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Case Report

45,X/46,X,psu idic(Y)(q11.2) in a phenotypically normal male with short stature: a case report

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Abstract. We report a case of 15-yr-old phenotypically normal male with short stature associated with the chromosomal abnormalities of 46,X,psu idic(Y)(q11.2)/45,X. At 3 yr of age, he underwent urethroplasty for scrotal hypospadias. At 15 yr of age, he was referred to our hospital due to short stature (–3.71 SD). The results of blood examination were mostly normal. A radiological examination revealed his bone age was 15.7 yr (based on the TW2-RUS method). Chromosome analysis of peripheral lymphocytes revealed 46,X,psu idic(Y)(q11.2)[16]/45,X[14], and array comparative genomic hybridization (aCGH) showed a large deletion of Yq which was located distal to the Y chromosome growth-control gene (*GCY*) region. It is likely that these structural abnormalities in the Y chromosome were responsible for the short stature. This case might provide new insights regarding *GCY* and emphasizes the importance of chromosome analysis in not only females but also males with short stature, especially when associated with genital anomalies.

Key words: short stature, 46,X, psu idic(Y)(q11.2)/45,X,idic(Y), Y chromosome deletion, growth-control gene

Introduction

Symptoms associated with abnormalities in sex chromosome mosaicism vary widely between individuals. Isodicentric Y chromosome [idic(Y)] is a common Y chromosomal abnormality. Palindromic sequences on the Y chromosome are associated with the occurrence of idic(Y) (1). Patients with idic(Y) often exhibits disorders of sexual development (DSD) and infertility, as the Y chromosome contains the sex-determining region of the Y chromosome (SRY) and many spermatogenesis genes. Idic(Y) is genetically unstable, so most patients have a higher percentage of 45,X, resulting in a female phenotype, such as Turner syndrome (2). Herein, we describe the case of a normal male with a normal phenotype and short stature, with the karyotype of 46,X,psu idic(Y)(q11.2)/45,X and discuss the mechanisms underlying short stature in this sex chromosome mosaicism.

Case Report

The patient was delivered at the gestational age of 38 w 2 d without asphyxia by elective repeat cesarean section. His birth weight, height and occipitofrontal circumference were 2,430 g (–1.60 SD), 45.0 cm (–1.62 SD), and 30.5 cm (–1.88 SD), respectively. He had scrotal hypospadias without bifid scrotum and cryptorchidism, and his Quigley scale grade was 2 at birth. Thus, he underwent urethroplasty using a free graft at the age of 3 yr. A testicular biopsy was not performed, so the histopathological findings of the testes are unknown. Otherwise, he was healthy. He was referred to our outpatient clinic at 15 yr old because of short stature. His height was 145.0 cm (–3.71 SD), his body weight was 48.0 kg (**Fig. 1**) and body mass index (BMI) was 22.8 (+ 0.69 SD). The heights of his father and mother were 168 cm and 156 cm, respectively. Pubic hair was Tanner stage 4, and right and left testicular volumes were 15 ml and 8 ml, respectively. Bilateral testicular hardness was normal. He had no bifid scrotum and cryptorchidism, and his Quigley scale grade was 2 at that time. He did not present Turner features. Routine laboratory tests, and serum levels of thyroid hormone, IGF-1, LH, FSH and testosterone were within normal ranges (**Table 1**). A radiological examination revealed his bone age was 15.7 yr (based on the TW2-RUS method). Based on the blood tests and radiological

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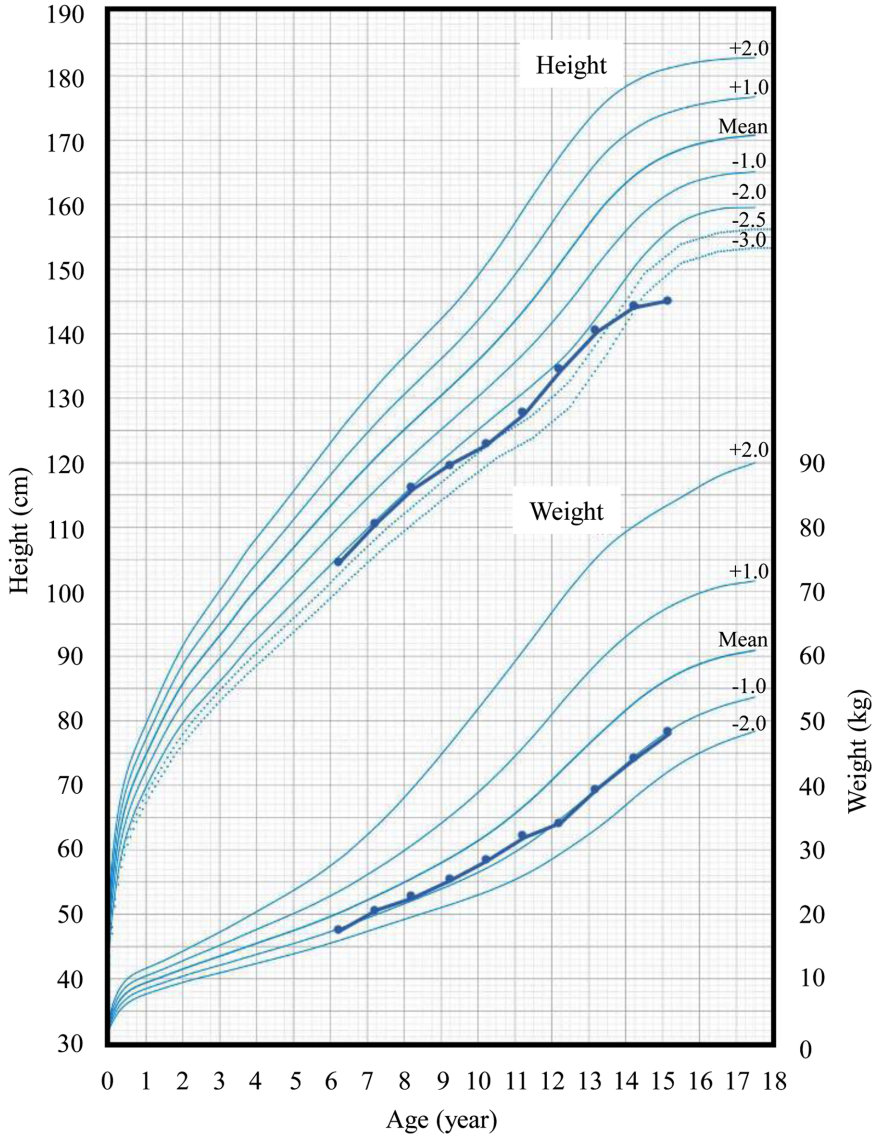

Fig. 1. Growth charts of the patient. The height and weight data of the patient are plotted on the Japanese standard growth charts for normal boys in 2000. The upper chart shows height, and the lower chart shows weight. The curves depict +2.0 SD, +1.0 SD, Mean, –1.0 SD, –2.0 SD, –2.5 SD, and –3.0 SD of stature values.

Table 1. Laboratory findings

Hematology	Value	Unit	Biochemistry	Value	Unit	Endocrine	Value	Unit	Normal Range
WBC	5,600	/μL	TP	7.5	g/dL	TSH	1.389	μIU/mL	(0.350–4.940)
Neutro	51.2	%	Alb	4.8	g/dL	FT3	2.47	pg/mL	(1.71–3.71)
Eosino	0.0	%	BUN	11.2	mg/dL	FT4	1.15	ng/dL	(0.70–1.48)
Hb	15.6	g/dL	Cre	0.77	mg/dL	IGF-1	347	mg/dL	(141–552)
RBC	576	$\times 10^4$/μL	Na	139	mEq/L	LH	5.76	mIU/mL	
Hct	48.9	%	K	4.4	mEq/L	FSH	12.6	mIU/mL	
Plt	29.3	$\times 10^4$/μL	Cl	101	mEq/L	Testosterone	5.83	ng/mL	
			Ca	10.3	mg/dL				
			P	3.8	mg/dL				
			AST	23	IU/L				
			ALT	13	IU/L				
			ALP	495	IU/L				

WBC, white blood cell; Neutro, neutrophil; Eosino, eosinophil; Hb, hemoglobin; RBC, red blood cell; Hct, hematocrit; Plt, platelets; TP, total protein; Alb, albumin; BUN, blood urea nitrogen; Cre, creatinine; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; TSH, thyroid-stimulating hormone; FT3, free tri-iodotyronine; FT4, free thyroxine; Na, sodium; K, potassium; Cl, chloride; Ca, calcium; P, phosphorus.

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findings, we considered that there was no treatment to improve his height. However, his mother requested further examinations, thus a chromosome examination was performed. Chromosome analysis of peripheral blood revealed that lymphocytes had an pseudoisodicentric Y chromosome with a breakpoint at q11.2 and were monosomic X or had one X chromosome, which were in the percentage of 46,X,psu idic(Y)(q11.2)[16]/45,X[14]. Molecular cytogenetic analysis was performed upon receiving written informed consent. Array comparative genomic hybridization was performed using the Human CGH Microarray (Agilent Technologies, Santa Clara, CA, USA). This revealed a large deletion in Yq and the genomic region between the 2-copy region and the deleted region had about half the copy number of the 2-copy region (**Fig. 2**).

Discussion

The present case exhibited extreme short stature, which is likely due to the karyotype of 46,X,psu idic(Y)(q11.2)/45,X. Structural abnormalities in the Y chromosome cause short stature. A female with 46,X, psu idic(Y)(q11.2)/45,X was previously reported to have short stature (3). The Y chromosome contains about 70 key genes such as the sex-determining gene *SRY* and spermatogenesis genes (4). However, some males often have structural abnormalities of the Y chromosome, such as deletions, inversions, and idic(Y) (2). The phenotypes associated with mosaicism of sex chromosomes that have Y chromosome structural abnormalities vary widely, ranging from Turner syndrome to male infertility (5). The Y chromosome contains many palindromic sequences. Since these palindromes are composed of mutually identical base sequences, they may form loop-shaped structures around the point of symmetry. Thus, non-allelic homologous recombination on the same chromosome can occur (6). In addition, it has been reported that idic(Y) may be generated from postzygotic cells via palindrome-mediated crossover (7). In our case, about half of the 2-copy region contained palindromes, and we suggest that the abnormal Y chromosome idic(Y)(q11.2) was generated by non-allelic homologous recombination of palindromic regions (**Fig. 3**). If the short stature in the present case is due to this chromosomal abnormality, there are two possible mechanisms. First, the short stature could be caused by the high ratio of 45,X, resulting in low SHOX copy number in the growth plate cartilage. SHOX protein is specifically expressed in hypertrophic chondrocytes of the growth plate, and involved in bone growth and maturation by controlling the differentiation and proliferation of chondrocytes (8). Deletion of the *SHOX* gene has been reported to cause growth disorders in idiopathic short stature and Turner syndrome (9). Second, a growth-related gene might exist in the deleted part of Yq, and a loss of this gene might be responsible for the short stature in the present case. The Y chromosome growth-control gene (*GCY*) region is supposed to be in the proximal Yq region between the microsatellite markers DYS11 and DYS246 (10, 11). However, the Yq deletion detected in the present case is located distal to the *GCY* region, suggesting that other candidate genes associated with growth might exist on Yq. Further studies are needed to elucidate the mechanism of short stature in the patients with 46,X,psu idic(Y)(q11.2)/45,X.

Detailed cytogenetic investigations regarding the short stature in the present case revealed the 46,X,psu idic(Y)(q11.2)/45,X chromosomal abnormality. This karyotype is often accompanied by genital anomalies, such as clitoromegaly and hypospadias (3, 12). In the clinical setting, we usually perform chromosome analysis to exclude Turner syndrome in females with short stature, but not males (13). We should consider chromosome analysis for males with short stature, especially if accompanied by genital anomalies, even for mild cases with a Quigley scale of grade 2 without bifid scrotum and cryptorchidism. The present patient was a phenotypically normal male, thus it is likely that there were enough SRY-containing cells in his testis, even though we did not examine his gonadal karyotype. SRY plays a critical role in male differentiation. The SRY-Box

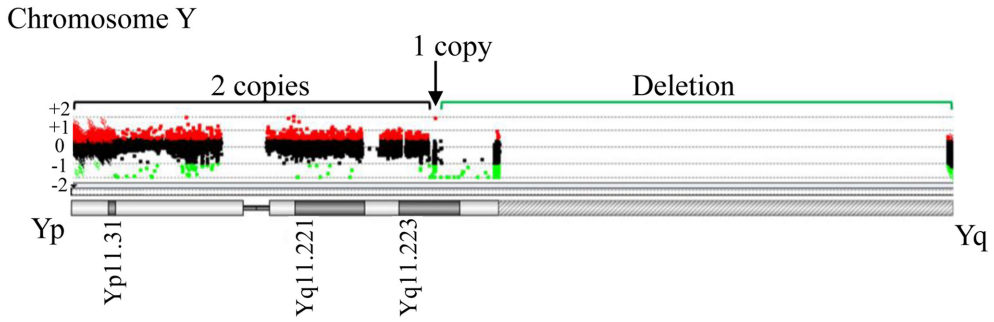

Fig. 2. Array comparative genomic hybridization analysis of the patient chromosome Y in peripheral blood. Black, red, and green dots indicate normal copy-number, increased copy-number ($\log_2$ signal ratio > +0.5), and decreased copy-number ($\log_2$ signal ratio < –1.0), respectively. The segments indicated by black and green lines represent the 2-copy region (2 copies) and the deleted region (Deletion), respectively. About half the copy number of the 2-copy region is located between the 2-copy region and the deleted region.

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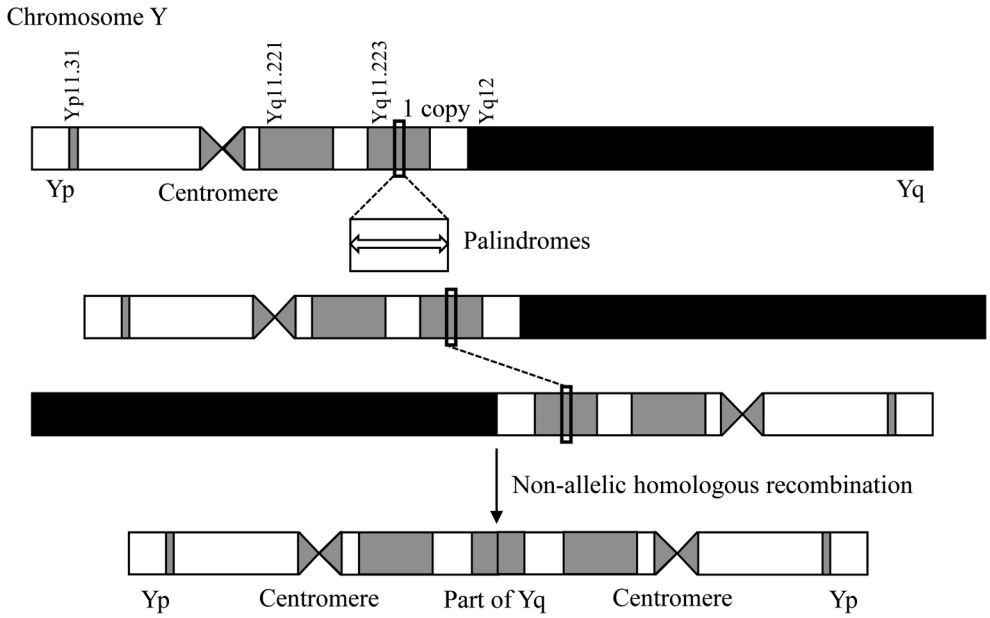

Fig. 3. A schematic representation of the mechanism of the Y chromosome structural abnormality in the patient.

Transcription factor 9 gene (*Sox9*), which is downstream of *SRY*, induces male differentiation via anti-Müllerian hormone. A patient with the same mosaicism in the gonads was a phenotypical female with clitoromegaly and separate urethral and vaginal orifices (3). Her right gonad (ovotestis) had about 30% of idic(Y) cells, but her left gonad (streak gonad) had no idic(Y) cells, only 45,X cells (3). The present case showed a difference between the sizes of the right and left testes. It is possible that the left testes, which was smaller than the right testis, had fewer idic(Y) cells.

In conclusion, we report a case with 46,X,psu idic(Y)(q11.2)/45,X, exhibiting a phenotypically normal male with short stature. The short stature is likely to be associated with this mosaicism, but the detailed mechanisms remain to be elucidated. Furthermore, chromosome analysis should be considered for males with short stature, especially if accompanied by genital anomalies.

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