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한국인 불임 남성 846명의 염색체 이상 및 Y 염색체 미세결실에 대한 유전 스크리닝

Genetic Screening for Chromosomal Abnormalities and Y Chromosome Microdeletions in 846 Infertile Korean Men

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Background: Chromosomal abnormalities are confirmed as one of the frequent causes of male infertility. The microdeletion of the azoospermia factor (AZF) region in the Y chromosome was discovered as another frequent genetic cause associated with male infertility. The aim of this study was to evaluate the frequency and type of chromosomal abnormalities and Y chromosome microdeletions in Korean infertile men.
Methods: A total of 846 infertile men with azoospermia and severe oligozoospermia were included for genetic screening. Cytogenetic analyses using G-banding and screening for Y chromosome microdeletions by multiplex PCR for AZF genes were performed.
Results: Chromosomal abnormalities were detected in 112 infertile men (13.2%). Of these, Klinefelter's syndrome was the most common (55.4%, 62/112), followed by balanced translocation including translocation between sex chromosome and autosome (14.3%), Yq deletion (13.4%), X/XY mosaicism with Yq deletion (12.5%), and XX male (4.5%). The overall prevalence of Y chromosome microdeletions was 9.2% (78/846). Most microdeletions were in the AZFc region (51.3%) with a low incidence in AZFa (7.7%) and AZFb (6.4%). Combined deletions involving the AZFbc and AZFabc regions were detected in 26.9% and 7.7% of men, respectively. Among the infertile men with Y chromosome microdeletions, the incidence of chromosomal abnormality was 25.6% (20/78).
Conclusions: There was a high incidence (20.1%) of chromosomal abnormalities and Y chromosome microdeletions in Korean infertile men. These findings strongly suggest that genetic screening for chromosomal abnormalities and Y chromosome microdeletions should be performed, and genetic counseling should be provided before starting assisted reproductive techniques.

Key Words: Male infertility, Chromosomal abnormalities, Y chromosome microdeletions, Azoospermia factor (AZF)

INTRODUCTION

Infertility is the inability to conceive a child during one to two years of frequent intercourse without the use of contraceptives. The prevalence of infertile couples are 10–15% worldwide, of which 40–50% are caused by male infertility. Both qualitative and quantitative abnormalities in sperm production are present in 40% of infertile men [1, 2]. A number of known risk factors such as genital infection, anatomical abnormalities, varicocele, immunological factors, and genetic aberrations are linked to male infertility [3]. Among them, genetic abnormalities are thought to account for 15–30% of male infertility [1, 2].

Chromosomal abnormalities are confirmed as one of the most frequent causes of male infertility, while Y-chromosome microdeletions constitute the second most common genetic causes of male infertility. The distal end of the long arm of the Y chromosome includes the azoospermia factor (AZF) locus, which contains the genes necessary for spermatogenesis. The AZF locus has been

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mapped to a region in band q11.23 of the Y chromosome [4, 5]. The AZF region is divided into three sub-regions designated as AZFa, AZFb, and AZFc. Spontaneous mutation or loss of one of these loci in the paternal germline leads to severely disturbed spermatogenesis [6-8]. In addition, these regions may be associated with a particular testicular histology. The association between Y-chromosome microdeletions and defective spermatogenesis has been studied previously, and the frequency of Y-chromosome microdeletions has been reported to account for 5–10% in azoospermia and 2–5% in severe oligozoospermia [4, 9]. In the last decade, many investigators have described the occurrence of microdeletions in infertile men around the world, and the molecular diagnosis of deletions has become an important test in the diagnostic workup of male infertility. Here, we conducted this study to evaluate the frequency and type of chromosomal abnormalities and determine the prevalence and pattern of Y chromosome microdeletions in infertile Korean men.

MATERIALS AND METHODS

1. Men and semen analysis

Cytogenetic and molecular screening of 846 infertile men (age ranged from 26 to 59) with idiopathic non-obstructive azoospermia (n=609, 72%) and severe oligozoospermia (n=237, 28%) who were referred to a single male infertility clinic in Korea was performed from March 2014 to December 2016. Semen analysis was conducted at least twice before a diagnosis of azoospermia (complete absence of sperm in semen) and oligozoospermia (low count of sperm in semen; mild: $10–20\times10^6$; moderate: $5–10\times10^6$; severe: less than 5×10^6 sperm/mL), according to WHO guidelines using computer assisted semen analysis (CASA) for total count, percent motility and forward progression [10]. Other possible causes of spermatogenic failure such as endocrine or obstructive causes were excluded. All participants were of Korean ethnic origin and gave informed consent according to the protocol approved by the institutional ethical review boards of our institutions (IRB No. 17-20).

2. Chromosome analysis

Chromosome analysis was performed with GTG banding using the peripheral blood lymphocyte technique. At least 30 metaphases were analyzed for each individual. All chromosomal abnormalities were reported in accordance with the current International System for Human Cytogenetic Nomenclature [11].

3. Y chromosome microdeletion screening

The genomic DNA was extracted from whole blood of 846 infertile men using a DNeasy Blood & Tissue Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. The concentration and quality of DNA was estimated using a Nanodrop 1000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA). Microdeletions of Y chromosome was detected using multiplex PCR based Y Chromosome Microdeletion Detection Kit (LG Life Science, Seoul, Korea) following the manufacturer's instructions. This kit was comprised of 4 sets and designed to amplify 3 regions of the AZF gene (AZFa, AZFb, and AZFc) using 15 sequence-tagged sites (STS) and 1 internal control (Table 1), produced in accordance with the guidelines provided by European Academy of Andrology (EAA) and European Molecular Genetics Quality Network (EMQN) [12]. Positive control used was G152A 23981301 of normal male DNA (Promega, Madison, USA) and negative controls were nuclease free water and G147A 23778401

Table 1. Sets of sequence-tagged sites of Y chromosome microdeletion kit

STS set	STS marker	Locus	Size (bp)	STS set	STS marker	Locus	Size (bp)
STS-1	ZFX	X	519	STS-2	ZFX	X	519
	sY14	Yp	472		sY14	Yp	472
	sY254	AZFc	380		sY84	AZFa	326
	syY86	AZFa	318		sY134	AZFb	238
	sY127	AZFb	274		sY255	AZFc	123
STS-3	ZFX	X	519	STS-4	ZFX	X	519
	SPGY1	AZFc	460		sY157	AZFc	286
	sY158	AZFc	215		sY242	AZFc	233
	sY152	AZFc	125		sY130	AZFb	173
	sY147	AZFc	100		sY124	AZFb	109

of normal female genomic DNA. The microdeletion of Y chromosome was confirmed by comparison with normal male DNA.

4. Molecular analysis of SRY gene

DNA was extracted from peripheral blood using QIAamp DNA Mini Kit (QIAGEN, Hilden, Germany). Two different sets of oligonucleotide primers for the sex determining region Y (*SRY*) gene were used for PCR. PCR conditions were as follows: reaction volume, 20 μL; primers, 20 pM; template genomic DNA, 100 ng; denaturation at 95℃ for 3 minutes, then 35 cycles at 94℃ for 1 minute, 62℃ for 90 seconds, and 72℃ for 3 minutes, followed by a 5-minute final extension at 72℃. The PCR products were electrophoresed on 2% agarose gel and visualized with ethidium bromide staining under ultraviolet light.

5. Statistical analysis

χ^2 test was used to compare differences between the two study groups. Statistical analysis was carried out with SPSS11.0 statistical software (SPSS Inc., Chicago, Illinois, USA). Data were considered statistically significant when $P<0.05$.

Table 2. Abnormal karyotypes in infertile men with non-obstructive azoospermia or severe oligozoospermia

Karyotypes	Non-obstructive azoospermia (N=609)	Severe oligozoospermia (N=237)	Total (N=846)	Total % (Abnormal %)
Normal (46,XY)	506	228	734	86.8
Abnormal	103	9	112	13.2
47,XXY	59	1	60	7.1 (53.6)
47,XXY/XY	2	0	2*	0.2 (1.8)
46,X,del(Y)(q11.23)	14	1	15	1.8 (13.4)
46,X,del(Y)(q11.23)/45,X	10	1	11†	1.3 (9.8)
46,X,psu idic(Y)(p11.32)/45,X	3	0	3‡	0.4 (2.7)
46,XX male	5	0	5	0.6 (4.5)
Abnormal sex chromosome	93	3	96	11.3 (85.7)
46,XY,t(1;13)(p13.3;q12.1)	1	0	1	0.1 (0.9)
46,XY,t(5;11)(q23.3;q22.3)	0	1	1	0.1 (0.9)
46,XY,t(6;15)(q25.1;q26.3)	1	0	1	0.1 (0.9)
46,XY,t(11;12)(q24.2;q13.1)	0	1	1	0.1 (0.9)
45,XY,der(13;14)(q10;q10)	3	1	4	0.5 (3.6)
45,XY,der(14;22)(q10;q10)	2	2	4	0.5 (3.6)
46,XY,t(15;20)(p10;p10)	0	1	1	0.1 (0.9)
Autosomal translocation	7	6	13	1.5 (11.6)
46,XY,t(Y;14)(p11.2;q11.2)	1	0	1	0.1 (0.9)
46,XY,t(Y;22)(p11.32;q13.1)	1	0	1	0.1 (0.9)
46,Y,t(X;1)(p11.23;p36.1)	1	0	1	0.1 (0.9)
X or Y;autosome translocation	3	0	3	0.4 (2.7)

*47,XXY[21]/46,XY[29],47,XXY[20]/46,XY[30]; †46,X,del(Y)(q11.23)[38]/45,X[12] (N=5), 46,X,del(Y)(q11.23)[30]/45,X[20] (N=3), 46,X,del(Y)(q11.23)[36]/45,X[14] (N=3); ‡46,X,psu idic(Y)(p11.32)[32]/45,X[18], 46,X,psu idic(Y)(p11.32)[36]/45,X[14], 46,X,psu idic(Y)(p11.32)[39]/45,X[11].

RESULTS

1. Chromosome analysis

Karyotyping was performed for 846 infertile men with azoospermia (N=609) or severe oligozoospermia (N=237). Chromosomal polymorphisms were excluded in karyotype. As shown in Table 2, 112 of the 846 (13.2%) infertile men had chromosomal abnormalities, including 103 of the 609 (16.9%) men with azoospermia and 9 of the 237 (3.8%) men with severe oligozoospermia. Among all patients, 96 men (11.3%) had the sex chromosome abnormality and 16 men (1.9%) had the autosomal translocation including translocation between sex chromosome and autosome (14.3%). Significant differences in the incidence of sex chromosomal abnormalities (15.3% vs. 1.3%, $P<0.01$), but not in autosomal translocation (1.6% vs. 2.5%, $P>0.05$), were detected between men with azoospermia and men with severe oligozoospermia.

Ninety-six men presented sex chromosomal abnormalities accounting for 85.7% of all abnormal karyotypes. In the men with sex chromosome abnormality, Klinefelter's syndrome including 47,XXY/46,XY mosaicism was the most common (55.4%, 62/112), followed by Yq deletion (13.4%, 15/112), X/XY mosaicism with Yq deletion (12.5%, 14/112) and XX male (4.5%, 5/112). The remaining 16 men presented balanced translocation between autosomes (N=13) or autosome and sex chromosome (N=3), which accounted for 14.3% of all abnormal karyotypes. Aberration of chromosome 14 was a little more frequent than other autosomes among autosome abnormalities, which were present in 9 (56.3%) of 16 men with autosome abnormalities.

Table 3. Frequencies of different Y chromosome microdeletions

Locus	Non-obstructive azoospermia (N=609)	Severe oligozoospermia (N=237)	Total (%)
AZFa	6	0	6 (7.7)
AZFb	4	1	5 (6.4)
AZFc	22	18	40 (51.3)
AZFab	0	0	0 (0)
AZFac	0	0	0 (0)
AZFbc	20	1	21 (26.9)
AZFabc	6	0	6 (7.7)
Total (%)	58 (9.5)	20 (8.4)	78 (9.2)

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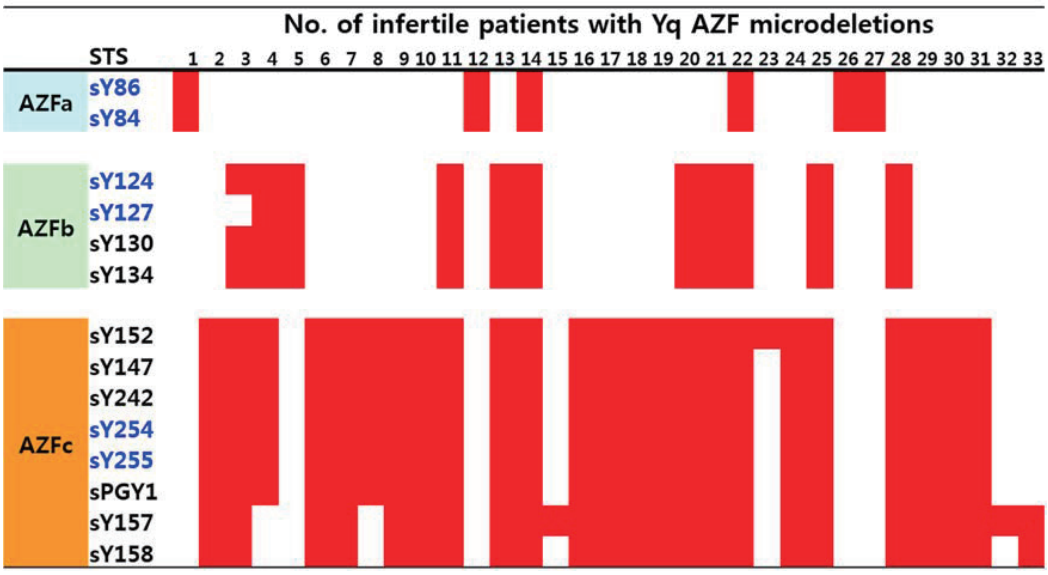

Fig. 1. Schematic depiction of the Y chromosome microdeletions. Microdeletions of non-EAA/EMQN guideline markers (sY152 and sY157) were detected in patient No. 15, 23, and 32. (Microdeletion in block, EAA/EMQN guideline markers; sY86, sY84, sY124, sY127, sY254, sY255).

2. Y chromosome microdeletion screening

As shown in Table 3, 78 of 846 (9.2%) infertile males presented with Y chromosome microdeletions. The frequency of microdeletions was 9.5% (58/609) in the azoospermic group compared with 8.4% (20/237) in the severe oligozoospermic group ($P>0.05$). In this study, the type of Y chromosome microdeletions analyzed included AZFa, AZFb, AZFc, AZFab, AZFac, AZFbc, and AZFabc. Deletion of AZFc was the most frequent AZF microdeletion (40/78, 51.3%) in both azoospermic (22/58, 37.9%) and severe oligozoospermic men (18/20, 90%).

In addition, the pattern of the STS marker, which was deleted in the 33 infertile men with Y chromosome microdeletions, was displayed as a block (Fig. 1). In patient No. 3, AZFb and AZFc were deleted, but sY127 of AZFc of EAA guideline was not deleted. In the case of infertile patient No. 15, 23, and 32, deletions were observed only in specific markers (sY157 for No. 15 and 32, sY152 for No. 23) that were not included in EAA/EMQN guideline markers.

3. Karyotyping in men with Y chromosome microdeletions

From analyses comparing karyotype and Yq AZF microdeletions, among the infertile men with Y chromosome microdeletions (N=78), the incidence of chromosomal abnormality was 25.6% (N=20) (Table 4). The abnormal karyotypes among these 20 men included 46,X,del(Y)(q11.23); 46,X,del(Y)(q11.23)/45,X; 46,X,+mar/45,X; and 46,XX male, all of them related to the sex chromosome abnormalities. Among the 20 infertile men with abnormal karyotype and Y chromosome microdeletions, 46,X,del(Y)(q11.23) (40%, 8/20) and deletion of AZFbc (55%, 11/20) was the most frequent. Five cases with 46,XX male carried combined AZFabc deletions. Furthermore, combined deletions involving AZFabc locus were detected in one 46,X,del(Y)(q11.23) patient. Deletions involving the AZFa locus were not detected in 20 infertile men with the abnormal karyotypes. The molecular analysis of *SRY* gene detected the presence of this gene in all men with 46,XX and 46,X,del(Y).

Table 4. Karyotype results in infertile men with Y chromosome microdeletions

Karyotypes	AZF deletion (N=78)					
	a	b	c	abc	bc	Total (%)
Normal (46,XY)	6	4	38	0	10	58 (74.4)
Abnormal	0	1	2	6	11	20 (25.6)
46,X,del(Y)(q11.23)		1	2	1	4	8 (10.3)
46,X,del(Y)(q11.23)/45,X					5	5 (6.4)
46,X,psu idic(Y)(p11.32)/45,X					2	2 (2.6)
46,XX male				5		5 (6.4)

DISCUSSION

Numerous studies have shown a wide range (2.2% to 16%) in the prevalence of chromosome abnormalities in infertile men [13-16]. In this present study, the prevalence of chromosomal abnor-

malities was 13.2% in infertile men, which is well within the range of the published data. The frequency of chromosomal abnormalities was 16.9% in men with azoospermia and 3.8% in men with severe oligozoospermia. These results are also similar to the published data of 13.7–15.4% in azoospermic men and 1.7–4.6% in oligozoospermic men [17, 18].

Spermatogenesis is regulated by a number of genes on the Y chromosome, X chromosome and autosomes that act at different stages of germ cell differentiation and maturation. Several studies have demonstrated the relationship between balanced autosomal translocation and severe oligozoospermia/azoospermia, as well as sex chromosome anomalies like Klinefelter's syndrome and male infertility [15, 19, 20]. In the present study, the most common chromosomal abnormality was Klinefelter's syndrome, which accounted for 55.4% of the abnormalities, followed by Y chromosome terminal deletions (Yq-) and structural autosomal abnormalities. The incidence of sex chromosomal abnormality in men with azoospermia (15.3%) was significantly higher ($P<0.01$) than that in men with severe oligozoospermia (1.3%), which was largely due to the high incidence of men with Klinefelter's syndrome. All men with 46,XX and 45,X/delY in this study had the *SRY* gene. *SRY* sequences were present in approximately 90% of 46,XX or 45,X maleness cases [21, 22]. The molecular analysis of *SRY* gene is quite useful to add this analysis to the clinical infertility investigation and subsequent prenatal diagnosis.

The vast majority of autosome abnormalities in the infertile men were balanced chromosomal translocations, which could cause the loss of genetic material at the break points of genes and corrupt the genetic message [23]. Our findings support the previous notion that abnormalities in sex chromosomes are primarily found in azoospermic men, while balanced autosomal translocations are the most frequent abnormalities in oligozoospermic males [24]. Interestingly, out of the 16 men with autosomal abnormalities, 9 (56.3%) had abnormal karyotypes involving chromosome 14, suggesting that some genes present on this chromosome might play an important role in spermatogenesis. In fact, Lian and colleagues [25] found that expression of miRNAs in region of 14q32.31 could be important in spermatogenesis. However, the detailed mechanisms of how abnormalities involving chromosomes 14 work requires further investigation.

Microdeletions of the Y chromosome are associated with either a reduced sperm count or the complete absence of spermatozoa and are more common among azoospermic than oligozoospermic men [26]. In this study, we investigated Y chromosome microdeletion in 846 infertile men and found its prevalence (9.2%) is within the range reported worldwide (5.7–21.0%) [27, 28] and slightly higher than a previous report of Korean infertile populations (7.7%) [29]. Frequency of AZF microdeletion was 9.5% in men with azoospermia and 8.4% in men with severe oligozoospermia. These results are slightly lower than the published data of 10–15% in azoospermic men and similar to the published data of 5–10% in oligozoospermic men [30].

In the present study, 15 STS markers in addition to 6 STS markers, recommended by EAA/EMQN [12], were used in the detection of AZF microdeletion. Nine STS markers (sY130, sY134, sY152, sY147, sY242, sPGY1, sY157, and sY158) were added to cover the sparse region of the Yq chromosome. The STS markers deleted in the 33 infertile men with Y-chromosome microdeletion were marked as a block to visualize the deletion pattern (Fig. 1). In AZFc microdeletions, only patient No. 15, 23, and 32 showed deletion of specific markers that were not included in EAA/EMQN guideline markers. If only the 6 STS markers recommended in the EAA/EMQN guidelines were applied, these deletions would have been undetected.

Y chromosome microdeletions in different AZF regions occurred with different frequencies. Confirming previous data [7, 14, 31], our findings showed that classical AZFc deletions represented the most frequent finding (51.3% of deletions in our cases), followed by the AZFbc region (26.9%), AZFa (7.7%), AZFabc (7.7%), and AZFb (6.4%). Our data revealed that there was a slightly higher frequency of large deletions such as AZFbc or AZFabc microdeletions in infertile men than previous studies [4, 12, 31]. The variations in deletion frequencies could be influenced by ethnic differences, the selection criteria of the men, sample size, and the type and number of STS marker sets used in the studies.

Advances over the past 10 years in molecular biology of the Y chromosome have led to the demonstration that each AZF subregion acts at a different phase of spermatogenesis. Genes in AZFa (DDX3Y) and in AZFb (KDM5D, RBMY1A1) seem to be essential for spermatogenic cell development and maturation [26]. Thus, deletion of AZFa and AZFb is usually associated with severe testicular damage. It is suggested that complete deletion of AZFa region may result in complete Sertoli cell-only (SCO) syndrome and azoospermia [27, 31]. Deletions of the AZFb region may cause SCO

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syndrome or arrest of spermatogenesis at the primary spermatocyte stage [16]. Deletions in the AZFc region produce a wide range of phenotypes from normal to oligozoospermia and azoospermia [7]. This is in accordance with the results of the present study in which AZFa deletions were only detected in azoospermic men, but AZFb or AZFc deletions were found in both men with severe oligozoospermia and men with azoospermia. In addition, the present study showed that combined deletions involving the three AZF regions (AZFabc) were also only detected in azoospermic men. The AZFc sub-region contains several important genes for male infertility such as *DAZ, BPY2,* and *CDY1* genes that control spermatogenesis; in addition, these genes have repetitive sequences in the AZFc region. Intrachromosomal recombination events among these repetitive sequence blocks might lead to abundant AZFc microdeletions. The pathological changes associated with AZFc microdeletions are less severe than those associated with AZFa or AZFb and show variable changes according to the deleted genes [32].

In the present study, the incidence of chromosomal abnormality among infertile men with Y chromosome microdeletions was 25.6% (Table 4). The prevalence of men with both defects was lower than that reported by Kim et al. (2012) in Korea (36.4%) and Ng et al. (2009) in Hong Kong (26.3%) [29, 33], and higher than that reported by Kumtepe et al. (2009) in Turkey (21.0%) [28]. This variability is probably related to differences in the selection of patient groups, ethnic differences, and sample size. In addition, 58 (74.4%) infertile men with Y chromosome microdeletion in this study presented normal karyotypes. Therefore, Y chromosome microdeletion screening should be performed along with chromosome analysis for infertile Korean men.

Large deletions including AZFabc and AZFbc appeared to be associated with higher chromosomal abnormalities than other deletions. In this study, the incidence of chromosomal abnormality was 52.4% (11/21) and 100.0% (6/6) in the AZFbc and AZFabc locus, respectively. All these abnormalities involved the sex chromosome, with a majority of Yq deletion, Yq deletion or isodicentric Y chromosome mosaicism with 45,X. An association between Y chromosome microdeletions and 45,X/46,XY chromosomal mosaicism or isodicentric Y chromosome has been previously proposed [34-36]. Moreover, it was suggested that Y chromosome microdeletions might be associated with Y chromosomal instability leading to mitotic loss of the Y chromosome.

Many studies have reported that mature spermatozoa were obtained in 50% of men with AZFc deletions, despite reduced fertilization rates after assisted reproduction techniques (ART) such as intracytoplasmic sperm injection (ICSI) [37]. In addition, when testicular sperm extracted from AZFc-deleted men was used for an ICSI cycle, a reduction in fertilization and per-cycle pregnancy rates was observed [38, 39]. However, ICSI treatment elevates the risk of transmitting genetic defects, for example, vertical transmission of AZF might lead to vertical transmission, expansion, and *de novo* Yq microdeletions in male fetuses [40]. Therefore, careful evaluation of chromosomal abnormalities and Y chromosome microdeletions in infertile men with azoospermia and severe oligozoospermia should be considered before they undergo ART. This can lead to the possibility of genetic counseling services and prediction of the chances of finding viable spermatozoa when performing testicular sperm extraction (TESE).

In conclusion, the rate of genetic abnormalities, including chromosome abnormalities or Y chromosome microdeletions, was 20.1% (170/846) in the present study. Relatively, a large number of large deletions such as AZFbc or AZFabc in Korean infertile men are less likely to be an indicator of success for ART such as ICSI. This study describes one of the largest studies of male infertility caused by Y chromosome microdeletions, especially in an Asian population. As such it is a significant contribution to the study of male infertility.

요 약

배경: 염색체 이상은 남성 불임의 흔한 원인 중 하나이며, Y 염색체의 azoospermia factor (AZF) 부위의 미세 결실은 남성 불임과 연관된 또다른 유전적 원인으로 알려져 있다. 본 연구는 한국인 불임 남성에서 염색체 이상 및 Y 염색체 미세 결실의 빈도와 유형을 알아보고자 하였다.

방법: 총 846명의 비 폐쇄성 무정자증 혹은 정자 부족증 국내 불임남성을 대상으로 염색체 이상 여부를 확인하기 위해 G-banding을 이용한 염색체 검사와 Y 염색체 미세 결실 검출을 위한 다중 PCR검사를 수행하였다.

결과: 염색체 이상은 112명(13.2%)의 불임 남성에서 발견되었는데, 클라인펠터 증후군(55.4%, 62/112)이 가장 흔하게 관찰되었고, 성염색체와 상염색체 간 전좌를 포함하는 균형 전좌(14.3%), Y 염색체 장완의 결실(13.4%), Y 염색체 장완의 결실을 동반하는 X/XY 모자이시즘(12.5%), XX남성(4.5%)의 순으로 관찰되었다. Y 염색체

미세 결실의 전체 유병률은 9.2% (78/846)였는데 대부분의 미세 결실은 AZFc 부위(51.3%)에서 관찰되었고 그 외 AZFa (7.7%)와 AZFb (6.4%) 부위에서 상대적으로 낮은 빈도로 관찰되었다. AZFbc와 AZFabc와 같은 중복 미세 결실은 각각 26.9%와 7.7%에서 관찰되었다. Y 염색체 미세 결실을 가진 불임 남성 중 25.6% (20/78)에서 염색체 이상을 같이 갖고 있었다.

결론: 한국인 불임남성에서 염색체 이상과 Y 염색체 미세결실은 20.1%로 높게 관찰되었으므로 염색체 이상과 Y 염색체 미세결실을 포함하는 유전 스크리닝은 반드시 수행되어야 하며, 보조 생식 시술 전에 스크리닝 결과에 대한 유전 상담이 제공되어야 한다

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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