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## LETTER TO THE EDITOR

Male Fertility

# Fertility achieved through *in vitro* fertilization in a male patient with 48,XXYY syndrome

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Asian Journal of Andrology (2018) 20, 208–209; doi: 10.4103/aja.aja\_44\_17; published online: 3 October 2017

Dear Editor,

The 48,XXYY syndrome is a rare sex chromosome aneuploidy with an incidence of 1:18 000–1:40 000 male births<sup>1</sup> and is associated with hypergonadotropic hypogonadism as an endocrine disorder.<sup>2,3</sup> Most men with this syndrome are never diagnosed in China. Due to sex chromosome aneuploidies and limited effective communication, these patients suffer from infertility.<sup>4</sup>

With a rare incidence rate, 48,XXYY syndrome is characterized by tall stature, abdominal adiposity, and small testicles; it often appears after puberty.<sup>5</sup> These patients often present with azoospermia and have difficulty with fertility. However, the literature provides little information about the fertility issues resulting from this syndrome. Advances in assisted reproductive techniques have, in rare cases, allowed for the production of offspring by patients with certain diagnoses thought to be associated with universal infertility.<sup>6,7</sup>

Here, we report the case of a 30-year-old male patient with 48,XXYY syndrome who was referred to our hospital in April 2016 for fertility treatment. In his family history, he was the only child of healthy nonconsanguineous parent. His mother's pregnancy and delivery were normal. The patient was born at term with normal measurements. We noted that the patient had greater difficulties in understanding and developing social relationships. He married three years before presentation but did not have children at that time. However, there were no available data regarding his parent.

The patient had a height of 185 cm, a weight of 80 kg, a body mass index of 23.4 kg m<sup>-2</sup>, and a blood pressure of 125/75 mmHg. The secondary sexual characteristics of the patient are poorly developed, and he has some feminine characteristics, such as no beard, less hair, and breast development. In addition, he presents orbital hypertelorism, eunuchoid skeleton, reduced muscle mass, elongated arms and legs, and small testicles and penis.

Laboratory investigations showed a normal blood cell count, normal thyroid-stimulating hormone (TSH), iron and calcium levels, and abnormal hepatic, renal, and gonadal functions. Most biological data from urine were within normal limits, with the exception of urinary protein, urinary total protein/creatinine, urinary albumin/creatinine,

microalbumin, and 24 h urinary protein (urinary protein: 555.0 mg l<sup>-1</sup>; urinary total protein/creatinine: 286.5; urinary albumin/creatinine: 186.9; microalbumin: 362.5 mg l<sup>-1</sup>; and 24 h urinary protein: 522 mg per 24 h). Thus, we diagnosed the patient with proteinuria resulting from some unknown reason. Biological data revealed that cholesterol and triglycerides were much higher than normal, suggesting the presence of hyperlipidemia (cholesterol: 6.87 mmol l<sup>-1</sup>; triglycerides: 5.74 mmol l<sup>-1</sup>). Hormonal data showed a low testosterone level accompanied by elevated basal gonadotropin levels (**Table 1**), and these data were suggestive of a sex chromosome aneuploidy.

We performed karyotype analysis twice for this patient using lymphocytes from peripheral blood; 30 metaphases were counted in the first analysis (320–400 G-banding) and 100 metaphases were counted in the second analysis (550 G-banding). Results from the two analyses showed the presence of the 48,XXYY aneuploidy in all the cells that were analyzed (**Figure 1**). The result of Y chromosome microdeletion detection showed no deletion of the six sequence tagged sites (sY84, sY86, sY127, sY134, sY254, sY255) and SRY gene, suggesting that the AZF regions are complete. Although the patient suffers from azoospermia, his family had a strong fertility requirement. Microdissection testicular sperm extraction was successfully performed; surprisingly, normally shaped sperm were found under a microscope after tearing of the seminiferous tubules.

Blood from the patient's wife was examined, and the results were consistent with the experimental requirements. Under intravenous anesthesia, ovarian puncture ovulation was carried out with the guidance of vaginal ultrasound imaging. Nine eggs were successfully removed, six were mature, and four were fertilized by intracytoplasmic sperm injection. Then two embryos developed into blastula stage and were frozen, followed by *in vitro* fertilization with preimplantation genetic diagnosis. All the procedures were approved by the Ethics Committee of our hospital, and the informed consent was obtained from the patient and his spouse. The patient's spouse is currently successfully pregnant, and the embryo is normal.

In this report, the patient had been married for three years and had conceived no children even without contraception. Infertility

**Table 1: Reproductive hormonal profile in the patient with 48,XXYY syndrome**

	Blood	Normal values
FSH (mIU ml <sup>-1</sup> )	39.9	0.7–11.1
LH (mIU ml <sup>-1</sup> )	26.4	0.8–7.6
Testosterone (nmol l <sup>-1</sup> )	1.9	3.0–8.5

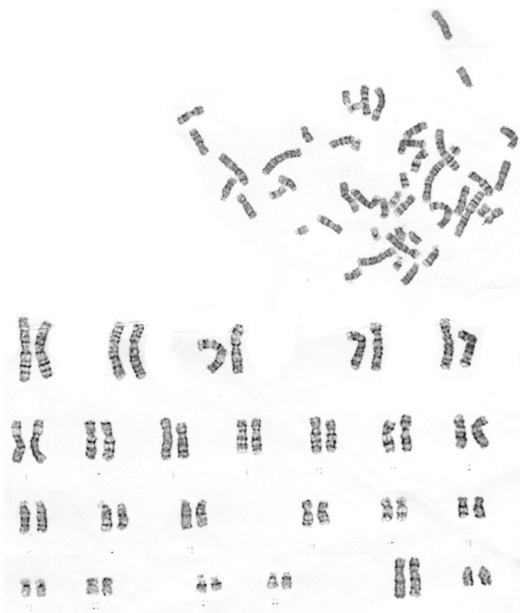
FSH: follicle-stimulating hormone; LH: luteotropic hormone

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Received: 20 May 2017; Accepted: 21 August 2017



Chromosomal karyotype: 48,XXYY

**Figure 1:** Chromosome test results.

was diagnosed, and the patient was hospitalized at our center to address this issue. A microdissection for testicular sperm extraction was performed for this patient with azoospermia. Ramasamy *et al.*<sup>8</sup> demonstrated that increased male age is associated with a trend toward a lower sperm retrieval rate in patients with Klinefelter's syndrome, and that various types of preoperative hormonal therapies did not result in different sperm retrieval rates, but men with a normal baseline testosterone level had the best sperm retrieval rate of 86%. Fortunately, although the patient's hormone levels were abnormal and his testosterone was low, normal sperm were nonetheless identified under the microscope after tearing of the seminiferous tubules. The entire search process was difficult, but it was a pleasant surprise that the screened sperm were nonprogressively motile and were normally shaped. With *in vitro* fertilization, the sperm and egg successfully combined, and embryonic development was progressing successfully at the time of the report.

Our case demonstrates the main typical features of 48,XXYY syndrome in a patient who suffers from infertility. The patient has a strong fertility requirement. How to help patients with 48,XXYY syndrome to have normal children has not been previously reported in the literature. Fortunately, normal sperm were found in our patient under high-magnification microscopy. Through the treatment of this case, it is proposed that microdissection testicular sperm extraction is an effective sperm retrieval technique for men with 48,XXYY syndrome.

#### COMPETING INTERESTS

All authors declare no competing interests.

#### AUTHOR CONTRIBUTIONS

DFL, KH, and HJ conceived the study, performed the operation, and drafted the article. KH, JMM, and LMZ performed the operation and participated in the acquisition of data. YZY and ZZ contributed to clinical follow-up of the patient and helped the review and editing of manuscript, and LMZ was responsible for the revision of the article. All authors read and approved the final manuscript.

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