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Molecular Cytogenetic Characterization of 17 rob(13q14q) Robertsonian Translocations by FISH, Narrowing the Region Containing the Breakpoints

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Summary

We have characterized 17 rob(13q14q) Robertsonian translocations, using six molecular probes that hybridize to the repetitive sequences of the centromeric and short-arm regions of the five acrocentric chromosomes by FISH. The rearrangements include six de novo rearrangements and the chromosomally normal parents, five maternally and three paternally inherited translocations, and three translocations of unknown origin. The D21Z1/D13Z1 and D14Z1/D22Z1 centromeric alpha-satellite DNA probes showed all rob(13q14q) chromosomes to be dicentric. The rDNA probes did not show hybridization on any of the 17 cases studied. The pTRS-47 satellite III DNA probe specific for chromosomes 14 and 22 was retained around the breakpoints in all cases. However, the pTRS-63 satellite III DNA probe specific for chromosome 14 did not show any signals on the translocation chromosomes examined. In 16 of 17 translocations studied, strong hybridization signals on the translocations were detected with the pTRI-6 satellite I DNA probe specific for chromosome 13. All parents of the six de novo rob(13q14q), including one whose pTRI-6 sequence was lost, showed strong positive hybridization signals on each pair of chromosomes 14 and 13, with pTRS-47, pTRS-63, and pTRI-6. Therefore, the translocation breakpoints in the majority of rob(13q14q) are between the pTRS-47 and pTRS-63 sequences in the p11 region of chromosome 14 and between the pTRI-6 and rDNA sequences within the p11 region of chromosome 13.

Introduction

The acrocentric chromosomes in man have been intensively investigated, both because of their frequent involvement in chromosomal aberrations and aneuploidy and because of their unique structural properties. Although all acrocentric chromosomes may undergo Robertsonian translocation formation, the distribution in the population is nonrandom, with rob(13q14q) ascertained most frequently (Therman et al. 1989). Molecular studies have shown that the pericentromeric and short-arm regions of these five pairs of acrocentric chromosomes have extensive sequence homology, although some sequences are not common to all of the acrocentrics (Choo 1990).

Several distinct and tandemly repetitive sequences are localized to these regions. Alpha-satellite is a major class of repetitive DNA found at the centromeric region of each human chromosome (Choo et al. 1991). Acrocentric chromosomes contain a number of satellite subfamilies, some of which are shared by different acrocentrics. These shared sequences have been postulated to be involved in the formation of Robertsonian translocations and in nonrandom participation of chromosomes 13, 14, and 21 in most Robertsonian translocations (Choo et al. 1988, 1989; Therman et al. 1989; Choo 1990).

The short arms of acrocentric chromosomes can be divided into three distinct portions. The proximal short arm (p11) contains satellites I–IV (Gosden et al. 1981; Choo et al. 1990, 1992; Gravholt et al. 1992), beta-satellite (Waye and Willard 1989), and the interspersed 724 repeated sequence (Kurnit et al. 1986). The stalk, or nucleolus organizer region (NOR) (p12), contains the 18S and 28S ribosomal genes (Worton et al. 1988). Finally, beta-satellite DNA (Waye and Willard 1989) and 724 DNA (Kurnit et al. 1986) have been mapped to the distal cytological satellite (p13).

In previous studies, 90% of Robertsonian translocations had been found to be dicentric, and the breakpoints had been localized to satellite III DNA in the short arms (Mattei et al. 1979; Gosden et al. 1981; Therman et al. 1989). However, both because of extensive heteromorphisms of the centromeric and short arm of the acrocentric chromosomes and because of lack of knowledge about the exact molecular organization of these regions, the precise localization of breakpoints has not been easy to define.

Over the past few years, FISH has become increasingly popular for localizing sequences to chromosomes; and it has technical advantages over tritium-based in situ hybridization. Recently isolated subfamilies of alpha-satellite,

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Table 1

Ascertainment and Cytogenetic Analysis of 17 rob(13q14q) Patients

Case	Sample Type	Ascertainment	Karyotype	Origin
1	Blood	Developmental delay, dysmorphic	45,XY,rob(13q14q)	De novo
2	Blood	Nasofrontal encephalocele	45,XX,rob(13q14q)	De novo
3	Amniotic fluid	Uncertain	45,XX,rob(13q14q)	De novo
4	Amniotic fluid	Uncertain	46,XX,−14,+rob(13q14q)	De novo
5	Amniotic fluid	Advanced maternal age	45,XY,rob(13q14q)	De novo
6	Chorionic villi	Advanced maternal age	45,XX,rob(13q14q)	De novo
7	Blood	Multiple anomalies	46,XY,−14,+rob(13q14q)	Maternal
8	Chorionic villi	rob(13q14q)mat	45,XX,rob(13q14q)	Maternal
9	Amniotic fluid	Advanced maternal age	45,XY,rob(13q14q)	Maternal
10	Amniotic fluid	Advanced maternal age	45,XY,rob(13q14q)	Maternal
11	Amniotic fluid	Advanced maternal age	45,XX,rob(13q14q)	Maternal
12	Blood	Developmental delay, dysmorphic	45,XY,rob(13q14q)	Paternal
13	Amniotic fluid	rob(13q14q)pat	45,XY,rob(13q14q)	Paternal
14	Amniotic fluid	Advanced maternal age, rob(13q14q)pat	45,XX,rob(13q14q)	Paternal
15	Blood	Multiple anomalies	45,XX,rob(13q14q)	Unknown
16	Blood	Multiple miscarriages	45,XY,rob(13q14q)	Unknown
17	Skin	Multiple anomalies	45,XY,rob(13q14q)	Unknown

satellite I, satellite III, and other repetitive DNA sequences from the acrocentric chromosomes enable us to further define the DNA sequences around the breakpoints. In the present study, we investigated 17 rob(13q14q), using FISH and six molecular probes specific for repetitive DNA sequences in the centromeric and short-arm regions of the acrocentric chromosomes, to characterize the sequence organization around the breakpoints in these Robertsonian translocations.

Material and Methods

Ascertainment

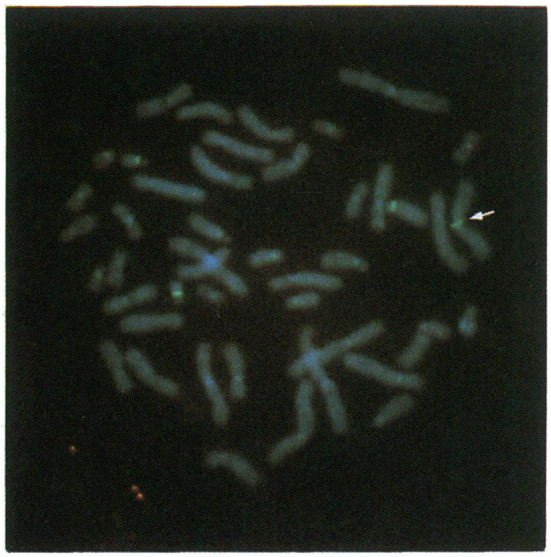
Seventeen rob(13q14q) were studied, from individuals who carry a de novo (6 cases), maternally inherited (5 cases), or paternally inherited (3 cases) rearrangement. In three cases, parental samples were unavailable, and therefore the parental origin could not be determined. In the six de novo cases, the karyotypically normal parents were also

Table 2

FISH Results for 17 Cases of rob(13q14q)

			rob(13q14q) Hybridization		
			Satellite III DNA		
Case	No. of Centromeres	rDNA	pTRS-47	pTRS-47	Satellite I DNA: pTRI-6
1	2	−	+	−	−[a]
2	2	−	+	−	+
3	2	−	+	−	+
4	2	−	+	−	+
5	2	−	+	−	+
6	2	−	+	−	+
7	2	−	+	−	+
8	2	−	+	−	+
9	2	−	+	−	+
10	2	−	+	−	+
11	2	−	+	−	+
12	2	−	+	−	+
13	2	−	+	−	+
14	2	−	+	−	+
15	2	−	+	−	+
16	2	−	+	−	+
17	2	−	+	−	+

[a] Parental chromosomes 13 showed positive hybridization with pTRI-6.



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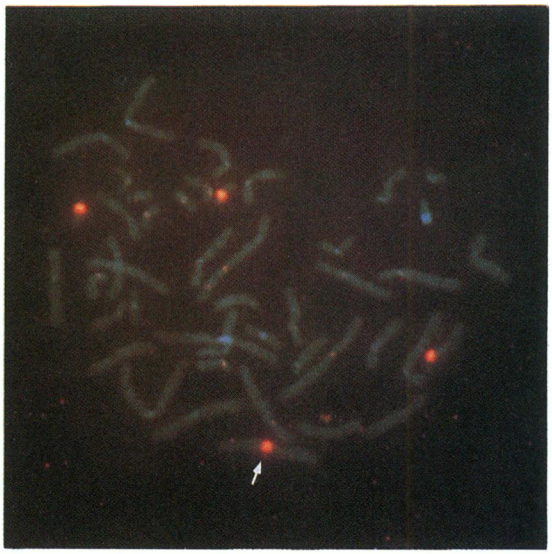

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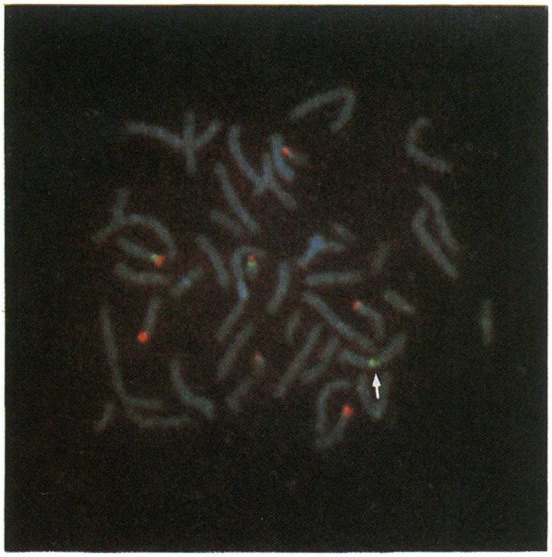

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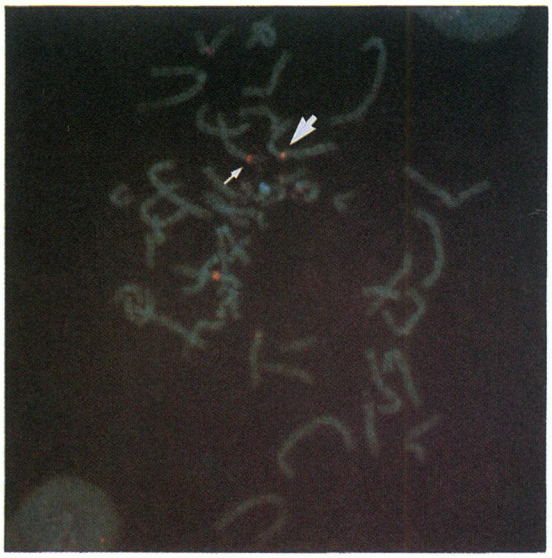

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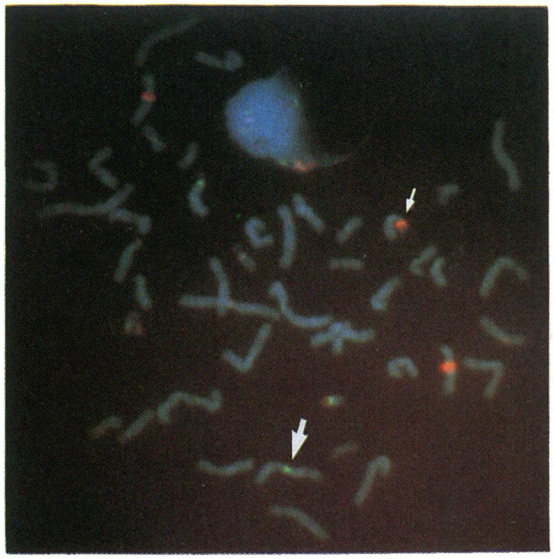

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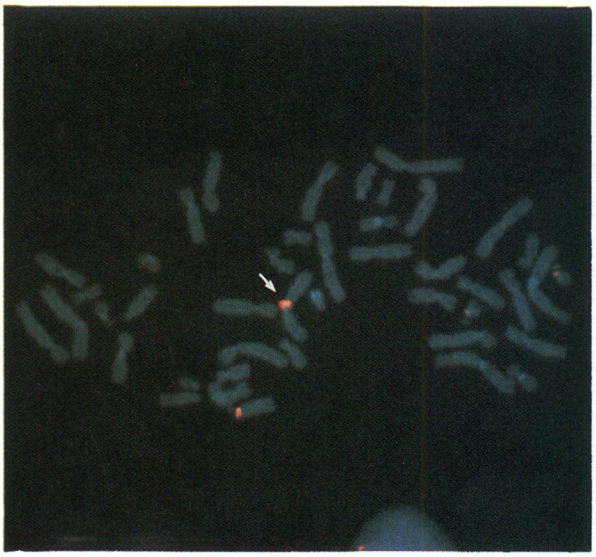

f

studied by FISH. Most of the cases were ascertained through a large study on the mechanisms of Robertsonian translocation formation, by six genetic centers, including Baylor College of Medicine, Houston; Henry Ford Hospital, Detroit; Lutheran General Hospital, Park Ridge, IL; Georgetown University Medical Center, Washington DC; Oakwood Hospital, Dearborn; and Austin Neurologic Clinic, Austin. Ten cases were identified prenatally, and seven were detected postnatally (table 1). Cases 1, 2, 7, and 12 were ascertained because of an abnormal phenotype and were referred for uniparental disomy studies. All cases demonstrated normal biparental inheritance of chromosomes 13 and 14, with the use of multiple molecular polymorphisms (data not shown).

Metaphase chromosomes were prepared from amniotic fluid (cases 3–5, 9–11, 13, and 14), chorionic villi (cases 6 and 8), or skin fibroblasts (case 17) by using standard procedures. Lymphoblastoid cell lines were established from peripheral blood samples and were harvested in cases 1, 2, 7, 12, 15, and 16.

DNA Probes

Six DNA probes were used for FISH analysis, including (1) D21Z1/D13Z1 (Oncor), specific for alpha-satellite DNA on the centromeres of chromosomes 21 and 13; (2) D14Z1/D22Z1 (Oncor), alpha-satellite DNA specific to the centromeres of chromosomes 14 and 22; (3) plasmids pA (Sylvester et al. 1986) and pU6.2 (Wilson et al. 1978), which contain 28S and 18S ribosomal RNA genes, respectively, and hybridize to rDNA sequences on all acrocentrics; (4) pTRS-47, a subfamily of satellite III DNA, specific for tandemly repeated sequences on the proximal short-arm region (p11) of chromosomes 14 and 22 (Choo et al. 1990); (5) pTRS-63, another subfamily of human satellite III DNA, mapped to the p11 region of chromosome 14 (Choo et al. 1992); and (6) pTRI-6, a satellite I DNA subfamily specific mainly for the short arm (p11) of chromosome 13, which may hybridize weakly to the short arm of chromosome 21 under high stringency (Kalitsis et al. 1993). D21Z1/D13Z1 and D14Z1/D22Z1 were purchased from Oncor, labeled with biotin and digoxigenin, respectively. The other four probes were digoxigenin-labeled using nick-translation (Boehringer Mannheim) and were diluted in 50%–65% formamide hybridization solution, for a final concentration of 20 ng/μl.

In Situ Hybridization

Metaphase chromosome coverslips and slides were prepared according to standard methods. FISH was performed as described elsewhere (Shaffer et al. 1994 [in this issue]).

For the D14Z1/D22Z1 probe, a more stringent 55% formamide, 2 × SSC washing condition was used. The biotinylated D21Z1/D13Z1 was detected by incubation with fluorescein isothiocyanate (FITC)–conjugated avidin (Oncor). The five digoxigenin-labeled probes were detected by anti-digoxigenin conjugated with rhodamine (Boehringer Mannheim). For pTRS-47 and pTRS-63 probes, the signals were amplified by monoclonal anti-digoxin antibody (Sigma) and by anti-mouse immunoglobulin conjugated to digoxigenin (Boehringer Mannheim), before detection, to provide optimal hybridization signal. The slides were counterstained with DAPI and were examined with a Zeiss Axiophot fluorescence microscope using a Zeiss triple-bandpass filter.

Results

The FISH results are summarized in table 2. Strong positive hybridization signals were obtained for both the D21Z1/D13Z1 and D14Z1/D22Z1 alpha-satellite probes (fig. 1*a* and *b*, respectively), in all rob(13q14q) chromosomes, indicating that they were all dicentric.

The rDNA probes pA and pU6.2, used simultaneously, did not hybridize to any of the 17 translocation chromosomes (fig. 1*c*). This result suggests an apparent loss of the NOR in these rob(13q14q).

When FISH was used with the two satellite III probes pTRS-47 and pTRS-63, significant cross-hybridization was observed on the heterochromatic region (band q12) of both chromosomes 9, the short arms of the other acrocentric chromosomes, and sometimes the centromeric heterochromatin of chromosome 1. For the six de novo rob(13q14q) cases, the parental chromosomes were examined using the two satellite III DNA probes pTRS-47 and pTRS-63 and pTRI-6 satellite I DNA probe to delineate any heteromorphisms or deletions of these sequences and to determine the organization of DNA sequences at the translocation breakpoints. Positive hybridization signals were detected with pTRS-47, on the translocation chromosomes and on the short-arm regions of the free-lying

Figure 1 Representative results of using FISH and six molecular probes specific for the centromere and short-arm region of acrocentric chromosomes. *a*, D21Z1/D13Z1 alpha-satellite DNA probe showing a positive hybridization signal on the translocation chromosome (*arrow*) (case 12). *b*, FISH with the D14Z1/D22Z1 alpha-satellite DNA probe, in the same case as in panel *a*. The arrow indicates a positive hybridization signal on the translocation chromosome, suggesting that it is dicentric, containing centromeres of both chromosomes 13 and 14. *c*, Two-color FISH using the rDNA probe detected with rhodamine and the D21Z1/D13Z1 probe detected with FITC. There was a deletion of ribosomal genes, as indicated by the absence of a red hybridization signal on the translocation chromosome (*arrow*) (case 3). *d*, Hybridization with the pTRS-47 satellite III DNA probe, showing retention of signal on the translocation chromosome (*larger arrow*) and on the free-lying chromosome 14 (*thin arrow*) (case 10). *e*, Two-color FISH with rhodamine-detected pTRS-63 satellite III DNA probe and FITC-detected D21Z1/D13Z1 alpha-satellite probe. The arrow indicates the absence of pTRS-63 hybridization signal on the translocation chromosome (*larger arrow*) (case 15). Note the positive hybridization on the free-lying chromosome 14 (*smaller arrow*). *f*, Hybridization with pTRI-6 satellite I DNA probe, indicating the presence of a strong positive signal on both the translocation chromosome (*arrow*) and the free-lying chromosome 13 (case 13).

chromosome 14 (figs. 1*d* and 2*a*). Therefore, these results demonstrate the retention of pTRS-47 sequences on the translocations. In contrast, pTRS-63, which hybridized to the free-lying chromosomes 14, did not show signals on any of the translocation chromosomes (figs. 1*e* and 2*d*). For the de novo cases, the parental chromosomes 14 showed positive hybridization signals (fig. 2*e* and *f*). These results suggest that pTRS-63 sequences on the short arms of chromosome 14 were lost during formation of the translocations. Therefore, the translocation breakpoints are located between pTRS-47 (proximal) and pTRS-63 (distal) on chromosome 14.

pTRI-6 is a satellite I DNA subfamily that is specific for the short arm of chromosome 13. Of the 17 rob(13q14q) cases, 16 had strong positive signals on the free-lying chromosomes 13 and on the translocation chromosomes (fig. 1*f*). Occasionally, chromosome 21 also showed hybridization signals, but the intensity of the signals was variable. One de novo rob(13q14q) (case 1) was deleted for the pTRI-6 sequences, although all four parental chromosomes 13 showed strong hybridization with the pTRI-6 probe (fig. 2). Therefore, the majority (16/17) of rearrangements studied retained pTRI-6 on chromosome 13 in the translocation.

Discussion

Robertsonian translocations, described as whole-arm exchanges between acrocentric chromosomes, are the most common structural rearrangements in humans and occur with a frequency of ~1/1,000 live births (Nielsen and Ramussen 1976; Evans et al. 1978; Nielsen and Wohlert 1991). They may arise de novo or may be inherited from a carrier parent. The majority of Robertsonian translocations involve two nonhomologous acrocentric chromosomes. In ~65%–80% of Robertsonian translocations, the exchanges are between chromosomes 13 and 14 and between chromosomes 14 and 21. The most common combination is rob(13q14q) (Therman et al. 1989).

Aneuploid offspring, infertility, miscarriages, mental retardation, and an increased risk of uniparental disomy are complications for balanced carriers of Robertsonian translocations (Gardner and Sutherland 1989; Donnai 1993). Of our 17 rob(13q14q) cases, 10 were ascertained through amniocentesis or chorionic villus sampling performed either because of advanced maternal age or because there was a known rob(13q14q) carrier. One rob(13q14q) was identified because of a history of multiple miscarriages. Five cases were ascertained through developmental delay and/or other anomalies not representing known trisomies. Uniparental disomy was excluded in these individuals (data not shown). The associated anomalies are probably incidental to the Robertsonian translocation; but further investigation is warranted, to rule out other aberrations of chromosomes 13 or 14 (Groupe de Cytogeneticiens Français 1989; Bonthron et al. 1993).

Early studies had shown ~90% of Robertsonian translocations to be dicentric (Mattei et al. 1979; Gosden et al. 1981; Therman et al. 1989). Four more recent studies examined 62 nonhomologous Robertsonian translocations by using FISH (Cheung et al. 1990; Earle et al. 1992; Gravholt et al. 1992; Wolff and Schwartz 1992). These studies revealed that 58 (~93.5%) of these 62 were dicentric. In the present study, all 17 rob(13q14q) were dicentric. This finding is consistent with the localization of the exchange to the short arms of both acrocentrics involved, since the alpha-satellite sequences corresponding to the D21Z1/D13Z1 and D14Z1/D22Z1 probes were retained with the long arms in the formation of Robertsonian translocations.

The NOR is located in the stalk or secondary constriction of the acrocentric chromosome and contains the tandemly repeated genes coding for the 18S and 28S rRNAs (Worton et al. 1988). The amount of rDNA present differs between the five pairs of acrocentric chromosomes and between individuals. However, the amount of rDNA per chromosome appears to be stable and heritable (Mattei et al. 1979). During the formation of nucleoli, the satellites of the acrocentric chromosomes associate. During this time, breakage and exchange could occur between acrocentrics, causing Robertsonian translocations to form (Ohno et al. 1961). Using the rDNA probes and FISH, we found no hybridization signals on the translocation chromosomes among the 17 rob(13q14q) studied. Five previous studies have examined the rDNA region by using silver stain and/or in situ hybridization (Mattei et al. 1979; Gosden et al. 1981; Cheung et al. 1990; Gravholt et al. 1992; Wolff and Schwartz 1992). They showed 65 NOR-negative cases in 67 Robertsonian translocations, which suggests that in the majority of cases there is an apparent deletion of the NOR during the translocation event.

As much as 10% of human chromosomal DNA consists of tandemly repeated sequences located at the pericentromeric regions (Moyzis et al. 1989). The proximal short arm (p11) of all the acrocentric chromosomes contains satellites I–IV. The function of satellite DNA has not been determined, but it may be involved in chromosomal organization and structure, gene regulation, and maintaining chromosome pairing and order within the nucleus (Gosden et al. 1979; Choo 1990). Recent isolation of satellite III (pTRS-47 and pTRS-63) and satellite I (pTRI-6) DNA subfamilies has provided useful probes for the investigation of Robertsonian translocations and of the structural organization on the short arms of the acrocentric chromosomes. Results with these satellite DNA probes indicate the retention of pTRS-47 sequences within the short arm of chromosome 14 in all rob(13q14q) (n = 21) and rob(14q21q) (n = 15) translocations examined elsewhere (Earle et al. 1992; Gravholt et al. 1992). The sequences for pTRS-63 have been shown to be lost on the translocation chromosomes in all rob(14q21q) examined (n = 12) (Earle et al. 1992). In the present study, using the two satellite

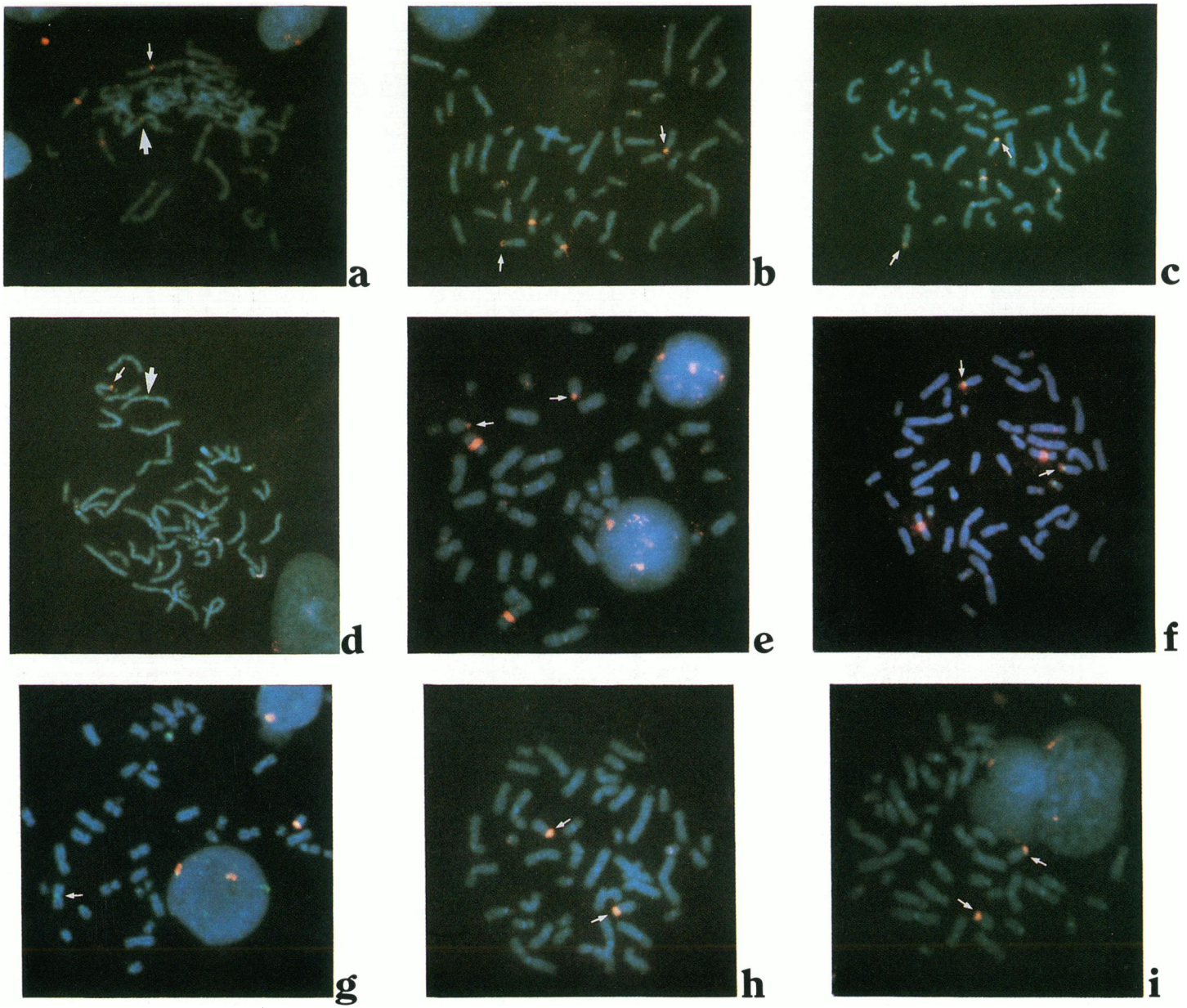

Figure 2 Representative results from de novo rob(13q14q) carriers (*left*), their mother (*middle*), and their father (*right*), from FISH with rhodamine-detected pTRS-47 and pTRS-63 satellite III DNA probes and pTRI-6 satellite I DNA probe (fluoresces red) and FITC-detected alpha-satellite probes D21Z1/D13Z1 and D14Z1/D22Z1 (fluoresces green). *a,* Hybridization with pTRS-47 satellite III DNA probe, demonstrating the presence of a signal on the translocation chromosome in case 6 (*larger arrow*), the free-lying chromosome 14 in the proband (*smaller arrow*), and both chromosomes 14 from the parents (*b* and *c*) . *d,* Cohybridization with pTRS-63 satellite III DNA probe and D21Z1/D13Z1, showing loss of pTRS-63 sequence on the translocation chromosome, as indicated by both the absence of a red hybridization signal in case *5* (*larger arrow*) and retention of signal on the free-lying chromosome 14 (*smaller arrow*). In the parents (*e* and *f*), strong hybridization signals are present in both chromosomes 14, suggesting that the pTRS-63 sequence is deleted from the translocation. Two-color FISH with pTRS-63 probe and D14Z1/D22Z1 in the father reveals that pTRS-63 satellite III DNA probe specifically hybridizes to chromosomes 14 (*f*). *g,* Two-color FISH with pTRI-6 satellite I DNA probe and D21Z1/D13Z1 in one de novo rob(13q14q) (case 1), showing loss of pTRI-6 sequence on translocation chromosome, as indicated by the absence of a red fluorescence (*arrow*). Strong hybridization signals are present in both chromosomes 14 from the parents (*h* and *i*), indicating the deletion of pTRI-6 sequences by the translocation event in the proband.

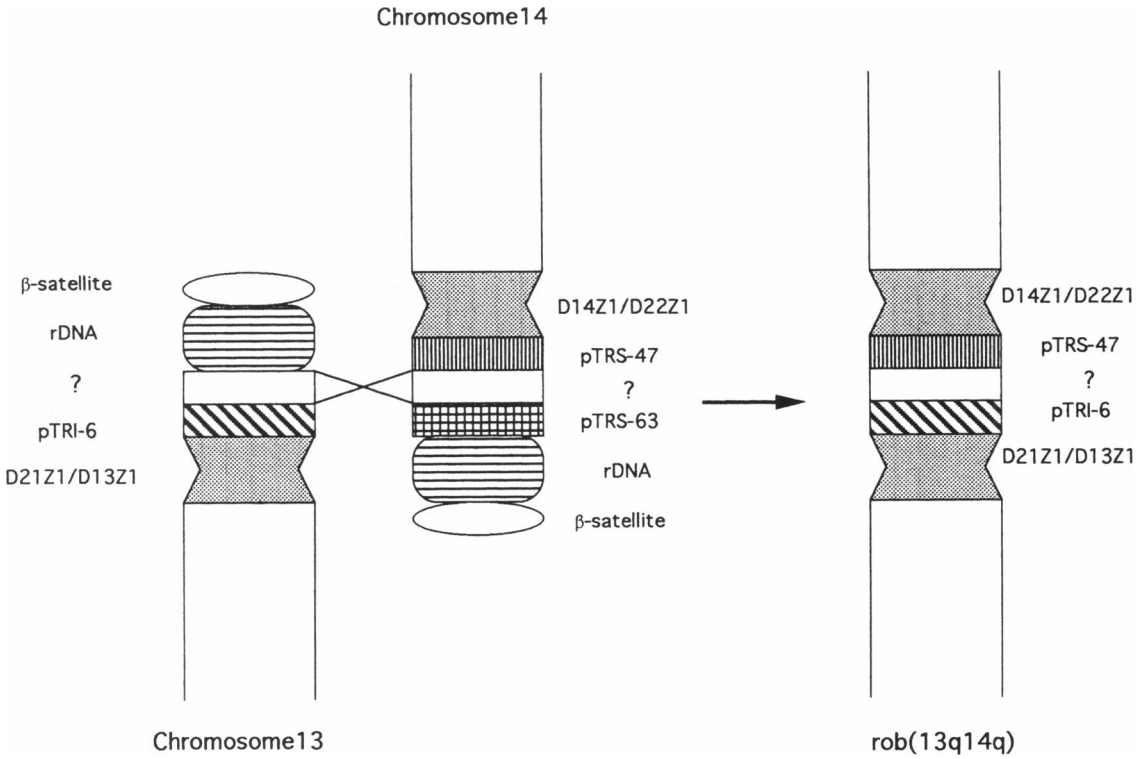

Figure 3 Diagram of the centromeric and short-arm regions of chromosomes 13 and 14, indicating relative locations of the six different sequences before and after translocation formation. A question mark (?) denotes that the sequence has not yet been identified.

III DNA probes showed both the retention of pTRS-47 sequences and the loss of pTRS-63 sequences within the p11 region of chromosome 14, in all rob(13q14q) tested (n = 17).

Under high-stringency hybridization conditions, pTRI-6 satellite sequence is found on the short arms of chromosomes 21 and 13. Previous investigation of 11 rob(14q21q) revealed the retention of the pTRI-6 satellite I sequences on chromosome 21, around the breakpoints in all cases (Kalitsis et al. 1993). Likewise, in the present study, pTRI-6 sequences were retained in 16 of 17 rob(13q14q) and were lost in 1 de novo rob(13q14q). Therefore, the breakpoints are localized between the pTRS-47 and pTRS-63 sequences, within the p11 region of chromosome 14 and distal to pTRI-6 but proximal to rDNA on chromosome 13, on the majority of rob(13q14q) (fig. 3). The retention of satellite I DNA on the short arm of chromosome 13 in most rob(13q14q) studied suggests that the region between pTRI-6 and rDNA may be a component of the translocation process and that the majority of breakpoints will be within the p11 region of chromosome 13.

For the study of the etiological mechanisms and of the nature of the breakpoints in Robertsonian translocations, one approach is to investigate both the proband with a de novo translocation and the karyotypically normal parents. In the present study, we examined both parents in six de novo rob(13q14q) cases, using the two satellite III DNA probes and the one satellite I DNA probe. In all parents, strong hybridization signals were detected on each pair of chromosomes 14 and 13 for the respective probes. Even in case 1, both parents showed strong positive signals with pTRI-6 on both chromosomes 13, demonstrating a complete deletion of this sequence on the de novo translocation in their child.

In summary, we have characterized 17 rob(13q14q), using six molecular probes and FISH. The breakpoints have been localized between the pTRS-47 and pTRS-63 sequences in the p11 region of chromosome 14 and between the pTRI-6 and rDNA sequences within the p11 region of chromosome 13, further narrowing the region containing the breakpoints compared to previous studies. Both further characterization of this region and refinement of the breakpoints in rob(13q14q) will be possible as more probes specific for DNA sequences in acrocentric short arms are identified.

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