Subtle phenotypic effects of mosaic trisomy X in monozygotic twins with Prader-Willi syndrome: case report and review of literature

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Case Report

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Abstract

Background

We described the first monozygotic twins with 46, XX/47, XXX mosaicism and Prader-Willi syndrome, who were manifested with typical Prader-Willi syndrome (PWS) symptoms and slight trisomy X characteristics. Trisomy X symptoms can differentiate greatly, ranging from no significant manifest to special appearance, whereas 46, XX/47, XXX mosaicism may be rather inapparent.

Case presentation

The twin girls (B1 and B2) were born with weak cry, axial hypotonia, sucking difficulties and PWS facial appearance. They were also manifested with clinodactyly, inappropriate low birth weight, epicanthal folds and congenital heart disease, too atypical to be likely caused by PWS alone and indicating an associated problem. The diagnosis of 46, XX/47, XXX mosaicism and Prader-Willi syndrome was established based on clinical suspicion and molecular analysis. Therapy were conducted, followed by 4 years’ follow-up.

Conclusions

This report illustrates the first monozygotic twins with 46, XX/47, XXX mosaicism and Prader-Willi syndrome. Subtle phenotypic effects of mosaic trisomy X in monozygotic twins with Prader-Willi syndrome may be significance in prognosis and genetic counseling.

Background

Prader-Willi syndrome (PWS) is a genomic imprinting disease that can cause functional disorders in multiple systems. Occurring at 1/10000-1/30000, PWS is genetically originated from defect in paternally expressed imprinted genes at 15q11.2-13.1 [1]. By genotype, PWS can be classified as (1) paternal deletion, (2) maternal uniparental disomy, and (3) imprinting defect [1]. PWS is manifested by hypotonia and feeding difficulties, which are improved over time and feeding but gradually develop to incontrollable overeating, resulting in severe obesity. Besides, other symptoms can also be observed, including typical facial features, hypogonadism, skin hypopigmentation, global developmental delay and mental retardation and behavioral disorders.

Severe atypical symptoms of PWS are possibly related to size of deleted fragments and co-occurrence of other genetic abnormalities [2, 3]. However, slight atypical symptoms are very likely to be ignored. As the most common sex chromosome polyploidy disease, clinical manifestations of trisomy X can vary from no observable symptom to special facial features [4], and is even less observable in mosaicism [5]. In this report, first case of PWS monozygotic twins with 46, XX/47, XXX mosaicism was reported, and they showed slight atypical clinical manifestations. These manifestations were more common in trisomy X, but unusual or insignificant in PWS. Clear description of PWS combined with mosaicism is of great significance for prognosis and genetic mosaicism counseling.

Case Presentation

The twin girls (B1 and B2) were the second and third of children who were born after 33 weeks of gestation to a 25-year-old mother and a non-consanguineous 27-year-old father by natural conception. Pregnancy period and birth
history were uneventful. There was nothing of related significance in their family history.

Birth weights of both girls were 1500 g (B1) and 1550 g (B2), and were within 3–5% average birth weights of premature infant with same gestational age in Chinese populations. Body lengths at birth were 40 cm (B1) and 39 cm (B2), and were lower than 3% of average of premature infants at same gestational age in Chinese populations. Both girls were hypoactive and symptoms were manifested by weak cry, axial hypotonia and sucking difficulties. Sucking power was gradually improved with age and normal eating at 4 to 5 months of age.

At age of 7 months, the twin girls were admitted for complain of “developmental delay of stature, weight and motor milestones”. Length of B1 was 59.7 cm and weight 5.5 kg, and length of B2 was 61.4 cm and weight 5.4 kg. Hands and feet of both girls were smaller than average, and both had usually skin hypopigmentation, poorly-developed genitals, hypotonia and PWS facial appearance. Besides, little fingers of both girls were skewed to radial-side. B2 showed no obvious abnormality in heart auscultation, whereas clear 3/6 systolic murmur and enhanced second heart sound P2 were heard at left limit of sternal border of B1.

Karyotyping indicated that both twins were 47, XXX[28]/46, XX[32] mosaic. Array-based comparative genomic hybridization (aCGH) revealed 5.93 Mbp deletion at 15q11.2q13.1 of B1 and 8.32 Mbp deletion at same loci of B2. No other deletion or duplication mutation was detected. However, sex chromosomal mosaicism was confirmed in both twins by further analysis, and mosaic ratio was consistent to karyotyping result. Based on clinical manifestations and history, PWS was considered. In methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA), high methylation level was observed in PWS region 15q11.1-13.2, and deletions were detected in BP1 to BP3. Molecular diagnosis was type 1 deletions.

No abnormality was found in blood cell count, biochemical tests on heart, liver and kidney functions, and electrolyte and arterial blood gas analysis. Levels of endocrine hormones were shown in Table 1. N-terminal brain natriuretic peptide (BNP) was 4023.70 pg/mL (reference value 0-250 pg/mL), heart color ultrasound showed atrial septal defect (ASD), moderate pulmonary arterial hypertension and moderate-severe tricuspid regurgitation in heart of B1, whereas BNP level and heart color ultrasound were within normal limits.
Table 1
Laboratory values of endocrine hormones and tumor markers of twins at 7 months old

<table>
<thead>
<tr>
<th>Items</th>
<th>B1</th>
<th>B2</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free triiodothyronine 3 (FT3)</td>
<td>5.62</td>
<td>6.12</td>
<td>2.95–7.57 pmol/L</td>
</tr>
<tr>
<td>Free thyroxine 4 (FT4)</td>
<td>11.72</td>
<td>13.34</td>
<td>13.17–22.33 pmol/L</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone (TSH)</td>
<td>7.382</td>
<td>5.254</td>
<td>0.36–7.63 µIU/mL</td>
</tr>
<tr>
<td>Growth hormone (GH)</td>
<td>1.82</td>
<td>3.37</td>
<td>No reference, ng/mL</td>
</tr>
<tr>
<td>Insulin-like growth factor 1 (IGF-1)</td>
<td>&lt;25.00</td>
<td>41.7</td>
<td>55–327 ng/mL</td>
</tr>
<tr>
<td>Insulin like growth factor binding protein 3 (IGFBP-3)</td>
<td>1.12</td>
<td>2.08</td>
<td>0.7–3.6 ug/mL</td>
</tr>
<tr>
<td>Estradiol (E2)</td>
<td>56.09</td>
<td>80.71</td>
<td>0-73.4 pmol/L</td>
</tr>
<tr>
<td>Follicle-stimulating hormone (FSH)</td>
<td>23.28</td>
<td>31.3</td>
<td>1.0-4.2 IU/L</td>
</tr>
<tr>
<td>Luteinizing hormone (LH)</td>
<td>2.25</td>
<td>4.65</td>
<td>0.02–0.18 IU/L</td>
</tr>
<tr>
<td>Prolactin (PRL)</td>
<td>13.47</td>
<td>15.99</td>
<td>2.8–29.2 ng/mL</td>
</tr>
<tr>
<td>Testosterone (T)</td>
<td>0.87</td>
<td>1.21</td>
<td>0-0.7 nmol/L</td>
</tr>
<tr>
<td>Human chorionic gonadotropin (hCG)</td>
<td>2</td>
<td>2</td>
<td>&lt; 10 mIU/mL</td>
</tr>
<tr>
<td>Androstenedione (AND)</td>
<td>1.06</td>
<td>1.14</td>
<td>1.0-11.5 nmol/L</td>
</tr>
<tr>
<td>Dehydroepiandrosterone sulfate (DHEAS)</td>
<td>2.41</td>
<td>2.51</td>
<td>0.95–11.67 µmol/L</td>
</tr>
<tr>
<td>Cortisol (Cor)</td>
<td>478.62</td>
<td>649.93</td>
<td>85.3–618 nmol/L</td>
</tr>
<tr>
<td>Insulin</td>
<td>0.86</td>
<td>2.24</td>
<td>3–25 µIU/mL</td>
</tr>
<tr>
<td>C-peptide</td>
<td>0.68</td>
<td>0.6</td>
<td>0.81–3.85 ng/mL</td>
</tr>
<tr>
<td>Alpha fetoprotein (AFP)</td>
<td>72.6</td>
<td>52.8</td>
<td>&lt; 8.1 ng/mL</td>
</tr>
<tr>
<td>Carcinoembryonic antigen (CEA)</td>
<td>2.1</td>
<td>1.7</td>
<td>&lt; 5.0 ng/mL</td>
</tr>
</tbody>
</table>

Diagnosis and therapy were conducted, followed by 4 years’ follow-up. B1 and B2 were given 2 µg/kg levothyrocine at 9 months and 10 months for low free thyroxine level (FT4). In following thyroid function examination (once per 3 months), thyroid hormone level remained within normal limits. Recombinant human growth hormone (rhGH) was given to B1 and B2 at age of 1 year and 9 month-old at 0.5 mg/(m²·d). Length/height, weight and BMI during the therapeutic course were recorded and shown in Fig. 1. Besides, B1 received congenital heart disease surgery at age of 2 years old and postoperative recovery was good.

Heights of both twins were below – 2SD before 1 year and over – 2SD after 1 year but still below average. They can walk independently at 46 months (B1) and 23 months (B2), talk at 24 months (B1) and 21 months (B2). Both started to exhibit hyperphagia and gain weight at 24 months and B2 reached obesity diagnosis criteria at 30 months and her weight continued to increase. BMI of B1 increased with age as well but did not reach obesity diagnosis criteria until follow-up.

**Discussion And Conclusions**
The present report presented the first PWS twins in China, at the same time the first PWS twins with 46, XX/47, XXX mosaicism. The twins showed low birth weights, epicanthal folds, clinodactyly, near normal stature and congenital heart disease (only in B1), all of which were uncommon manifestations in PWS but typical in 47, XXX syndrome [1, 6].

PWS is a rare genomic imprinting disease and PWS twins are even rarer. Only six reports can be retrieved from PubMed [3, 7–11], five of which are accessible as full text and are concluded in Table 2. Three pairs were PWS monozygotic twins and this research reported the fourth pair. Among these four pairs, two were male and two were female, and all were conceived by natural insemination. Other two articles involved one PWS victim in the twins, one pair were male and the other female, both pairs were conceived by assisted reproductive technology (ART). Ages of the parents were between 22 and 32. Half of them were delivered prematurely. Two pairs of the monozygotic twins were clinically diagnosed, karyotype of both was male [7, 9]. The other PWS monozygotic twins [3] and this case were deletion-type PWS, and the former had TCF4 gene mutation and were diagnosed as Pitt-Hopkins syndrome, exhibiting atypical clinical manifestations including significant mental deficiency, obesity and PWS facial feature were not observed.
Table 2
Summary of reports about twins with Prader-Willi syndrome

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Type of Twins</th>
<th>Sex</th>
<th>Age</th>
<th>Father’s Age</th>
<th>Mother’s Age</th>
<th>Assisted reproduction</th>
<th>Gestational weeks</th>
<th>Birth weight (g)</th>
<th>Birth length (cm)</th>
<th>Molecular Methods</th>
<th>Genetic findings</th>
<th>Age of walk (months)</th>
<th>Age of speak (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brissenden JE. et al (1973)</td>
<td>Monozygotic</td>
<td>Male</td>
<td>9m</td>
<td>26</td>
<td>22</td>
<td>No</td>
<td>36</td>
<td>1900/2200</td>
<td>nr</td>
<td>Karyotype</td>
<td>46, XY, Dp +</td>
<td>nr</td>
<td>46/23</td>
</tr>
<tr>
<td>Trevisan C. et al (1983)</td>
<td>Monozygotic</td>
<td>Male</td>
<td>15y</td>
<td>nr</td>
<td>nr</td>
<td>No</td>
<td>36</td>
<td>2900/2950</td>
<td>nr</td>
<td>Karyotype; 46, XY</td>
<td>46, XY</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>Atik T. et al (2014)</td>
<td>Dizygotic</td>
<td>Male</td>
<td>2y</td>
<td>32</td>
<td>31</td>
<td>Yes</td>
<td>Full term pregnancy</td>
<td>31</td>
<td>2110</td>
<td>48.8</td>
<td>Karyotype, methylation, and microsatellite marker analysis</td>
<td>46, XY; PWS, Maternal UPD 15</td>
<td>nr</td>
</tr>
<tr>
<td>Han JY. et al (2016)</td>
<td>Dizygotic</td>
<td>Female</td>
<td>6y</td>
<td>nr</td>
<td>nr</td>
<td>Yes</td>
<td>Full term pregnancy</td>
<td>31</td>
<td>1030</td>
<td>38</td>
<td>aCGH, MS-MLPA</td>
<td>PWS, deletion type 2, mutation in TCF4 gene, Pitt–Hopkins syndrome</td>
<td>nr</td>
</tr>
<tr>
<td>Jehee FS. et al (2017)</td>
<td>Monozygotic</td>
<td>Female</td>
<td>9m</td>
<td>nr</td>
<td>nr</td>
<td>No</td>
<td>33</td>
<td>2775/2950</td>
<td>54/55</td>
<td>Microsatellite marker analysis, aCGH, MS-PCR, Exome Sequencing, and qRT-PCR</td>
<td>PWS, deletion type 1; 46, XX [32]/47, XXX [28]</td>
<td>nr</td>
<td>46</td>
</tr>
<tr>
<td>Present study (2021)</td>
<td>Monozygotic</td>
<td>Female</td>
<td>9m</td>
<td>27</td>
<td>25</td>
<td>No</td>
<td>37</td>
<td>1500/1550</td>
<td>40/39</td>
<td>Karyotype, MS-MLPA, aCGH</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: aCGH, array-based comparative genomic hybridization; MS-MLPA, methylation-specific MLPA; MS-PCR, methylation-specific PCR; nr, no recorded; qRT-PCR, real-time quantitative PCR; rhGH, recombinant human growth hormone.
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical manifestations</td>
<td>pneumonia and fecal impaction</td>
<td>163/164 cm tall, weighed 86/97 kg</td>
<td>-</td>
<td>-</td>
<td>Non obese, eye anomalies and typical face;</td>
<td>Ultrasound showed atrial septal defect, severe pulmonary hypertension, mid-to-severe tricuspid regurgitation in one of twins</td>
</tr>
<tr>
<td>Treatment</td>
<td>nr</td>
<td>Gonadotropins</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>rhGH</td>
</tr>
</tbody>
</table>

Abbreviations: aCGH, array-based comparative genomic hybridization; MS-MLPA, methylation-specific MLPA; MS-PCR, methylation-specific PCR; nr, no recorded; qRT-PCR, real-time quantitative PCR; rhGH, recombinant human growth hormone.

Latest research on the relationship between epigenetic changes and ART indicated that ART can significantly increase risks of imprinting disorders including Angelman syndrome and Beckwith-Wiedemann syndrome [12, 13]. PWS is a methylation-related genetic imprinting disease, and 47, XXX syndrome can induce methylation or demethylation of genes on X chromosome and other chromosomes [1, 14]. DeAngelis believed that absolute risk of imprinting disorder did not increase with ART [15]. Gold had analyzed occurrence of PWS after ART individually and discovered that occurrence of PWS was not related to ART. However, morbidity of PWS was higher in ART twins [16].

This is the first report of PWS twins with 46, XX/47, XXX mosaicism. Trisomy X (47, XXX) is a sex chromosome polyploidy disease in which female victims have one extra X chromosome. Mostly, 47, XXX is often individually observed in mosaicism of Turner's syndrome, 46, XX/47, XXX mosaicism is relatively rarer [6]. Neonatal screening indicated that trisomy X occurred in 1 per 1000 born female infants, but only 10% were clinically diagnosed [17]. This can possibly be ascribed to highly differentiated phenotypes of this syndrome, from significant abnormality in physical examination and mental deficiency to slight unobservable clinical manifestation. Comparing to complete 47, XXX, clinical symptoms of individuals with 46, XX/47, XXX mosaicism are less severe and expectations of their outcomes are better [5]. Still, there are reports on severe symptoms of 46, XX/47, XXX mosaicism including autoimmune myelofibrosis, congenital chylothorax and azoospermia [18–20].

Comparison of clinical manifestations of this case to those of typical PWS syndrome and trisomy X was listed in Table 3. Low birth weight may occur to PWS children, but their birth weight is usually only 10–20% lower than normal and even within normal ranges [1]. Birth weights of trisomy X individuals are normally 400–500 g less than normal [6]. Nevertheless, birth weights of the twins in the present case were at only 3–5% of normal infants at the same age. Relationship between low birth weight and cooccurrence of two genetic disorders is still unknown. Heart defects including atrial and ventricular septal defects, pulmonic stenosis and aortic coarctation have been reported in trisomy X individuals, whereas these were seldom reported in PWS individuals [1, 6]. One of the twins, B1, showed atrial septal defect, severe pulmonary hypertension, mid-to-severe tricuspid regurgitation, 47, XXX possibly caused additional congenital heart defects. Without growth hormone therapy, short stature often occurs to PWS victims, in contrast, trisomy X is usually manifested by tall stature [1, 6, 21]. Treatment with rhGH was initiated at 12 months and 9 months for B1 and B2, respectively, when heights of both twins were below −2SD. Both of them reached over −
2SD at around the age of 1 year, but still below average. Meanwhile, twins in the present case had epicanthal folds and clinodactyly, both of which were common in physical examination of trisomy X patients [6].
<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Trisomy X (47, XXX)(^{[1]})</th>
<th>Case B1</th>
<th>Case B2</th>
<th>Prader-Willi Syndrome(^{[2]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karyotype/MS-MLPA/aCGH</td>
<td>47, XXX (5–15% with Turner syndrome)</td>
<td>46, XX [32]/47, XXX [28]; Type 1 deletions (T1d) extend from BP1 to BP3</td>
<td>46, XX [32]/47, XXX [28]; Type 1 deletions (T1d) extend from BP1 to BP3</td>
<td>46, XX or 46, XY; Deletion, UPD, and imprinting defect</td>
</tr>
<tr>
<td>Mean birth weight</td>
<td>400–500g lower(^{[3]})</td>
<td>1500g, gestational was 33 weeks [birth weight; mean, SD: 2133 ± 434], between 3–5%(^{[4]})</td>
<td>1550g, gestational was 33 weeks [birth weight; mean, SD: 2133 ± 434], between 3–5%(^{[4]})</td>
<td>15–20% smaller than unaffected siblings (although often still in the normal range)</td>
</tr>
<tr>
<td>Neonatal/infantile hypotonia and poor suck</td>
<td>Hypotonia in infancy (55–71%); normal suck</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Feeding problems and failure to thrive as infant</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Weight gain at 1–6 years</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Hyperphagia; obesity</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Characteristic dysmorphic facial features</td>
<td>Epicanthal folds (32–46%)</td>
<td>Epicanthal folds, typical PWS facial features(^{-})</td>
<td>Epicanthal folds, typical PWS facial features(^{-})</td>
<td>Typical PWS facial features(^{-})</td>
</tr>
<tr>
<td>Small genitalia</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Developmental delay/intellectual disability</td>
<td>The mean full-scale IQ at 85–90 and approximately 5–10% with intellectual disability</td>
<td>Moderate intellectual disability</td>
<td>Borderline disability</td>
<td>Borderline disability or low-normal (40%) Moderate disability (20%)</td>
</tr>
<tr>
<td>Stature</td>
<td>Tall stature &gt; 75th percentile (80–89%)</td>
<td>Stature within normal range (treated with growth hormone)</td>
<td>Stature within normal range (treated with growth hormone)</td>
<td>Short stature (if not treated with growth hormone) (~100%)</td>
</tr>
<tr>
<td>Hands and feet</td>
<td>Clinodactyly (42–65%)</td>
<td>Small hands and feet; Clinodactyly</td>
<td>Small hands and feet; Clinodactyly</td>
<td>Small hands and feet</td>
</tr>
</tbody>
</table>

\(^{-}\)Typical PWS facial features: narrow bifrontal diameter, almond-shaped palpebral fissures, narrow nasal bridge, thin vermilion of the upper lip with down-turned corners of the mouth.

\(^{[1]}\) Tartaglia et al. Orphanet Journal of Rare Diseases 2010, 5:8


Clinical features | Trisomy X (47, XXX)\(^1\) | Case B1 | Case B2 | Prader-Willi Syndrome\(^2\) |
---|---|---|---|---|
Hypopigmentation of skin | N | Y | Y | Y |
No congenital heart defects | Have been described including cases of atrial and ventricular septal defects, pulmonic stenosis, and aortic coarctation | Atrial septal defect, severe pulmonary hypertension, mid-to-severe tricuspid regurgitation | N | N |

#Typical PWS facial features: narrow bifrontal diameter, almond-shaped palpebral fissures, narrow nasal bridge, thin vermillion of the upper lip with down-turned corners of the mouth.


Past research indicated that higher apparency of PWS clinical manifestations can possibly be related to absence of larger chromosome parts \(^2\). However, not all atypical manifestations in PWS victims can be ascribed to size of absent chromosome fragment \(^22\). Jehee et al reported a case of PWS twins with TCF4 gene mutation, in which clinical manifestations of dual molecular defects occurred simultaneously \(^3\). Individuals with multiple molecular diagnosis may show clinical manifestations of multiple genetic disorders \(^3\), some of which can mislead physicians to believe that one of the disorders exhibited new, atypical or more extensive clinical manifestations \(^23\).

The present report indicated that slight atypical clinical manifestations occurring to the PWS twin girls were likely to be associated with cooccurrence of 46, XX/47, XXX mosaicism. The presence of slight atypical manifestations of PWS makes diagnosis of the other molecular disorder more challenging, but critical in prognosis and antenatal.

**Abbreviations**

aCGH Array-based comparative genomic hybridization; ART, assisted reproductive technology; ASD: atrial septal defect; BNP: N-terminal brain natriuretic peptide; FT4: low free thyroxine level; MS-MLPA: Methylation-sensitive multiplex ligation-dependent probe amplification; PWS: Prader-Willi syndrome; rhGH: Recombinant human growth hormone.

**Declarations**

**Acknowledgements**

The authors sincerely thank the twin girls’ parents for their informed consensus and participation in this report. The authors are also thankful to Laboratory of Genetics and Endocrinology, Guangzhou Women and Children’s Medical Center, for technical support in molecular diagnostics. This research is approved by Ethical Committee of Guangzhou Women and Children’s Medical Center.
Authors’ contributions

Xinjiang H designed the study and wrote the manuscript. Li L and Xiaojian M contributed equally to this work. All authors have read and approved the final version.

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Availability of data and materials

Not applicable.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Guangzhou Women and Children’s Medical Center, Guangzhou Medical University. Written informed consent to participate in this study was obtained from their parents/guardians. And, all methods were carried out in accordance with relevant guidelines and regulations. The parents of the patient have given parental consent for this study.

Consent for publication

The parents of the twin girls have given parental consent for this study. Written informed consent for writing this case report and publication was obtained from the parents before initiation of writing.

Competing interests

The authors declare that they have no competing interests.

References


**Figures**
Figure 1

comparison of age (month) – anthropometric characteristics curves of PWS twins to standard curves.

a) comparison of age (month) – weight (kg) curves of PWS twins to standard curves. Broken line with solid dot stands for B1, dashed line with solid triangle stands for B2. Other five paralleled solid lines stand for standard age-weight curves of Chinese girls with the same age from +2SD to -2SD, respectively from above to below. The curves indicated that the twins experienced fast weight gaining after 2 years. Age-weight curve of B1 was below B2, this can possibly be ascribed to congenital heart disease.

b) comparison of age (month) – height (cm) curves of PWS twins to standard curves. Broken line with solid dot stands for B1, dashed line with solid triangle stands for B2. Other three paralleled solid lines stand for standard age-
weight curves of Chinese girls with the same age from mean to -2SD, respectively from above to below. Height of both twins were below -2SD before 12 months and gradually grew over -2SD afterward, but still under average height.

c) comparison of age (month) – BMI (kg/m$^2$) curves of PWS twins to standard curves. Broken line with solid dot stands for B1, dashed line with solid triangle stands for B2. Other six paralleled solid lines stand for standard age-weight curves of Chinese girls with the same age from +3SD to -2SD, respectively from above to below. BMI curves of the twins increased from below -2SD, and BMI of B2 reached obesity criteria at 30 months and continued increasing. BMI of B1 increased with age as well but did not meet obesity criteria until follow-up.