c/N_{total}	N_c	% of N_C	N_c/N_{total}	N_c	% of N_C	N_c/N_{total}	N_c	% of N_C	N_c/N_{total}
interchromosomal																
rcp	acrocen.	4	10.0	1.4	4	10.3	1.4	2	2.6	0.7	1	2.5	0.3	1	1.0	0.3
	others	12	30.0	4	11	28.2	3.7	24	31.6	8.1	15	37.5	5.1	24	24.0	8.2
	total	16	40.0	5.4	15	38.5	5.1	26	34.2	8.8	16	40.0	5.4	25	25.0	8.5
CCR		3	7.5	1	1	2.6	0.3	1	1.3	0.3	4	10.0	1.4	-	-	-
Σ_{inter}		19	47.5	6.4	16	41.1	5.4	27	35.5	9.1	20	50.0	6.8	25	25.0	8.5
intrachromosomal																
del		9	22.5	3.1	16	41.0	5.5	10	13.2	3.4	4	10.0	1.4	52	52.0	17.6
euchr.der		4	10.0	1.4	5	12.8	1.7	25	32.9	8.5	8	20.0	2.7	15	15.0	5.1
dup		3	7.5	1	1	2.6	0.3	10	13.2	3.4	2	5.0	0.7	5	5.0	1.6
r		5	12.5	1.6	-	-	-	3	3.9	1	2	5.0	0.7	1	1.0	0.3
i		-	-	-	-	-	-	1	1.3	0.3	4	10.0	1.4	2	2.0	0.7
inv		-	-	-	1	2.6	0.2	-	-	-	-	-	-	-	-	-
Σ_{intra}		21	52.5	7.1	23	59.0	7.8	49	64.5	16.6	20	50.0	6.8	75	75.0	25.3
Σ_{total}		40		13.5	39		13.2	76		25.7	40		13.6	100		33.8

Table 7: Origin of aberrations with at least one euchromatic breakpoint (subunit III).

	Origin of aberrations (%) chromosomes									
	13		*14*		*15*		*21*		*22*	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
de novo	55	77	37	65	36	48	38	62	31	52
familial	16	23	20	35	39	52	23	38	29	48
unknown	29	-	43	-	25	-	39	-	40	-

showed a dominance for size vs with 70 – 95 % of all acrocentrics, followed by the size s in 0 – 27 % and m in 0 – 5 %. Larger polymorphisms were not observed. The frequency of brilliant fluorescence intensity i(5) ranged from 10 to 65 %, thus showing a significant difference in inter- and intrachromosomal distribution in size, as well as brilliant fluorescence intensity i(5) (Kalz 2003). In families with 13/14 translocations, the frequency of polymorphisms of the chromosomes 13 and 14 was in accordance with their distribution in the general population. A selection of specific polymorphisms could be excluded. Size and fluorescence intensity in the translocation chromosomes remained unchanged after meiosis.

Comparison of the Distribution of Aberration Frequencies within the Acrocentrics

Altogether, there were 13 different types of aberrations, and their frequencies had to be compared for the 5 acrocentrics. These are the results with regard to the distribution of the analysed types of rearrangements (Fig. 1, Table 8):

Translocations of Yq12 onto the short arm regions of the acrocentrics happened in 1,5 % and only in the chromosomes 15 (1.1 %) and 22 (0.4 %).

Within the interchromosomal aberrations, Robertsonian translocations occurred most frequently (39.8 %), and the subunits heterologous and homologous rob included 33.5 and 6.3 %, respectively.

Maxima were found in the chromosomes 14 (15.6 %) and 13 (11.3 %) for rob total. Reciprocal translocations were second in frequency with 17.9 % in all. 2.2 % showed an exchange between acrocentrics only and 15.7 % between acrocentrics and different other chromosomes. These were most often the chromosomes 15 and 22 (4.8 and 4.6 %) (Fig. 2) . Heterochromatic chromosome derivates occurred in 4.8 % of the cases, whereby chromosome 15 was rearranged most often (2.8 %). CCRs showed a frequency of 1.6 % with a peak in chromosome 21 (0.7 %).

Table 8: Types of aberrations analysed for the 5 acrocentric chromosomes and their frequencies (all subunits).

	Frequencies of the different aberration types (%)					
N = 547	*13*	*14*	*15*	*21*	*22*	*% of all acrocentrics*
Y/A	-	-	1.1	-	0.4	1.5
rob heterologous	10.2	14.9	2.2	4.9	1.3	33.5
rob homologous	1.1	0.7	0.4	3.7	0.4	6.3
rob total	*11.3*	*15.6*	*2.6*	*8.6*	*1.7*	*39.8*
heterochr. der	0.2	0.7	2.8	0.4	0.7	4.8
rcp acrocentrics	0.7	0.7	0.4	0.2	0.2	2.2
rcp others	2.2	2.0	4.4	2.7	4.4	15.7
rcp total	*2.9*	*2.7*	*4.8*	*2.9*	*4.6*	*17.9*
del	1.6	2.9	1.9	0.7	9.5	16.6
dup	0.5	0.2	1.9	0.4	0.9	3.9
r	0.9	-	0.5	0.4	0.2	2.0
euchr. der	0.7	0.9	4.6	1.5	2.7	10.4
CCR	0.5	0.2	0.2	0.7	-	1.6
i	-	-	0.2	0.7	0.4	1.3
inv	-	0.2	-	-	-	0.2

Among the intrachromosomal aberrations, deletions were the most frequent, with 16.6 % in total, and the maximum was in chromosome 22 (9.5 %). Euchromatic marker chromosomes were observed in 10.4 % of the aberrations, that showed maxima in the chromosomes 15 and 22 (4.6 and 2.7 %). Duplications occurred in 3.9 % of the cases, and most of them in the chromosomes 15 and 22 (1.9 and 0.9 %). Ring chromosomes happened in 2.0 %, namely in 13 and 15 (0.9 and 0.5 %). Isochromosomes were found in 1.3 % and only in 15, 21, and 22 (0.2, 0.7 and 0.4 %). Inversions occurred with a frequency of 0.2 % and only in chromosome 14 (Table 8).

The relation of interchromosomal to intrachromosomal aberrations was 61:39 %.

Table 9 summarizes the overall distribution of the analysed rearrangements within for sulounits the 5 acrocentric chromosomes (see the chapters for subunits II and III) with the following results for the individual chromosomes**:**

Chromosome 13 is second in frequency of Robertsonian translocations (rob) after chromosome 14. We observed 54.4 % of heterologous and 5.8 % of homologous rob, making this the largest group within the aberrations of chromosome 13 (60.2 %). Heterochromatic derivates caused by rearrangements of two homologous chromosomes 13 or isochromosomes were only found in 1.0 %. Reciprocal translocations represented the second largest group (15.6 %) of aberrations in chromosome 13, with 3.9 % within the acrocentrics and 11.7 % with

Table 9: Distribution of the analysed rearrangements regarding the 5 acrocentric chromosomes (summarizing I, II, and III).

		Chromosome									
N = 539		*13*	*% N_C*	*14*	*% N_C*	*15*	*% N_C*	*21*	*% N_C*	*22*	*% N_C*
rob	heterologous	56	54.4	82	63.6	12	11.4	27	30.3	7	6.2
	homologous	6	5.8	4	3.1	2	1.9	20	22.5	2	1.8
heterochr. der		1	1.0	4	3.1	15	14.3	2	2.3	4	3.5
rcp	acroc.	4	3.9	4	3.1	2	1.9	1	1.1	1	0.9
	others	12	11.7	11	8.2	24	22.9	15	16.6	24	21.2
del		9	8.7	16	12.4	10	9.5	4	4.5	52	46.0
dup		3	2.9	1	0.8	10	9.5	2	2.3	5	4.4
r		5	4.9	-	-	3	2.6	2	2.3	1	0.9
euchr. der		4	3.9	5	3.9	25	23.8	8	8.9	15	13.3
CCR		3	2.9	1	0.8	1	1.0	4	4.5	-	-
i		-	-	-	-	1	1.0	4	4.5	2	1.8
inv		-	-	1	0.8	-	-	-	-	-	-
Total		103		129		105		89		113	

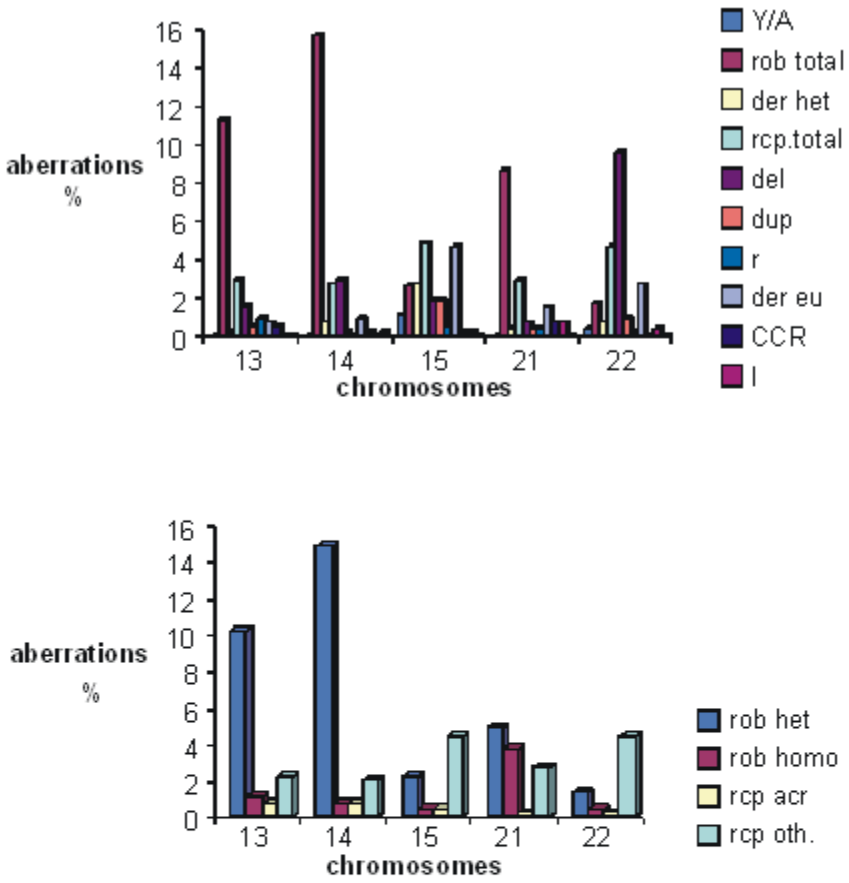

Fig. 2. T **r distribution**

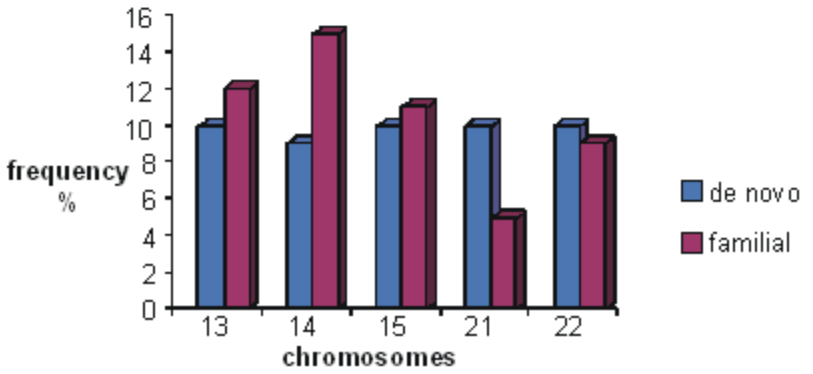

Fig. 3. Frequencies of the different aberration types in the investigation group

other chromosomes. The intrachromosomal aberrations concerning deletions in the euchromatin followed with 8.7 %, occurring de novo in all cases. In order of frequency, the remaining aberrations were ring chromosomes in 4.9 %, euchromatic derivates in 3.9 %, duplications and CCRs both in 2.9 %. No isochromosomes or inversions were found (Table 9).

Chromosome 14 had the highest share of heterologous Robertsonian translocations (rob) with 63.6 % for the chromosome, thus accounting for 44.6 % of all the rob in the acrocentrics. Homologous rob only occurred in 3.1 %. The pattern and order of frequency for aberrations were very similar to the ones of chromosome 13 (Table 9). There were no ring chromosomes and 0.8 % of inversions, though.

Chromosome 15 showed aberrations with a different distribution pattern as compared to 13 and 14. Reciprocal translocations were the most frequent abnormality (24.8 %), and exchanges with acrocentric rcps (1.9 %) were low and those with non-acrocentrics high (22.9 %). The occurrence of reciprocal translocations proved to be nearly double in comparison to the frequency of Robertsonian translocations (13.3 %). Robs in 15 were found a lot less than those in 13 (60.2 %) and 14 (66.7 %). Heterologous robs in 15 were dominant (11.4 %) over homologous ones (1.9 %) but to a much smaller factor than in the previous chromosomes. Heterochromatic derivates (14.3 %) showed the highest frequency of all the acrocentrics. Euchromatic derivates occurred as the second most frequent aberration type in chromosome 15 (23.8 %). With 9.5 %, deletions were comparable to the previous chromosomes. Duplications showed up in 9.5 % as well, thus being more than three times the amount of those of chromosome 13 and twelve times the amount those of 14. Ring chromosomes had a frequency of 2.6 %, the second highest of all the acrocentrics. CCRs and isochromosomes played no particular role (1.0 % both), and inversions were not found at all.

Chromosome 21 showed, similar to 13 and 14, a dominance of Robertsonian translocations among the structural aberrations (52.8 %), but in contrast to the former chromosomes, the numbers of heterologous (30.3 %) and homologous (22.5 %) translocations were considerably close in frequency. The pattern of distribution for heterochromatic derivates (2.3 %), and both reciprocal translocation types (1.1 % and 16.6 %) was comparable to the chromosomes 13 and 14. Deletions with 4.5 % showed only about half the frequency in comparison to the D-chromosomes. Derivates containing euchromatic regions (8.9 %) ranged 3rd following 15 and 22, while rare structural aberrations such as rings, CCRs and isochromosomes had frequencies between 2 and 5 %. No inversions were found.

Chromosome 22 revealed a specific aberration pattern as well. Robertsonian translocations comprised only 8.0 % of the abnormalities, and the difference between heterologous (6.2 %) and homologous (1.8 %) was small, thus being quite different from the results in the chromosomes 13 to 15. Heterochromatic derivates (3.5 %) were in the same order as 13, 14, and 21. Reciprocal translocations (22.1 %) were the second-most aberration type within the chromosome, and translocations with non-acrocentrics (21.2 %) dominated over those with acrocentrics (0.9 %,) thus comprising 96 % of this aberration type. The most frequent class of structural abnormalities in chromosome 22 was deletions (46.0 %). This was the highest rate within all of the acrocentrics. Duplications (4.4 %) rated 10 % of the deletions but ranged still 2nd highest rate after chromosome 15 within the acrocentrics. Ringchromosomes (0.9 %) were rare and second to chromosome 14 in lowest frequency. The amount of euchromatic derivates (13.3 %) ranged 3rd for chromosome 22 and 2nd for all the acrocentrics following 15. CCRs and inversions were not observed. The frequency of isochromosomes (1.8 %) was 2nd after 21 (Table 9).

Comparison of Origin of Aberrations within the 5 Acrocentric Chromosomes

The comparison of the frequency of familial and de novo cases revealed nearly similar distributions with 51 and 49 % (Fig. 3). Likewise, as far as the individual chromosomes were concerned, 13, 15, and 22 showed comparable results for de novo and familial cases (10, 10, and 10 % for de novo, and 11, 11 %, and 9 % for familial), contrary to chromosome 14 with a majority of

Table 10: Analysis of origin of all known structural aberration types and their distribution among the 5 acrocentric chromosomes (all subunits).

	Frequency in cases of known origins (%)				
chromosome	*13*	*14*	*15*	*21*	*22*
de novo	10	9	10	10	10
familial	12	15	11	5	9

familial (15 %) over de novo cases (9 %) and chromosome 21 with more de novo aberrations (10 %) than familial ones (5 %) (Table 10).

DISCUSSION

The 3 regions of the short arms of the acrocentric chromosomes (p11.2, p12, and p13) can be heteromorphous and/or different in their staining features. The short arms of the acrocentrics demonstrate the highest mutation rate in the human genome. They can form Robertsonian translocations and heterochromatic derivates, thus losing satellites (p13), NOR-regions (p12), and partially p11.2 and p11.1 as well. The distribution of intrachromosomal breakpoints in all types of abnormalities in the acrocentrics and the participation of the different chromosomes in chromosomal rearrangements do not happen at random, according to the present findings and to literature. Chromosome 14 is involved most frequently in the interchromosomal exchange, followed by chromosome 13 (Hecht et al. 1972, Therman et al. 1989). The most frequent combination is 13/14, then 14/21 and 13/21, caused by similar sequences of satellite-DNA II und III in the short-arm regions, in particular in p11.2 (Choo et al. 1988, 1991). Why there are significant differences in the occurrence of short-arm polymorphisms remains to be explained. The specific construction of p11.2 in 15 and 22p11.2 of a subcomponent of satellite-DNA III and the conformity with Yq12 can explain the selective translocation between these chromosomes.

Our study analysed 8 cases of translocations between the acrocentrics and Yq12. Complementary FISH-analyses could exclude any transfer of euchromatin, thus omitting a genetic risk for the carrier. In literature, the frequency of translocations of Yq12 onto 15q11.2 and 22p11.2 is said to be 1:3-4000 in unselected studies of newborn (Miller and Therman 2001). Patients with these translocations and gonadoblastoma, prostate cancer, and/or infertility obviously did not have pure heterochromatic translocations (Wyandt and Tonk (Ed.) 2004).

Robertsonian translocations in our study involved mostly chromosome 14, followed by chromosome 13 (Fig. 1, 2). This is in accordance with observations in literature stating that fusion 13/14 includes 75 % of all Robersonian translocations (Nielsen et al. 1976, Gardner and Sutherland 2004). This type of aberration is the most frequent in chromosome 14 (60 of 78 cases), with 13 being the partner of that fusion (49 of 55 cases). Homologous fusions are rare (5 %). Gardner and Sutherland (2004) indicate a frequency of 2 % for 13/13 fusions, based on literature. Homologous Robertsonian translocations in our study were de novo in 100 %, and heterologous ones were familial in 67 %. These findings are in agreement with literature. A Danish study revealed 63 % of familial translocations (Nielsen et al. 1976).

An exemplary comparison of frequencies for different types of aberrations was performed for *chromosome 13* regarding our study group and the data used in the catalogue of Borgaonkar (1997). We compared 11 different structural aberrations. The results of Borgaonkar showed Robertsonian and reciprocal translocations to be the most abundant aberrations, just like in our study. Their frequency of occurrence was reverse, though, with 20.0 % (rob) and 50.9 % (rcp) in Borgaonkar's to 60.2 % (rob) and 15.6 % (rcp) in our study. The reason for this possibly was the fact that studies of families with Robertsonian translocations are not published as much as those with reciprocal translocations. The more rare structural aberrations showed very similar frequencies in Borgaonkar's and our studies with the exception of deletions (14.0 % for Borgaonkar and 8.7 for us).

Chromosome 15 revealed a very special pattern of rearrangements in the present study, which was especially different from aberrations in the chromosome 13 and 14. Reciprocal translocations had about twice the amount of Robertsonian ones, whereby exchanges with acrocentrics were less frequent than with non-acrocentrics. The most frequent aberration type in 15 was chromosome derivates containing euchromatin of 15q proximal regions. Dicentric and monocentric derivates are a peculiarity of chromosome 15 (Eggermann et al. 2002).

Deletions in *chromosome 21* showed only half the frequency in comparison to the other chromosomes, so we compared and confirmed the amounts of these abnormalities with the documentation of Borgaonkar as well (4.5 % to 4.0 %). Thus we can say that this low deletion rate seems to be special to chromosome 21.

The characterization of the heterochromatic regions in acrocentric chromosomes underwent a significant expansion within the last few years

because of the inclusion of different FISH-analyses and molecular genetic analyses as well (Wyandt and Tonk (Ed.) 2004).

SUMMARY

The investigation group presented here was comprised of 432 cases of structural chromosome aberrations in the acrocentrics. On the whole, 547 aberrant chromosomes were analysed. 218 interchromosomal rearrangements consisted of 109 Robertsonian translocations, 92 heterologous and 17 homologous. Of these, chromosomes 14 and 13 showed a maximum of involvement. For all 5 acrocentrics, heterologous Robertsonian translocations were more frequent than homologous ones. Reciprocal translocation involved 98 chromosomes, 6 cases of pure acrocentric exchanges, and 86 with the involvement of other chromosomes.

The maxima of intrachromosomal aberrations were found in the chromosomes 15 and 22 while peaks for interchromosomal aberrations could be documented in 14, 13 and 21. Translocations between Yq12 and the acrocentrics were rare and involved only chromosome 15 and 22. With 9 cases altogether, CCRs were mainly observed in chromosome 21.

Pure intrachromosomal aberrations were found in 214 cases. The main types of aberration were deletions (maximum chromosome 22), euchromatic chromosome derivates (maximum chromosome 15), and duplications (maximum chromosome 15). Ringchromosomes, isochromosomes, and inversions had frequencies of less than 5 %.

The relation of de novo and familial cases was about even in regard to the whole investigation group but showed significant differences for the individual aberration.

The analysis of polymorphic regions in p11.2 and p13 in the acrocentrics 13 and 14 revealed no particular peculiarities in fluorescence intensity i(5) and size vs for Robertsonian translocation carriers. A selection of specific polymorphisms could be excluded in families with 13/14 translocation with frequencies being in accordance with their distribution in the general population.

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