

## Original Article

# Extreme Tall Stature in a Japanese Boy with a 48,XXYY Karyotype

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**Abstract.** We report an 18-yr-old Japanese boy with a 48,XXYY karyotype and extreme tall stature (194 cm). A GnRH test at 12.5 yr of age showed hypergonadotropism (LH, 4.2→72.2 mIU/mL; FSH, 28.9→61.7 mIU/mL), and an hCG test at 15.5 yr of age revealed a normal testosterone response (1.67→4.08 ng/mL). The tall stature is remarkable, because the mean adult height of Caucasian 48,XXYY patients is 181 cm. Although the underlying factors for the tall stature are unknown, this report indicates an association of the 48,XXYY karyotype with marked tall stature.

**Key words:** 48,XXYY syndrome, hypogonadism, tall stature

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### Introduction

48,XXYY syndrome is considered to be a subtype of Klinefelter's syndrome, and it rarely occurs, with an incidence of one in 25,000–50,000 persons, in contrast to the incidence of Klinefelter's syndrome with the XXY karyotype of one in 1,000 (1, 2). The tendency of a tall stature in patients with 48,XXYY syndrome compared to XXY patients has been reported (3). We report a patient with 48,XXYY syndrome, leading to a tall stature.

### Case Report

The patient was born after Caesarian section at 41 wk of gestation. There was no remarkable familial history, and the patient's sister, who is

2 yr younger, is healthy. The parents are unrelated. At the patient's birth, his father and mother were both 29 yr old, and their heights were 173 cm and 160 cm, respectively (target height: 173 cm). Mild developmental retardation had been noted since infancy, and his IQ tested at 4 yr of age was 70. The patient had been tall since infancy. The growth chart of the patient is shown in Fig. 1. Since the height was +3SD at 8 yr of age, a chromosomal test was performed, and 48,XXYY was identified (Fig. 2). Blood test findings at that time were: IGF-1, 192 ng/ml (normal range 150–448); TSH, 3.0  $\mu$ U/ml (0.4–4.7); T3, 160 ng/dl (70–190); T4, 10.1  $\mu$ g/dl (5.8–12.8); and testosterone, <0.1 mg/ml. The bone age measured by the TW2 method standardized for Japanese was 6.0 yr. A GnRH test was performed at 12 yr and 6 mo of age, and an exaggerated response was noted (Table 1). The patient did not consult thereafter, and his height reached 190 cm at 15 yr and 6 mo of age. Since the patient did not desire any further increase in height, he re-visited our clinic. His facial complexion was not peculiar, and

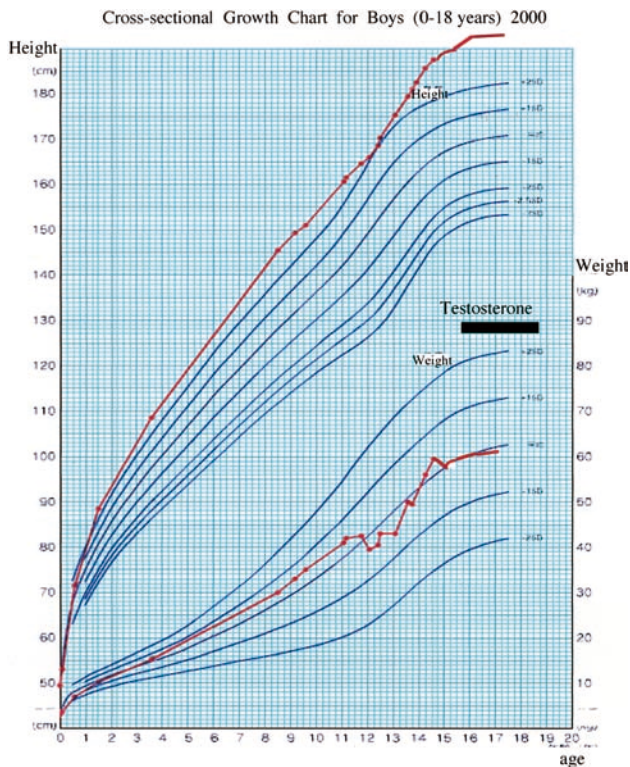
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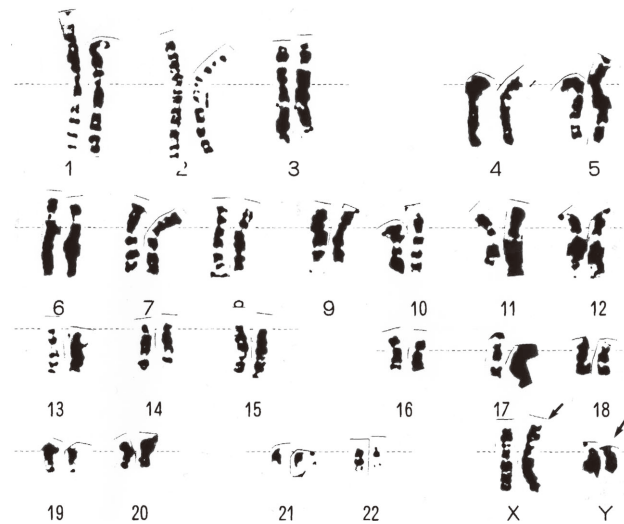
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**Fig. 1** Growth curve of the patient. Stature was maintained in the range of +3SD.

arachnodactyly, flatfeet and gynecomastia were present, but radioulnar synostosis was absent. His testicular volume was 4 ml and penile length, 6 cm with female distribution of pubic hair, Tanner stage IV. The endocrinological findings on this visit are shown in Table 2. The bone age measured by the TW2 method standardized for Japanese was 14.0 yr. Although the hCG test showed normal response (testosterone levels increased from 1.67 ng/ml to 4.08 ng/ml), and the pubertal growth spurt occurred at a normal age, a diagnosis of primary hypogonadism was made based on high gonadotropin and low testosterone levels at basal conditions as well as small testes. Thus, testosterone therapy was initiated with a dose of 50 mg depot testosterone enanthate per month, followed by stepwise elevation to 250 mg per month in 10 mo, and this dose was maintained. At 17 yr of age, the epiphyseal line had closed; the patient's adult



**Fig. 2** Chromosomal analysis (G-banding) (Peripheral blood, 30 cells).

height was 194 cm, and his body weight was 60 kg. Other measurements were arm span, 195 cm; arm length, 89 cm; leg length, 109 cm (upper segment/lower segment ratio=0.82); sitting height, 99 cm; testicular volume, 3 ml; penile length, 9 cm; and pubic hair, Tanner stage V.

## Discussion

48,XXYY syndrome is considered to be a subtype of Klinefelter's syndrome (4), and was first reported by Muldal in 1967 (5). Conjunction of an XX egg and YY sperm, and a normal egg and XYY sperm, and non-disjunction in cell division after fertilization are considered to be the developmental mechanism (1), and the incidence is very low, one in 25,000–50,000 persons. Its presence is identified in most cases on observing tall stature and hypogonadism in adulthood, and hypotonia, developmental retardation and male pseudohermaphroditism in infancy. In this patient, mild developmental retardation had been noted since infancy, but the abnormality was discovered on observing the tall stature.

Primary hypogonadism and tall stature are

**Table 1** GnRH stimulation test (LH-RH 100  $\mu$ g iv) (12 yr 6 mo)

Time (min)	0	15	30	45	60	90	120
LH (mIU/ml)	4.2	55.2	72.2	67.5	56.3	43.8	33.8
FSH (mIU/ml)	28.9	51.0	58.6	61.7	60.4	50.0	49.8

**Table 2** Hormonal laboratory data (15 yr 6 mo)

Serum-hormone	Unit	Present case	Normal range
IGF-1	ng/ml	604	250–680
LH	mIU/ml	14.3	0.6–4.1
FSH	mIU/ml	52.1	2.9–10.2
E <sub>2</sub>	pg/ml	<10	20–60
T	ng/ml	1.37	2.01–7.50
GH	ng/ml	0.15	<1.46
ACTH	pg/ml	64	7–56
Cortisol	$\mu$ g/dl	15.8	4.0–23.3
Prolactin	ng/ml	14.94	3.58–12.78
TSH	$\mu$ U/ml	1.47	0.436–3.78
fT3	pg/ml	1.6	2.1–4.1
fT4	ng/dl	1.6	1.0–1.7
DHEA-S	$\mu$ g/dl	120	130–519
17-OHCS (spot)	mg/l	8.1	
17-KS (spot)	mg/l	12.8	
PRA	ng/ml/h	1.0	0.2–3.9
Aldosterone	ng/dl	9.6	3–21
BMD (DEXA, L2-L4)	g/cm <sup>2</sup>	0.742	

the main features of 48,XXYY patients as well as Klinefelter patients with XXY karyotype. Concerning hypogonadism, androgen deficiency is often more severe than that in XXY patients. In 48,XXYY patients, as well as XXY patients, there is no spermatogenesis, and Leydig cell dysfunctions are also observed. Testicular histology is similar to that of XXY patients, demonstrating hyperplasia of the interstitial cells, tubular atrophy, absence of spermatogenesis, and peritubular fibrosis (6). In most 48,XXYY patients, both in adults and at prepubertal ages, LH response to LH-RH and basal FSH levels are elevated (7). In this patient, at 12 yr and 6 yr old, the basal plasma LH level was slightly elevated, and excess LH response to LH-RH was observed. FSH showed marked elevation both

in the basal level and in the response to LH-RH. The LH to FSH ratio was below 1.0 as seen in the XXY patients (8). Responses to the hCG stimulation test have often shown a low response in previously reported 48,XXYY cases. In this case, the response to the hCG test at 15 yr and 6 mo was normal, but a low basal testosterone level and small testes were observed. Thus, a diagnosis of primary hypogonadism was made, and testosterone therapy was initiated.

With regard to the tall stature, 48,XXYY patients are taller than XXY patients. According to William's Textbook of Endocrinology, the mean height is 180 cm in cases of XXY Klinefelter's syndrome, and 181 cm in XXYY cases (9). The presence of 4 copies of the SHOX gene, 2 copies of the Y-specific growth gene are considered to

be the underlying causes of the tall stature. The SHOX gene was identified in 1988 (10), and an increase in its copy number is considered to induce tall stature. The Y-specific growth gene is assumed to be present on the Y chromosome, and its presence is considered to increase height by about 9 cm (11). This patient became very tall (194 cm) in adulthood. To our knowledge, 182.5 cm is the tallest Japanese patient reported among previous 48,XXYY cases (12), and we considered the mechanism underlying this patient's tall stature involves two factors. One is his parents' tall stature. His target height was estimated as 173 cm, which is relatively taller than the Japanese standard height for adult males. The other is partial testosterone secretion in this patient. At 15 yr of age, the basal testosterone level was 1.67 ng/ml, and it was suspected that the partial secretion of testosterone induced the pubertal growth spurt at the normal age, but bone age progressed slowly. Thus, his growth persisted continuously, the epiphyseal line did not close, and his height reached 190 cm at 15 yr of age.

Radioulnal synostosis, thrombophlebitis, lower limb ulcer, and diabetes have been reported to be complications of 48,XXYY syndrome. These were absent in this patient, but right carotid arterial stenosis and hyperuricemia are currently present, and being carefully managed.

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