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Complete XY gonadal dysgenesis and aspects of the *SRY* genotype and gonadal tumor formation

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Abstract XY gonadal dysgenesis can be classified as either complete or incomplete according to gonadal morphology. The disease is a sex-reversal disorder resulting from embryonic testicular regression sequences and is induced by mutations in the sex-determining region Y (*SRY*) gene. The incidence of *SRY* mutations is thought to be approximately 20%. As the disease is characterized by a frequent complication of gonadal tumors, patients are usually advised to undergo prophylactic gonadectomy. In this study, we searched for mutations in *SRY* open reading frames from three patients with the complete form of XY gonadal dysgenesis, and detected missense mutations in two patients. Combined with the results of our previous study, in which *SRY* abnormalities were also detected in two out of three complete-type patients, the final incidence of *SRY* abnormalities was 67% (four of six patients), which is much higher than previously thought. The incidence of gonadal tumor formation in patients with *SRY* abnormalities was 50% (two of four patients), which is similar to the result of a metanalysis of patients with *SRY* abnormalities that revealed an incidence of 52.5%. Therefore, it is possible that the lower incidences of *SRY* abnormalities previously reported were caused by the inclusion of patients with the incomplete form or other sex-reversal disorders. Moreover, our results suggest that clinicians should carefully examine patients with *SRY* abnormalities.

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Introduction

The sex-reversal disorder XY gonadal dysgenesis is the result of an embryonic testicular regression sequence, and can occur in a complete or incomplete form. The complete form is defined by a 46,XY karyotype and the absence of testes. Affected individuals present with female-type external genitalia, normal Müllerian structures, and streak gonads similar to those of Turner syndrome. Gynecologists tend to encounter the complete form, as affected patients grow as phenotypically normal females and at adolescence complain of gynecologic symptoms, such as primary amenorrhea or delayed puberty. In contrast, patients with the incomplete form are often diagnosed in early childhood due to genital ambiguity. The incomplete form is characterized by unilateral or bilateral dysgenetic gonads consisting of disorganized seminiferous tubules admixed with ovarian stroma (Marcantonio et al. 1994).

Several genetic loci play important roles in testis-determining pathways. The testis-determining gene *SRY* is a Y-chromosome gene essential for testicular development (Koopman et al. 1991). *SRY* consists of a single exon in which the central third of the open reading frame (ORF) encodes a 79-amino-acid region showing high similarity to a motif known as the high-mobility-group (HMG) box. While the *SRY* HMG-box-containing protein has been shown to possess sequence-specific DNA-binding activity and act as a transcriptional regulator (Gubbay et al. 1990; Harley et al. 1994), its target genes remain largely unknown.

Following the cloning of *SRY*, a number of aberrations, such as missense mutations, nonsense mutations, frameshifts due to nucleotide deletions, and cryptic deletions involving the *SRY* locus on the short arm of the Y chromosome (Yp), have been reported in patients with XY gonadal dysgenesis (Cameron and Sinclair 1997). These

Table 1. Patient case reports

Patient	Age	Hormone levels				Gonads	*SRY* mutation
		LH	FSH	E2	T		
NH	42	80	72	<20	<20	Streak gonads	Negative
MF	15	26.6	116	<20	35.9	Streak gonads	Arg132CGT→GlyGGT
YS	22	47.3	141	<20	<20	Streak gonads	Ala113GCA→ThrACA

LH, luteinizing hormone; FSH, follicle stimulating hormone; E2, estradiol; T, testosterone

aberrations occur especially in the *SRY* HMG box, and are thought to have an overall incidence of approximately 20%. To date, there have been at least 35 different missense or nonsense mutations reported for *SRY* (Okuhara et al. 2000).

It is well known that germ cell tumors, including gonadoblastoma and dysgerminoma, frequently occur in patients with XY gonadal dysgenesis. Gonadoblastoma is a mixed germ cell–sex cord stromal tumor with limited malignancy potential. The tumor arises in streak gonads in 30% of XY sex-reversed patients (Scully 1970; Verp and Simpson 1987). It has been reported that gonadoblastoma can occur not only in individuals with XY gonadal dysgenesis but also in Turner syndrome patients with mosaic karyotypes that include structurally aberrant Y chromosome clones. Therefore, it has been hypothesized that the expression of a Y chromosome gene (or genes) is involved in tumor etiology (Page 1987). In a certain number of patients, gonadoblastoma can also develop into dysgerminoma (Manuel et al. 1976), a malignant germ cell tumor that can lead to metastatic disease. As the reason for the association between XY gonadal dysgenesis and gonadal tumors remains unclear, many patients are advised to undergo prophylactic gonadectomy soon after diagnosis. However, it is not known whether prophylactic gonadectomy is necessary for all patients with the disease. We have previously identified two *SRY* aberrations (a cryptic deletion of a region of Yp that includes *SRY*, and a mutation consisting of a 2-base substitution and a 7-base deletion) from three patients with the complete form of XY gonadal dysgenesis (Uehara et al. 1999), and speculated that these aberrations were associated with gonadal tumors. We have now examined for *SRY* mutations three additional independent patients with the complete form of the disease. We detected two missense mutations, both in the *SRY* HMG box. On the basis of the present results and a metanalysis of previous reports, we discuss the incidence of *SRY* aberrations and the relationship between *SRY* aberrations and gonadal tumor formation, especially in patients with complete-type XY gonadal dysgenesis.

Subjects and methods

Clinical reports

We encountered three new patients (NH, MF, and YS) with the complete form of XY gonadal dysgenesis. All three patients complained of primary amenorrhea or delayed menarche. The patients were unrelated and their parents were non-consanguineous. By physical examination, the patients were phenotypically female with unambiguous female-type external genitalia, positive development of pubic hair, and hypoplastic uteri. The possibilities of androgen insensitivity or inborn errors of testosterone biosynthesis were excluded by analyses of serum testosterone, androstenedione, and dihydrotestosterone before and after human chorionic gonadotropin stimulation. Other endocrinological examinations revealed hypergonadotropic hypogonadism. The karyotypes of all three patients were 46,XY, as determined from peripheral blood leukocytes stimulated with phytohemagglutinin. Exploratory laparoscopy was performed to determine the presence of Müllerian structures and the nature of the gonadal tissues. Excised gonadal tissues from all three patients were examined by conventional histologic methods, and revealed only fibrous tissue without primitive sex cords. The case reports of the patients are summarized in Table 1. The patients gave their fully informed consent before being included in this study.

Nucleotide sequencing of *SRY*

Genomic DNA was extracted from peripheral blood samples from the three patients as well as from normal males and females using SepaGene (Sanko-Junyaku, Tokyo, Japan). The entire *SRY* coding region (*SRY*-ORF) was amplified from genomic DNA samples by using primers XES10 and XES11, as described by Hawkins et al. (1992a). Polymerase chain reaction (PCR) products were electrophoresed on 2% agarose gels, purified, and subcloned into the pGEM-T plasmid (Promega, Madison, WI, USA). Plasmids were then transformed into *E. coli* (DH-5α), and bacterial colonies containing the correct insert identified. Plasmid DNA was prepared and applied to nucleotide sequencing analysis. To distinguish mutations from randomly misincorporated nucleotides, plasmids from six independent bacterial colonies were examined.

Metanalysis

To investigate the incidence of *SRY* aberrations in patients with XY gonadal dysgenesis, we collected reports that analyzed patient numbers and numbers of *SRY* abnormalities (References are cited in Table 2). DNA sequences from

Table 2. *SRY* abnormalities in patients with XY gonadal dysgenesis

Reference	No. of patients	No. of patients with *SRY* abnormalities	Incidence (%)
Jäger et al. 1990	12	1	8.3
Jäger et al. 1992	3	1	33.3
Hawkins et al. 1992a	5	3	60
McElreavy et al. 1992a	25	5	20
Müller et al. 1992	3	1	33.3
Affara et al. 1993	21	4	19.0
Tajima et al. 1994	3	1	33.3
Schmitt-Ney et al. 1995	30	2	6.7
Scherer et al. 1998	16	3	18.8
Uehara et al. 1999	3	2	66.7
Total	121	23	19.0

entire *SRY*-ORFs were screened in these studies. Because the results of clinical examinations, such as gonadal morphology and anatomy of internal genitalia, were not satisfactorily described in some of the previous reports, the subjects possibly included not only patients with the complete form of XY gonadal dysgenesis but also patients with the incomplete form or other sex reversal disorders.

To investigate the relationship between *SRY* aberrations and gonadal tumor formation in XY gonadal dysgenesis, previous reports describing *SRY* molecular analyses, histopathological findings of resected gonads, and patient age (age was unknown in some reports) were also gathered (References are cited in Table 3).

Table 3. *SRY* abnormalities and gonadal tumor formation in patients with XY gonadal dysgenesis

Reference	Age	*SRY* abnormality	Gonad morphology	
			First	Second
Disteche et al. 1986	1	Cryptic deletion on Yp	S	S
Disteche et al. 1986	15	Cryptic deletion on Yp	G	S
Jäger et al. 1990	18	4-Base deletion	S	S
Jäger et al. 1992	28	Phe109TTC→SerTCC	G	S
Hawkins et al. 1992a	ND	Gly95GGA→ArgCGA	S	S
Hawkins et al. 1992a	ND	Trp70TGG→stopTAG	S	S
Hawkins et al. 1992b	17	Ile90ATC→MetATG	G	G
Hawkins et al. 1992b	25	Lys106AAA→IleAAT	S	S
Hawkins et al. 1992b	25	Pro108CCA→1 base deletion	F	F
McElreavy et al. 1992a	20	Gln93CAG→stopTAG	S	S
McElreavy et al. 1992a	ND	Cryptic deletion on Yp	G	E
McElreavy et al. 1992a	ND	Ile68ATC→ThrACC	S	S
McElreavy et al. 1992b	ND	Tyr127TAT→stopTAA	S	S
Müller et al. 1992	9	Lys92AAG→stopTAG	G	IC
Affara et al. 1993	41	Arg133CGG→TrpTGG	G	S
Affara et al. 1993	25[a]	Gln74CAG→stopTAG	G	S
Affara et al. 1993	20[a]	Gln74CAG→stopTAG	G	S
Affara et al. 1993	17	Met78ATG→ThrACG	G	G
Affara et al. 1993	18	Arg62CGA→GlyGGA	S	S
Zeng et al. 1993	19	Ala113GCA→ThrACA	G	S
Tajima et al. 1994	ND[b]	*Leu163TTG→stopTAG*	G	G
Tajima et al. 1994	ND[b]	*Leu163TTG→stopTAG*	S	S
Iida et al. 1994	28	Trp107TGG→stopTAG	S	S
Poulat et al. 1994	17	Tyr129TAT→CysTGT	S	S
Barbosa et al. 1995	19[c]	Cryptic deletion on Yp	G	G
Barbosa et al. 1995	19[c]	Cryptic deletion on Yp	S	S
Schmitt-Ney et al. 1995	11	Ser91AGC→GlyGGC	G	S
Schmitt-Ney et al. 1995	18[d]	Pro125CCG→LeuCTG	G	S
Schmitt-Ney et al. 1995	14[d]	Pro125CCG→LeuCTG	S	S
Sultana et al. 1995	14	Cryptic deletion on Yp	G	D
Bilbao et al. 1996	16	Gln97CAG→stopTAG	G	G
Brown et al. 1998	15	*Gln2CAA→stopTAA*	S	S
Scherer et al. 1998	20	Lys43AAG→stopTAA	S	S
Scherer et al. 1998	16	Met64ATG→ArgAGG	S	S
Scherer et al. 1998	15	Phe67TTC→ValGTC	G + D	ND
Uehara et al. 1999	15	2-Base substitution & 7-base deletion	G + D	S
Uehara et al. 1999	22	Cryptic deletion on Yp	G + D	S
Okuhara et al. 2000	12	Asn87AAC→TyrTAC	G	S
The present case	17	Arg132CGT→GlyGGT	S	S
The present case	22	Ala113GCA→ThrACA	S	S

SRY mutations in italics were detected outside the HMG box
ND, not described; S, streak gonad; G, gonadoblastoma; F, fibroma; E, embryonal carcinoma; IC, invasive carcinoma; D, dysgerminoma; G+D, tumor containing gonadoblastoma and dysgerminoma lesions
[a,b,c,d] Familial cases

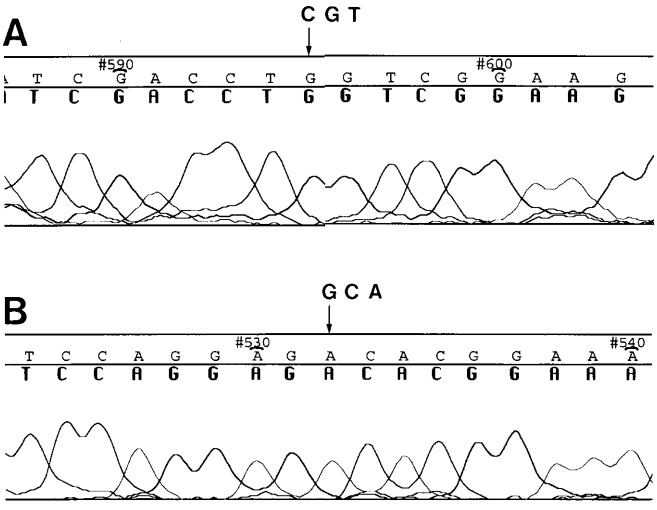

Fig. 1. Partial sequences of *SRY* observed in patients MF (**A**) and YS (**B**). *Arrows* indicate substituted nucleotides; the nucleotides *above the arrows* are the wild-type codons

Results

SRY mutations

Of three previously unreported patients with XY complete gonadal dysgenesis, two patients exhibited *SRY* point mutations.

In patient HN, the DNA sequence of the entire *SRY*-ORF was identical to the wild-type sequence obtained from control males.

Patient MF showed a missense mutation within the *SRY* HMG box, with the arginine codon (CGT) at amino acid 132 altered to a glycine (GGT), giving Arg132CGT→GlyGGT (Fig. 1A).

Patient YS also showed a missense mutation within the HMG box, with the alanine codon (GCA) at amino acid position 113 altered to a threonine (ACA), giving Ala113GCA→ThrACA (Fig. 1B).

The two types of nucleotide substitutions were not detected in our preliminary *SRY* sequencing of 30 normal males.

Incidence of *SRY* abnormalities

Metanalysis of 121 patients with XY gonadal dysgenesis revealed that *SRY* abnormalities (both cryptic deletions in Yp including the *SRY* locus and *SRY* mutations) were present in 23 patients (18.5%). This is in contrast to the observed incidence from our studies (67%; four out of six patients). Interestingly, Hawkins et al. (1992a), who analyzed only patients with the complete form, also reported a higher incidence (60%; three in five patients). Table 2 summarizes patient numbers, *SRY* abnormalities, and references.

Relationship between *SRY* abnormalities and gonadal tumor formation

In the metanalysis, 40 patients (including four familial cases of two related individuals) were shown to have *SRY* abnormalities: 7 patients with cryptic deletions involving Yp, and 33 patients with *SRY* mutations, including missense mutations, nonsense mutations, deletions, and frameshifts. Most of the *SRY* mutations were located within the *SRY* HMG box, with only three mutations located outside. Of the 40 patients with *SRY* abnormalities, 21 (52.5%) had complications in the form of gonadal tumors, with gonadoblastoma observed in 13 patients, malignant tumors (including dysgerminoma, with or without gonadoblastoma, and embryonal carcinoma) in 7 patients, and fibroma in 1 patient. Bilateral streak gonads without tumors were observed in 19 patients. Age, details of the aberration, whether the aberrant site was inside or outside the *SRY* HMG box, histopathological findings on gonads, and references are summarized in Table 3.

Discussion

In the present study, we detected two missense mutations in two out of the three new patients: Arg132CGT→GlyGGT was a novel mutation, while Ala113GCA→ThrACA was reported by Zeng et al. (1993). We have previously reported finding *SRY* abnormalities in two out of three patients with the complete form of XY gonadal dysgenesis (Uehara et al. 1999); thus, the final proportion of *SRY* aberrations was 67% (four of six patients). While this proportion is much higher than that observed in previous reports (Table 2), our result was similar (60%; three in five patients) to that reported by Hawkins et al. (1992a), who also analyzed only patients with the complete form. XY sex reversal can be induced by several other etiologies, including microdeletions in Yp, androgen-insensitivity syndrome, LH receptor deficiency, P450c17 deficiency, and so on. Furthermore, XY gonadal dysgenesis can be classified as being either complete or incomplete. In our study, subjects were limited only to patients diagnosed with the complete form by means of physical, endocrinological, surgical, and histopathological examinations. Thus, the finding of a much higher proportion of *SRY* abnormalities in a group of patients carefully selected as having the complete form may be significant. It is possible, therefore, that some patients classified as having "gonadal dysgenesis" in some previous reports may in fact have had the incomplete form or some other disorder, and a high incidence of *SRY* abnormality may be a characteristic of the complete form.

However, the fact remains that some patients in the metanalysis showed no *SRY* mutations. Although the etiologies for these patients could not be ascertained, McElreavey et al. (1996) reported a case that showed a cryptic and interstitial deletion upstream of *SRY* (i.e., outside the *SRY*-ORF region), and Kwok et al. (1996) included a case with a single-base variant upstream of *SRY*. There-

fore, as with other complete-form etiologies, it is possible that the aberrations were present in the *SRY* activator-binding or promoter regions.

As shown in Table 3, the complete form can be induced by various *SRY* point mutations. However, the incomplete form is more likely to be induced by *SRY* missense mutations outside the HMG-box region (Domenice et al. 1998). Moreover, the Val60GTG→AlaGCG missense mutation in the *SRY* HMG box (shown to be not a polymorphism but a mutation after analysis of 200 normal males) was identified in a true hermaphrodite whose one gonad was an ovotestis (Hiort and Klauber 1995). Therefore, it is possible that variations in gonadal morphology and phenotype may be due to residual bioactivity of the substituted *SRY* protein, so that the entire *SRY*-ORF should be analyzed to determine the etiologies of XY gonadal dysgenesis or true hermaphroditism.

The results of the metanalysis concerning the relationship between *SRY* aberrations and gonadal tumor formation (Table 3) showed that benign and malignant gonadal tumors were observed in 21 out of 40 (52.5%) patients with *SRY* abnormalities. In light of this high incidence, it is possible that aberrant SRY proteins are involved in gonadal tumor formation in XY gonadal dysgenesis. However, Page (1987), who hypothesized the presence of a locus *GBY* (gonadoblastoma locus on the Y chromosome), predicted that the gene encoded by the *GBY* locus would function normally in the testis but act as an oncogene only in the dysgenetic gonad. Until now, the *GBY* locus has been mapped to the small pericentric region (1–2 Mb of DNA). Five genes (amelogenin Y, RNA-binding Y, protein kinase Y, protein tyrosine phosphatase-related Y, and testis-specific protein Y-encoded) residing on that small region are candidates for *GBY* (Vogt et al. 1997; Lahn and Page 1997; Lau and Zhang 2000). A patient with an idic(Y)(q11.23) karyotype that preserved the critical region of *GBY* showed gonadoblastoma formation (Giltay et al. 2001), supporting the interpretation of *GBY* as an oncogene that affects gonadal tumor formation.

The incidence of gonadoblastoma formation increases with age in XY sex reversal patients (Manuel et al. 1976). Indeed, as shown in Table 3, in the two familial cases with *SRY* point mutations, the older patients exhibited gonadal tumors whereas the younger patients did not (Tajima et al. 1994; Schmitt-Ney et al. 1995). As neoplastic initiation may be induced by multiple mutations of related genes (Knudson 1971, 1972), it has been hypothesized that mutations in oncogenes, tumor suppressor genes, or DNA repair genes accumulate with age and then induce tumor formation as well as other neoplasms in the streak gonads. It has been shown that although *SRY* plays a role in gonadal development, the target genes for the SRY protein remain unclear. Of the six patients that we studied, malignant dysgerminoma lesions were observed in two patients (15 and 22 years old), both with aberrant *SRY*, but no tumor formation was observed in the two older patients (22 and 33 years old) with normal *SRY*. On the basis of these results, it appears that patients with *SRY* aberrations have a greater risk for gonadal tumor formation than patients without *SRY* aberrations. Therefore, as *SRY* may function as an oncogene as well as *GBY*, it is recommended that clinicians carefully examine and observe the gonads of patients with *SRY* aberrations.

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