

# Molecular and Clinical Characteristics of 26 Cases with Structural Y Chromosome Aberrations

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## Key Words

AZF region microdeletions · Infertility · Structural Y chromosome aberrations

## Abstract

Structural abnormalities include various types of translocations, inversions, deletions, duplications and isochromosomes. Structural abnormalities of the Y chromosome are estimated to affect less than 1% of the newborn male population and are particularly hazardous for male reproductive function. The objective of this study was to characterize a group of patients with structural abnormalities of the Y chromosome. All patients who visited our laboratory between 2007 and 2010 underwent cytogenetic investigations. Among these, we detected 26 patients with structural abnormalities of the Y chromosome. To confirm the structural Y chromosome alterations, we used special bandings, FISH and multiplex PCR to detect Y chromosome microdeletions. Of the 26 patients presented here, 11 had an isodicentric Y chromosome, 7 had an inversion, 3 had a translocation, 2 had a derivative, 2 had a Yqs and 1 had a deletion. Sixteen were diagnosed with azoospermia, 8 as normal fertile males and 1 as a man who was unable to donate semen due to mental retardation. One of the patients having 45,X/46,X, idic(Y) was

reported to be phenotypically female with primary amenorrhea and without uterus. Deletions of the AZFbc region were correlated with the sperm concentration ( $p < 0.05$ ), but no correlation with the levels of FSH, LH, testosterone, prolactin and estradiol were found. The present report shows that the precise identification of structural Y chromosome aberrations may be clinically important for genetic counseling and assisted reproductive technology treatment.

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The human Y chromosome is one of the smallest human chromosomes, consisting of a short (Yp) and a long (Yq) arm. The Y chromosome is 60 Mb in size but has the smallest number of genes compared to all other chromosomes. Of the 27 Y chromosome genes identified, 9 are located on Yp and the remaining 18 on Yq [Skaletsky et al., 2003]. The genes on the Y chromosome are essential for male sex determination, early sexual differentiation and control of spermatogenesis [Disteche et al., 1986; Arnemann et al., 1991; Gardner and Sutherland, 1996].

Structural abnormalities occur because of breakage and rejoining of a chromosome and include various types of translocations, deletions, ring chromosomes, duplica-

tions, inversions and isochromosomes. There are 2 types of structural aberrations: balanced structural aberrations, such as translocations or inversions, with a normal complement of chromosomal material, and unbalanced structural aberrations, such as deletions, duplications or isochromosomes, with loss or gain of chromosomal material. Structural anomalies of the Y chromosome are particularly hazardous for male reproductive function [Sinclair et al., 1990]. Ring chromosomes and isochromosomes of both short and long arms are the most prevalent causes of spermatogenic failure and azoospermia [Lin et al., 2005; DesGroseilliers et al., 2006].

The azoospermia factor (AZF) region maps within intervals 5 and 6 of the Y chromosome and contains many genes involved in the growth and development of sperm, such as the *USP9Y*, *RBMY1*, *BPY2* and *DAZ* genes [Vogt et al., 1996]. The AZF region is further subdivided into 3 regions defined as AZFa, AZFb and AZFc. A microdeletion in the AZF region is defined as a chromosomal deletion that spans several genes but is not large enough to be detected using conventional cytogenetic methods. Such microdeletions have been implicated in the pathogenesis of spermatogenic failure. The prevalence of microdeletions was found to range between 10 and 15% in azoospermia and 5 and 10% in severe oligozoospermia. However, such observations have not identified any particular Y-chromosome-encoded protein associated with spermatogenic function because each of these deletions removes multiple genes.

In this study, we characterized structural abnormalities in the Y chromosome of 26 patients analyzed at the cytogenetic, molecular and clinical levels at our center during a 4-year period.

## Materials and Methods

### Patients

This study was approved by the institutional ethics committee of Cheil General Hospital and included 26 patients with structural abnormalities of the Y chromosome who were examined in our clinic between January 2007 and December 2010. These patients included 15 men with primary infertility who attended the Department of Urology, 3 men with Y chromosomal abnormalities confirmed by other hospitals, 5 men with paternal testing for Y chromosome aberration in amniocytes, 2 men whose partners experienced recurrent abortion and 1 woman with short height (146 cm) and primary amenorrhea. The mean age of the patients was 34.9 years (range: 23–47).

### Cytogenetic and FISH Analysis

Metaphase chromosome preparations from peripheral blood lymphocytes were obtained using standard procedures and

stained using standard GTL- and RBG-banding techniques. The karyotype description followed the International System for Human Cytogenetic Nomenclature [ISCN 2005, 2009]. At least 50 metaphases were analyzed for each patient and up to 100 metaphases in cases of mosaicism. Special techniques such as CBG-, DA-DAPI- and NOR-staining were additionally applied. FISH was carried out with multiple probes for the Y chromosome, including SRY (LSI SRY SO/CEP X SG, Vysis, Downers Grove, Ill., USA), Yq12 heterochromatin/Y centromeric region (CEP Y Sat III SG/CEP Y alpha SO, Vysis) and 22q telomeric region (TelVysion 22q SO, Vysis). For each analysis, a minimum of 10 metaphase and 100 interphase cells were scored.

### Y Chromosome Microdeletion Analysis

Microdeletion analysis of the AZF region was performed by multiplex PCR using 16 sequence-tagged sites. The sequence-tagged site primers used were sY14 (*SRY*); sY84, sY86 (AZFa); sY124, sY127, sY129, sY130, sY134 (AZFb); sY147, sY242, sY254, sY255, SPGY1, sY157, and sY158 (AZFc). The *ZFX* gene on the X chromosome was used as an internal control to confirm PCR amplification. For each patient, 4 sets of multiplex PCR reactions were carried out including an internal control. Genomic DNA samples of a fertile man and a normal female were used as positive and negative controls, respectively. The PCR products were separated on a 3% agarose gel, stained with ethidium bromide and visualized using an ultraviolet illuminator.

### Semen, Hormonal and Testicular Analysis

Semen analysis was performed twice in 18 patients according to the guidelines of the World Health Organization [World Health Organization, 1999]. Six fertile men with babies or whose partners had experienced abortion, 1 man with mental retardation and 1 woman were excluded. Testicular volume was evaluated using an orchidometer. Serum concentrations of follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, prolactin and estradiol were measured using electrochemiluminescence immunoassay and radioimmunoassay, according to the manufacturer's instructions. The histological examination of the testicular tissue revealed spermatogenic arrest in meiosis, confirming the diagnosis of non-obstructive azoospermia. Testicular histology was carried out in 11 patients.

### Statistical Analysis

Statistical analysis was carried out by the Statistical Package for Social Science for Windows, version 11.0 (SPSS; Chicago, Ill., USA). Pearson correlation coefficients were used to determine correlations among sperm parameters, hormones and microdeletion of AZF genes. A p value <0.05 was considered significantly different.

## Results

The karyotype, special banding, FISH, serum hormones, AZF deletion, semen parameters and testicular histology of the 26 patients with structural Y chromosome abnormalities are summarized in table 1.

**Table 1. A** Summary of 26 patients with structural Y chromosome aberrations (part 1)

Case no.	Age	Karyotype	Phenotype/fertility history	Semen parameters			Serum hormones				
				volume ml	pH	N/ml n × 10 <sup>6</sup>	FSH mIU/ml	LH mIU/ml	testosterone ng/ml	prolactin ng/ml	estradiol pg/ml
1	31	46,X,t(Y;7)(q11.222;p15.3)	AZ	4.0	7.6	0	3.7	3.5	4.2	6.5	-
2	36	46,X,t(Y;17)(q11.221;p11.1)	AZ	3.1	7.4	0	9.6	5.9	5.3	5.0	17.0
3	36	46,X,t(Y;22)(p11.2;q13.32)	AZ	2.0	7.0	0	9.7	1.0	1.9	-	4.2
4	47	46,X,inv(Y)(p11.2q11.23)	AZ	1.7	7.4	0	23.0	2.9	3.3	6.0	6.6
5	40	46,X,inv(Y)(p11.2q11.23)	FM/G1 (AF;46,X,inv(Y)(p11.2q11.23))	-	-	-	-	-	-	-	-
6	39	46,X,inv(Y)(p11.2q11.23)	FM/G2 P2 (2nd;46,X,inv(Y)(p11.2q11.23))	-	-	-	-	-	-	-	-
7	44	46,X,inv(Y)(p11.2q11.23)	FM/G1 P1 (46,X,inv(Y)(p11.2q11.23))	-	-	-	-	-	-	-	-
8	42	46,X,inv(Y)(q11.222q12)	FM/G4 SA4	-	-	-	-	-	-	-	-
9	34	46,X,inv(Y)(p11.2q11.23)t(8;9)(q24.23;q33.2)	FM/G2 SA2	0.6	7.4	130	-	-	-	-	-
10	28	45,X,inv(Y)(p11.2q11.23),der(13;14)(q10;q10)	FM	1.4	7.4	123	-	-	-	-	-
11	29	46,X,der(Y)(pter→q11.23;p11.2→pter)	AZ	3.2	7.4	0	6.1	6.9	4.7	14.2	31.8
12	23	46,X,der(Y)(pter→q11.23;p11.2→pter)	AZ	4.0	7.2	0	17.0	5.2	2.3	11.0	18.0
13	35	46,X,del(Y)(q11.23)	AZ	2.2	7.4	0	30.0	5.3	3.3	3.0	16.0
14	35	46,X,idel(Y)(q11.2)	AZ	0.7	7.6	0	13.0	4.6	2.6	4.6	6.7
15	38	46,X,idel(Y)(q11.21)	AZ	0.1	7.0	0	<0.5	<0.5	5.3	4.5	39.0
16	30	46,X,idel(Y)(q11.222)	AZ	3.1	7.4	0	28.2	15.1	4.9	15.3	28.6
17	29	46,X,idel(Y)(q11.2)	AZ	2.2	7.6	0	3.0	8.5	2.8	6.1	12.0
18	34	46,X,idel(Y)(q12)	AZ	3.0	7.2	0	18.0	-	2.6	-	29.0
19	35	45,X[15]/46,X,idel(Y)(q11.2)[85]	AZ	4.6	7.2	0	10.0	4.6	3.1	14.0	16.0
20	36	45,X[14]/46,X,idel(Y)(q11.222)[95]	AZ	3.0	7.4	0	28.0	11.0	1.8	6.1	9.8
21	41	45,X[4]/46,X,idel(Y)(q11.222)[113]	AZ	0.9	7.6	0	48.0	6.7	4.7	5.2	5.8
22	30	46,X,idel(Y)(q11.23)[58]/46,i(Y)(p10)[45]	AZ	1.6	8.0	0	22.0	3.2	5.5	8.1	12.0
23	34	45,X[93]/47,X,idel(Y)(q11.23),idel(Y)[13]	male (without semen analysis)	-	-	-	26.0	6.8	0.7	7.2	7.2
24	27	45,X[29]/46,X,idel(Y)(q11.23)[84]	female	-	-	-	130.0	13.0	0.2	8.4	8.2
25	38	46,X,Yqs	FM/G1 (AF;46,X,Yqs)	-	-	-	-	-	-	-	-
26	36	46,X,Yqs	FM/G2 L:0 D:1 (AF;46,X,Yqs)	-	-	-	-	-	-	-	-

AF = Amniotic fluid; AZ = azoospermic male; D = death; FM = fertile male; FSH = follicle-stimulating hormone; G = gravida; L = live; LH = luteinizing hormone; P = para; SA = spontaneous abortion.

Normal reference ranges for men: FSH = 1.5–12.4 mIU/ml, LH = 1.7–8.6 mIU/ml, testosterone = 1.31–8.13 ng/ml, prolactin = 4.04–15.2 ng/ml, estradiol = 7.4–80.0 pg/ml; and for women: FSH = 2–12 mIU/ml, LH = 1.8–13.4 mIU/ml, testosterone = 0.06–0.77 ng/ml, prolactin = 2.7–19.7 ng/ml, estradiol = 30–120 pg/ml.

### Translocation of Y Chromosome; t(Y;autosome)

Reciprocal balanced Y chromosome translocations were found in 3 patients with karyotypes of t(Y;7), t(Y;17) and t(Y;22), respectively. For the patient with t(Y;22), G-banding chromosomes and ideograms are shown as well as FISH using SRY/CEP X (fig. 1B). Additionally, TelVysion 22q probes confirmed the presence of a 22q terminal region on the derivative Y chromosome and an SRY region on the end of the derivative 22 chromosome (not shown). Serum hormone levels of FSH, LH, testosterone, prolactin and estradiol were normal in the translocation patients, but the estradiol level in case 3 was slightly decreased (4.2 pg/ml; normal range, 7.4–80 pg/ml). Molecular studies revealed that 3 patients had intact SRY genes with an absence of AZFabc deletions. Spermograms of the 3 patients showed azoospermia.

### Inversions on Y Chromosome; inv(Y)

Inv(Y) was found in 7 patients. Six of them had a pericentric inv(Y) with breakpoints on the short (p11.2) and long arms (q11.23). One patient had a paracentric inv(Y) with breakpoints on Yq11.222 and Yq12. And, CBG-/DA-DAPI-banding revealed a partially inverted heterochromatin, and FISH with a DYZ1 probe confirmed 2 signals on the paracentric inv(Y) (fig. 1C). Molecular studies showed that 6 patients had the SRY gene and no AZFabc deletions. But 1 patient (case 9) had 2 microdeletions of sY130 on the AZFb and sY147 on the AZFc. Six patients including case 9 were healthy and fertile men. However, case 4 showed azoospermia and was treated with testicular sperm extraction. The result of intracytoplasmic sperm injection (ICSI) was not good because of poor sperm quality. The patient showed normal levels of hor-

**Table 1. B** (part 2)

Case No.	Microdeletion analysis															Testis volume ml		TESE	ICSI	Testicular histology or physical examination
	ZFX	SRY	AZFa			AZFb			AZFc						right	left				
	sY 14	sY 84	sY 86	sY 124	sY 127	sY 129	sY 130	sY 134	sY 147	sY 242	sY 254	sY 255	SPGY1	sY 157	sY 158					
1	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	18	18			MA
2	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	13	13			MA
3	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	17	17			HS
4	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	10	10	yes	yes	MA
5	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
6	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
7	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
8	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
9	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+					
10	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	17	17			NM
11	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	15	15	yes		HS
12	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	8			
13	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	15	15			SCOS
14	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	11	11			MA, tubular hyalinization
15	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	5	5			
16	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	12	12			
17	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	2	2	yes		
18	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	3	3			MA, tubular hyalinization
19	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	13	13			normal spermatogenesis
20	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	8	8			
21	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	5	5			MA
22	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	15	15			SCOS
23	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	4	4			mental retardation, NM
24	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					primary amenorrhea, short height
25	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
26	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					

HS = Hypospermatogenesis; ICSI = intracytoplasmic sperm injection; MA = maturation arrest; NM = not married; SCOS = Sertoli cell only syndrome; TESE = testicular sperm extraction. For better visibility, deletions are highlighted in grey.

mone except for an elevation in FSH level (23 mIU/ml; normal range, 1.5–12.4 mIU/ml).

*Derivative Y Chromosome; der(Y)*

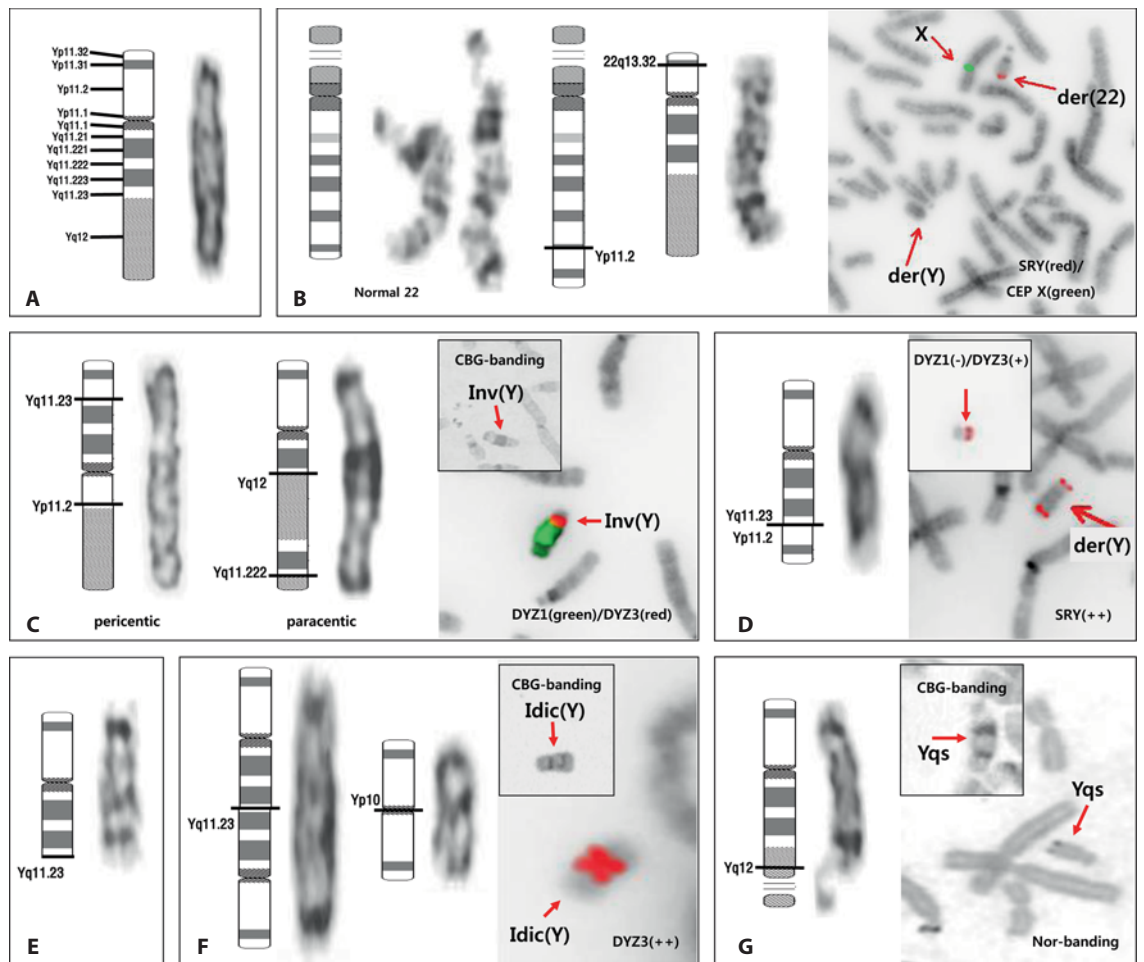
A rearranged monocentric der(Y) was found in 2 patients, and their karyotypes were 46,X,der(Y) (pter→q11.23::p11.2→pter). These patients lacked the heterochromatic Yq12 region according to CBG- and DA-DAPI-banding. FISH using an SRY-specific probe indicated a double copy of the SRY gene, shown with a centromeric probe for the X chromosome as a control. FISH with the Y alpha satellite (DYZ3)/Y satellite III (DYZ1) probes confirmed the presence of 1 centromere copy, and a Y heterochromatin probe showed no signal on the rearranged Y chromosome (fig. 1D). Serum hormone levels in the 2 patients were within the normal range. The results of the deletion analysis of the AZF region showed all 14 loci to be present (fig. 2). These 2 patients were azoospermic men.

*Deletion on the Y Chromosome; del(Y)*

Del(Y) was observed in 1 patient with a breakpoint at q11.23 (fig. 1E). DA-DAPI-banding revealed that the del(Y) was lacking the heterochromatic Yq12 region. The diagnostic screening of the AZF region showed that 8 loci in the AZFc region were deleted. FSH concentration was elevated (30 mlU/ml; normal range, 1.5–12.4 mlU/ml), but LH, testosterone, and estradiol were within the normal range. Prolactin was slightly diminished. The semen analysis results showed azoospermia.

*Isodicentric Y Chromosome; idic(Y)*

Idic(Y) was found in 11 patients: 5 men with non-mosaic idic(Y) with a breakpoint on Yq, 4 men and 1 woman with a mosaic karyotype having a 45,X cell line, and 1 man with a mosaic of 2 cell-lines with a breakpoint on Yq and centromere. FISH analysis and CBG-banding revealed the presence of 2 copies of the SRY gene and cen-



**Fig. 1.** Partial ideograms, GTL-banding karyotypes, special banding and FISH showing structural abnormalities of the Y chromosome. **A** Normal Y chromosome. **B** Translocation (case 3). **C** Pericentric (case 4) and paracentric (case 8) inversions. **D** Derivative chromosome (case 11). **E** Deletion (case 13). **F** Mosaic with isodicentric and isochromosome (case 22). **G** Satellited Y chromosome (case 25).

tromeric region but no constitutive heterochromatic characteristics on the idic(Y) (fig. 1F). FSH hormonal level was slightly increased in 7 male patients, extremely decreased in 1 male patient (case 15, <0.5 mIU/ml) and extremely increased in 1 female patient (case 24). The LH level was slightly increased in 2 men and extremely decreased in 1 male patient (case 15, <0.5 mIU/ml). Estradiol was slightly decreased in 3 male patients and extremely decreased in 1 female patient. Testosterone level was decreased in 1 male (case 23) and prolactin levels were normal in all patients.

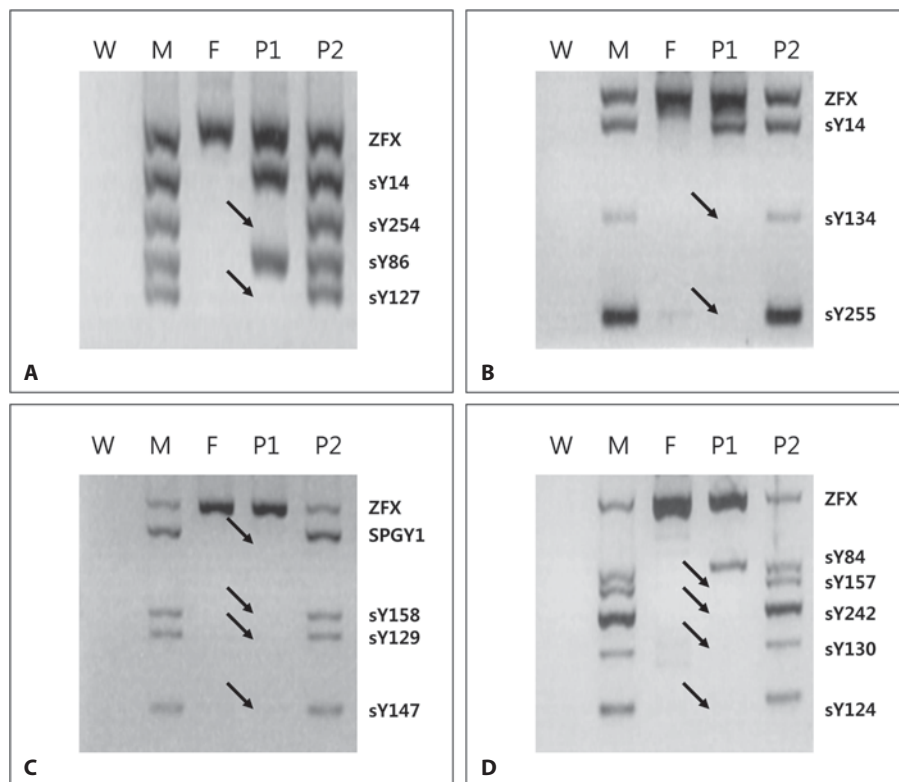
Eight male patients had AZF deletions: 2 had AZFabc deletions, 5 had AZFbc deletions (fig. 2) and 1 had an AZFc deletion. Two azoospermic males and 1 female had no AZF deletions. Semen analysis of 9 male patients re-

vealed that all had azoospermia. The female patient was referred at the age of 27 years because of primary amenorrhea, with a height of 146 cm, and ultrasound evaluation showed the absence of uterus findings and abnormal shape of both ovaries.

#### *Satellited Y Chromosome; Yqs*

Yqs was observed in 2 patients who were recommended for analysis based on amniotic cell analysis results of 46,XYqs. In 2 families, CBG- and DA-DAPI-staining showed the presence of constitutive heterochromatin, and silver staining demonstrated active NORs within the satellited stalks of the Y chromosome (fig. 1G). Molecular analysis of the AZF region did not reveal any deletions in the 2 patients.

**Fig. 2.** Representative gel electrophoresis profiles of 2 patients. **A** Multiplex PCR of ZFX, SRY (sY14), sY254, sY86 and sY127. **B** ZFX, sY14, sY134 and sY225. **C** ZFX, SPGY1, sY158, sY129 and sY147. **D** ZFX, sY84, sY157, sY242, sY130 and sY124. Patient 1 with idic(Y) (P1: case 16) had AZFb (sY124, 127, 129, 130 and 134) and AZFc (sY147, 242, 255, 157,158 and SPGY1) deletions, whereas patient 2 with der(Y) (P2: case 11) had no deletion. In addition, the genomic DNA from 1 fertile male (M), normal female (F) and distilled water without gDNA (W) were also included as positive and negative controls, respectively. The arrows denote the deletions in the particular sequence-tagged site region.



### Deletions of the AZF Region

Deletions of the AZF region were detected in 8 of 16 azoospermia patients (50%): AZFabc region (2 cases), AZFbc (4 cases) and AZFc (2 cases). Deletions of the AZFbc region were correlated with the sperm concentration ( $p < 0.05$ ), but no correlation with the levels of FSH, LH, testosterone, prolactin and estradiol could be detected.

### Discussion

Balanced translocations between the Y and autosomal chromosomes occur with a frequency of 1/2,000 in the general population [Nielsen and Rasmussen, 1976; Powell, 1999]. They do not usually have any phenotypic consequences but often lead to azoospermia, a variety of male gamete abnormalities and infertility depending on the breakpoint [Hsu, 1994; Pinton et al., 2008]. On the other hand, unbalanced Y;autosomal translocations have been reported in children with malformations and/or sexual ambiguity [Mademont-Soler et al., 2009]. In our study, there were 3 patients with confirmed balanced translocations and azoospermia without AZF microdeletion.

Inversions occur when there are 2 breaks in a single chromosome. If 1 break occurs in the short arm and the other in the long arm of the chromosome, this is called a pericentric inversion. If both breaks occur in the same arm of the chromosome, this is called a paracentric inversion. The frequency of pericentric *inv*(Y) ranges from 0.07 to 5.7% in the general population, and most of the reported cases are familial [Wyandt and Tonk, 2004]. Pericentric *inv*(Y) is not considered to be associated with any phenotypic manifestations or fertility problems. In some rare cases, reduced fertility or phenotypic abnormalities related to sex determination are associated with deletion or disruption of genes located in the inverted area [Gimelli et al., 2006]. Paracentric *inv*(Yq) is very rare and generally harmless [Madan, 1995; Aiello et al., 2007]. However, a patient with a familial paracentric *inv*(Yq) and ambiguous genitalia has been reported [Liou et al., 1997]. Among the cases in our study, there were 6 pericentric and 1 paracentric *inv*(Y). One patient with pericentric *inv*(Y) and no AZF deletions had azoospermia, but the other males were healthy and fertile.

A derivative chromosome is a structurally rearranged chromosome generated either by a rearrangement involving 2 or more chromosomes or by multiple aberrations

tions within a single chromosome. Der(Y) is a possible mechanism for sister-chromatid rearrangement during paternal meiosis or in the very early stages of embryogenesis [Cui et al., 2009]. To our knowledge, der(Y) has rarely been reported. In this study, we identified der(Y) in 2 azoospermic males as a segmental duplication of Ypter-p11.2 and a deletion of q11.23-qter by cytogenetic and FISH analysis, without any deletion in the AZF region.

Deletion may be caused by loss of a part of a chromosome between 1 or 2 breakpoints, and loss of a tiny fragment may have no noticeable effect. However, a deletion of a chromosome has a major effect that varies according to the chromosome affected, the site of and the extent of the deletion. Del(Yq) has been identified by cytogenetic analysis in around 3% of infertile men having abnormal Y chromosome [Gekas et al., 2001]. It is generally accepted that del(Y)(q12) is not associated with infertility because the deletion is limited to the heterochromatin, whereas del(Y)(q11) is associated with azoospermia or severe oligospermia due to the involvement of the AZF region [Delobel et al., 1998]. Here, we report a case of azoospermia with karyotype del(Y)(q11.23) and AZFc deletion.

Dicentric Y chromosomes correspond to 2 different types: dic(Yq) resulting from the fusion between the short arms of 2 Y chromosomes in which some Yp material is maintained and dic(Yp) in which only the Yq arms fuse. If the dicentric has completely symmetric arms, it is considered an isodicentric chromosome [Robinson et al., 1999]. Idic(Y) is the most common aberration, occurring in 15%–30% of infertile men having an abnormal Y chromosome [Codina-Pascual et al., 2004]. Because of its meiotic or post-zygotic origin and its mitotic instability, most (90%) idic(Y) chromosomes are present in mosaicism with a 45,X cell line. Depending on the breakpoints and the types of mosaicism, patients with idic(Y) have a wide range of phenotypic manifestations [Tuck-Muller et al., 1995; Iourov et al., 2008]. As previously reviewed, 40.9% of affected individuals were phenotypic females, 31.8% were phenotypic males and 27.3% had different degrees of intersexuality [Hsu, 1994]. In the present study, we analyzed 11 isodicentric Y chromosomes with dic(Yp) type, and 6 of these cases (54.5%) had mosaicism. Affected persons included 1 phenotypic woman, 9 men with azoospermia and 1 man without semen analysis because of mental retardation. Eight patients (72.7%) had a deletion of the AZF region.

Yqs is the product of a translocation between part of the NOR-bearing short arm of an acrocentric autosome

and the Y heterochromatin band, Yq12. Yqs was first described by Genest et al. [1967] and belongs to the category of very rare chromosomal abnormalities. In all except 2 de novo cases, the Yqs chromosome has been shown to be an inherited variant without any clinical consequences [Yakut et al., 2011]. The satellites are derived from acrocentric chromosomes mostly from chromosome 15 or, less frequently, from chromosomes 21, 13 or 14 [Schmid et al., 1984]. In this study, we reported 2 familial cases without any deletion of the AZF region.

Male infertility can be caused by a variety of factors, such as infection, varicose, endocrine disorders, etc. Apart from these, Yq deletions are the most frequent genetic cause of male infertility. A particular area of interest on Yq is the AZF region, which contains genes involved in the growth and development of sperm. These AZF genes code for RNA binding proteins and might be involved in regulation of gene expression, RNA metabolism, packaging and transport to cytoplasm and RNA splicing [Zamani et al., 2006]. The detection of Yq deletions is very important since this chromosome defect can be transmitted to 100% of the male offspring. However, the clinical significance of Yq deletions has been debated for a long time, mainly because of the large variation in deletion frequencies reported by different authors and because Yq deletions have also been reported in fertile men. We found 8 deletions in 16 azoospermic patients, and deletions of the AZFbc region were correlated with the sperm concentration ( $p < 0.05$ ).

Structural chromosomal anomalies are related to the increased risk of aneuploidy or unbalanced chromosomal complements and carry a poor prospect of sperm retrieval [Krausz et al., 2000]. Artificial reproduction techniques, such as preimplantation genetic diagnosis, ICSI and testicular sperm extraction, can help couples to achieve genetic parenthood. We carried out testicular sperm extraction in 3 men with azoospermia and conducted ICSI in 1 man. Unfortunately, our reports showed a poor result of ICSI in a non-obstructive azoospermic case. However, it is imperative to analyze the accurate identification and characterization of Y chromosome structural alterations for genetic counseling and clinical decisions regarding the optimal artificial reproduction technique treatment.

In conclusion, structural Y chromosome abnormalities are associated with human infertility, and deletions in the AZFbc region are associated with low sperm concentration due to reduced spermatogenesis.

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