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Identification of chromosome rearrangements between the laboratory mouse (*Mus musculus*) and the Indian spiny mouse (*Mus platythrix*) by comparative FISH analysis

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Running title: chromosome evolution of *Mus platythrix*

Key words: chromosome painting, comparative mapping, chromosome homology, *Mus platythrix*, Indian *Mus* species

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Abstract

Comparative chromosome painting was applied to the Indian spiny mouse (*Mus platythrix*) with mouse (*M. musculus*) chromosome-specific probes for understanding the process of chromosome rearrangements between the two species. The chromosome locations of the 5S and 18S-28S ribosomal RNA genes and the order of the *119* and *Tcp-1* genes in the In(17)2 region of the *t*-complex were also compared. All the painting probes were successfully hybridized to the Indian spiny mouse chromosomes, and a total of 27 segments homologous to mouse chromosomes were identified. The comparative FISH analysis revealed that tandem fusion were major events in the chromosome evolution of the Indian spiny mouse. In addition, other types of chromosome rearrangements, i.e. reciprocal translocations and insertions, were also included.

Introduction

The Indian spiny mouse (*Mus platythrix*) is the native species that is distributed in the Indian Peninsula (Ellerman 1961). The diploid chromosome number of the Indian spiny mouse is $2n=26$, which is much fewer than those of other *Mus* species ($2n=40$), though all the chromosomes are acrocentric (Tsuchiya & Yosida 1972). From the molecular phylogenetic studies of *Mus* species, it was suggested that the Indian spiny mouse diverged at an early stage during the speciation in the genus *Mus* (Bonhomme and Guénet 1996, Schubert *et al.* 2000). Comparative mapping of 26 X-linked genes in the Indian spiny mouse with fluorescence *in situ* hybridization (FISH) revealed that the gene order on the Indian spiny mouse X chromosome was more similar to that of rat than the laboratory mouse (*Mus musculus*) (Kuroiwa *et al.* 2001). According to these results, chromosome rearrangements of this species are speculated to be unique in the evolutionary process of the genus *Mus*. The comparison of G-banded patterns and individual chromosome length between the Indian spiny mouse and the laboratory mouse suggested that eight autosomal pairs of the Indian spiny mouse were derived from the tandem fusion of two autosomal pairs of the laboratory mouse (Yosida 1979). However, the morphological comparison of chromosomes has not given sufficient information on the chromosome rearrangements that occurred during the divergence of *Mus* species. Comparative chromosome painting, named Zoo-FISH, is a powerful tool for identifying homologous chromosome regions between different species. This approach allows the direct delineation of conserved segments at the molecular level, and provides clues for understanding the process of chromosome evolution (Wienberg *et al.* 1990, Scherthan *et al.* 1994, Wienberg & Stanyon 1995).

The 5S and 18S-28S ribosomal RNA (rRNA) genes have been used as cytogenetic markers to examine intraspecific and interspecific chromosome variations. The locations of the 5S rRNA genes were determined in three *Mus* species, *M. spicilegus*, *M.*

caroli and *M. spretus*, and six *Mus musculus* subspecies, *M. m. domesticus*, *brevirostris*, *bactrianus*, *musculus*, *castaneus* and *molossinus*, whose karyotypes were identical except for the differences in sizes of Y chromosomes among the species, in our previous study (Matsuda *et al.* 1994). The location of the 5S rRNA genes on the distal telomeric region of chromosome 8 was conserved among *Mus* species. On the contrary, the distribution patterns of the 18S-28S rRNA genes were highly variable among *Mus musculus* subspecies and different *Mus* species (Matsuda & Chapman 1995). The mouse *t*-complex has been characterized by four inversions in the proximal region of chromosome 17 (Herrmann *et al.* 1986, Hammer *et al.* 1989). *Mus* species have been divided into two groups according to the orientation of the In(17)2 region. One group is composed of six *M. musculus* subspecies, *M. spicilegus* and *M. macedonicus*, and the other one includes *M. spretus* and *M. caroli* with the ancestral type in which no inversions are contained (Hammer *et al.* 1989, Matsuda & Chapman 1995).

In this study, comparative chromosome painting was applied to the Indian spiny mouse with chromosome-specific probes of the laboratory mouse for detecting the chromosome homologies between the two species. We localized the 5S and 18S-28S rRNA genes to the Indian spiny mouse chromosomes with direct R-banding FISH method, and compared their locations with those of other *Mus* species. Moreover, the order of two genes, *119* and *Tcp-1*, which have been localized to the In(17)2 region (Herrmann *et al.* 1986, Willison *et al.* 1986), was determined in the Indian spiny mouse by two-colored FISH to examine whether this region of the Indian spiny mouse was included in the ancestral type or the inverted type. We also localized the 5S and 18S-28S rRNA genes and the *119* and *Tcp-1* genes to chromosomes of other Indian *Mus* species, *M. booduga* and *M. dunni*, and discussed the process of karyotype evolution in *M. platythrix*.

Materials and methods

Animals

The Indian spiny mouse used in this study has been maintained at Laboratory of Wild Animals, Department of Zootechnical Sciences, Faculty of Agriculture, Tokyo University of Agriculture, Japan. This colony of the Indian spiny mouse was derived from the wild animals captured in Mysore, India. *Mus booduga* and *M. dunni* were used for mapping the 5S and 18S-28S rRNA genes and the *119* and *Tcp-1* genes. We used the wild individuals of these species captured in Mysore, India. *Mus macedonicus* derived from Bulgaria was also used for chromosomal localization of the 5S and 18S-28S rRNA genes.

Chromosome preparation and FISH

Preparation of R-banded chromosomes and FISH were performed as described by Matsuda *et al.* (1992) and Matsuda & Chapman (1995). Mitogen-stimulated splenocytes were cultured in RPMI 1640 medium supplemented with 20% fetal bovine serum (FBS). They were synchronized by thymidine blockage, and 5-bromodeoxyuridine (BrdU) was incorporated during the late replication stage after release from excessive thymidine. R-banded chromosomes were obtained by exposure of chromosome slides to UV light after staining with Hoechst 33258. For G-banding analysis, chromosome preparations were made using the fibroblast cells of lung tissue cultured in Dulbecco's MEM medium supplemented with 15% FBS. The G-banded chromosomes were obtained by trypsin-treatment as described by Seabright (1971).

We used the 1.8-kb and 6.6-kb mouse genomic DNA fragments for chromosomal localization of the 5S and 18S-28S rRNA genes, respectively (Kominami *et al.* 1982, Matsuda *et al.* 1994). The cosmid DNA clones were used for mapping the *119* and

Tcp-1 genes. The genomic DNA of the *Tcp-1* gene was isolated from 129Sv mouse liver (Personal communication from Dr. T. Morita). The DNA was partially digested with *Sau3A* (30-50 kb) and ligated to *Bam*H I sites of cosmid vector pJB8. The DNA was packaged in vitro and resulting phage particles were infected to *E. coli* 490A. The phage clones positive for mouse *Tcp-1* cDNA were selected by hybridization using mouse *Tcp-1* cDNA as a probe. Tu119 was a genomic clone of the *119* gene isolated from mouse chromosome 17 by microdissection (Herrmann *et al.* 1986). The clone DNA Tu119 originated from Dr. Hans Lehrach was donated by Dr. T. Morita. Two-colored FISH was applied to determine the order of the two genes.

The biotinylated chromosome-specific painting probes of the laboratory mouse were purchased from Cambio Ltd., UK. *In situ* hybridization with the probes was carried out following the manufacturers' protocol with slight modification. Prehybridization and hybridization were carried out for 45 min at 37°C and for 2 days at 37°C, respectively. After hybridization, the slides were washed for 15 min in 50% formamide/2 X SSC at 37°C, and in 2 X SSC for 15 min at room temperature. The chromosome slides were reacted with fluoresceinated avidin (FITC-avidin) (Vector Laboratories) for 1 h at 37°C. The slides were washed on the shaker with 4 X SSC, 0.1% Nonidet P-40/4 X SSC and 4 X SSC for 5 min each at room temperature, and stained with propidium iodide (PI).

Microphotography and image capture

The chromosome slides were observed with a Nikon fluorescence microscope using Nikon filter sets B-2A and UV-2A. Kodak Ektachrome ASA100 films were used for microphotography. For analysis of digital images, the FISH images were captured with the 550CW-QFISH application program of Leica Microsystems Imaging Solution Ltd. (Cambridge, UK) using a cooled CCD camera (MicroMAX 782Y, Princeton

Instruments) mounted on a Leica DMRA microscope.

Results and discussion

G-banded karyotype of the Indian spiny mouse

The G-banded karyotype of the Indian spiny mouse is shown in Figure 1. Each chromosome was numbered referring to Yosida (1979), although chromosome 9 was larger than chromosome 8 in this study. The idiogram of G-banded karyotype was made by analyzing 11 metaphase spreads. Unclear banded patterns were observed for 2.8% of chromosomes (8/286 chromosomes) in G-banded metaphase spreads.

Chromosome homology between the Indian spiny mouse and the laboratory mouse

All mouse paints successfully yielded hybridization signals, and a total of 27 segments homologous to mouse chromosomes were detected (Figures 1 & 2a, b). Mouse chromosome (*Mus musculus* chromosome: MMU) Y probe was hybridized to the whole region of the Indian spiny mouse Y chromosome, suggesting that there are Y chromosome-specific repetitive sequences common to the two species, which constitute the heterochromatin of the Y chromosome.

Yosida (1979) compared G-banded patterns between the two species, and proposed that the major event of the rearrangements was tandem fusion of acrocentric chromosomes. This fusion hypothesis leads us to speculate that most of MMU probes hybridize to single chromosome regions in the Indian spiny mouse. All MMU probes except MMU 6, 14 and 17 were hybridized to whole or parts of single chromosomes. The Indian spiny mouse chromosome (*Mus platythrix* chromosome: MPL) 10 and MPL 11 completely corresponded to MMU 4 and MMU 11, respectively. These homologies were also corroborated by similarities of the G-banded patterns. Thus, MPL 10 and

MPL 11 seem to remain as the ancestral types of chromosomes. MMU X paint was hybridized to the whole region of MPL X, but it has been confirmed that there are several chromosome inversions between the laboratory mouse and the Indian spiny mouse X chromosomes (Kuroiwa *et al.* 2001). Each MPL 1, 2, 3, 4, 6 and 7 was painted by two different MMU probes, and ten out of the twelve MMU probes that painted these Indian spiny mouse chromosomes were hybridized to single chromosomes. MMU 6 probe was hybridized to MPL 3 and 8, and MMU 17 probe to MPL 7 and 8 (Figures 1 & 2a). MMU 14 probe painted the proximal region of MPL 7 and the centromeric regions of MPL 5, 8, 9 and 12 (Figure 2b). Although the orientation of chromosome segments cannot be detected by Zoo-FISH, the results in this study provide evidence that the four autosomal pairs of MPL 1, 2, 4 and 6 were derived from the tandem fusion of two different autosomal pairs of the ancestral *Mus* species. However, fission is not excluded in the process of chromosome rearrangements between the two species. MPL 6 is composed of the tandemly ordered chromosome segments homologous to MMU 7 and 19 (Figure 1). Such hybridization patterns are observed in other rodents; the long arm of chromosome 1 in four *Apodemus* species (Matsubara *et al.* in preparation), the long arm of rat chromosome 1 (Stanyon *et al.* 1999) and the long arm of Chinese hamster chromosome 3 (Yang *et al.* 2000). Thus, it is more likely that the ancestral type of MPL 6 was cleaved into two chromosomes, i.e. MMU 7 and 19, after *M. musculus* diverged from the common ancestor. On the other hand, MMU 6, 14 and 17 probes were hybridized to two or more chromosome regions in the Indian spiny mouse chromosomes, suggesting that other types of inter-chromosome rearrangements were included in the chromosome evolution of the Indian spiny mouse.

Order of the 119 and Tcp-1 genes in the In(17)2 region

The orientation of the chromosome segment homologous to the mouse In(17)2

region was investigated in the Indian spiny mouse by two-colored FISH. The *I19* gene was located proximal to the *Tcp-1* gene on MPL 8 (Figure 2g). This order of the genes was the same as the inverted type that was different from the ancestral type (Matsuda & Chapman 1995). The ancestral type was observed in *M. booduga* (Figure 2h) and *M. dunni* (data not shown), whose karyotypes were almost identical to that of laboratory mouse except for sex chromosomes. A large chromosome segment homologous to MMU 17 was localized to the distal part of MPL 7, while another small segment containing the In(17)2 was located in the interstitial region of MPL 8 (Figures 1 & 2a). MPL 8 was painted with four different probes for MMU 6, 14, 16 and 17, indicating that complicated rearrangements had occurred in MPL 8. It was not possible to identify whether the In(17)2 in the Indian spiny mouse was the ancestral type or the inverted type, because the orientation of the MMU 17 segment could not be determined in the present study. Other markers located outside the In(17)2 are necessary to be mapped for clarifying the orientation of this chromosome segment.

Chromosome locations of the 5S and 18S-28S ribosomal RNA genes

The 5S ribosomal RNA genes were localized to the telomeric region of MPL 2 (Figure 2e). The chromosome locations of the 5S rRNA genes have been assigned to the distal telomeric region of chromosome 8 in six *Mus musculus* subspecies and three different *Mus* species (Matsuda *et al.* 1994). The 5S rRNA genes were also mapped to the telomeric region of chromosome 8 in *M. booduga* (data not shown), *M. dunni* (Figure 2f) and *M. macedonicus* (data not shown) in this study. In *M. dunni* fluorescent signals were detected in the interstitial regions of the Y chromosome. This result suggests that a repetitive element homologous to the sequence of Y chromosome is contained in the spacer regions of the 5S rRNA genes (Matsuda & Chapman 1995). MPL 2 was derived from the tandem fusion of the ancestral MMU 8 to the distal end of

the ancestral MMU 5, suggesting that the locations of the 5S rRNA genes are conserved between the two species.

Yosida (1979) revealed by silver-staining that nucleolus organizer regions (NORs) were localized to the centromeric regions of MPL 5, 8 and 12. The 18S-28S rRNA genes were also mapped to the centromeric regions of MPL 5, 8 and 12 by FISH in this study, confirming the results reported by Yosida (1979) (Figure 2c). The centromeric regions of MPL 5, 8 and 12 were painted by MMU 14 probe (Figures 1 & 2b), although the 18S-28S rRNA genes have not been localized to chromosome 14 in *Mus* species investigated in the past (Dev *et al.* 1977; Suzuki *et al.* 1990; Matsuda & Chapman 1995). Distribution of the 18S-28S rRNA genes were also studied in *M. booduga* (Figure 2d), *M. dunni* and *M. macedonicus*, and the location of these genes on chromosome 14 was observed in *M. booduga* (Table 1). There are two interpretations for the present mapping data of the 18S-28S rRNA genes in the Indian spiny mouse. 1) The repetitive DNA which is contained in the centromeric region of the ancestral type of MMU 14 was translocated to the proximal regions of four MPL chromosomes, and the translocations were accompanied by the 18S-28S rRNA genes in MPL 5, 8, 12 but not in MPL 9. 2) The 18S-28S rRNA genes in MPL 5, 8 and 12 were derived from chromosomes 13, 6 and 18 in Indian *Mus* species. The 18S-28S rRNA genes were localized to chromosomes 13, 6 and 18 in *M. booduga* and chromosomes 6 and 18 in *M. dunni*, and the genes have not been localized to chromosome 6 in other *Mus* species (Table 1). This result provides a possibility that the locations of the 18S-28S rRNA genes on the proximal regions of chromosomes 13, 6 and 18 in *M. booduga* and *M. dunni* were conserved in MPL 5, 8 and 12 to whose proximal ends the centromeric region of chromosome 14 was translocated. It is hard to determine which interpretation is correct at present, but the results obtained in this study suggest that *M. booduga* and *M. dunni* are genetically more closely related to the Indian spiny mouse compared with

other Asian and European *Mus* species.

Our present study revealed the supportive evidence that the tandem fusion was the main event of chromosome rearrangements in the Indian spiny mouse, however, other types of rearrangements, i.e. reciprocal translocations and insertions, were also involved.

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Figure legends

Figure 1. G-banded karyotype of the Indian spiny mouse with comparative cytogenetic map between the Indian spiny mouse and the laboratory mouse. The chromosome idiogram of the Indian spiny mouse composed of 266 bands was made according to G-banded patterns. The numbers of homologous mouse chromosomes are indicated to the right of the Indian spiny mouse chromosomes. Arrows and arrowheads indicate the regions to which the following genomic and cosmid clones were hybridized; the 18S-28S rRNA genes (black arrows), the 5S rRNA genes (a white arrow), the *Tcp-1* gene (a black arrowhead), and the *119* gene (a white arrowhead). Scale bar indicates 10 μ m.

Figure 2. FISH patterns with mouse chromosome-specific painting probes and the genomic DNA clones. Painting signals of MMU 17 (a) and 14 (b) probes are visualized by FITC-avidin on G-banded chromosomes stained with Hoechst 33258. (b) Arrows indicate the signals of MMU 14 probe hybridized to the centromeric regions of the Indian spiny mouse. Chromosomal localization of the 18S-28S rRNA genes in Indian spiny mouse (c) and *Mus booduga* (d), and the 5S rRNA genes in Indian spiny mouse (e) and *M. dunni* (f). Hybridization signals were visualized by FITC-avidin on R-banded chromosomes stained with PI. (f) Arrowheads indicate the signals hybridized to the interstitial regions of Y chromosome. Gene ordering of the *119* and *Tcp-1* genes in the Indian spiny mouse (g) and *M. booduga* (h). The locations of the *119* and *Tcp-1* genes are visualized as greenish-yellow and pinkish-red signals, respectively. Scale bars indicate 10 μ m.

Table 1. Chromosomal distribution of the 18S-28S ribosomal RNA genes in *Mus* species.

Mice	Location	Chromosomes ^e
<i>Mus musculus</i>		
<i>M. m. domesticus</i> ^a	Pac (USA)	12, 15, 16, 18, 19
<i>M. m. brevirostris</i> ^a	BFM (France)	12, 15, 16, 19
<i>M. m. musculus</i> ^a	Myl (Yugo)	11, 12, 15, 16, 18, 19
<i>M. m. molossinus</i> ^a	MSM (Japan)	1, 5, 9, 11, 12, 13, 15, 16, 17, 18, 19
<i>M. m. castaneus</i> ^a	Mal (Malaysia)	4, 11, 12, 15, 18, 19
<i>Mus spretus</i> ^{a, b}	Spain	4, 13, 19
<i>Mus spicilegus</i> ^{a, c}	Bulgaria	3, 9, 16, 19
	Yugo	3, 4, 16, 19
<i>Mus macedonicus</i> ^d	Bulgaria	3, 5, 8, 16, 19
<i>Mus booduga</i> ^d	India	1, 3, 4, 6, 8, 9, 11, 12, 13, 14, 15, 16, 17, 18, 19
<i>Mus dunni</i> ^d	India	4, 6, 7, 12, 15, 17, 18, 19

^aReferred to Matsuda and Chapman (1995).

^bIn *M. spretus*, the 18S-28S rRNA genes are located on the distal end of chromosomes.

^c*M. spicilegus* was classified into two different species, *M. spicilegus* and *M. hortulanus*, in Matsuda and Chapman (1995), but the latter is a synonym of the former.

^dPresent data.

^eNumbering of chromosomes in all the species is based on the nomenclature in the laboratory mouse, because the G-banded patterns of autosomes are identical among the species.

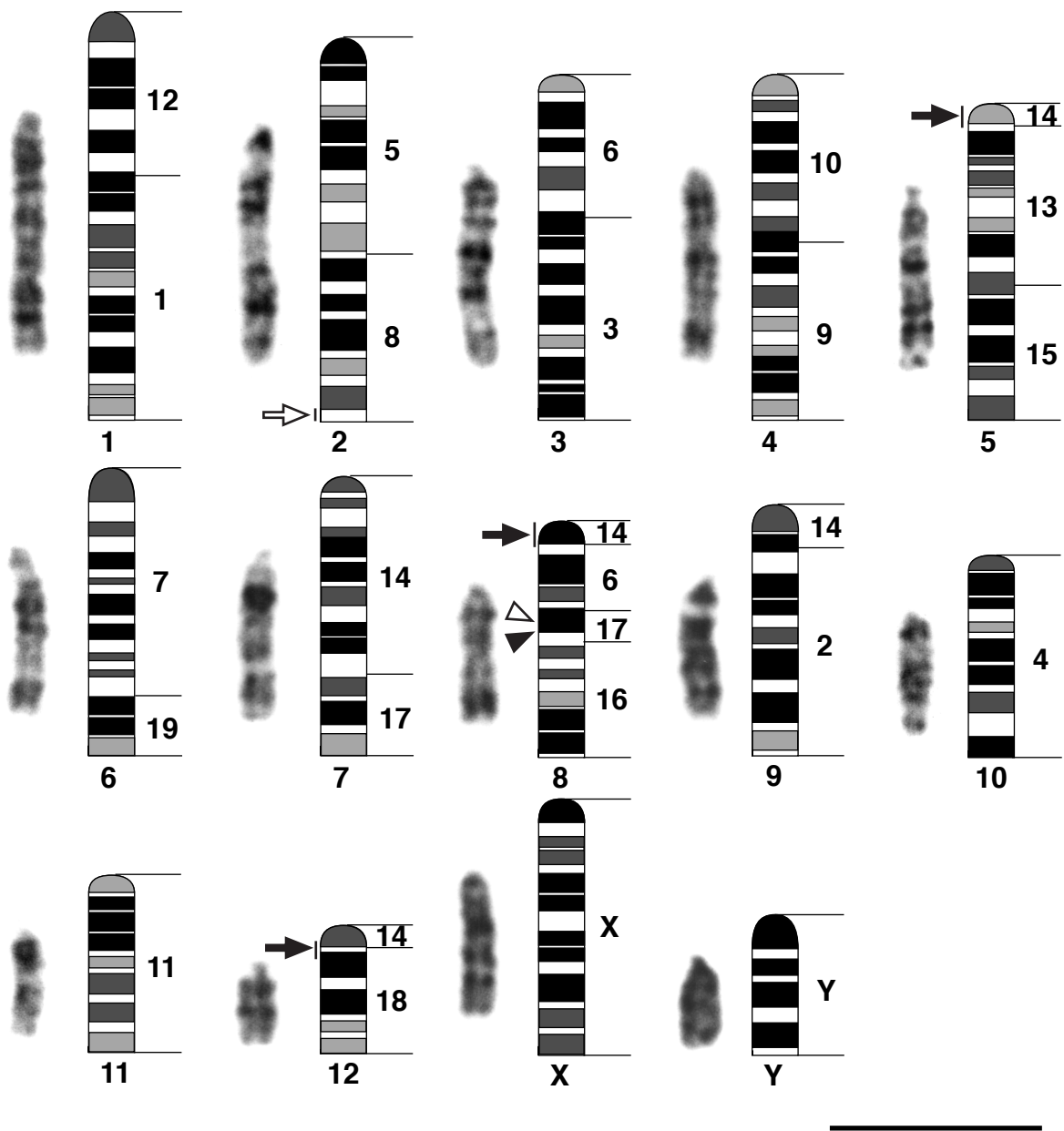


Figure 1

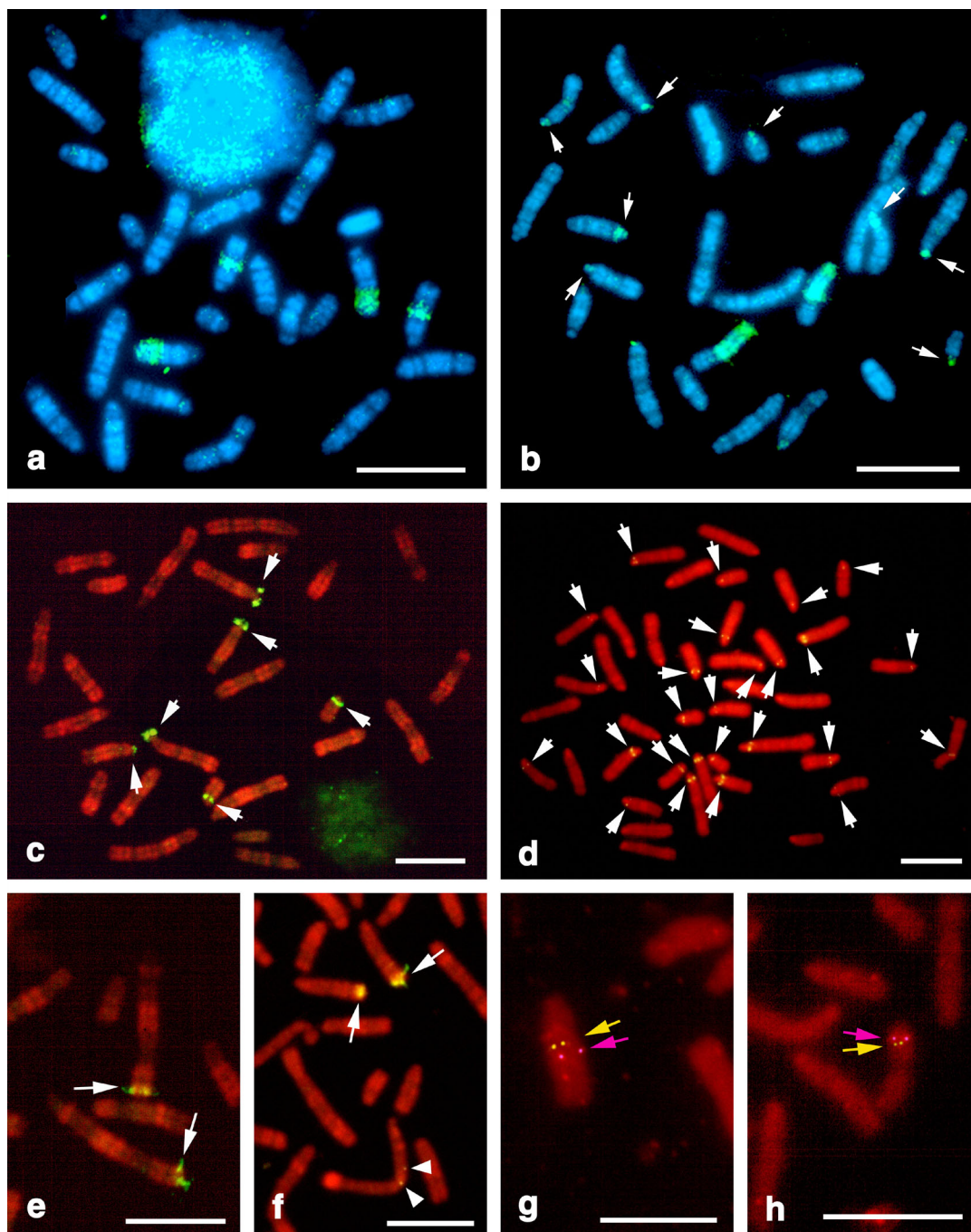


Figure 2