Molecular-cytogenetic study of *de novo* mosaic karyotype 45,X/46,X,i(Yq)/46,X,idic(Yq) in an azoospermic male: Case report and literature review

YUTING JIANG[1], RUIXUE WANG[1], LINLIN LI[1], LINTAO XUE[2], SHU DENG[1] and RUIZHI LIU[1]

[1]Center for Reproductive Medicine, Center for Prenatal Diagnosis First Hospital, Jilin University, Changchun, Jilin 130021; [2]Reproductive Medical and Genetic Center, People's Hospital of Guangxi Zhuang Autonomous Region, Nanning, Guangxi 520021, P.R. China

Received August 11, 2016; Accepted May 9, 2017

DOI: 10.3892/mmr.2017.6981

Abstract. The present study describes a 36-year-old male with the 45,X/46,X,i(Yq)/46,X,idic(Yq) karyotype, who suffered from azoospermia attributed to maturation arrest of the primary spermatocyte. To the best of our knowledge, this rare karyotype has not yet been reported in the literature. The results of detailed molecular-cytogenetic studies of isodicentric (idic)Y chromosomes and isochromosome (iso)Y, which are identified in patient with complex mosaic karyotypes, are presented. The presence of mosaicism of the three cell lines 45,X, 46,X,i(Yq) and 46,X,idic(Yq) may be a contributing factor for spermatogenic failure, in addition to the instability of iso/idic Y chromosomes to pass the spermatogenesis process. Possible mechanisms of the formation of the mosaic karyotype and karyotype-phenotype correlations are discussed. The current study highlights that routine karyotype analysis and fluorescent *in situ* hybridization-based technology are more useful in detecting mosaic chromosomal abnormality, predicting the clinical features of patients during genetic counseling and improving artificial reproductive technologies.

Introduction

Chromosomal abnormalities account for ~6% of infertility in men, and the prevalence increases to 15% among men with azoospermia (1). Such structural Y chromosome abnormalities, including Y-autosomal or Y-X translocations, inversions, rings, isochromosomes, and dicentrics are frequently associated with male infertility (2). Among these structural abnormalities, iso(Y) or idic(Y) chromosomes are the most common. Iso(Y) carries one centromere and duplication of the short or long arm, and the idic(Y) consists of two identical arms that are positioned as mirror images to one another, with an axis of symmetry lying between two centromeres (3). The two types of chromosome are often unstable during cell division.

Patients with iso(Y) or idic(Y) may develop mosaic karyotypes with variable phenotypes, such as spermatogenic failure, sexual infantilism, hypospadias, ambiguous genitalia, and a normal male phenotype (4). The variation of clinical phenotypes depends on the structure of the abnormal Y chromosome, the breakpoints, and the types of mosaics, which consist of a 45,X associated with another cell line that contains a structurally abnormal Y chromosome (5).

As a result, idic(Y) are structurally dependent on their breakpoints. Recently, Kalantari *et al* (6) delineated the association between the idic(Yq) (breakpoint Yq11.2) and male infertility. The primary cause of their azoospermia has been demonstrated to be idic(Y) with a breakpoint in the long arm of the Y chromosome, which may lead to deletion or rearrangement of critical azoospermia factor (AZF) regions (7). In the present study, a rare case of a 45,X/46,X,i(Yq)/46,X,idic(Yq) karyotype identified in an azoospermic man without an AZF microdeletion is presented. In addition, the complex sex chromosome mosaicism is evaluated, to attempt to explain the occurrence of the derivative Y chromosome and propose how these patients may receive genetic counseling.

Case report

Patient. A 36-year-old man was referred to Center for Reproductive Medicine, First Hospital, Changchun, China due to primary infertility for 6 years. He was generally well developed except for short stature and no malformations were observed. The patient was 162 cm tall and weighed 52 kg. His father was 33-years-old when the patient was born and his mother was 32-years-old. A detailed history could not identify any infertility risk factors and there were no documented exposures to chemotherapy, radiation, smoking or excessive alcohol intake. The family history was uneventful. Physical examination revealed a normal penis and pubic hair. The left and right testicular volumes were 8 ml each. Initial clinical

Correspondence to: Professor Ruizhi Liu, Center for Reproductive Medicine, Center for Prenatal Diagnosis First Hospital, Jilin University, 71 Xinmin Street, Changchun, Jilin 130021, P.R. China
E-mail: lrz410@126.com

Key words: azoospermia, mosaicism, fluorescent *in situ* hybridization, isodicentic Y chromosome, isochromosome Y

assessment included a repeat semen analysis and hormones confirming azoospermia and normal hormone levels with the exception of elevated estradiol (Table I). Cytology revealed neither spermatozoa nor germ cells.

The patient's wife presented with a normal gynecological status, normal hormone levels and a 46,XX karyotype. His parents did not exhibit any chromosomal abnormalities.

Appropriate voluntary written consent was obtained from the patient for the study, which was approved by the Chinese Association of Humanitarianism and Ethics.

A G-banding karyogram of the proband revealed a mosaic 45, X/46, X, der(Y), although the exact breakpoint of the Y chromosome was unclear (Fig. 1A and B). G-banding demonstrated a 45, X, cell line (13/60 cells) and a 46, X, der(Y) cell line (47/60 cells). The result of C-banding suggested der(Y) characterized by the presence of a distal Yq pseudoautosomal region (Fig. 1C).

Cytogenetic and fluorescent in situ hybridization (FISH) analyses. Peripheral blood lymphocytes were cultured in lymphocyte culture medium (Yishengjun; Baidi Biotechnology, Guangzhou, China) at 37˚C for 72 h, followed by 50 μg/ml colchicine treatment (Yishengjun; Baidi Biotechnology) 1 h before culture termination to arrest mitoses. The lymphocytes were hypotonically treated in 0.075 M KCl and fixed in methanol:acetic acid (3:1), then G-banding and C-banding were performed (8).

FISH was performed using centromeric probes for chromosomes 18, X and Y (CSP18-Spectrum blue, CSPX-Spectrum green and CSPY-Spectrum red; Beijing GP Medical Technologies, Beijing, China). Detailed experimental procedures were performed as described by Luo *et al* (9). FISH was also performed on metaphase chromosome spreads using dual-color probe combinations for chromosome X and *SRY* (GLP *SRY* Spectrum Red and CEP X Spectrum Green; Beijing Cyto Test Biotechnology, Beijing, China).

Of the plates, 20% had 2 blue signals, 1 green signal and no red signal (Fig. 2A); 42% gave 2 blue signals, 1 green signal and 1 red signal (Fig. 2B) and 38% exhibited 2 blue signals, 1 green signal and 2 red signals (Fig. 2C). This confirmed that the uncertain karyotype of der(Y) contained a idic(Yq) and i(Yq). The metaphase FISH showed the idic(Yq) with one *SRY* signal (Fig. 3A) and the i(Yq) with no *SRY* signals (Fig. 3B). The idic(Yq) was shown to have breakpoints distal to the *SRY* locus, likely in the distal Yp pseudoautosomal region. Thus, the karyotype of the patient was described as 45,X[20]/46,X, i(Yq)[42]/46,X,idic(Y)(qter→p11.32::p11.32→qter) [38].

Molecular analysis. To evaluate the sex determining region (*SRY)* and AZF zones of the Y chromosome, a set of nine Y chromosome-specific sequence-tagged sites (STSs) was used (10). The nine STS markers were: sY84 and sY86 for AZFa; sY127, sY134 and sY143 for AZFb; and sY152, sY157, sY254, and sY255 for AZFc.

According to the procedure of Al-Achkar *et al* (11), mutation screening was performed using direct DNA sequence analysis. The whole coding sequence of the *SRY* gene was amplified by polymerase chain reaction (PCR) using the primers previously described (12).

No microdeletions were detected in the AZF region of the Y chromosome in this infertile man. To identify a potential mutation, the *SRY* specific PCR fragment was analyzed by DNA sequencing using a healthy male as a control. No mutation was exhibited by the patient (data not shown).

Next generation sequencing (NGS). Whole genome sequencing (WGS) by NGS technology was performed on an Ion torrent PGM (Thermo Fisher Scientific, Inc., Waltham, MA, USA) platform according to the standard protocol (https://ioncommunity.thermofisher.com/community/protocols-home). Genomic DNA from the peripheral blood of the patient was sheared into fragments (250-300 bp) using an Ion Shear Plus Reagents kit (Thermo Fisher Scientific, Inc.). Ion Torrent Barcoded Libraries were created using an Ion Plus Fragment Library kit (Thermo Fisher Scientific, Inc.) and an Ion PGM Template OT2 200 kit (Thermo Fisher Scientific, Inc.) was used for template amplification and enrichment of the target sequence. Ion Sphere Particles (ISPs) were recovered and template-positive ISPs were enriched using an Ion OneTouch ES (Thermo Fisher Scientific, Inc.). Sequencing was performed using an Ion PGM Sequencing 200 kit v2 (Thermo Fisher Scientific, Inc.) on a '318' sequencing chip for a total of 500 nucleotide flows, yielding average read lengths of 220-230 bp. The DNA sample of the patient was pooled and labeled on the '318' chip. The average whole genomic sequence depth was ~0.02x, and the average read number was ~500 K. The primary sequencing BAM data were submitted to the Celloud cloud server (http://www.celloud.org/), which was offered by a third-party company (JBRH, China), in order to analyze the chromosomal copy number variants. Data analysis was performed according to a previous study (13).

No copy number variation of AZF or *SRY* was detected through NGS technology (data not shown). These results demonstrate that WGS could not applied to the detection of certain mosaic chomosomal abnormalities. For the proportion of mosaicism cell lines of 45,X/46,X,i(Yq)/46,X,idic(Yq), karyotype analysis and FISH were recognized as the standard detection methods in the current case report.

Testicular cytology. A fine-needle aspiration biopsy was performed under local anesthesia in the pole of the patient's right testis. The retrieved samples were washed three times in phosphate-buffered saline, spread onto glass slides and air-dried. The specimens were then fixed in 95% alcohol and stained with hematoxylin and eosin. The cells were examined under high magnification using a 40x light microscope and the spermatogenic status was classified according to the Meng system (14).

Cytological analysis of a testicular biopsy specimen demonstrated complete maturation arrest. Neither sperm nor spermatids were detected. Sperm maturation had stopped in the early stages of spermatogenesis (data not shown).

Discussion

Increasing cytogenetic and molecular studies in recent years have demonstrated the association of Y chromosome abnormalities with male infertility. Correct genetic diagnosis is essential to ensure proper counseling and avoid unnecessary and expensive treatments to improve fertility. There are important ethical consequences regarding patients who are

Table I. Semen analysis and hormonal level results.

Variable	Result	Normal range
Semen volume	1.2 ml	1.5-5.5 ml
Sperm count	0	>20 million/ml
Prolactin	0.47 nmol/l	0.18-0.69 nmol/l
Follicle stimulating hormone	5.8 U/l	1.5-12.4 U/l
Luteinizing hormone	7.9 U/l	1.7-8.6 U/l
Estradiol	159.75 pmol/l	27.96-155.92 pmol/l
Testosterone	18.5 nmol/l	9.9-27.8 nmol/l

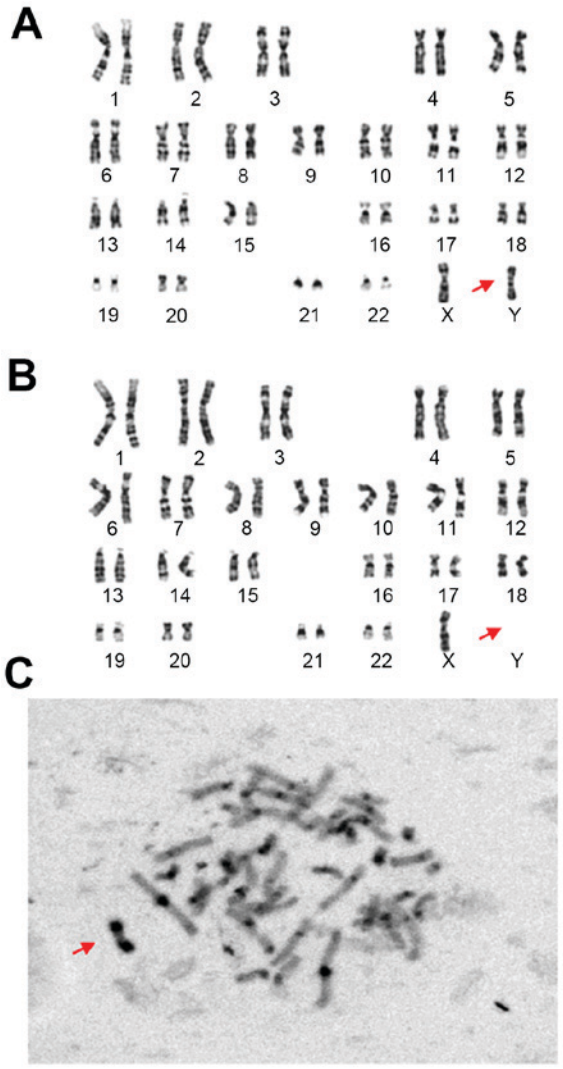

Figure 1. Karyotype of the patient following G-banding, demonstrating (A) a 45,X, cell line (13/60 cells) and (B) a 46,X,der(Y) cell line (47/60 cells). (C) C-banding demonstrated a large C-positive heterochromatic region in qter and pter of the der(Y).

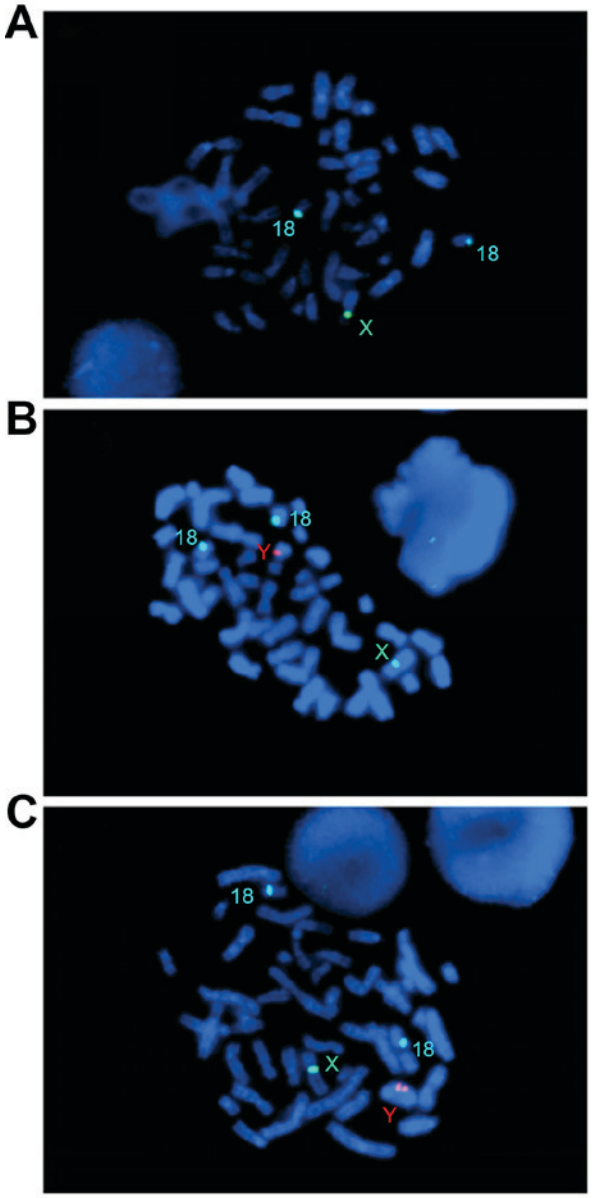

Figure 2. Fluorescent *in situ* hybridization using centromeric probes for chromosomes 18 (blue), X (green) and Y (red) on metaphase nuclei. (A) Two blue and one green signal represent the 45, X cell line. (B) Two blue, one green signal and one red signal represent the 46, X, i(Yq). (C) Two blue, one green signal and two red signal represent the 46, X, idic(Yq). Magnification, x1,000.

candidates for assisted reproduction techniques, such as *in vitro* fertilization/intra-cytoplasmic sperm injection and preimplantation genetic diagnosis (15). The patient, an otherwise healthy 36-year-old man, was referred for cytogenetic studies due to absolute azoospermia. The results revealed a mosaic karyotype, 45,X/46,X,i(Yq)/46,X,idic(Yq). A unique feature of the present case is that three cell lines which included 45,X, iso(Y) and idic(Y) were identified in the peripheral blood. The breakpoint occurred at Yp11.32, very close to the telomere in the idic(Yq) chromosome. The idic(Yq) contains a duplication of the proximal short arm and entire long arm (q) with duplicated preservation of AZF regions.

As previously demonstrated (16), the phenotype of patients exhibiting the idic Y chromosome were highly variable, ranging from Turner-like females to infertile males, depending on the structure of the dicentric Y chromosome, the Yp and Yq breakpoints, and the types of mosaicism. Of the affected subjects, 40.9% were phenotypical females, 31.8% were phenotypical males and 27.3% had different degrees of intersexuality. Among aberrant Y chromosomes, mosaicism of

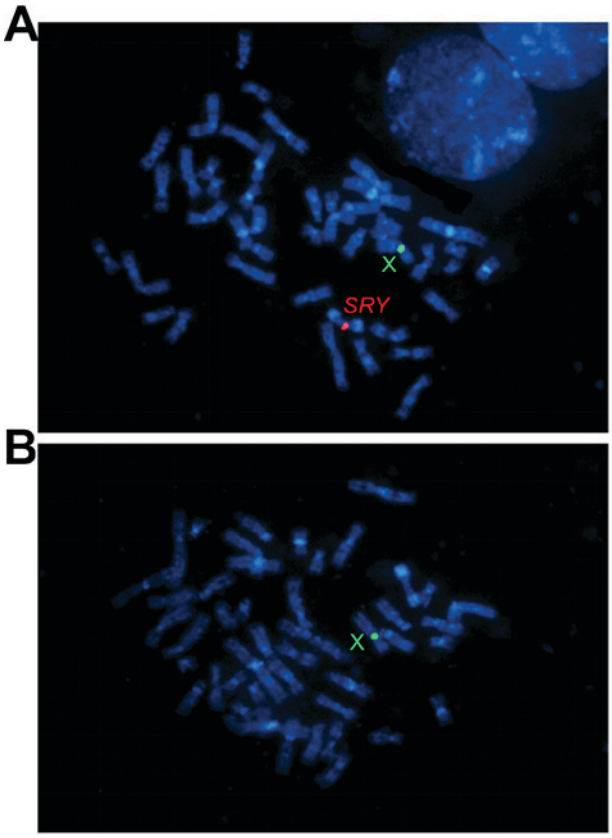

Figure 3. Fluorescent *in situ* hybridization using probes for *SRY* (red) and chromosome X (green) on metaphase cells. (A) idic(Yp11.3), ish(*SRY*+) and (B) i(Yq), ish(*SRY*-). Magnification, x1,000. *SRY*, sex determining region.

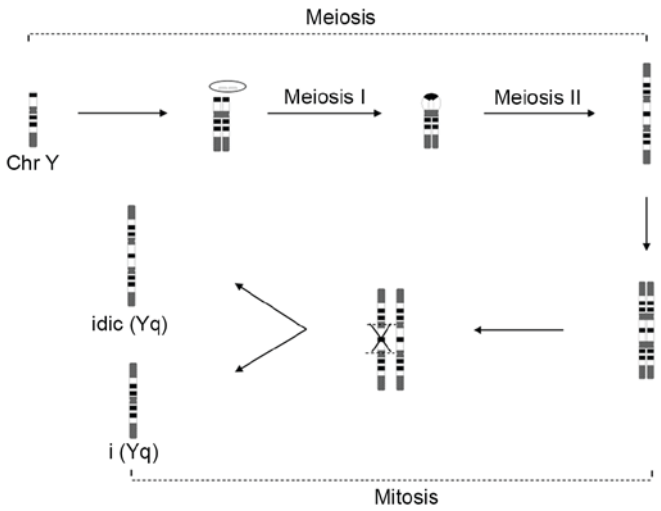

Figure 4. Schematic diagram of the mechanism of origin of idic(Yq) and i(Yq).

sex chromosomes, which consisted of a 45,X associated with another cell line, occurs most frequently and represents one of the main causes of ambiguous genitalia (17). Generally, mosaicism may occur during meiosis for abnormal X-Y bivalents or as a result of a postzygotic mitotic error due to structural instability of the Y chromosome during cell division (18). In the current case, it exerted a limited effect on the patient's phenotype due to the small percentage of the 45,X cell line.

Recently, the mechanisms of iso/idic Y chromosomes have been proposed to involve activation of intra- and inter-chromatid crossover and noncrossover pathways by massive palindrome-borne mirror-image gene pairs (19). This indicates that the idic(Y) chromosome resulted from an error during gametogenesis before the spermatid stage, as two chromatids are required to generate these rearrangements, or arose from an error in the first zygotic division. Errors occurring after the first zygotic division would result in mosaicism. Thus, the present study proposed that the abnormal idic(Yq) chromosome arose in paternal meiosis I (U type exchange) and II (nondisjunction), and the i(Yq) chromosome arose post-zygotically (Fig. 4).

Cases of adult infertile males with idic(Yq) that have been reported in previous studies are presented in Table II (2,3,20-22). These patients underwent cytogenetic study due to absolutely male infertility, a majority of them with azoospermia. Patients with idic(Yq) and male infertility were selected for this literature review. A possible reason for spermatogenic failure is the unstable iso/idic Y chromosome, caused by an inactivated centromere, which interferes with X-Y bivalent formation and chromosomal separation during mitosis and leads to a breakdown in spermatogenesis (23). The other possible reason is the presence of extra copies of AZF regions in our patient, which may be a contributing factor for spermatogenic failure, irrespective of AZF deletions. Kalantari *et al* (6) indicated that 45,X cells cannot commence meiosis and induce sperm production. However, without a high percentage of 45,X, mosaicism of three cell lines may be the third cause for infertility (24).

Notably, all the patients were of short stature with an mean height of 162 cm, which is significantly lower than the mean height of men (25). The presence of a 45,X cell line, deletion of the putative growth controlling gene locus and short stature homeobox-containing gene, which have been mapped to the pseudoautosomal regions of Xp and Yp, or a combined effect may result in a short stature (26,27). In study report by Guevarra *et al* (28), a 17-year-old with 45,X/46,X,idic(Y) karyotype was treated with recombinant growth hormone and has achieved a near final adult height, emphasizing that further investigation that includes the karyotype is required in male patients with unexplained short stature.

Molecular-based approaches to investigate mosaicism are difficult, particularly when three cell lines exist: One cell line does not contain Y, one cell line contains a normal Y and one cell line contains an idic Y (29). FISH-based technology is considered to be more useful in evaluating mosaic genotypes. In the current case report, no copy number variation of AZF or *SRY* was detected using NGS technology. These results demonstrate that WGS could not be applied to the detection of certain mosaic chomosomal abnormalities. For the proportion of mosaicism in cell lines 45,X/46,X,i(Yq)/46,X,idic(Yq), karyotype analysis and FISH were recognized as the standard detection methods in the present case report.

In conclusion, to the best of our knowledge, this is the first attempt to detail the clinical characterization and molecular-cytogenetic studies of patients with complex mosaic karyotype 45,X/46,X,i(Yq)/46,X,idic(Yq). The major symptoms of the infertile man include small testes, azoospermia, elevated estradiol levels and short status.

Table II. Review of adult infertile male with isodicentric Yq (breakpoint in Yp).

Author, date	Karyotype	Age, years	Semen analysis	Height cm	L/R testis volume, ml	Azoospermia factor microdeletion	*SRY*	FSH	LH	T	Testicular histology	(Refs.)
Present study	45,X[20]/46,X,i(Yq)[42]/46, X,idic(Y) (qter→p11.32::p11. 32→qter) [38]	36	Azoospermia	162	8/8	No deletion	+	N	N	N	Maturation arrest of the primary spermatocyte	n/a
Geng *et al*, 2014	45,X[32]/46, X, der(Y) t(Y; Y)(p11; ?) [18]	30	Severe oligospermia	151	8/8	No deletion	+	N	N	N	NP	(20)
Lehmann *et al*, 2012	Mos 45,X[9]/46,X,mar.ish mar(DYZ3+)[3]/46,X,idic(Y) (p11.3).ish idic(Y)(p11.3) (DYZ3++, *SRY*++)[33] /47, XY + idic(Y)(p11.3) .ish idic(Y)(p11.3)(DYZ3++, *SRY*++)[2] /48, X, + idic (Y)(p11.3)x2.ish idic(Y) (p11.3)(DYZ3++, *SRY*++) [2]/46,XY[1]	28	Azoospermia	NP	Small/ small	No deletion	+	N	N	N	Maturation arrest of the primary spermatocyte	(3)
Codina-Pascual *et al*, 2004	46,XY/46,X,idic(Y) (qter→p11.32::p11.32→qter)	37	Azoospermia	NP	5/5	NP	+	↑	NP	NP	NP	(2)
Haaf, *et al*, 1990	45,X/46,X,idic(Yq) (Yqter→cen→Yp 11.3:: Yp 11.3→cen→Yqter.)	26	Azoospermia	NP	Small/ small	NP	NP	↑	↑	N	NP	(21)
Micic *et al*, 1990 (Case 1)	45,X[33]/46,X,idic(Yq)[17]	34	Azoospermia	165	Normal/ normal	NP	NP	↑	↑	N	Maturation arrest of the primary spermatocyte	(22)

PRL, prolactin; SRY, sex determining region; FSH, follicle stimulating hormone; LH, luteinizing hormone; T, testosterone; N, normal; NP, not performed.

Azoospermia had not been caused by AZF microdeletions, although there may be other reasons, such as the abnormal structure of the Y chromosome and mosaicism of the three cell lines, 45,X/46,X,i(Yq)/46,X,idic(Yq). The results of the current study highlight that routine karyotype analysis and FISH-based technology are more useful in detecting mosaic chromosomal abnormality, predicting the clinical features of the patient during genetic counseling and planning artificial reproductive technologies.

Acknowledgements

The authors would like to thank all the staff of the Genetics Laboratory and Andrology Laboratory, Center for Reproductive Medicine, First Hospital, Changchun, China for their excellent work. The present study was supported by the National Natural Science Fund (grant no. 81471515).

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