CLINICAL REPORT

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XX Male Sex Reversal With Genital Abnormalities Associated With a De Novo *SOX3* Gene Duplication

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Differentiation of the bipotential gonad into testis is initiated by the Y chromosome-linked gene *SRY* (Sex-determining Region Y) through upregulation of its autosomal direct target gene *SOX9* (*Sry*-related HMG box-containing gene 9). Sequence and chromosome homology studies have shown that *SRY* most probably evolved from *SOX3*, which in humans is located at Xq27.1. Mutations causing *SOX3* loss-of-function do not affect the sex determination in mice or humans. However, transgenic mouse studies have shown that ectopic expression of *Sox3* in the bipotential gonad results in upregulation of *Sox9*, resulting in testicular induction and XX male sex reversal. However, the mechanism by which these rearrangements cause sex reversal and the frequency with which they are associated with disorders of sex development remains unclear. Rearrangements of the *SOX3* locus were identified recently in three cases of human XX male sex reversal. We report on a case of XX male sex reversal associated with a novel de novo duplication of the *SOX3* gene. These data provide additional evidence that *SOX3* gain-of-function in the XX bipotential gonad causes XX male sex reversal and further support the hypothesis that *SOX3* is the evolutionary antecedent of *SRY*. © 2012 Wiley Periodicals, Inc.

Key words: *SOX3*; XX male sex reversal; disorders of sex development

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INTRODUCTION

The basis of our conception of genetic sex determination was initially, at least in mammals, limited to a form of chromosomal currency. The Y chromosome was thought by definition to always produce a male and the lack of Y chromosome would result in a female.

The refinement of our genetic tools revealed important realizations such as that the presence of an entire Y chromosome was not essential for the development of the male phenotype and that a transfer of the *SRY*-gene alone, rather than the entire Y chromosome, could result in phenotypically male individuals. Critically, mutations in the *SRY* gene are linked with XY-female sex reversal in mice and humans [McElreavey et al., 1992] indicating that *SRY* is essential for male development. The *SRY* gene encodes for a transcription factor that is thought to play a pivotal role in sex differentiation in all placental mammals. It appears that the only role of SRY is to upregulate the *SRY*-related HMG box containing gene 9 (*SOX9*) bipotential gonads, which results in Sertoli cell differentiation and, ultimately, in testes differentiation [Piprek, 2009; Sekido and Lovell-Badge, 2009]. Our prior understanding of

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mammalian sexual development, of the female phenotype as the "default" sex, from which the male phenome arises, is now being challenged. It is becoming apparent that sexual phenotypes are the result of either gain or loss of function of a multitude of key regulatory signals. A recent report by Cox et al. [2011] described a family, two brothers and an uncle, with 46,XX male sex reversal who lacked the *SRY* gene and had a 600 kb duplication upstream of *SOX9* [Cox et al., 2011]. In their report, all three phenotypic XX-males had normal male secondary sexual characteristics, including growth and development. Yet, all three men were also found to be infertile with azoospermia [Cox et al., 2011]. The described duplication seems to have overridden the requisite need for the *SRY* gene for the formation of a male phenotype, although upon histologic examination the seminiferous tubules were atrophied with no spermatogenesis [Cox et al., 2011]. Another such example is the *SRY*-related HMG box containing gene 3 (*SOX3*), a single exon gene located on the X-chromosome which shares some conservation with the *SRY* gene and is involved in embryogenesis [Stevanovic et al., 1993; Weiss et al., 2003; Rizzoti et al., 2004]. A recent report showed that Xq27.1 locus rearrangements were associated with XX male sex reversal in three humans [Sutton et al., 2011]. However, it remained unclear whether the resulting phenotype was due to increased dosage through the duplication, change in the expression or ectopic expression of the *SOX3* gene leading to a male phenotype [Sutton et al., 2011]. Sutton et al. [2011] also showed that ectopic *Sox3* expression in the developing gonad of transgenic mice can result in male sex reversal. However, the potential functional relationship between *SOX3* copy number gain and 46,XX male sex reversal is complicated by reports of 46,XX normal female carriers, who were ascertained through their sons affected with X-linked hypopituitarism [Solomon et al., 2002; Woods et al., 2005]. We report here on a baby with a de novo 494 kb duplication containing the *SOX3* gene that resulted in XX male sex reversal.

CLINICAL REPORT

The propositus was born to a nonconsanguineous couple of Asian descent. The pregnancy was uncomplicated, apart from gestational diabetes. The delivery was spontaneous and vaginal with a birth weight of 3.37 kg (50th centile). Initial physical examination showed a phenotypic male infant with a bifid, but well developed scrotum and penoscrotal hypospadias. Normal erectile tissue was palpable. No other abnormalities were noted and his facial appearance was normal. His growth and development has been normal and at 5 months of age his weight was 6.65 kg (under the 25th percentile). Treatment with intramuscular injection of testosterone, in preparation for the hypospadias repair, resulted in a substantial increase in the length and width of his penis.

His blood LH, FSH, testosterone, and rostenedione, 17-hydroxyprogesterone, DHA-sulfate levels were all normal. Abdominal

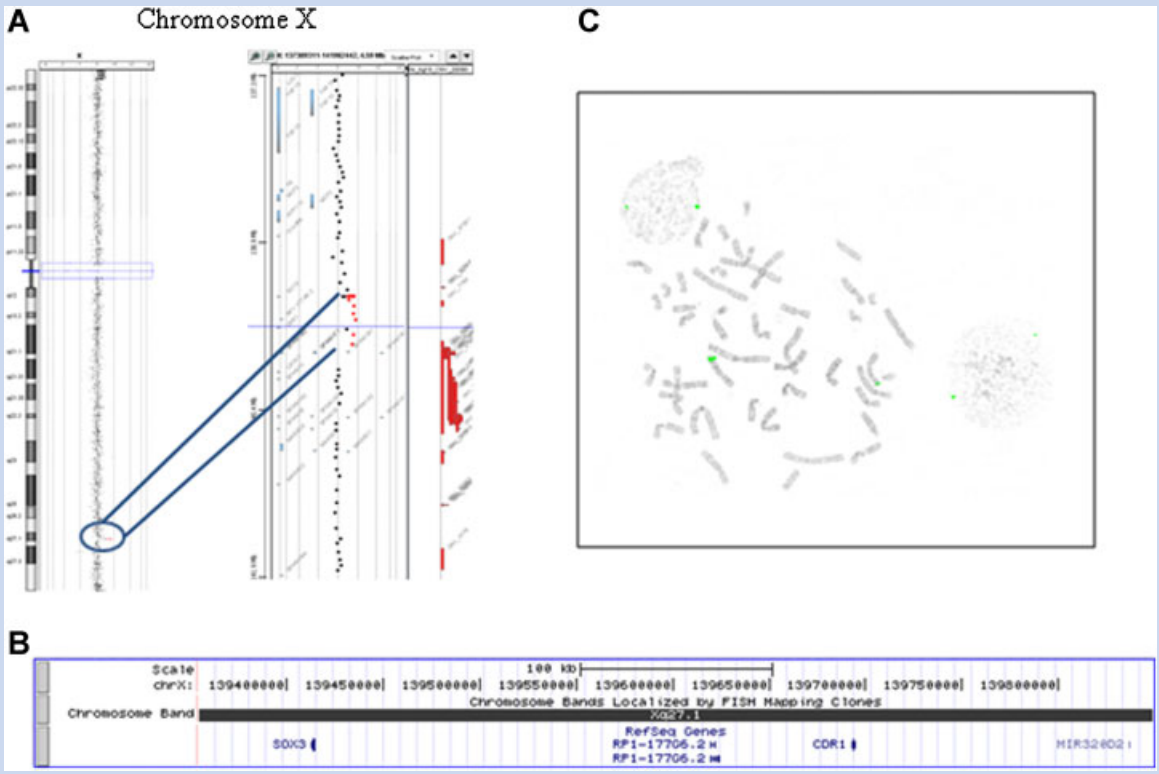

FIG. 1. Chromosome microarray and FISH analysis. A: Chromosome and Gene views of the duplication in chromosome region Xq27.1. B: Gene content displayed on the UCSC Genome Browser (NCBI36/hg18). C: Metaphase FISH analysis using BAC probe RP11-951L8 (green) shows two signals in the expected location of the X chromosomes. The signal on one X homologue is larger suggesting the duplication is in tandem.

ultrasound findings were normal at 12 months and ultrasonography showed that the testes were of normal size and configuration with the right testis measuring 1.2 cm × 0.8 cm × 0.6 cm and the left measuring 1 cm × 0.8 cm × 0.6 cm with the epididymis appearing grossly normal.

METHOD AND RESULTS

Chromosome and FISH analysis, using standard protocols, showed a normal female karyotype (46, XX), and negative for *SRY* (Abbott Laboratories, Abbott Park, Il). Array genomic hybridization was performed using the oligonucleotide 4 × 44K microarray platform (Agilent Technologies, Santa Clara, CA) with a custom design described previously [Baldwin et al., 2008]. Patient and XX control reference DNA (Promega, Madison, WI) were labeled with Cy3-dCTP and Cy5-dCTP, respectively, and hybridized to the array platform, as recommended by the manufacturer's protocol (Agilent Technologies). The arrays were scanned using the Agilent G2505B microarray scanner. Data analysis was performed using DNA Analytics version 4.0 (Agilent Technologies) with ADM-1 algorithm set at a threshold of 6.7 and a minimum of four contiguous probes. This analysis showed three copy number gains. The first of which was a de novo 494 kb copy number gain in region Xq27.1 (nucleotide positions 139,354,859–139,848,664, NCBI 36/hg18) which contains the *SOX3*, *RP1-177G6.2*, *CDR1* and *MIR320D2* genes (Fig. 1). Metaphase FISH analysis using BAC probe RP11-951L8 was performed on the patient and control samples using standard methods, and the slides were blinded prior to analysis. The metaphase chromosomes were stained with DAPI, and were viewed with the ISIS imaging software (MetaSystems, Altlussheim, Germany) using reverse DAPI mode to identify the chromosomes. The probe hybridized to the expected location on both X homologues; however, one signal was larger in 10/10 metaphase chromosomes in the patient sample, consistent with a tandem duplication of this region (Fig. 1C).

Two additional maternally inherited copy number gains were observed. The first of which was a 1.344 Mb duplication in chromosome region 13q12.12 (nucleotide positions 22,464,762–23,808,884) which contains approximately nine genes. The other copy number gain is a 0.959 Mb duplication in chromosome region 15q11.2 (nucleotide positions 20,249,686–21,208,577) which contains approximately 11 genes, and includes the region between proximal breakpoint 1 to breakpoint 2 of the type I microdeletion associated with Prader–Willi/Angelman syndromes. Microarray analysis was performed on parental samples to determine the inheritance of all copy number changes observed in the propositus (data not shown). As indicated the mother has no physical abnormalities and no health issues.

DISCUSSION

Sex determination in mammals is the result of coordinated events, which begin at the chromosome sex determination (XX in females and XY in males) and end in the determination of the phenotypic and psychosocial sex. The link between the chromosome sex and the phenotypic sex is the determination of the gonadal sex. The gonads develop from the genital ridges (GR), that lie ventrally subjacent to the mesonephros, and are considered to be bipotential, since the cell lineages within the gonads can differentiate into testis-or ovary [Albrecht and Eicher, 2001]. The *SRY* gene on the short arm of the Y chromosome is necessary and sufficient for male sex differentiation. In mice, the level of *Sry* activity must exceed a critical threshold within approximately 6 hr for the irreversible commitment of the indifferent gonad into a testis fate [Nagamine et al., 1999; Bullejos and Koopman, 2005; Hiramatsu et al., 2009]. The target of the *SRY* gene is the autosomal *SOX9* gene which is upregulated directly by *SRY* and in turn starts the differentiation of the Sertoli cells in the testes [Sekido and Lovell-Badge, 2008]. These cells, under the influence of *Sox9* over expression and by the help of the *Sox9*/*Fgf9* and *Sox9*/*Pgd2* positive feedback loops [Wilhelm et al., 2005; Kim et al., 2006], migrate to surround the germ cells in the male gonad and form testicular cords. Shortly after and just 48 hr after *Sry* starts its activity, the Leydig cells differentiate and enable the early testis to produce testosterone. These changes also result in morphological changes in the gonad that allows the recognition of distinction between testis and ovaries on palpation and ultrasound.

The formation of the ovaries is not a default process and requires a balance between pathways that are pro and pathways, which are against ovarian development. Thus, loss-of-function mutations in *Wnt4* and *Rspo1* cause partial XX male sex reversal, and gain-of-function mutations in *Wnt4*, *Rspo1*, and *Ctnnb1* induce XY female sex reversal [Jordan et al., 2001; Maatouk et al., 2008].

XX male sex reversal is rare and in most cases is the result of translocation of the SRY gene to the X-chromosome during male meiosis. The *SOX3* gene, which has many similarities to the *SRY* gene, encodes a protein that is most similar to *SRY*, sharing 67% amino acid identity (and 90% similarity) across the DNA-binding HMG domain [Stevanovic et al., 1993; Bowles et al., 2000]. Thus, comparative sequence data and molecular and cytogenetic studies, have led to the hypothesis that *SRY* arose during early mammalian evolution from a gain-of-function mutation in the proto-Y allele of *SOX3*. The *SOX3* gene contains a single exon and is located in a highly conserved region of the X chromosome [Stevanovic et al., 1993; Foster and Graves, 1994; Collignon et al., 1996]. *Sox3* expression is very low or absent in the developing gonads of mice [Collignon et al., 1996] but is widely expressed in the central nervous system of vertebrate embryos and is required for normal brain development and function in mice and humans, as well as in pituitary and craniofacial development [Rizzoti et al., 2004; Solomon et al., 2004; Woods et al., 2005]. Mice and humans with mutations in *SOX3* do not show any defects in sex determination, although spermatogonial differentiation and follicle survival are affected in *Sox3*-null mice [Laronda and Jameson, 2011]. However, ectopic expression of Sox3 in the urogenital ridge of transgenic mice induces complete XX male sex reversal [Sutton et al., 2011]. *SOX3* regulatory region rearrangements in humans have also been recently reported in three patients with XX male sex reversal. Patient B had a microdeletion just upstream of the *SOX3* gene, patient A had two microduplications, one of which spanned the *SOX3* gene and patient C had a 6-Mb duplication that encompassed *SOX3* and at least 18 distally located genes. Thus, although *SOX3* does not normally function in sex determination, certain gain-of-function mutations in *SOX3* may result in XX male sex reversal in

TABLE I. Cases of *SOX3* Related XX Male Reversal*

	Woods et al., Family A: Patient 1	Woods et al., Family A: Patient 2	Sutton et al., Patient A	Sutton et al., Patient B	Sutton et al., Patient C	Moalem et al., Patient 1
Secondary sexual characteristics	Normal	Not reported	Normal	Tanner stage five pubic hair, penile development with small testis; onset age 13 year	Unknown	Unknown
Growth and Developmental issues	GH deficiency; Normal serum prolactin and cortisol. Psychomotor development	History of neonatal hypoglycaemia; severe cortisol, TSH, GH, and gonadotrophin deficiency. He has normal psychomotor development but has been noted to be hyperactive	Unknown	Gender dysphoria from 6 years; referred to behavior therapist	Developmental delay; microcephaly; growth retardation	Normal
Imaging Results	MRI revealed a hypoplastic anterior pituitary, and hypoplasia of the lower half of the infundibulum and a partially descended posterior pituitary at the tip of the infundibulum	MRI revealed hypoplasia of the anterior pituitary, absence of the infundibulum, and an ectopic/undescended posterior pituitary. The corpus callosum was normal	Not reported	Not reported	Not reported	The scrotum appears underdeveloped. The right testes is located within the scrotum and the left testes is slightly high in the inguinal region. There was no evidence of cystic change to suggest an ovotestes. The right testes measures 1.2 cm × 0.8 cm × 0.6 cm and the left testes measures 1 cm × 0.8 cm × 0.6 cm. Epididymi are grossly normal
Genitals and testis	Details not reported	Hypoplastic genitalia, with both testes palpable high in the inguinal canal and a micropenis	Normal	Atrophic changes on pathology	Hypoplastic scrotum; testes are retractile and can be brought down	Penoscrotal hypospadias with a bifid scrotum; Phallus was otherwise unremarkable with erectile tissue palpable; On ultrasound epididymi appearing grossly normal
Genotype	Tandem duplication 685.6 kb in length on the X-chromosome which spanned the *SOX3* gene	Tandem duplication 685.6 kb in length on the X-chromosome which spanned the *SOX3* gene	Two microduplications of approximately 123 kb and 85 kb, on the X-chromosome, the first of which spanned the entire *SOX3* gene	Single 343-kb microdeletion on the X-chromosome immediately upstream of *SOX3*	6-Mb duplication that encompasses *SOX3* and at least 18 additional distally located genes	0.494 Mb copy number gain in region Xq27.1 which contains the *SOX3*, *RP1-177G6.2*, *CDR1*, and *MIR320D2* genes. 1.344-Mb copy number gain in chromosome region 13q12.12, which contains approximately 9 genes including *SGCG* and *SACS*. 0.959 Mb copy number gain in 15q11.2, which contains approximately 11 genes, including NIPA1

GH, growth hormone; TSH, thyroid stimulating hormone.
*Table adapted from Sutton et al. [2011].

mice and humans by mimicking the function of the *SRY* gene and its impact on the *SOX9* gene [Sutton et al., 2011].

In our case, XX male sex reversal was detected with genital abnormalities including shawl and bifid scrotum, incomplete prepuce, a chordee and grade II hypospadias. The scrotum was bifid in its anterior part and fused in its posterior part and the anus was posteriorly displaced. Gonads were palpated in each hemiscrotum and had normal volume on ultrasound and had normal function at this stage. The growth and development have been normal.

In view of the duplication of the *SOX3* gene in our case we would have expected complete sex reversal as the *SOX3* gain of function mimics expression of SRY in the bipotential gonad, thereby triggering the testis pathway. However, if the ectopic expression in the early gonad is weak or slightly late compared to the *SRY* normal expression of the XY gonads, a partial sex reversal with abnormal genitalia, as seen in our patient, may result. Furthermore, the location and orientation of the duplicated segment containing the *SOX3* gene, as well as the genomic environment of the duplicated chromosome segment may have importance in determining the phenotype, and thus the differences between patients with a duplicated *SOX3* locus. In cases of 46,XX male sex reversal, new microenvironment of the duplicated chromosome segment may lead to ectopic expression in the gonad thus driving the male phenotype. Consistent with this hypothesis, Sutton et al. showed that a change in the chromosome environment immediately adjacent to the *SOX3* locus in the form of a 600 kb deletion resulted in 46, XX sex reversal [Sutton et al., 2011].

Male patients with 46,XY and *SOX3* duplication with panhypopituitarism [Solomon et al., 2004] and mild intellectual disability [Woods et al., 2005] have been reported (Table I). However, 46,XX female carriers of SOX3 duplications are unaffected [Solomon et al., 2002, Genomics]. Consistent with these data, overt hypopituitarism was not evident in the 46,XX male patients described by Sutton et al. [2011] that carry duplications of the *SOX3* gene. At 10 months, our patient had normal development and growth. However, long-term follow-up will be needed to identify a change in this matter.

Given the lack of reported cases of XX male sex reversals to date, this case is an important addition to help clarify the role of *SOX3* in gonadal and phenotypic sex determination. Regarding our patient's fertility, 46,XX *SRY* positive male sex reversal are known to have azoospermia since they lack the Y chromosome. Vetro et al. [2011] reported on a family with two azoospermic brothers, both 46,XX, *SRY* negative with a 96 kb triplication 500 kb upstream of *SOX9*. Thus, our patient will be infertile since he does not have the Y chromosome and may also need induction of puberty.

As we move from expanding our knowledge base from genome to phenome, cases as the one reported herein can help clarify and bring attention to the importance of temporal events in phenotypic sex determination.

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