Prenatal diagnosis of a rare case report of 45,X/46,X,dic(X) and literature review

Ting Wang
Guangdong Women and Children Hospital
Miao-Xu Lun
Guangdong Women and Children Hospital
Han-biao Chen
Guangdong Women and Children Hospital
Qian-yi Du
Guangdong Women and Children Hospital
Lai-ping Zheng
Guangdong Women and Children Hospital
Yin-huan Zhong
Guangdong Women and Children Hospital
Jian Lu
Guangdong Women and Children Hospital
Li Guo (guoli3861@163.com)
Guangdong Women and Children Hospital

Case Report

Keywords: Prenatal diagnosis, Turner sydrome, Dicentric X chromosomes, Single nucleotide polymorphism array, case report

Posted Date: May 9th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1629129/v1

Abstract

Objective

We present a prenatal case of 45,X/46,dic(X) with two asymmetric chromosome arms.

Methods

Single nucleotide polymorphism array(SNP-array),fluorescence in situ hybridization(FISH) and conventional cytogenetic analysis were performed for verification.

Results

The conventional G-banding analysis revealed a mosaic karyotype of mos 45,X/46,X,dic (X;X) (p11.2;q10) and the C-banding analysis showed that the derivative X chromosome had two darkly stained bands near the centromere.Two green signals and single green signal (X chromosome cetromere) were observed simultaneously in the metaphases and interphases FISH confirmation test,which indicated a mosaicism for X chromosome in the uncultured amniocytes.The SNP-array results revealed two copy-number-loss on the X chromosome.One was a 54.3Mb deletion in Xp22.33-p11.22 including 414 genes.Another was a mosaic deletion in Xp11.22-q28.

Conclusion

A combination of molecular and cytogenetic techniques should be employed to provide adequate genetic counseling to mosaic Turner sydrome patients for avoiding misdiagnosis.

Introduction

Dicentric chromosomes (DIC) are the results of genomic rearrangement, in which two active centromeres are placed on the same chromosome[1].DIC can occur between any two chromosomes, and the most common occurrence in humans is Robertson translocation[2].The majority of DIC are unstable during cell division.They inactivate one centromere through epigenetic inheritance, or overcome the instability by deleting one of the two centromeres, thus producing functional monocentric chromosome[3].

Dicentric X chromosomes (dic(X)s) can be detected in about 15% of patients with Turner syndrome(TS) and generally contain two identical copies of X centromere, separated by different amounts of material from the proximal short arm (Xp)[4].Dic(X)s is usually found in mosaic karyotypes, and its centromere is partially unstable, and typically exists in the karyotype as a pseudodicentric chromosome[5].

Here,we presented a fetus with mosaic karyotype 45,X/46,X,dic(X).Single nucleotide polymorphism array(SNP-array),fluorescence in situ hybridization(FISH) and conventional cytogenetic analysis were performed for verification.

Materials And Methods

Subject

A 33-years-old pregnant woman,gravida 2 para 1 abortion 0,was referred to our center due to the positive results of noninvasive prenatal screening(NIPS). The woman and her husband were both healthy and non-consanguineous. She had no history of irradiation or teratogenesis, had no infection during pregnancy and had no family history of congenital malformation.The maternal serum screening at 12^{+3} weeks(MSPAPPA=0.24 MOM, NT = 1.60 mm,MSHCG=0.88 MOM) indicated a critical risk of Down syndrome(1/782) and Edward syndrome(1/537).Subsequently,the NIPS was recommended to the patient and the results suggested the number of fetal sex chromosome is less, and the fetus may have sex chromosome abnormality.Amniocentesis was performed at 17 weeks of gestation and amniotic fluid(AF) was collected under ultrasound guidance for cytogenetic and molecular analysis.The mosaic karyotype of mos 47,X,der(X)/45,X revealed that the fetus had sex chromosome abnormality.The SNP-array and FISH results also confirmed the existence of mosaic X chromosome.Since the fetus had no normal karyotype and the prognosis was likely to be poor, the pregnant woman decided to terminate the pregnancy at 24 weeks of gestation.Chromosome studies of the couple showed that they both had normal karyotype.This study was approved by the Medical Ethics Committee of Guangdong Women and Children Hospital and written informed consent were obtained from the couple.

Cytogenetic analysis(G-banding)

AF cells were cultured and harvested according the in-situ culture technology[6].The preparations were conducted according to standard procedures (G-banding) at 550 band resolution.The karyotypes were described as the International System for Human Cytogenomic Nomenclature (ISCN 2016)

[7].The karyotypes of the couple were obtained by peripheral lymphocytes culture and the preparations were also performed with G-banding standard protocol.

Cytogenetic analysis(C-banding)

C-banding was employed to ascertain the number of functional centromeres in the derivative X chromosome.The prepared slides were left on the oven at 60℃ overnight then treated in the saturated $Ba(OH)_2$ at 37℃ for 5 minutes.This was followed by a standardized washing procedure, which involved rinsing slides in tap water, rinsing twice in distilled water, and air drying at room temperature.The slides were then incubated in 2× standard saline concentration(SSC) at 70℃ for 1 hour.After rinsing,Giemsa dye liquor was used for staining.

FISH

Interphase and metaphase FISH on uncultured amniocytes was applied to confirm the origin of the centromeres in the derivative X chromosome using DXZ1/DYZ3/D18Z1 mixed centromeric probes(Abbott Vysis CEP Probe,USA).The operations were performed according to the standard FISH protocols.

SNP-array

10ml of amniotic fluid were collected for SNP-array. The DNA were extracted from uncultured amniocytes using QIAamp DNA Blood Mini Kit (QIAGEN, Germany) according the recommended procedure. NANODROP 2000(Thermo, USA) was employed to test the DNA concentration. SNP-array analysis was performed using CytoScan 750 K chip (Affymetrix, USA). ChAS software was used to interpret the chip data.The databases including OMIM (http://www.ncbi.nlm.nih.gov/omim), DGV(http://projects.tcag.ca/ variation),UCSC(http://genome.ucsc) and DECIPHER(http://decopher.sanger.ac.uk/) were used to evaluate experimental data and analyze genotype-phenotype correlation.

Results

The conventional G-banding analysis revealed a mosaic karyotype of mos 45,X/46,X, dic (X;X) (p11.2;q10) as shown in Figure 1.Of the 25 colonies cultured from AF cells,14 colonies had the karyotype of 46,X,dic(X;X)(p11.2;q10) and 11 colonies had the karyotype of 45,X.The mosaic proportion of dicentric X and monosomy X was 56%(14/25) and 44%(11/25),respectively.The karyotype of the couple showed no abnormality.The C-banding analysis showed that the derivative X chromosome had two darkly stained bands near the centromere as shown in Figure 2.

Two green signals and single green signal (X chromosome cetromere) were observed simultaneously in the metaphases and interphases FISH confirmation test using mixed centromeric probes as shown in Figure 3,which indicated a mosaicism for X chromosome in the uncultured amniocytes.

The SNP-array results using DNA extracted from amniotic fluid revealed two copy-number-loss on the X chromosome as shown in Figure 4.One was a 54.3Mb deletion in Xp22.33-p11.22 including 414 genes.Another was a mosaic deletion in Xp11.22-q28.The proportion of mosaic deletion in Xp11.22-p11.1 was approximately

60% and the segment size was 4.0Mb.The mosaic deletion proportion in Xq11.2-q28 was approximately 15% and the segment size was 92.2Mb.

Due to lack of normal karyotype,we assumed the prognosis of the fetus will be similar to patients with TS.After genetic counselling, the couple decided to terminate the pregnancy and the induced labor was performed at 24 week of gestation.

Discussion

The karyotype of patients with classical TS were 45,X,accounting for about 50%.There were many variants in karyotype of TS.In the karyotypes of atypical TS female patients,in addition to a normal X chromosome, another X chromosome may have structural aberrations including del(X),r(X),idic(X),i(X),and balanced translocation between X and autosome.The abnormal cell lines in the TS variant may be homozygous or may be accompanied by mosaicism of the 45,X and 46,XX cell lines[8].TS patients with dic(X) karyotype were very rare,with an incidence of about 1/13000 in live female infants,most of which occured in the form of mosaicism of 45,X/46,X,dic(X) [9, 10, 11].In the current study,the fetus was found to have a mosaic karyotype of two cell lines 45,X[11]/46,X, dic(X;X) (p11.2;q10)[14] using GTG-banding, while FISH and C-banding were used to confirm the number of the centromeres from the derivative X chromosome.

There are two mechanisms of the formation of dicentric chromosome that have been reported by previous published literature.One is an local U-shape sister chromatid exchange (local breakage of two chromatids and reconnection of the broken ends) in S or G2 phase[12].The other is that the broken ends of chromatids are reconnected in a U-shape after the deletion and duplication of chromosomes in G1 phase[13].Dicentric chromosomes formed by chromosome fusion are stabilized in three ways[14].The first is epigenetic centromere inactivation.The second is the elimination of the centromere by DNA rearrangement,and the third is the chromosome breakage into two monocentric chromosomes.Epigenetic centromere inactivation occurs in more than three quarters of stable dicentric chromosomes[14].The presence of two functional centromeres on a single chromosome does not necessarily result in chromosomal instability and loss.As the distance between the centromere decreased,the dicentric chromosome does not consistently inactivate one or the other and both centromeres were capable of assembling the kinetochore[15].The metaphase FISH(Figure 3)

suggested that the distance between the two centromeres of the dic(X) chromosome is very short,which may be the reason for the stability of the chromosome.

When the G-banding achieves 550-bands level,the structural aberration of dic(X) chromosome is not difficult to detect.In case of low resolution of G-banding level,missed diagnosis and misdiagnosis may occur.Hence,a combination of FISH and SNP-array is needed to ensure the accuracy of diagnosis.In the current study,~4Mb mosaic deletion in Xp11.22-p11.1 was observed from the results of SNP-array,which may be undetected in low-resolution G-banding.Combined with the results of C-banding and FISH,we verified that the dic(X) chromosome contains two identical centromeres and is an asymmetrical isodicentric chromosome(Figure 5).Chromosomes with multiple centromeres are stabilized by epigenetic centromere inactivation,which is caused by the kinetochore disassembly,followed by the heterochromatization of the inactive centromeres [16]. Therefore,it is necessary to use C-banding to detect whether one of the centromeres is inactivated.Meanwhile,SNP-array can be used to detect the microdeletion and microduplication of chromosome segments near the centromere, so as to distinguish whether the dicentric chromosomes are symmetrical or not.

Based on the origin of centromere,dicentric chromosomes can be categorized to three types[17]:1)heterologous dicentric chromosome derived from non-homologous chromosomes;2)homologous dicentric chromosome derived from two homologous chromosomes and 3)isodicentric chromosome derived from homologous chromosome with two identical arms.According to the above categories,the case of this study should belong to type 2 and the derivative dicentric X chromosome was asymmetrical.However, without SNP-array that can identify submicroscopic chromosomal structural aberrations, it may not be possible to observe the segments between Xp11.22 and Xp11.1 in the dic(X) chromosome.The ideogram illustration of the derivative dicentric X chromosome was presented in Figure 5 according to the results of SNP-array and G-banding.Breakage and reunion have occurred at bands p11.22 and q10 on the two X chromosomes to form a dicentric chromosome.

Table 1 summarized the clinical data of the patients with mosaic karyotype of 45,X/46,dic(X) from the published reports.Typical manifestations of TS patients include webbed neck,cubitus valgus,a shield-like chest,facial paralysis,short stature,no breast development after puberty,primary amenorrhea and gonadal dysplasia.For the clinical presentation of the TS patients with mosaic karyotype,the severity of phenotype and gonadal differentiation depends on the ratio of 45,X cells to normal cells during somatic and germ cell differentiation[29].Sandhya et al[31] described a juvenile ankylosing spondylitis (JAS) patient with phenotypic features of TS and mosaic karyotype of 45,X/46,X,dic(X),which indicated that haplo-insufficiency of the X chromosome may induce autoimmunity. A deletion of approximate 54.3Mb in Xp22.33-p11.22 was present in the fetus of this study.The short stature homeobox (SHOX) gene, located in Xp22, is responsible for skeletal features[32].Loss of distal short arm of X chromosome can lead to short stature and physical features of TS, but gonadal function is usually preserved. Menstruation is common in patients with Xp21.1-p22.1 or Xp22.2 deletions, but many patients remain infertile or have secondary amenorrhea[33].To our knowledge,this was the first study of prenatal diagnosis of a fetus with mosaic karyotype of 45,X/46,dic(X).

In conclusion,multiple previous literatures have reported that patients with this kind of karyotype exhibit Turner syndrome[18–31].Therefore,it is likely that the fetus of the current study would present the similar clinical characteristics of Turner syndrome.In this study, a combination of G-banding,C-bangding,SNP-array and FISH detection techniques was employed to provide adequate genetic counseling for the pregnant women, who decided to terminate the pregnancy due to the possibility of birth defects in the fetus.Therefore,this study can provide guidance for future pregnancy and fertility decision-making in prenatal diagnosis.

Declarations

Funding

This study is supported by Guangzhou Basic and Applied Basic Research Project Grant 202102080233.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

References

1. Chiatante G, Giannuzzi G, Calabrese F M, **et al**. **Centromere Destiny in Dicentric Chromosomes: New Insights from the Evolution of Human Chromosome 2 Ancestral Centromeric Region[J]**.Mol Bio Evol, 2017,**34**(**7**):**1669-1681**.
2. Page S L, Shin J, Han J, **et al**. **Breakpoint Diversity Illustrates Distinct Mechanisms for Robertsonian Translocation Formation[J]**.Hum Mol Genet,1996,**5**(**9**):**1279-1288**.
3. Kato T, Inagaki H, Miyai S, **et al**.**The involvement of U-type dicentric chromosomes in the formation of terminal deletions with or without adjacent inverted duplications[J]**. **Hum Genet,2020**.
4. Sullivan B A, Willard H F.**Stable dicentric X chromosomes with two functional centromeres[J]**.Nat Genet,1998,**20**(**3**): **227-228**.
5. Higgins A W,Gustashaw K,Willard H F, **et al**.**Engineered human dicentric chromosomes show centromere plasticity[J]**.Chromosome Res,2005,**13**(**8**): **745-762**.
6. Wang T,Lian J,Ren C,**et al**.**Prenatal diagnosis of mosaic trisomy 2 and literature review[J]Mol Cytogenet,2020,13;36**

7. McGowan-Jordan J, Simons A, Schmid M (**eds**) (2016**) An international system for human cytogenomic nomenclature**. S. Karger, **Basel**.[**Reprint of Cytogenet Genome Res 149**(**1**–**2**)].
8. Gravholt CH, Andersen NH, Conway GS, Dekkers OM, Geffner ME, Klein KO, **et al**. **Clinical practice guidelines for the care of girls and women with Turner syndrome**: **proceedings from the 2016 Cincinnati International Turner Syndrome Meeting**. **Eur J Endocrinol** 2017;**177**:**G1**–**70**.
9. TY Yu, HS Lin, PL Chen,**et al**. **An isodicentric X chromosome with gonadal dysgenesis in a lady without prominent somatic features of Turner's syndrome. A case report[J]**. J For Med Assoc, 2015, **114**(**1**).
10. Nishi, Yumie M, Correa, **et al**. **Tall stature and poor breast development after estrogen replacement in a hypergonadotrophic hypogonadic patient with a 45,X/46,X,der(X) karyotype with SHOX gene overdosage[J]**. Arq Bras De Endocrinol Metabol, 2008, **52**(**8**):**1282-1287**.
11. Ogata T, Inokuchi M, Ogawa M. **Growth pattern and body proportion in a female with short stature homeobox-containing gene overdosage and gonadal estrogen deficiency**. Eur J Endocrinol, 2002, **147**(**2**): **249-254**.
12. Lin C C, Li Y, Liu P P, **et al**. **Identification and characterization of a new type of asymmetrical dicentric chromosome derived from a single maternal chromosome 18[J]**. Cytogenet Genome Res, 2007: **291-296**.
13. Lebo R V, Milunsky J,Higgins A W ,**et al**.**Symmetric replication of an unstable isodicentric Xq chromosome derived from isolocal maternal sister chromatid recombination[J]**.Am J Med Genet Part A, 2010, **85**(**5**):**429-437**.
14. Sato H, Saitoh S. **Switching the centromeres on and off: epigenetic chromatin alterations provide plasticity in centromere activity stabilizing aberrant dicentric chromosomes[J]**. Biochem Soc Trans, 2013, **41**(**6**): **1648-1653**
15. Stimpson K M, Matheny J E, Sullivan B A, **et al**. **Dicentric chromosomes: unique models to study centromere function and inactivation[J]**.Chromosome Res,2012,**20**(**5**): **595-605**.
16. Sato H, Masuda F, Takayama Y, **et al**. **Epigenetic Inactivation and Subsequent Heterochromatinization of a Centromere Stabilize Dicentric Chromosomes[J]**. Curr Biol, 2012, **22**(**8**): **658-667**.
17. Therman E,Trunca C,Kuhn E M,**et al**. **Dicentric chromosomes and the inactivation of the centromere[J].Hum Genet,1986,72**(3):**191-195**.
18. Dalton P, Coppin B, James R S, **et al**.**Three patients with a 45,X/46,X,psu dic(Xp) karyotype.[J]**. J Med Genet,1998,**35**(**6**): **519-524**.
19. Pettigrew A L,Mccabe E ,Elder F ,**et al**. **Isodicentric X chromosome in a patient with Turner syndrome–implications for localization of the X-inactivation center.[J]**. Hum Genet,1991, **87**(**4**):**498-502**.
20. Petit P, Fryns J, Koumans J, **et al**. **X-chromosomes attached by their long arm: case report and replication kinetics of the rearranged X-chromosome[J]**. Clin Genet,2008, **21**(**6**): **384-387**.
21. Midro A T, Kulikowski M, Sawicka A, **et al**.**Familial occurrence of isodicentric X chromosomes with different breakpoints[J]**. Clin Genet,2008, **34**(**3**):**153-160**.
22. Yu C W, Chen H, Morrison J .**Kinetics of DNA replication in a dicentric X chromosome formed by long arm to long arm fusion[J].Hum Genet**,1980, **56**(**1**):**71**.
23. Luleci G, Hoslgor O, Karauzum S B, **et al**. **A rare case of Turner's syndrome with 45,X/46,X,Dic (X) (qter-**—p11.1::p11.4—qter). [J].Hereditas,2008,**113**(**3**): **217-220**.
24. Mattei J F,Taramasco H, Mattei M G,**et al**.**A girl with mosaicism for a dicentric X chromosome (45,X/46,X,dic(X)(Xqter→p22::p22→qter))[J]**.Hum Genet,1977,**38**(**1**):**39-48**.
25. Yu T,Lin H,Chen P,**et al**.**An isodicentric X chromosome with gonadal dysgenesis in a lady without prominent somatic features of Turner's syndrome. A case report.[J]**.J Formos Med Assoc, 2015, **114**(**1**):**77-80**.
26. Nishi, Yumie M, Correa, **et al**.**Tall stature and poor breast development after estrogen replacement in a hypergonadotrophic hypogonadic patient with a 45,X/46,X,der(X) karyotype with SHOX gene overdosage[J]**. Arq Bras Endocrinol Metabol,2008,**52**(**8**): **1282-1287**.
27. Petković I,Barisić I, Bago R. **Cytogenetic evaluation, fluorescence in situ hybridization, and molecular study of psu idic(X)(pter–>q22.3::q22.3–>pter) chromosome abberation in a girl with moderate growth retardation.[J]**.Cro Med J,2003, **44**(**4**):**494**.
28. Chen C P,Hwu Y M,Yeh I F,**et al**.**Successful triplet pregnancy and delivery after oocyte donation in an infertile female with chromosome mosaicism for monosomy X, partial trisomy X, and terminal Xp deletion[J].Fertil Sterili,2003,79**(5):**1231-1233**.
29. Yuan X, Zhu Z.**Turner syndrome with rapidly progressive puberty: a case report and literature review[J]**.J Int Med Res,2020,**48**(**5**):**030006051989691**.
30. Shah B, Moran E, Zinn A R, **et al**. **Effect of Growth Hormone Therapy on Severe Short Stature and Skeletal Deformities in a Patient with Combined Turner Syndrome and Langer Mesomelic Dysplasia[J]**.J Clinic Endocrinol Metab,2009,**94**(**12**): **5028-5033**.
31. Sandhya P,Danda D ,Danda S ,**et al**.**Juvenile ankylosing spondylitis in Turner syndrome.[**J].Natl Med J India,2013,**26**(**6**):**338-339**.
32. Rao E, Weiss B, Fukami M, **et al**.**Pseudoautosomal deletions encompassing a novel homeobox gene cause growth failure in idiopathic short stature and Turner syndrome[J]**. Nat Genet,1997, **16**(**1**):**54-63**.
33. Simpson J L,**Rajkovic A.Ovarian differentiation and gonadal failure.[**J].Am J Med Genet,1999,**89**(**4**):**186-200**.

Tables

Table 1. The summary of cases with mosaic karyotype of 45,X/46,X,dic(X) in published literature

Reference	Karyotype	Age	Height(cm)	Phenotype	Mosaic rate of 45,X cell line(%)	IQ	Molecular findings
Dalton et al[18]	mos45,X[98]/46,X,psu dic(X)(pter→q13.3::q13.3→pter)[32]	9	120.9	Triangular face with bilateral,severe ptosis and wide set eyes, hypermetropia,low posterior hairline, and low-set,posteriorly rotated ears.One hairy pigmented naevus. Bilateral clinodactyly and broad thumbs. Eczema and oesophageal reflux	75	79	FISH:DXZ2×2,XIST×1
Dalton et al[18]	mos45,X[73]/46,X,psu dic(X)(pter→q22.3::q22.3→pter)[27]	16	150.5	Broad face with hypertelorism,unilateral epicanthic fold,wide set eyes,high arched palate,low posterior hairline. Excess of pigmented naevi.Oedema of the fingers and toes.Broad chest,widely spaced,pale nipples.Only one small ovary.Hypertension and primary amenorrhea	73	94	FISH:DXZ2×2,XIST×2
Dalton et al[18]	mos45,X[4]/46,X,psu dic(X)(pter→q22.1::q22.1→pter)[96]	10	128.3	High,rounded palate,short,webbed neck,low posterior hairline.Bilateral lymphoedema, puffiness of lateral nail folds.Mild cubitus valgus. Subaortic stenosis,bicuspid aortic valve, coarctation of the aorta.Eczema	4	58	FISH:DXZ2×2,XIST×2
Pettigrew et al[19]	mos45,X[2]/46,X,idic(X)(pter→q13.2::q13.2→pter)[28]	28	142	Broad chest, widely spaced nipples. Small immature breasts.Brachycephaly,short webbed neck.Low posterior hairline,highly arched palate, mild micrognathia.Normal external genitalia, pubic hair. Tanner stage IV,small ovaries.Fourth metacarpal shortened on right hand,normal on left.Increased carrying angle, bilateral subluxation of the radial head.Primary amenorrhea	7	N	SB:DXYS1×1,DXYS2×1
Pettit et al[20]	mos45,X[80]/46,X,idic(X)(pter→q21::21→pter)[20]	16	146	Gonadal infantilism. Facial pigmented naevi, short neck, broad chest with hypoplastic, widely spaced nipples.Brachymetacarpy and brachymetatarsy IV-V.Discrete oedema of dorsum of the hands.Primary amenorrhea	80	NA	DNA-replication:q21 latest
Midro et al[21]	mos45,X[78]/46,X,idic(X)(pter→q21::21→pter)[22]	52	145	Slight webbing of the neck. Scanty axillary and pubic hair.Poor breast development. Shield chest with widely spaced nipples.External genitalia infantile. Small uterus,bilateral streak gonads. Hypertensive and primary amenorrhea	78	NA	DNA-replication:q21 latest
Yu et al[22]	mos45,X[69]/46,X,idic(X)(pter→q23::23→pter)[31]	16	155	Absence of axillary hair,scanty pubic hair,infantile external genitalia,no palpable ovaries,barely palpable	69	NA	DNA-replication:q21 latest

				uterus. Slight breast development and primary amenorrhea			
Luleci et al[23]	mos45,X[68]/46,X,idic(X)(qter→p11.1::p11.4→qter)[32]	30	143	Cubitus valgus, small breasts, female type pubic and axillary hair and small uterus.Small uterus, normal fallopian tubes, bilateral streak gonads. Horse-shoe kidney and primary amenorrhea.	68	N	NA
Mattei et al[24]	mos45,X[98]/46,X,idic(X)(qter→p22::p22→qter)[2]	12	124	Prominent rounded forehead and convergent strabismus.Moderate cubitus valgus.Infantile external genitalia.Absence of breast tissue, axillary and pubic hair.	98	N	NA
Yu et al[25]	mos45,X[30]/46,X,idic(X)(qter→q22::q22→qter)[10]	21	157.7	Gonadal dysgenesis.Short neck and acanthosis nigricans.Tanner stage III breast development. Small uterus and ovaries	75	N	NA
Ninshi et al[26]	mos45,X[4]/46,X,psu idic(X)(pter→q21::q21→ pter) [46]	16	183	Absence of secondary sexual development Tanner II breast development,Tanner V pubic hair and normal female external genitalia	8	N	FISH:KAL×3,SHOX×3
Petković et al[27]	mos45,X/46,X,psu idic(X)(pter→q22.3:: q22.3→ pter)	4	99	Short stature.Slightly hypotonic.Moderate growth retardation and slight dysmorphic features	16	NA	FISH:DXZ1×3(84%),DXZ1×1 (16%)
Chen et al[28]	mos45,X[10]/46,X,psu idic(X)(qter→p22.3::p22.3→qter)[40]	23	150	Webbed neck, cubitus valgus, and multiple pigmented nevi on face.Tanner stage 3 breast development and Tanner stage 4 pubic hair.A small uterus.Hypoplastic uterus, normal fallopian tubes, and bilateral streak ovaries.	20	NA	FISH:terminal Xp deletion
Yuan et al[29]	mos45,X/46,X,idic(X)(pter→q21.32::q21.32→pter)	9	119	Stage B1 bilateral breasts with a wide breast distance.A shield-like chest and webbed neck.Mild cubitus valgus and slightly obvious warped hips.	90	NA	CMA:45,X(90%)
Shah et al[30]	mos45,X[17]/46,X,idic(X)(qter→p11.23::p11.23→qter)[3]	11	86.5	Cycloplegia,hypermetropia and hyperopic astigmatism.Mild retrognathia and high-arched palate. Tanner stage II few straight pubic hair.Absence of axillary hair.Rhizomelic/mesomelic shortening of all limbs bilateral Madelung deformity with ulna deviation. Mildlevoscoliosis with the apex at Thorasic spine. Bilaterally short fourth metacarpals.Marked shortening and thickening with metaphyseal flaring of femur, tibia,fibula,humerus, ulna, and radius bilaterally. Absence of bilateral ovaries	85	NA	FISH:idic(X)(p11.23)(wcpX+, DXZ1x2)
Sandhya et al[31]	mos45,X[19]/46,X,psu idic(X)(qter→p11::p11→ qter)[6]	20	134	Short stature,webbed neck and micrognathia. Absence of axillray hair.Tanner stage I breast development and pubic hair.Hypoplastic uterus, absent ovaries and	76	NA	FISH:mosaic monosomy X and psu idic(X)

horseshoe kidneys.Severe osteoporosis

N:normal;SB:Southern bolt;FISH:fluorescence in situ hybridization;NA:not available.CMA:chromosome microarray analysis;

Figures

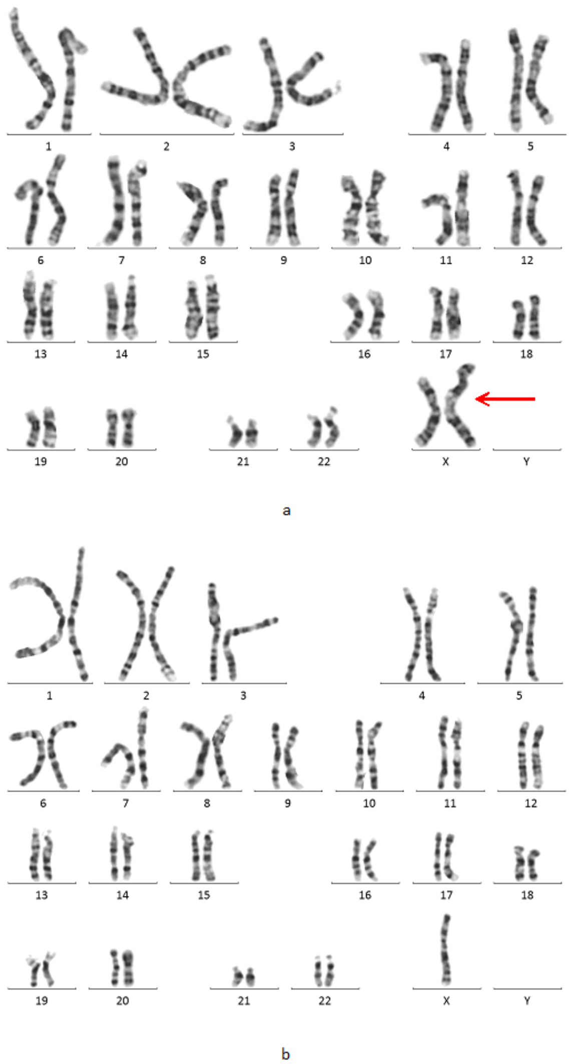

Figure 1

a:Karyotype of 46,X,dic(X) from amniotic cell culture and the derivative dicentric X chromosome was indicated by the red arrow;b:Karyotype of 45,X.

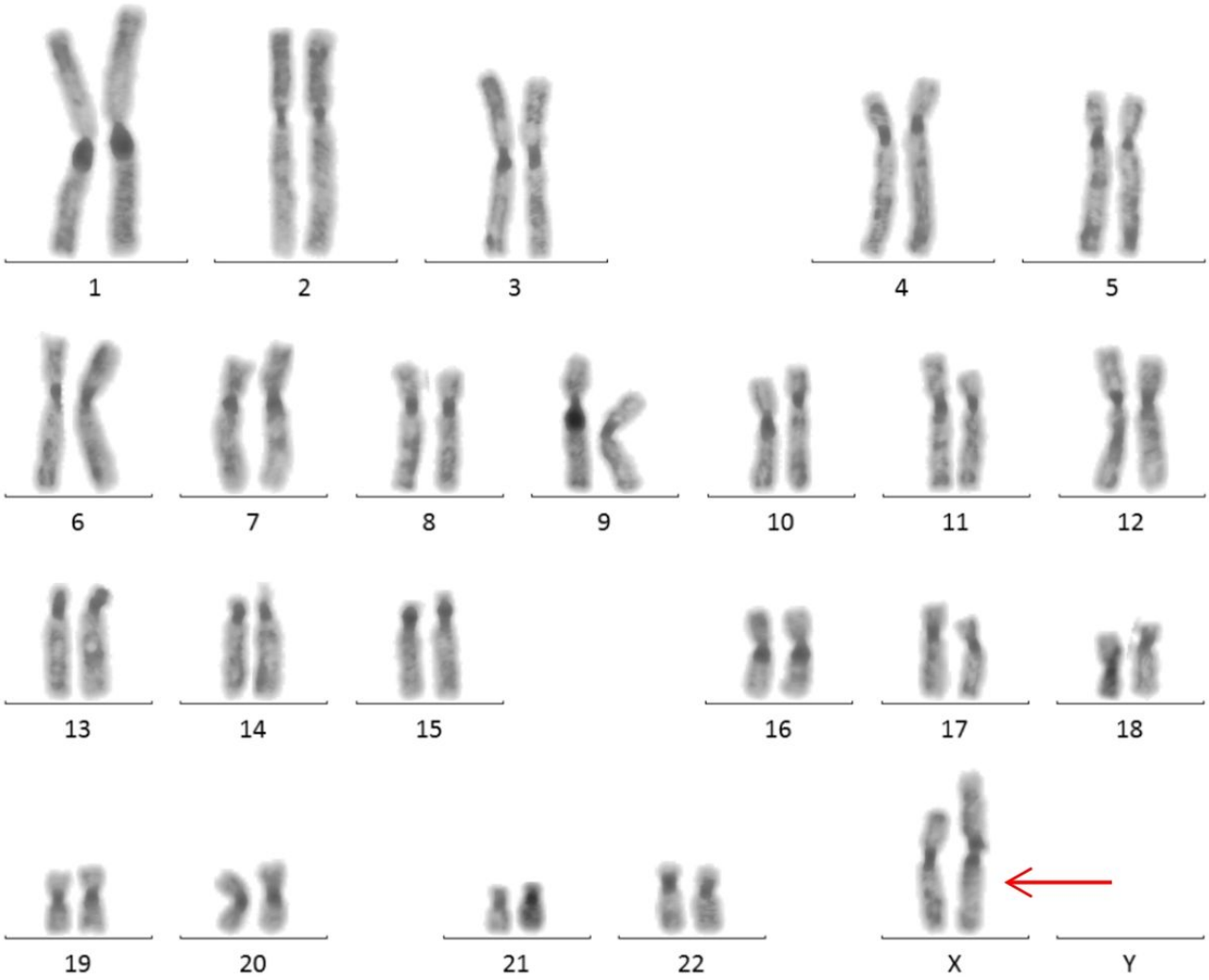

Figure 2

Karyotype of C-banding and two darkly stained bands near the centromere of the derivative dicentric X chromosome were pointed by the red arrow.

Figure 3

a:Metaphase FISH from uncultured amniotic cell shows presence of one centromere(green signal) on the the normal X chromosome and presence of two closely spaced centromeres(red arrow pointed) on the dicentric X chromosome.The aqua signal was from the control probe of D18Z1.b:Interphase FISH from uncultured amniotic cell shows presence of two cell line,one of which was 45, X cell line with only one green signal and the other 46,X,dic(X) cell line with three green signals.

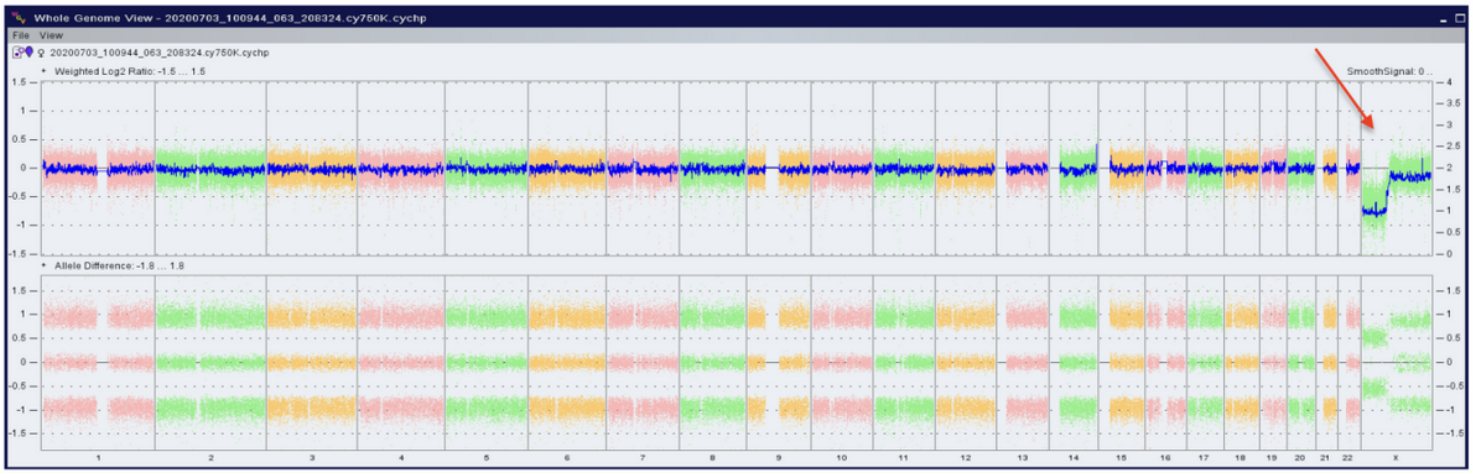

Figure 4

Single nucleotide polymorphism array using DNA extracted from uncultured amniotic fluid cells.The red arrow shows the whole genome view of X chromosome deviated from baseline and it indicates that the X chromosome may be presence of mosaicism.

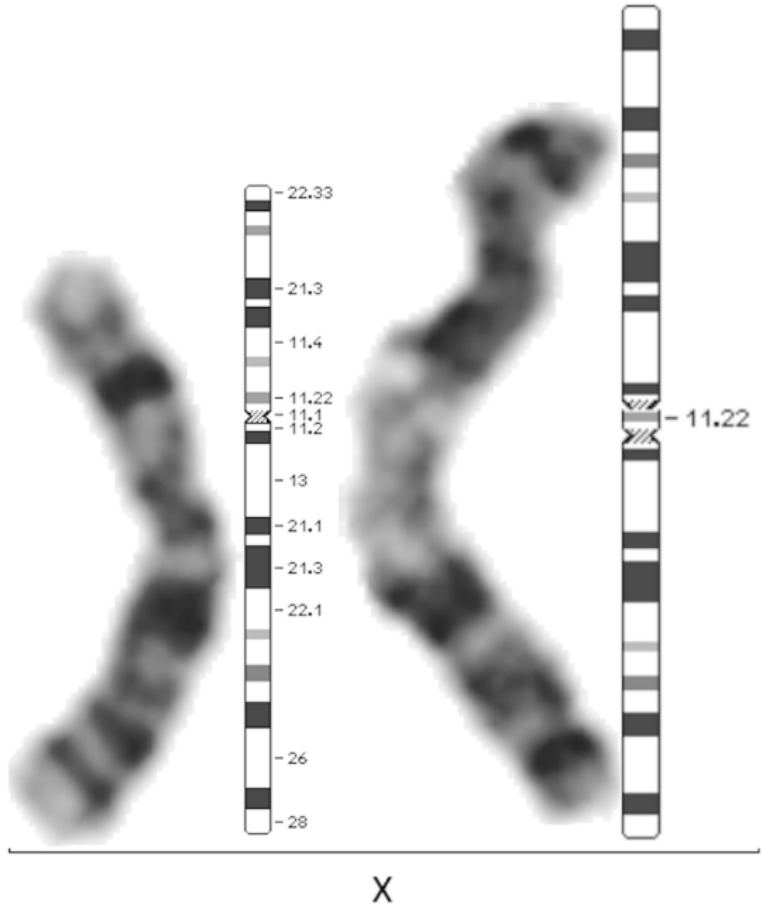

Figure 5

Ideogram of the X chromosome.The normal X chromosome is on the left, and the derivative dicentric X chromosome is on the right.