

## A CASE OF SEX REVERSAL SYNDROME WITH SEX-DETERMINING REGION (XX MALE)

MASANORI YAMAMOTO, KEISUKE YOKOI, SATOSHI KATSUNO,  
HATSUKI HIBI and KOJI MIYAKE

*Department of Urology, Nagoya University School of Medicine, Nagoya, Japan*

### ABSTRACT

We examined a 32-year-old man with a 4-year history of infertility. The man's sex life, male hair pattern, and penis were normal, and he had no history of erection problems. Left and right testicular volumes were 2 ml and 3 ml, respectively. Semen analysis showed no sperm. The endocrine panel revealed increased serum luteinizing hormone and follicle-stimulating hormone levels, and a normal serum testosterone level. A testicular biopsy demonstrated that both Leydig cell and Sertoli cell hyperplasia were present, and that no germ cells were found in the tubules. A chromosome analysis done on the peripheral blood lymphocytes revealed a karyotype of 46, XX. We identified the sex-determining region, Y, by polymerase chain reaction using Y-specific probes in this patient. The diagnosis was XX male.

Key words: XX male, Infertility, Sex determining region

### INTRODUCTION

In humans, differentiation of genetic sex is determined by the presence or absence of the Y chromosome. People with 45, XO chromosomal pattern (Turner syndrome) are phenotypically female with short stature and bilateral streak gonads. Those with 47, XXY chromosomal pattern are usually tall and phenotypically male with primary testicular failure (Klinefelter's syndrome). Mosaicism of 45, XO and 46, XY is related to various phenotypes from the Turner syndrome and mixed gonadal dysgenesis to normal males. Exceptions to this are normal appearing females with 46, XY chromosomes (testicular feminization syndrome) and normal appearing males with 46, XX chromosomes (sex reversed males).

The sex reversal syndrome (XX male) is an extremely rare disorder of chromosomal sex. De la Chapelle first described this case in 1964.<sup>1)</sup> Thirty-one cases of 46, XX male have been reported in the Japanese literature as of today.<sup>2)</sup> Most cases occur sporadically at an estimated frequency of 1 per 20,000 males.<sup>3)</sup>

Although they lack a Y chromosome, the vast majority have detectable Y DNA material (sex-determining region Y) (SRY). In a recent study performed by Guellaen et al., some XX males were noted to have Y DNA material upon chromosomal analysis.<sup>4)</sup> Thus, these patients possess the genetic information necessary for the formation of testes in addition to two X chromosomes. We report here on a case of a 46, XX chromosomal male with SRY detected by polymerase chain reaction using a Y-specific probe.

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Correspondence: Masanori Yamamoto, M.D., Department of Urology, Nagoya University School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466, Japan

## CASE REPORT

The patient was a 32-year-old man with a 4-year history of infertility. His sex life was normal and there was no history of erection problems. The man underwent a bilateral herniorrhaphy and an appendectomy when he was a child.

He was an intelligent male, with a height and weight of 161 cm and 45 kg, respectively. He had a small cervicodorsal hump, no gynecomastia, and his male hair pattern and penis were normal. His left and right testicular volumes were 2 ml and 3 ml, respectively.

Semen analysis (done three times) showed no sperm. Normal levels for viscosity, pH and seminal volume were recorded. Serum hormone levels included: testosterone: 4.15 ng/ml (2.7–10.7); follicle-stimulating hormone (FSH): and 48.9 IU/L (2.9–8.2); luteinizing hormone (LH): 20.4 IU/L (1.8–5.2); and prolactin: 12.3 ng/ml (2.0–20.0). The testosterone level and adrenal function were normal, but FSH and LH levels were prominently increased. His wife had a normal menstruation cycle and was gynecologically of normal status.

Chromosomal analysis performed on the peripheral blood lymphocytes revealed 46, XX (Fig. 1). There was no evidence of mosaicism. SRY was identified by polymerase chain reaction using a Y-specific probe. This examination was performed according to Sinclair *et al.*'s method which has been recently reported.<sup>5)</sup> A testicular biopsy specimen revealed severely hyalinized seminiferous tubules and hyperplasia of Leydig cells. Only a few tubules contained Sertoli cells (Fig. 2).

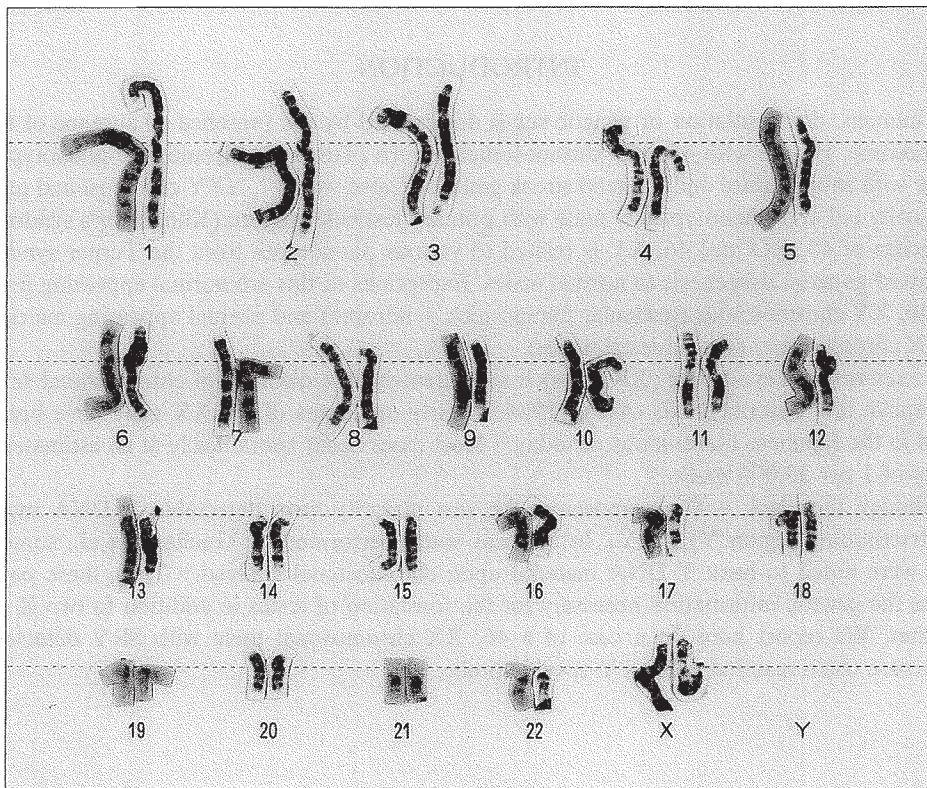


Fig. 1. Chromosomal analysis shows Karyotype of 46, XX.

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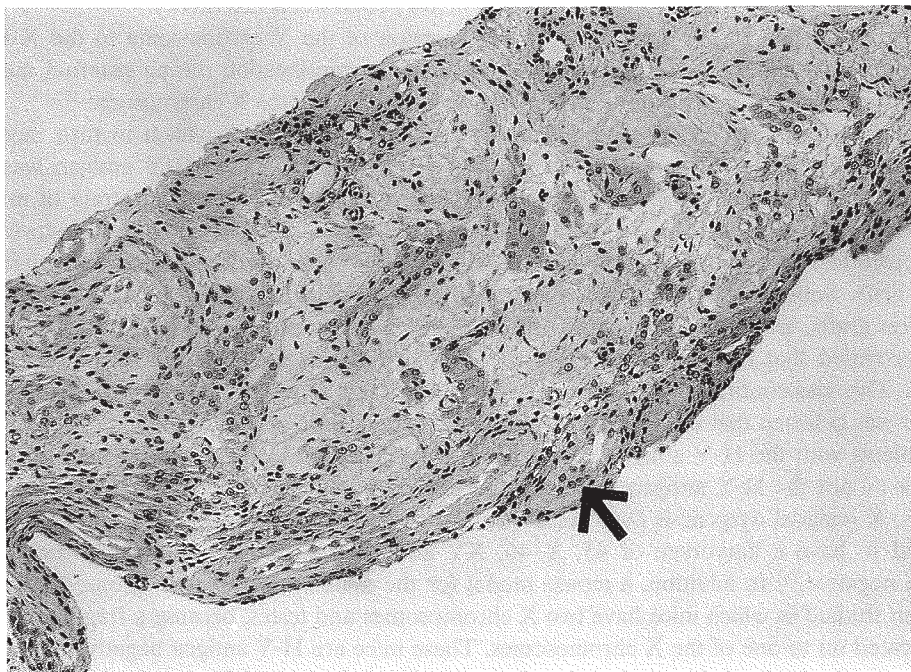


Fig. 2. Testicular biopsy shows severely hyalinized seminiferous tubules and hyperplasia of Leydig cells. Only a few tubules contain Sertoli cells (arrow).

No germinal cells were seen in the seminiferous tubules (Fig. 2).

## DISCUSSION

The sex reversal syndrome (XX male) probably represents a variant of Klinefelter's syndrome, in which the patients are phenotypically and psychosexually normal males with small testes and a small-to-normal-sized penis. Affected patients are shorter in height than average. One-third of adults have gynecomastia. All are infertile;<sup>6)</sup> hypospadias occurs in 10% and cryptorchidism in 15%.<sup>7)</sup> The XX male patients are clinically indistinguishable from those with Klinefelter's syndrome.<sup>8)</sup>

In sex reversal syndrome and testosterone may be at a low-to-normal level. FSH and LH are usually increased,<sup>9)</sup> and the prolactin level is normal. Semen analysis shows no sperm, and a light microscopic examination of the testes usually reveals hyalinized seminiferous tubules which contain only Sertoli cells. There is frequently Leydig cell hyperplasia.<sup>8-10)</sup>

There are several theories which try to explain the etiology of this condition. According to the autosomal gene theory, the male sex determining factors are located on chromosomes other than the Y chromosome. A gonad, under the influence of this gene for maleness, would develop into a testis.<sup>11)</sup>

The mosaicism theory postulates the existence of a cell line containing a Y chromosome that

was present during an early stage of development but was subsequently lost.<sup>8)</sup> The presence of Y material in the genome of XX males (described below) contradicts this theory.

The translocation ("X-Y Interchange") of a portion of the Y chromosome to the X is the most compelling theory. XX maleness is the result of a translocation during paternal meiosis, such that some of the Y's chromosome material is transferred to the X chromosome.<sup>12)</sup>

Y chromosome regulates the production of a cell surface antigen, which in turn mediates transformation of the indifferent gonad into a testis.<sup>13)</sup> This so-called H-Y antigen was first identified in 1955, when male-to-female skin grafts were rejected in the same strain of mice in whom female-to-male skin grafts were accepted.<sup>14)</sup> It was theorized that the male-to-female graft rejection was due to a Y-situated histocompatibility gene, hence the histocompatibility-Y (H-Y) gene. Subsequently, male specific antibodies were detected in sera of female mice with male skin grafts, and assays for quantifying H-Y antigen were developed. Using these assays, it was discovered that the presence of a testis resulted in serologically detectable levels of H-Y antigen. This was confirmed in normal and intersex patients as well as in males of other species. Thus, it was believed that the H-Y gene was the testis-determining gene.<sup>13)</sup>

Problems with the H-Y antigen theory have developed, however, raising the question as to whether or not the H-Y antigen is in fact, the testis determining factor. A number of women with 45, X gonadal dysgenesis have been found to be H-Y antigen positive.<sup>15)</sup> And one patient reported to have a karyotype of 45, X/46, XY and bilateral intra-abdominal testes as H-Y antigen negative.<sup>16)</sup> In addition, a mouse model for the male sex reversal syndrome (XX male) has been studied in which mice have two X chromosomes and testes, because a fragment of Y is translocated on to one of the X chromosomes. These mice are H-Y antigen negative and azoospermic. On the basis of this work, it has been suggested that the H-Y antigen does not determine testis formation, but may play a role in spermatogenesis.<sup>17)</sup>

Currently, Vergnaud and Anderson are attempting to localize the testis-determining factor by chromosomal analysis of a series of XX males. They have found that 12 of 19 XX males studied have evidence of Y DNA material, and that a certain portion of the Y chromosome is common in all XX males studied thus far.<sup>18-19)</sup> In addition, they have studied a series of XY females to determine which portion of the Y chromosome would be deleted in these patients without testes. Based on these studies, it appears that the SRY is located distally on the short arm of the Y chromosome within segment 1A (the H-Y transplant antigen has been located on the proximal portion of the long arm of the Y near the centromere).<sup>20)</sup> While further work remains to be done in localization of the SRY, it seems clear at this point that the H-Y antigen does not seem to function in the process of sex determination of the undifferentiated gonad. The H-Y antigen may play a role at a later stage of testicular development.

In conclusion, we reported a case of XX male with infertility. In this patient, SRY was identified by a polymerase chain reaction using a Y-specific probe. We determined that the undifferentiated gonad in a testis is controlled by the SRY, and that the H-Y antigen may influence the later development and normal hormonal and sperm-producing function of the testis.

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