

# Double trisomy 48,XXX,+18 with multiple dysmorphic features

Zi-Yan Jiang, Xiao-Hui Wu, Chao-Chun Zou

Hangzhou, China

**Background:** Chromosomal abnormality is a common cause of congenital anomalies, psychiatric disorders, and mental retardation. However, the double trisomy 48,XXX,+18 is a rare chromosome abnormality.

**Methods:** Case report and literature review.

**Results:** A 7-hour-old girl presented to our unit because of poor response after birth. She presented with multiple dysmorphic features, including small for gestational age infant, flat nasal bridge, widely-spaced eyes, the left thumb deformities, flat facial profile, raised sternum, ventricular septal defect, the third lateral brain ventricle enlargement, and small liver. This case expands the spectrum of malformations reported in association with the double trisomy 48,XXX,+18. The literature on 16 fetuses or infants with the 48,XXX,+18 were also reviewed.

**Conclusion:** These data suggested that in patients with clinical features similar to trisomy 18, especially with anomalies of the ears and/or reproductive malformations, double trisomy (48,XXX,+18) should be considered and karyotyping should be performed although it is a rare disease.

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**Key words:** 48,XXX,+18;  
chromosome abnormality;  
double trisomy;  
multiple dysmorphic features

## Introduction

Chromosomal abnormality is a common cause of congenital anomalies, psychiatric disorders, and mental retardation.<sup>[1,2]</sup> Abnormalities of the chromosomes, usually caused by parental non-disjunction during gametogenesis, may affect the autosomal chromosome and sex chromosome. Trisomy 18, also named Edwards syndrome, is considered a relatively common chromosomal aberration. Its incidence is estimated between 1/6000 and 1/8000 in live borns, but the overall incidence is higher (1/2500-1/2600).<sup>[3]</sup> It is characterized by a limited survival and only about 10% cases surviving to one year old. 47,XXX is another common chromosomal aberration with a prevalence about 1/1000 females, which is associated with high stature and a variety of physical and behavioral phenotypes.<sup>[4]</sup> Double aneuploidy in one individual is seen in 3% to 7% of fetuses with cytogenetic abnormalities.<sup>[5,6]</sup> The most prevalent double trisomy involving one of the sex chromosomes is a 48,XXY,+G male having Klinefelter's and Down's syndromes.<sup>[7]</sup> Double trisomy leading to trisomy and/or monosomy of two different chromosomes arises because of two meiotic non-disjunctional events. These aneuploidies could have the same or different parental origin.<sup>[8-10]</sup> To our knowledge, only 16 cases of 48,XXX,+18 have been described. Here, we reported a case of this rare chromosomal abnormality, who presented multiple dysmorphic features, and reviewed associated literatures to highlight the clinical features and diagnosis of this rare event.

## Case report

A 7-hour-old girl presented to our unit because of poor response after birth. She was the gravida 6 and para 2 of 33-year-old mother and 35-year-old father. She was born at 44 weeks' gestation via normal delivery with normal hydramnios. Umbilical cord was round the body and foot one wrap. The Apgar score was 9 at the first minute, and her birth weight was 2.3 kg. She presented with a poor response and little activity, and crying without cyanosis. Her parents are peasants and

**Author Affiliations:** Department of Pediatrics, Children's Hospital, Zhejiang University School of Medicine and the Key Laboratory of Reproductive Genetics (Zhejiang University), Ministry of Education (Jiang ZY, Wu XH, Zou CC)

**Corresponding Author:** Chao-Chun Zou, MD, Children's Hospital, Zhejiang University School of Medicine, 57 Zhugan Xiang, Hangzhou 310003, China (Tel: +86-571-88873011; Fax: +86-571-87033296; Email: zou108cc@yahoo.com)

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not consanguineous marriage. Her sister was healthy and died at the age of 10 years because of drawing. Her mother had 3 times of abortion, and denied a history of alcohol, drugs, or any medications during this pregnancy.

On physical examination, the girl was 44 cm in length and 2.29 kg in weight with a head circumference of 32 cm. Her respiratory and heart rate was 50 and 129 times per minute with a temperature of 35°C. She had poor response, feeble cry and pale facial expression without cyanosis. Anterior fontanel was 2×2 cm. A cephalohematoma with a diameter of 2×2 cm was noted. She had the characteristic features, including prominent occiput, flat facial profile, broad flat nasal bridge, prominent ear, raised sternum, and the left thumb deformities. In the pericardial region, I-II/6 SM was noted. Muscular tension and the external genitalia were normal. The dermal, aural, and ocular examinations were unremarkable.

Laboratory tests of liver and kidney function, peripheral blood counting (white blood cell:  $10.7 \times 10^9/L$ ; neutrophil: 62.2%; lymphocyte: 31.6%; hemoglobin: 192 g/L; platelet:  $157 \times 10^9/L$ ) were all normal. The ratio of stab neutrophils to polymorphonuclear neutrophils was 3.57% (2%:56%). Urine analysis was positive for protein (+), occult blood (+), and bilirubin (+). Blood immunoglobulin M of *Toxoplasma gondii* was positive while the PCR was doubtful. PCR for cytomegalovirus was negative.

Chest X-ray showed enlarged heart shadow. The Doppler echocardiography showed ventricular septal defect (VSD, membranous 0.6 cm), patent foramen ovale (0.3 cm) with enlarged left atrium, and hypertrophy of septal and ventricular wall near the apical. Brain B-mode ultrasonography showed 0.3 cm diameter of the third lateral ventricle, and enhanced and fuzzy echo of brain parenchyma, which implied hypoxic-ischemic encephalopathy. Abdominal B-mode ultrasonography showed that the oblique diameter of right leaf was 3.8 cm and 0.8 cm under the edge of ribs, which implied a smaller liver compared with infants of the same age.

Cytogenetic study from two peripheral blood cultures revealed a complement of 48 chromosomes with two extra chromosomes in the E and C groups, respectively. Two X chromosomes were readily recognized on morphological criteria, and the other extra E group chromosome was confirmed to be an 18 chromosome. The karyotype of 48,XXX,+18 was confirmed.

A postterm infant, small for gestational age (SGA), chromosomal abnormality with double trisomy 48,XXX,+18, and congenital heart disease (VSD) was diagnosed. Unfortunately, further investigation for the

parent-of-origin of the extra chromosomes was not performed. Her parents refused further management. She was discharged on the 10th day of hospitalization and died about 10 days after discharge.

## Discussion

The double trisomy 48,XXX,+18 is a rare chromosome abnormality, which was first described in 1961 by Uchida.<sup>[11]</sup> We reviewed the available literature, and only 16 cases with 48,XXX,+18,<sup>[10-25]</sup> including one (case 4) 48,XXX,+18/47,XXX mosaic,<sup>[16]</sup> had been reported. Among these cases, 11 were diagnosed after birth and while 5 (case 12-16) were diagnosed at the prenatal period and 4 (case 13-16) died intrauterine. In this study, these 16 cases reported previously were reviewed and analyzed together with our current case.

Most authorities have suggested that the extra chromosome is present because of non-disjunction. Studies of the parental origin of the additional X chromosome in trisomy X revealed that 58%-63% of cases were due to maternal meiosis I errors, 16%-17.4% were due to maternal meiosis II errors, and 18%-19.6% were due to post-zygotic non-disjunction.<sup>[8,9,26]</sup> On the other hand, the non-disjunction of the trisomy 18 is more frequent in meiosis II, and the minority of cases is of a paternal post-zygotic error.<sup>[3,27]</sup> In this serial cases, the maternal and paternal age of 48,XXX,+18 were mentioned in 16 (94.1%) and 10 (58.8%) cases, respectively. The maternal age ranged from 17 to 45 years with a mean age of  $30.1 \pm 8.1$  years. The paternal age ranged from 21 to 52 years with a mean age of  $31.4 \pm 9.4$  years (Table 1).<sup>[11-25]</sup> This consistent with the fact that abnormal separation of chromosomes may occur in older individuals because of dysfunction of structures related to chromosome separation although a 17-year-old mother (case 6) was reported.<sup>[18]</sup> It was reported that two non-disjunction events resulted in 48,XXX,+18 can happen in the same parent or in the same cell division.<sup>[10,23]</sup> However, there is still no obvious biological mechanism to explain the occurrence of malformations in infants with double trisomy 48,XXX,+18. It may need further accumulation of this double trisomy to understand its mechanism.

Although no unified risk factor of double trisomy was reported in this series, X-ray and measles contact were reported in one case, respectively. Pre-term and post-term were reported in 2 (case 8, 11) and 3 (case 1, 4, and current case) of 11 cases. Asphyxia was reported in 8 of 13 newborns (case 4, 6-12). SGA was noted in 12 of 13 newborns (except for case 6) while intrauterine growth retardation (IUGA) was reported in 2 fetuses (case 11, 12). It was notable that thickening nuchal translucency

**Table 1.** Family history, pregnancy and birth status of 13 infants and 4 fetuses with 48,XXX,+18

No.	Mother/father age (y)	Family and pregnancy history	Gestation age (wk), delivery, Apgar score	Birth weight & length
Current	33/35	Umbilical cord round the body and foot one wrap	44, normal delivery, 9 at 1 min	2.3 kg, 44 cm
1 <sup>[11-13]</sup>	36/33	An X-ray technician mother, membranes ruptured few weeks	43, caesarean section as membranes ruptured	2.27 kg
2 <sup>[14]</sup>	31/26	Normal pregnancy	40	1.9 kg
3 <sup>[15]</sup>	29/None	Measles contact in pregnancy	≥41, normal delivery	1.9 kg, 43 cm
4 <sup>[16]</sup>	21/24	-	43, breech delivery, resuscitation	1.7 kg, 40 cm
5 <sup>[17]</sup>	22/21	Normal pregnancy	Full-term	1.56 kg
6 <sup>[18]</sup>	17/None	Mother with sickle-cell trait	Cesarean section as breech presentation, 6 at 1 min	2.69 kg, 50 cm
7 <sup>[19]</sup>	29/32	Imminent abortion during the 1st trimester	41, breech presentation, 5 at 1 min	1.7 kg, 45 cm
8 <sup>[20]</sup>	45/52	Oophorectomy for right ovarian cyst; gestosis, polyhydramnios, early membrane ruptured	36 <sup>6</sup> , 5 at 1 min	1.48 kg, 43 cm
9 <sup>[20]</sup>	32/39	First conception after married for 7 years	38, cesarean section, 3 at 1 min	1.76 kg, 43 cm
10 <sup>[21]</sup>	20/28	Poor maternal weight gain during the last trimester	41, normal deliver, 6 at 1 min	2.2 kg, 45 cm
11 <sup>[22]</sup>	27/28	IUGR, polyhydramnios	36 <sup>6</sup> , 2 at 1 min	1.1 kg, 37.7 cm
12 <sup>[23]</sup>	26/None	IUGR, olyhydramnios, enlarged cisterna magna, abnormal Down syndrome screening test	4 at 1 min	1.23 kg, 36 cm
13 <sup>[24]</sup>	33/None	Diagnosed as 5 mm nuchal translucency & hydrops fetalis at 12 <sup>5</sup> wk of gestation	-	-
14 <sup>[24]</sup>	45/None	Diagnosed as 4.8 mm nuchal translucency at 11 <sup>3</sup> wk of gestation	-	-
15 <sup>[25]</sup>	36/None	Diagnosed as sonographic feature at 12 <sup>6</sup> wk of gestation	-	-
16 <sup>[10]</sup>	None/None	Hydrops fetalis	-	-

IUGR: intrauterine growth retardation; "-": not available.

(case 13, 14) and hydrops fetal (case 13 and 16) were found in two fetuses, respectively (Table 1). Besides the IUGA, whether the thickening nuchal translucency and hydrops fetal are the characteristics features and helpful for the diagnosis of 48,XXX,+18 require more large sample investigations.

The clinical features were analyzed for 13 infantile cases as shown in Table 2.<sup>[11-23]</sup> The prominent occiput was common and noted in 11 cases (case 1-8, 10, 12 and current case). Broad flat nasal bridge and/or small nose were reported in 5 cases (case 4, 8-10, and current case). Down slanting palpebral fissures, narrow palpebral fissures, and epicanthal folds were reported in 3 (case 6, 8, 10), 2 (case 6, 9), and 2 cases (case 4, 9), respectively. Low-set ear was common as well and reported in 12 cases (case 1-12). Micrognathia, small mouth, and high arched palate were reported in 10 (case 1-4, 6-8, 10-12), 5 (case 1, 3, 6, 9, 10), and 6 cases (case 1, 2, 6, 7, 9, 10), respectively. These typical craniofacial features were similar to those in patients with trisomy 18.<sup>[3]</sup> However, it was noted that structural ear anomalies were common and reported in 9 of these cases (case 1, 2, 4, 5, 7-11). Malformed auricle (e.g. hypoplastic auricle, crumpled auricle, overfolded upper helices and elfin ear) was reported in 8 cases (case 1, 2, 4, 5, 7-10), and external meatus atresia in 5 (case 4, 5, 7, 8, 11). These occasionally presented in patients with trisomy 18<sup>[3]</sup> or 47,XXX,<sup>[26,28]</sup> maybe as important cites of 48,XXX,+18.

Overlapping fingers were reported in 11 cases (case 1, 3-12) and thumb deformities was reported in 2 (case 8 and current case). Skin texture disorders were reported in 8 cases (case 1, 4-10), including simian creases in 4 cases (case 1, 4, 8, 9), palmar creases in 3 (case 5, 9, 10), poorly developed dermal ridges in 2 (case 6, 7), hypoplastic nails in 2 (case 6, 7), lacking interphalangeal creases in fingers in 2 (case 7, 9), and ulnar deviation of the wrists in one (case 4). Rocker bottom foot was reported in 10 cases (case 1, 3-7, 9, 11, 12). Short big toes (case 1, 7), hips dislocated (case 1, 8), and syndactyly (case 1, 11) were noted in 2 cases, respectively (Table 2). The limb malformation was similar in patients with trisomy 18.

Moreover, chest abnormalities were noted in 5 cases, including short sternum in 3 (case 1, 7, 10), shield-shaped chest in 2 (case 1, 5), and raised sternum in the current case. Congenital heart disease was common and confirmed in 11 cases, including VSD in 9 (case 1-3, 7-9, 11, 12 and current case), patent ductus arteriosus in 7 (case 3, 4, 6-8, 11, 12), atrial septal defect in one (case 7), and atrioventricular septal defect in one (case 4). Neuromuscular abnormalities were noted in 7 and hypotonia was noted in 5 cases (case 1, 6, 7, 10, 12). Hypoxic-ischemic encephalopathy was reported by hypersonic in the current case. Also, cerebellar hypoplasia, perivascular collections of astrocytes and optic nerve degeneration were reported in 2 (case 7, 12) of 7 cases who had autopsy performed. Urinary malformations was noted in 3 cases (case 1, 4, 6). Right

**Table 2.** The clinical manifestations of 13 infants with 48,XXX,+18

No.	Head (prominent occiput)	Ear (low-set ear)	Eye & nose	Micrognathia	High arched palate	Hand (overlapping fingers)	Foot (rocker bottom foot)	Cardio-vascular	Neuromuscular	Reproductive & urinary	Gastrointestinal	Others	Outcome
1 <sup>[1+13]</sup>	Current +, pale facial expression	Prominent ear	Broad flat nasal bridge		Left thumb deformities			VSD, PFO	Hypoxic-ischemic encephalopathy, normal muscular tension	Normal genitalia, Positive of protein and occult blood in urine	Smaller liver	Raised sternum	Died at about 20-d-old
2 <sup>[14]</sup>	+	+, asymmetrical auricle	+, malformed auricle	+	+, small mouth	+, short big toes, syndactyly, dorsal dislocation of 1st metatarsophalangeal joint, dislocated hips	Right talipesquinovarus	VSD	Mental retarded, hypotonia	Small ovaries with scarce ova. Right hydromephritis & reduplication on right ureter	Meckel's diverticulum	Short sternum, broad chest, 2nd left costal cartilage absent, both lungs fibrobed, tectus abdominis muscles separation, loose skin folds	Died at 35-d-old
3 <sup>[15]</sup>	+	+	+	+	Small mouth		+	VSD, PFO, PDA		Scarce ova & clumps of epithelial cells in ovaries	Long, mobile mesentery	Large pedunculated exomphalos with a narrow aperture	Died of pneumonia at 2-mon-old
4 <sup>[16]</sup>	+	+, hypoplastic left auricle, external meatus atresia, elfin right ear	+, hypoplastic external meatus atresia	+	+, simian creases, deviation of the wrists	+, simian creases, ulnar+, limited hip abduction	+	PDA, AVSD	Perivascular collections of astrocytes, opticnerve degeneration	Normal	Meckel's diverticulum	Shield-shaped chest	Died at 2-d-old
5 <sup>[17]</sup>	+	+, hypoplastic right auricle, external meatus atresia	+, hypoplastic external meatus atresia	+	+, palmar creases	+, palmar creases	+	PDA	Hypotonia	Part of the labia giving appearance of clitoris		Redundant folds of skin in neck, capillary hemangioma	Died of cardiac arrest at 5-mon-old
6 <sup>[18]</sup>	+	+	+	+	+, small mouth	+, right bridged palmar crease, poorly developed dermal ridges	+	PDA		Double collecting system on right kidney			
7 <sup>[19]</sup>	+	+, hypoplastic right auricle, external meatus atresia	+, hypoplastic external meatus atresia	+	+, lacking distal creases on 2nd to 5th fingers, poorly developed dermal ridges, hypoplastic nails	+, short & dorsiflexed big toes, limited hip abduction	+	VSD, ASD, PDA, coarctation of aorta	Cerebellar, hypoplasia, hypotonia				
8 <sup>[20]</sup>	+	+, hypoplastic auricle, left external meatus atresia	+, hypoplastic external meatus atresia	+	Narrow palate	+, simian creases, distal implanted thumbs, hypoplastic nails	+	VSD, PFO, PDA, mitral atresia, coarctation of aorta		Hypoplasia of the labia majora	Type C esophageal atresia	Hirsutism, excessive skin at frontal bossing & nape	Died of heart failure at 9-d-old
9 <sup>[20]</sup>	+	+, malformed auricles	+, malformed auricles	+	+, small mouth, palatal cleft	+, simian crease, lacking interphalangeal creases in right 2nd to 5th & left 5th fingers	+	VSD	Hypotonia	Normal, external genitalia		Hirsutism	Died at 8-d-old
10 <sup>[21]</sup>	+, round & small face	+, overfolded upper helices	+, overfolded palpebral fissures, small nose, hypoplastic alae nasi	+	+, small mouth	+, right extra palmar crease	+					Short sternum, small chest	Ljye at 12-mon-old without progression
11 <sup>[22]</sup>	+	+, malformed atresia	+, malformed atresia	+	+	+, syndactyly	+	VSD, PDA, PH		Prominent clitoris	Type A esophageal atresia	Hirsutism, hyperbilirubinemia	Died of convulsions at 20-d-old
12 <sup>[23]</sup>	+	+	+	+	+	+	+	VSD, PDA	Cerebellar hypoplasia, hypotonia	Normal renal			Died of cardiopulmonary failure at 2-wk-old

VSD: ventricular septal defect; ASD: atrial septal defect; AVSD: atrioventricular septal defect; PDA: patent ductus arteriosus; PH: pulmonary hypertension; PFO: patent foramen ovale.

pyelonephritis and hydronephrosis, reduplication on the right ureter and low and rotated left kidney, double collecting system on the right kidney were reported in one case, respectively. Although horseshoe kidney is a common finding in trisomy 18 (about two-thirds of patients),<sup>[3]</sup> we did not find this abnormality in the current case. Gastrointestinal malformations were noted in 7 cases, including Meckel's diverticulum in 3 (case 1, 4, 7), esophageal atresia in 2 (case 8, 11), long and mobile mesentery in one (case 3), and smaller liver in the current case (Table 2). Hirsutism (case 8, 9, 11) and redundant folds (case 1, 6, 8) were reported in 3 cases, respectively.

Compared the clinical findings of double trisomy 48,XXX,+18<sup>[10-22]</sup> with those of the trisomy 18 syndrome,<sup>[3,18]</sup> we found that the most common clinical manifestations of these two diseases were similar (Table 3). We noted that structural ear anomalies were more common in patients with 48,XXX,+18 whereas horseshoe kidney more common in patients with trisomy 18 syndrome. Whether these differences are helpful for differential diagnosis need more large sample studies.

Moreover, reproductive malformations were noted in 6 of 13 cases with double trisomy 48,XXX,+18, whereas it was rarely reported in the cases of trisomy 18 syndrome. Small ovaries and/or scarce ova were reported in 3 (case 1, 2, 4) of 7 cases who had autopsy performed. Prominent clitoris (case 11), hypoplasia of the labia majora (case 8), and part of the labia giving the appearance of a clitoris (case 5) were reported separately in one case. In normal females, one of the two X chromosomes is inactive. The inactive X is allocyclic and heterochromatinized. Over 85% genes

on the inactive X are silenced. Two of the three X chromosomes in these cases of the 47,XXX karyotype are inactive.<sup>[29]</sup> The extra X chromosome of the 48,XXX,+18 may play a small role in contributing to clinical features. However, extra X chromosome may be an important cause of reproductive malformations. This may be associated with the remainder 10% genes in X chromosome which were not silenced.

Similar to trisomy 18, most cases died shortly after birth. In this study, besides our case was lost of follow-up after discharge, 6 cases died within the first month of age, 3 died in the second month, one in the 5th month, and 2 are still living at the age of 8 and 12 months (Table 2). Prenatal sonographic features (e.g., increased nuchal translucency, IUGR, polyhydramnios, brachycephaly and narrow frontal cranium, overlapping of hand fingers, congenital heart defects, and other malformations) may contribute to this chromosome abnormality. When prenatal or neonatal diagnosis of trisomy 18 is made, the counseling of the family should be realistic. However, how to deal with these patients is still a medical and ethical challenge and the parents have to be prepared for the probability of death and possibility of living.

In summary, patients with clinical features similar to trisomy 18, especially anomalies of the ears and/or reproductive malformations, and double trisomy (48,XXX,+18) should be considered and karyotyping should be performed.

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**Ethical approval:** Informed consent was obtained from the parents and the study was approved by the Ethical Committee of the Children Hospital of Zhejiang University School of Medicine (No. 2013-05-12).

**Competing interest:** None declared.

**Contributors:** Zou CC supervised this study. Jiang ZY participated in the patient data management, and Wu XH was responsible for the literatures review. All authors read and approved the final manuscript.

**Table 3.** Comparison of clinical manifestations between 48,XXX,+18 and trisomy 18

Clinical manifestations	48,XXX,+18 <sup>[11-23]</sup>	Trisomy 18 <sup>[3,18]</sup>
Small for gestational age (weight < 3rd centile)	12/13 (92.3%)	>87%
Typical craniofacial features*	13/13 (100.0%)	99%
Flexed or overlapping fingers	11/13 (84.6%)	>80%
Rocker bottom foot	10/13 (76.9%)	50%-80%
Structural heart defects	11/13 (84.6%)	80%-100%
Neuromuscular malformations (cerebellar hypoplasia, optic nerve degeneration, and so on)	3/13 (23.1%)	5%-25%
Gastrointestinal malformations (Meckel diverticulum, esophageal atresia, and so on)	5/13 (38.5%)	5%-25%
Urinary malformations (hypoplasia, hydronephrosis, horseshoe kidney)	8/13 (61.5%)	25%-75%
Anomalies of the ears	9/13 (69.2%)	Occasional
Reproductive malformations	6/13 (46.2%)	Rare

\*: means prominent occiput, microphthalmia, flat nasal bridge, micrognathia.

## References

- Xu F, Zou CC, Liang L, Huang XM, Shao YN. Ring chromosome 15 syndrome: case report and literature review. *HK J Paediatr (New series)* 2011;16:175-179.
- Huang XY, Tang LF, Zou CC, Zhao ZY. Chromosome analysis in 8158 pediatric patients: an experiment of 29 years from Hangzhou, China. *Endocrinologist* 2010;20:179-181.
- Cereda A, Carey JC. The trisomy 18 syndrome. *Orphanet J Rare Dis* 2012;7:81.
- Otter M, Schrandner-Stumpel CT, Didden R, Curfs LM. The

- psychiatric phenotype in triple X syndrome: new hypotheses illustrated in two cases. *Dev Neurorehabil* 2012;15:233-238.
- 5 Ljunger E, Cnattingius S, Lundin C, Annerén G. Chromosomal anomalies in first-trimester miscarriages. *Acta Obstet Gynecol Scand* 2005;84:1103-1107.
  - 6 Ohno M, Maeda T, Matsunobu A. A cytogenetic study of spontaneous abortions with direct analysis of chorionic villi. *Obstet Gynecol* 1991;77:394-398.
  - 7 Shen Z, Zou CC, Shang SQ, Jiang KW. Down-Klinefelter syndrome (48,XXY,+21) in a child with congenital heart disease: case report and literature review. *Intern Med* 2012;51:1371-1374.
  - 8 Hall H, Hunt P, Hassold T. Meiosis and sex chromosome aneuploidy: how meiotic errors cause aneuploidy; how aneuploidy causes meiotic errors. *Curr Opin Genet Dev* 2006;16:323-329.
  - 9 Hassold T, Hall H, Hunt P. The origin of human aneuploidy: where we have been, where we are going. *Hum Mol Genet* 2007;16:R203-R208.
  - 10 Diego-Alvarez D, Ramos-Corrales C, Garcia-Hoyos M, Bustamante-Aragones A, Cantalapedra D, Diaz-Recasens J, et al. Double trisomy in spontaneous miscarriages: cytogenetic and molecular approach. *Hum Reprod* 2006;21:958-966.
  - 11 Uchida IA, Bowman JM. XXX 18-Trisomy. *Lancet* 1961;2:1904.
  - 12 Uchida IA, Lewis AJ, Bowman JM, Wang HC. A case of double trisomy: trisomy No. 18 and triplo-X. *J Pediatr* 1962;60:498-502.
  - 13 Uchida IA, Bowman JM, Wang HC. The 18-trisomy syndrome. *N Engl J Med* 1962;266:1198-1201.
  - 14 Ricci N, Borgatti L. XXX 18-Trisomy. *Lancet* 1963;2:1276-1277.
  - 15 Haas L, Lewis FJ. Double trisomy: trisomy 17-18 with triple X in a female infant. *J Pediatr* 1966;69:660-662.
  - 16 Engel E, Haddow JE, Lewis JF, Tipton RE, Overall JC, McGee BJ, et al. Three unusual trisomic patterns in children. Triple X plus triple E-triple X mosaic: normal XY-D trisomy mosaic; partial trisomy with E translocation. *Am J Dis Child* 1967;113:322-328.
  - 17 Madahar DP, Dosik H, Wexler I. 48,XXX, plus 18 double trisomy. *J Med Genet* 1974;11:309-311.
  - 18 Rosenfeld W, Verma RS, Jhaveri RC, Salazar D, Dosik H. Double trisomy 48,XXX,+ 18 in a newborn. *Am J Med Genet* 1981;8:67-71.
  - 19 Imai I, Shimao S, Suzuki Y, Okada T. A case of 48,XXX, +18 double trisomy. *Acta Paediatr Jpn* 1987;29:178-181.
  - 20 Sonoda T, Ohdo S, Madokoro H, Akimoto K, Ohba K. Clinical and postmortem findings of two cases with karyotype: 48,XXX, +18. *Acta Paediatr Jpn* 1987;29:173-177.
  - 21 Jaruratanasirikul S, Jinorose U. An infant with double trisomy (48,XXX, + 18). *Am J Med Genet* 1994;49:207-210.
  - 22 Tsukahara M, Fukuda M, Furukawa S, Kondoh O. Double trisomy (48,XXX, +18). *Am J Med Genet* 1994;52:244.
  - 23 Chen CP, Chern SR, Yeh LF, Chen WL, Chen LF, Wang W. Prenatal diagnosis and genetic analysis of double trisomy 48,XXX,+18. *Prenat Diagn* 2000;20:750-753.
  - 24 van Huizen ME, Knecht AC, Bijlsma EK, Bilardo CM. Double trisomy 48,XXX,+18 in association with increased nuchal translucency; two cases. *Prenat Diagn* 2004;24:1020-1021.
  - 25 Dezerega V, Be C, Wong AE, Silva R, Sepulveda W. Prenatal diagnosis of double trisomy 48,XXX,+18 in the first trimester. *J Ultrasound Med* 2005;24:717-719.
  - 26 Tartaglia NR, Howell S, Sutherland A, Wilson R, Wilson L. A review of trisomy X (47,XXX). *Orphanet J Rare Dis* 2010;5:8.
  - 27 De Souza E, Morris JK, Eurocat Working Group. Case-control analysis of paternal age and trisomic anomalies. *Arch Dis Child* 2010;95:893-897.
  - 28 Otter M, Schrandt-Stumpel CT, Curfs LM. Triple X syndrome: a review of the literature. *Eur J Hum Genet* 2010;18:265-271.
  - 29 Kelkar A, Deobagkar D. Methylation profile of genes on the human X chromosome. *Epigenetics* 2010;5:612-618.

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