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Case Report

A rare case of Turner syndrome with a special karyotype: a case report and review of literature

Linqi Chen, Hui Sun, Haiying Wu, Ting Chen, Fengyun Wang, Rongrong Xie, Xiuli Chen, Jianmei Tian

Department of Endocrine and Genetic Metabolism, Children's Hospital of Soochow University, Jiangsu, PR China

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Abstract: Turner syndrome is a chromosomal abnormality. The majority of patients show monosomy of chromosome X (45, X), while a small number of patients present (45, X/47, XXX) karyotype. The present paper reported an extremely rare case of Turner syndrome with a special karyotype of 46, X, rea (X) (qter-->q22.3::p11.23-->qter). The female patients had some typical characteristics of Turner syndrome, including short stature, cubitus valgus, left toe brachydactylia, underdeveloped breasts and so on. The ultrasound examination showed a small-sized uterus and bilateral ovaries in patients. Oral glucose tolerance test (OGTT) presented impaired glucose tolerance. Growth hormone stimulation assay revealed growth hormone deficiency. G-banding chromosome analysis indicated normal 46, XX. And FISH with locus specific probed for sex chromosome further confirmed 100% XX. Unexpectedly, high-throughput sequencing indicated an abnormal female karyotype. There were a 45.04 Mb deletion in Xp22.33p11.23, a 47.16 Mb repeated fragment in Xq22.3q28, and a 0.68 Mb repeated fragment in 3p12.3. Then, the comparative genomic hybridization assay was performed and it further confirmed the abnormal molecular karyotype.

Keywords: Turner syndrome, karyotype, high-throughput sequencing

Introduction

Turner syndrome (TS) is one of the most common sex chromosome disorders, affecting one in 2,000 to 5,000 female live-births [1, 2]. Patients with Turner syndrome have some symptoms such as short stature, gonadal failure, broad chest, low hair-line, low-set ears, a webbed neck, and failure or delay in developing secondary sexual characteristics [3]. The degree which patients are affected is determined by the specific chromosomal abnormality: they may have only a few features associated with the syndrome, but short stature and infertility always exist [4]. Female patients not receiving treatment showed approximately 18-20 cm shorter than that of general population [5-8]. Medical problems related with Turner syndrome include congenital heart disease, hypothyroidism, diabetes, vision and hearing problems, cognitive deficits and autoimmune diseases.

It was reported that TS was caused by numeric or structural abnormalities of the X chromosome, including monosomy of the X-chromosome or other X-chromosome abnormalities such as rings, deletions, isochromosomes and mosaicisms [9]. The karyotypes are nonmosaic or mosaic, including 45, X, 46, X, del (Xp), 46, X, i(Xq), 45, X/46, XX, 45, X/46, XrX, 45, X/46, XY, 45, X/47, XXX. Among them, 45, X karyotypes is a classical type in the majority of patients. In the present report, we reported a rare case of Turner syndrome with a special karyotype (46, X, rea (X) (qter-->q22.3::p11.23-->qter)).

Case report

The patient is a 13-year-old girl who has been referred to our unit for evaluation of short stature in August 2010. During physical examination, it was observed that she had a short stature (136.8 cm, >-3SD), multiple facial moles, cubitus valgus, left toe brachydactylia, broad chest and underdeveloped breasts. Besides, she had no webbing on the neck, poorly developed secondary sexual characters and weighed 45 kg (BMI 24.0 kg/m^2) (**Figure 1**). She was introverted with a poor academic performance. Under laboratory examination, the bone aged 12 years old. Ultrasonography analysis revealed

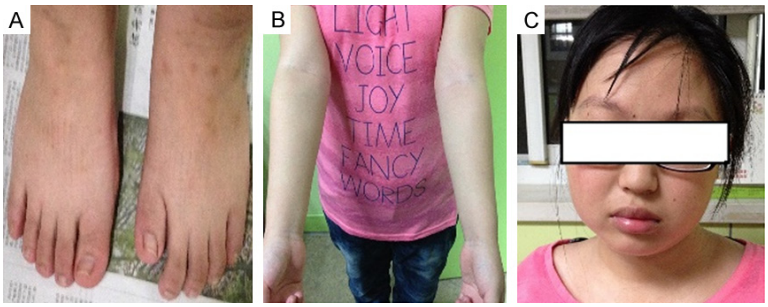

Figure 1. Special characteristics of the patient on physical examination. (A) left toe brachydactylia (B) cubitus valgus (C) multiple facial moles.

Table 1. LHRH stimulation test

	0 h	0.5 h	1 h	1.5 h
FSH (mIU/ml)	60.60	104.53	96.81	102.45
LH (mIU/ml)	15.93	81.34	63.22	47.13

Table 2. Growth hormone stimulation test

Stimulator	Growth hormone (μg/L)				
	0 h	0.5 h	1 h	1.5 h	2 h
Arginine	0.05	1.58	2.58	3.27	3.20
Levodopa	0.04	1.25	1.84	1.78	1.02

Table 3. LHRH stimulation test

	0 h	0.5 h	1 h	1.5 h
FSH (mIU/ml)	47.54	48.51	67.59	62.72
LH (mIU/ml)	10.35	29.44	35.54	30.93

a small-sized uterus (18*11*7 mm^3) and bilateral ovaries (the left: 13*11 mm^2, the right: 14*8 mm^2). The biochemical analysis for glutamic-pyruvic transaminase (GPT) (119.5 U/L), glutamic-oxaloacetic transaminase (GOT) (68.1 U/L) and uric acid (UA) (399.1 μmol/L) were performed. Moreover, 2 h glucose tolerance test revealed that the levels of blood glucose (9.40 mmol/L), insulin (127.81 mU/L) and serum C-peptide (6.74 ng/mL) were high. During hormone examination, there was high level of TSH (5.74 UIu/ml), while the levels of FT3 (3.52 pg/ml) and FT4 (1.22 ng/dl) were normal. In addition, the levels of Estradiol (E2) (48.57 pg/mL), Testosterone (T) (29.95 ng/dL) and PRL (13.12 ng/mL) were high, and the level of IGF-1 (250 ng/ml) was low. LHRH stimulation testing showed abnormal gonadotropic hormones, the levels of follicle-stimulating hormone level (FSH) and uteinizing hormone level (LH) were high at different time points of baseline (0.5 h, 1 h, and 1.5 h post-stimulation) (**Table 1**). Additionally, the levels of growth hormone were low at baseline, 0.5 h, 1 h, 1.5 h, and 2 h by stimulation with either arginine or levodopa (**Table 2**). The patient was given a diagnosis of growth hormone deficiency, gonadal dysgenesis, and impaired glucose tolerance. The cytogenetics with G-banding chromosome analysis of peripheral blood lymphocytes (PBL) was conducted and indicated a normal 46 XX.

The second patient at the age of 17 has been admitted to our department in August 2014. She was 144 cm (>-3SD) and 62 kg (BMI 24.9 kg/m^2). The patient hadn't experienced menarche throughout her life. The evaluation of bone age revealed a basic healing of epiphysis. Ultrasound examinations showed the uterus and the two ovaries were small size (uterus: 20*15*5 mm^3, the left ovary: 18*11 mm^2, the right ovary: 15*10 mm^2). Under biochemical examination, abnormal liver function, the serum level of GOT, total cholesterol, Triglyceride, UA, and IGF-1 were performed. Oral glucose tolerance test (OGTT), and increased 2 h postprandial blood glucose was conducted. The high levels of FSH and LH at different time points after stimulation were observed at the second LHRH stimulation testing (**Table 3**). The patient was diagnosed with Turner syndrome, metabolic syndrome, and type 2 diabetes.

The molecular cytogenetics with fluorescence in situ hybridization (FISH) analysis of sex chromosome showed 100% XX (**Figure 2**). The high throughput sequencing (HTS) was carried out for molecular karyotyping. An abnormal female karyotype with duplication and deletion in the X-chromosome was found (**Figure 3**). Detailed analysis indicated there was a 45.04 Mb deletion in Xp22.33-p11.23 (2700001-47740000), a 47.16 Mb repeated fragment in Xq22.3q28 (107780001-154940000)*3, and a 0.68 Mb repeated fragment in 3p12.3 (75280001-75960000)*3. A repetitive G-banding chromosome analysis showed 46 XX. The array comparative genomic hybridization (aCGH) revealed an abnormal female patient (**Figure 4**). There was a 47.74 Mb deletion in Xp22.33p11.23

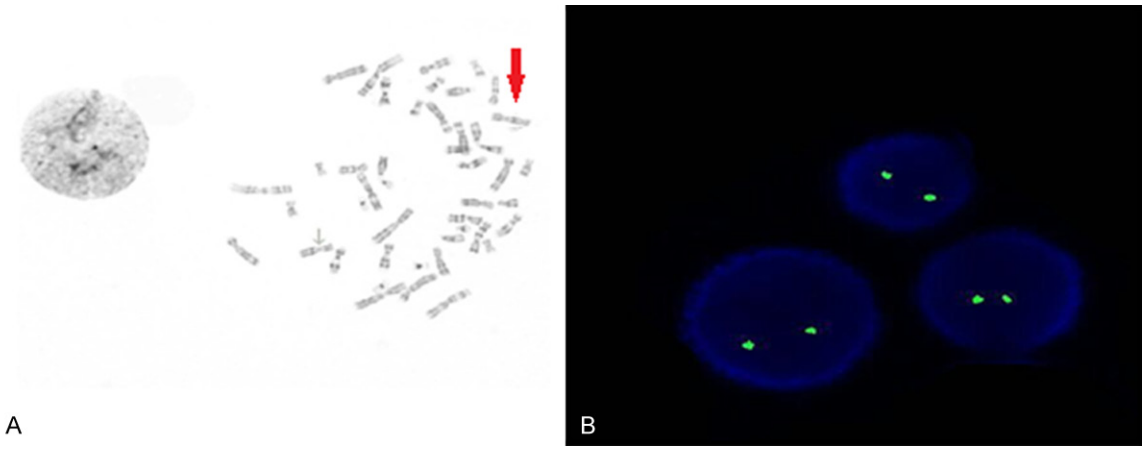

Figure 2. Conventional and molecular cytogenetics. (A) G-banding chromosome analysis, red arrow indicates the X-chromosome, (B) FISH analysis of sex chromosome, bright green indicates the centromere of the X-chromosome.

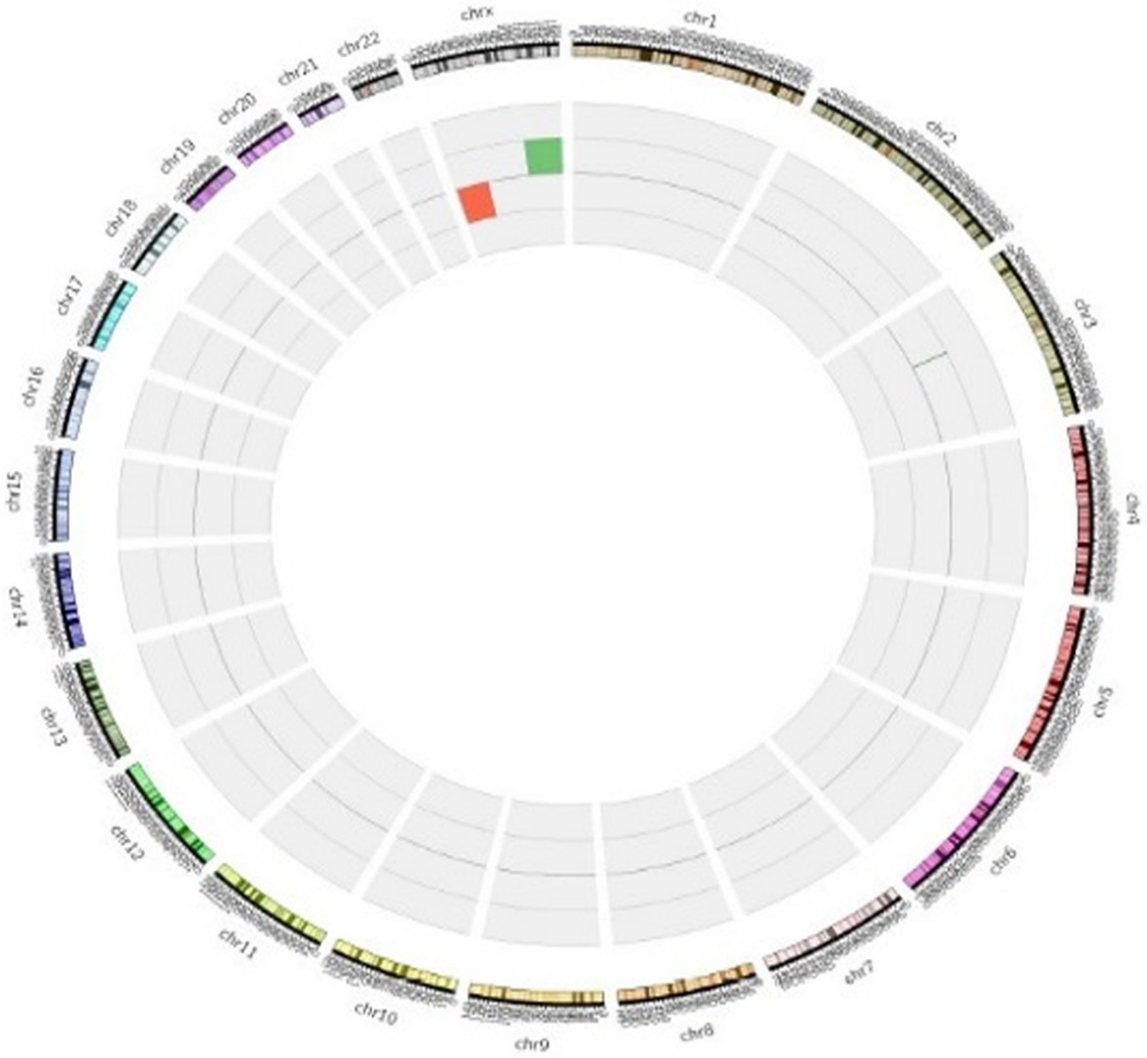

Figure 3. molecular karyotyping with high throughput deep sequencing. Square regions in color indicate alteration locus, red region indicates deletion in the X-chromosome, green indicates duplication in the X-chromosome.

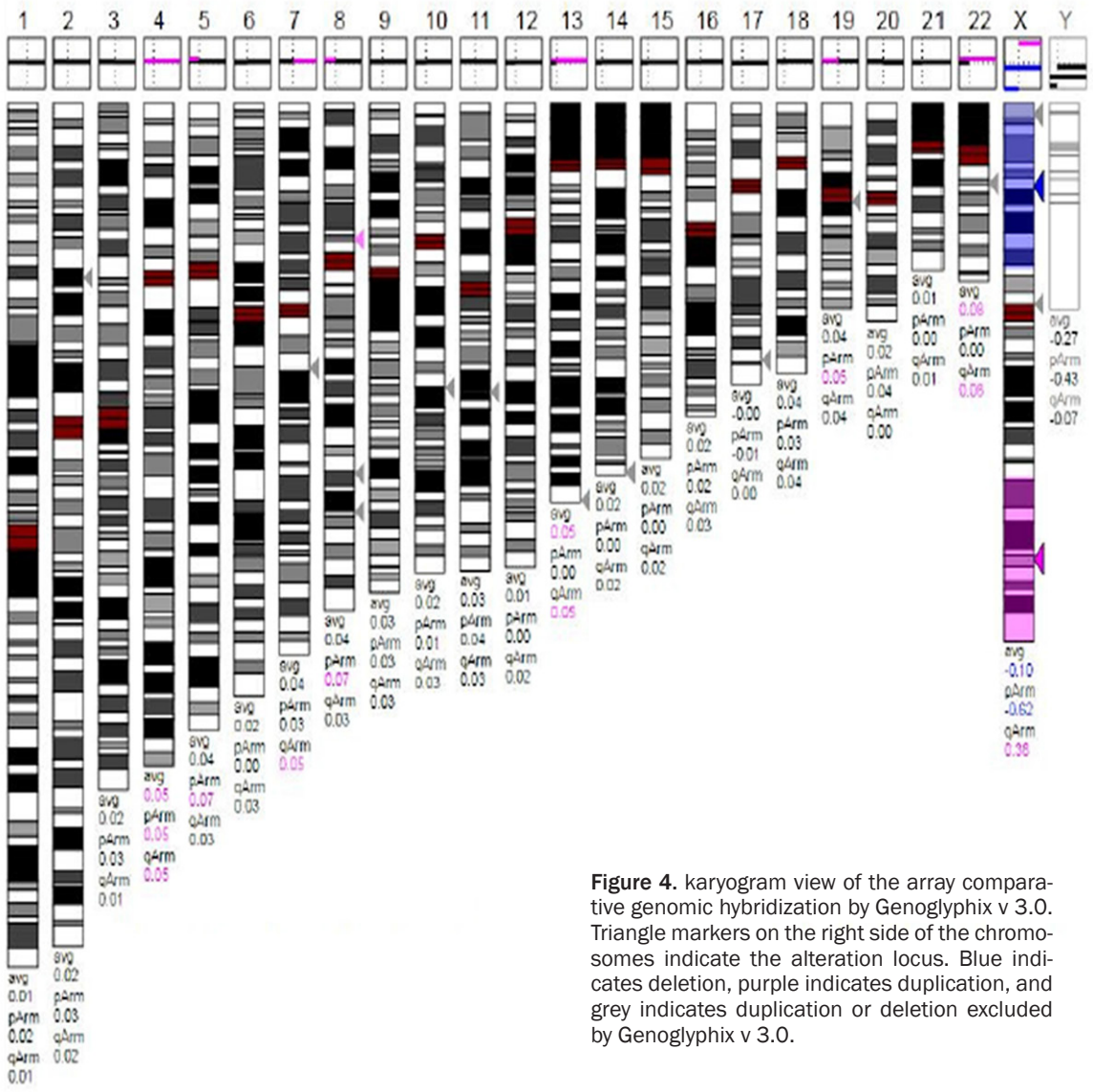

Figure 4. karyogram view of the array comparative genomic hybridization by Genoglyphix v 3.0. Triangle markers on the right side of the chromosomes indicate the alteration locus. Blue indicates deletion, purple indicates duplication, and grey indicates duplication or deletion excluded by Genoglyphix v 3.0.

(296520-47741780), and a 47.41 Mb repeated fragment in Xq22.3q28 (107815321-155228049)*3, which was nearly in accordance with the results of high throughput sequencing. The karyotype was identified as 46, X, rea(X) (qter-->q22.3: :p11.23-->qter).

Discussion

Turner syndrome (TS), also known as primary gonadal dysgenesis occurs as a result of partial or complete absence of an X-chromosome. Patients with Turner syndrome are featured with short stature and gonadal dysgenesis. The typical physical manifestations include webbed neck, swollen hand and foot, cubitus valgus, short metacarpal and visceral malformations. Apart from these, the incidence of metabolic disturbance in Turner patients was higher than that of normal children, and the incidence of type 2 diabetes in Turner patients was 4-fold as many as that of normal children [10]. In the current report, the female patient presented some typical features of Turner syndrome, including short statue, bone deformity and gonadal dysgenesis. The metabolic diseases were also presented [11-13].

G-banding chromosome analysis is widely used for karyotyping of Turner syndrome due to the low cost and high feasibility. However, in this study, G-banding chromosome analysis failed to detect any abnormality in the X-chromosome of female Turner patient. Furthermore, FISH

assay indicated 100% XX, because G-banding analysis could not detect the derived chromosome. HTS and aCGH analysis indicated the abnormal molecular karyotype of the X-chromosome. HTS revealed there was a 45.04 Mb deletion in Xp22.33p11.23, a 47.16 Mb repeated fragment in Xq22.3q28, and a 0.68 Mb repeated fragment in 3p12.3. And aCGH indicated that there was a 47.74 Mb deletion in Xp22.33p11.23, and a 47.41 Mb repeated fragment in Xq22.3q28. Based on these results, we speculated that rearrangement occurred in the two sites of the X-chromosome, leading to the formation of a derived chromosome. And the size of the deleted fragment was very similar with that of the duplication, which may cause the detection failure by using G-banding analysis and FISH. Then, the female patient was diagnosed with Turner syndrome with a special karyotype of 46, X, rea(X) (qter-->q22.3::p11.23-->qter). So far, it is firstly report this special karyotype of Turner syndrome.

Warburton and his colleagues have indicated that the chromosome rearrangement was closely related with the large, highly homologous inverted repeats (IRs) in the X-chromosome [14]. Of these IRs, ~25% occurred on the X-chromosome, although it represents only 5% of the genome [14]. In 2000, Giglio et al reported four cases of Turner syndrome with the rearrangement in Xp11.23 breakpoint [15], which was partially in accordance with the findings in our report. In Scott's report, aCGH was performed to investigate the molecular mechanism of idic(X) (p11) formation. The results showed there existed large IRs composed of repetitive gene clusters and segmental duplications on Xp11.2, indicating the rearrangement on Xp11.2 led to isodicentric chromosome formation [16]. It is recognized that most of the chromosome rearrangements have a parental origin, at male meiosis, the X and the Y chromosomes pair at the Xp-Yp pseudoautosomal region but are free for the rest of their length. It has been demonstrated that this configuration favors refolding of the chromosomes into themselves, in turn, leading to intra chromosome synapses and recombination between repeated sequences. In addition, the IRs in the unpaired flexible region (accounting for most region of the X-chromosome) allows for the folding and homologous recombination of chromosomes at male meiosis [15]. Here, we speculated that IRs located at the breakpoints may allow for synapses and recombination between the short arm and the long arm of the X-chromosome at male meiosis, resulting in refolding into itself.

At first, it was believed that the short arm of the X-chromosome was associated with short stature, and the long arm of the X-chromosome was related with ovarian dysgenesis [17]. However, only homeobox gene (*Shox*) deletion in the short arm of the X-chromosome was identified to be associated with the phenotype of short statue. *Shox* gene is located in the pseudoautosomal region 1 (Xp22.3/Yp11.3, OMIM312865) [18-20]. An accumulating studies have provided evidence that the function of *Shox* gene is dose-dependent, which can lead to growth impairment and other physical deformity, including cubitus valgus, short metacarpal and high-arched palate in Turner patients, due to the lack of energy during the escape of the X-chromosome inactivation [20, 21]. Cytogenetic analysis in our study indicated there was a deletion in Xp22.33p11.23 (a region covering the location of *Shox* gene) in the Turner patient. So the results of our study was in accordance with previous findings that the deletion of *Shox* in Xp was associated with the phenotypic short statue. Thus far, other potential genes attributed to the special phenotype of short stature are still unknown.

Other studies have proved that the specific genes on X-chromosome are associated with ovarian dysgenesis [22], among which, *Bmp15* gene (Xp11.22, OMIM300247), *Fmr1* gene (Xq27.3 OMIM309550) and Progesterone Receptor Membrane Component-1 gene (*Pgrmc1,* Xq24 OMIM300435) have been well identified. Our study revealed there was a duplication in Xq22.3q28 (a region covering the location of *Fmr1* gene and *Pgrmc1* gene). So, our study reconfirmed that the alterations in *Fmr1* and *Pgrmc1* were associated with the ovarian dysgenesis. It is well defined that the mutation in *Fmr1* gene is a risk factor associated with premature ovarian failure [23], while, thus far, it is not very clear if the repeats in *Fmr1* gene are associated with ovarian dysgenesis. For the first time, our study indicated that the repeats in *Fmr1* gene may be associated with the ovarian dysgenesis. In human ovarian granulosa cells, a 22-kDa protein (PGRMC1) encoded by

Pgrmc1 gene intermittently associates and dissociates with the mitotic spindle at mitosis, and thereby contributes to ovarian follicular growth. It was expounded that the over-expression of PGRMC1 could disrupt this dynamic interaction with the mitotic spindle and thus slow or inhibit the development of ovarian follicles [24, 25]. Notably, the abnormal phenotypic features caused by dup (Xq) are gender-dependent, males with dup (Xq) often have clinical abnormal features due to the existence of single parent diploid. While, females with dup (Xq) may not present phenotypic abnormalities due to skewed X-chromosome inactivation. Reportedly, the dup(Xq)-associated phenotypic abnormalities in females include short stature, developmental delay, facial dysmorphism, gonadal dysgenesis, etc [26-29]. Among these features, gonadal dysgenesis is not associated with skewed X-chromosome inactivation, because the X-chromosomes can be active in two copies during early embryo stage and at meiosis [30].

Ogata and Matsuo demonstrated that Turner-associated ovarian dysgenesis was the result from pairing failure at meiosis, and the extent of failure was positively related with the extent of ovarian dysgenesis [31]. It was speculated that the size of deletion was associated with the severity and initiation time of the disease, although it was not an independent risk factor [32]. So it is reasonable that Turner patients with small fragment deletion still have menarche period due to the residual ovarian follicles, while may experience a secondary menopause or early menopause. In our report, the unpaired region covered the most region of the Xp of the patient, leading to the failure in developing the secondary sexual characteristics.

To conclude, with the development of HTS and aCGH technology, and its comprehensive application combined with G banding analysis and FISH, it is promising to conduct a more sophisticated study in derived chromosome, which will allow for a detailed elucidation on the association between the genotype and phenotype.

Disclosure of conflict of interest

None.

Address correspondence to: Jianmei Tian, Department of Endocrine and Genetic Metabolism, Children's Hospital of Soochow University, 92# Zhongnan Street, Suzhou Industry Park (SIP), Suzhou 215000, Jiangsu, PR China. Tel: 86-0512-80693588; E-mail: jianmei_tian123@163.com

References

[1] Kaliki Venkata G, Fudge JC, Vyas HV, Bleiweis MS and Chandran A. Hybrid stage 1 palliation in a patient with hypoplastic left heart syndrome and unusual decompressing levoatrial cardinal vein in turner syndrome: utility of multimodality imaging. World J Pediatr Congenit Heart Surg 2016; 7: 375-376.

[2] Faienza MF, Ventura A, Colucci S, Cavallo L, Grano M and Brunetti G. Bone fragility in turner syndrome: mechanisms and prevention strategies. Front Endocrinol (Lausanne) 2016; 7: 34.

[3] Wang S, Yang L, Li J and Mu Y. Concurrent insulinoma with mosaic Turner syndrome: a case report. Exp Ther Med 2015; 9: 801-804.

[4] Reh CS and Geffner ME. Somatotropin in the treatment of growth hormone deficiency and Turner syndrome in pediatric patients: a review. Clin Pharmacol 2010; 2: 111-122.

[5] Bereket A, Turan S, Elcioglu N, Hacihanefioglu S, Memioglu N, Bas F, Bundak R, Darendeliler F, Gunoz H, Saka N, Ercan O, Arslanoglu I, Isguven P, Yildiz M, Can S, Ozerkan E, Coker M, Darcan S, Ozkan B, Orbak Z, Oztas S, Palanduz S, Sezgin I, Atabek E, Erkul I and Erdogan G. Adult height in Turkish patients with Turner syndrome without growth hormone treatment. Turk J Pediatr 2008; 50: 415-417.

[6] Davenport ML. Approach to the patient with Turner syndrome. J Clin Endocrinol Metab 2010; 95: 1487-1495.

[7] Davenport ML. Growth hormone therapy in Turner syndrome. Pediatr Endocrinol Rev 2012; 9 Suppl 2: 723-724.

[8] Los E, Quezada E, Chen Z, Lapidus J and Silberbach M. Pilot study of blood pressure in girls with Turner syndrome: an awareness gap, clinical associations, and new hypotheses. Hypertension 2016; 68: 133-136.

[9] Larizza D, Calcaterra V and Martinetti M. Autoimmune stigmata in Turner syndrome: when lacks an X chromosome. J Autoimmun 2009; 33: 25-30.

[10] Levitsky LL, Luria AH, Hayes FJ and Lin AE. Turner syndrome: update on biology and management across the life span. Curr Opin Endocrinol Diabetes Obes 2015; 22: 65-72.

[11] Somerville S, Rosolowsky E, Suntratonpipat S, Girgis R, Goot BH and Tham EB. Cardiac Magnetic Resonance Imaging in Pediatric Turner Syndrome. J Pediatr 2016; 175: 111-115, e111.

[12] Choi IK, Kim DH and Kim HS. The abnormalities of carbohydrate metabolism in Turner syndrome: analysis of risk factors associated with impaired glucose tolerance. Eur J Pediatr 2005; 164: 442-447.
[13] Bakalov VK, Cheng C, Zhou J and Bondy CA. X-chromosome gene dosage and the risk of diabetes in Turner syndrome. J Clin Endocrinol Metab 2009; 94: 3289-3296.
[14] Warburton PE, Giordano J, Cheung F, Gelfand Y and Benson G. Inverted repeat structure of the human genome: the X-chromosome contains a preponderance of large, highly homologous inverted repeats that contain testes genes. Genome Res 2004; 14: 1861-1869.
[15] Giglio S, Pirola B, Arrigo G, Dagrada P, Bardoni B, Bernardi F, Russo G, Argentiero L, Forabosco A, Carrozzo R and Zuffardi O. Opposite deletions/duplications of the X chromosome: two novel reciprocal rearrangements. Eur J Hum Genet 2000; 8: 63-70.
[16] Scott SA, Cohen N, Brandt T, Warburton PE and Edelmann L. Large inverted repeats within Xp11.2 are present at the breakpoints of isodicentric X chromosomes in Turner syndrome. Hum Mol Genet 2010; 19: 3383-3393.
[17] Huang HY, Zeng H. Clinical analysis of 14 Turner's cases. Chinese Journal of Brith Health & Heredirty 2012; 7: 48-54.
[18] Altuna-Azkargorta M, Torne-Hernandez L, Aznar-Gomez P, Ibiricu-Yanguas MA and Ducouret A. [Infection by the hepatitis E virus as a precipitating factor of Parsonage-Turner syndrome]. Rev Neurol 2016; 62: 572-574.
[19] Kawabata S, Sakamoto S, Honda M, Hayashida S, Yamamoto H, Mikami Y and Inomata Y. Liver transplantation for a patient with Turner syndrome presenting severe portal hypertension: a case report and literature review. Surg Case Rep 2016; 2: 68.
[20] Juloski J, Dumancic J, Scepan I, Lauc T, Milasin J, Kaic Z, Dumic M and Babic M. Growth hormone positive effects on craniofacial complex in Turner syndrome. Arch Oral Biol 2016; 71: 10-15.
[21] Clement-Jones M, Schiller S, Rao E, Blaschke RJ, Zuniga A, Zeller R, Robson SC, Binder G, Glass I, Strachan T, Lindsay S and Rappold GA. The short stature homeobox gene SHOX is involved in skeletal abnormalities in Turner syndrome. Hum Mol Genet 2000; 9: 695-702.
[22] Milner CS, Kannan K, Iyer VG and Thirkannad SM. Parsonage-Turner syndrome: clinical and epidemiological features from a hand surgeon's perspective. Hand (N Y) 2016; 11: 227-231.
[23] Svanberg C, Norevall LI, Ekman B, Wahlberg J and Bagesund M. Cephalometric analysis of adults with Turner syndrome. Swed Dent J 2016; 40: 33-41.
[24] Elassar A, Liu X, Scranton V, Wu CA and Peluso JJ. The relationship between follicle development and progesterone receptor membrane component-1 expression in women undergoing in vitro fertilization. Fertil Steril 2012; 97: 572-578.
[25] Lodde V and Peluso JJ. A novel role for progesterone and progesterone receptor membrane component 1 in regulating spindle microtubule stability during rat and human ovarian cell mitosis. Biol Reprod 2011; 84: 715-722.
[26] Chen CP, Su YN, Lin HH, Chern SR, Tsai FJ, Wu PC, Lee CC, Chen YT and Wang W. De novo duplication of Xq22.1-->q24 with a disruption of the NXF gene cluster in a mentally retarded woman with short stature and premature ovarian failure. Taiwan J Obstet Gynecol 2011; 50: 339-344.
[27] Fiot E, Zenaty D, Boizeau P, Haignere J, Santos SD and Leger J. X-chromosome gene dosage as a determinant of impaired pre and postnatal growth and adult height in Turner syndrome. Eur J Endocrinol 2016; 175: X1.
[28] Armstrong L, McGowan-Jordan J, Brierley K and Allanson JE. De novo dup(X)(q22.3q26) in a girl with evidence that functional disomy of X material is the cause of her abnormal phenotype. Am J Med Genet A 2003; 116A: 71-76.
[29] Volleth M, Stumm M, Mohnike K, Kalscheuer VM, Jakubiczka S and Wieacker P. Preferential inactivation of a dupX(q23 --> q27-28) chromosome in a girl with mental retardation and dysmorphy. Hum Hered 2001; 52: 177-182.
[30] Deric D, Dudvarski Z and Cvorovic L. Otological manifestations of turner syndrome: clinical and radiological findings. Med Pregl 2016; 69: 45-47.
[31] Prueter J, Stevens SM, Andaluz N and Samy RN. Parsonage-Turner syndrome: a case of Idiopathic Upper extremity paresis following middle cranial fossa resection of a vestibular schwannoma. Otol Neurotol 2016; 37: 1195-1198.
[32] Kim MK, Seok HH, Kim YS, Chin MU, Sung SR, Lee WS, Shim SH and Yoon TK. Molecular genetic and cytogenetic characterization of a partial Xp duplication and Xq deletion in a patient with premature ovarian failure. Gene 2014; 534: 54-59.