Taiwanese Journal of Obstetrics & Gynecology 55 (2016) 877–880

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Case Report

Prenatal diagnosis of paternal duplication of 11p15.5→14.3: Its implication of Beckwith–Wiedemann syndrome

Kuan Ju Chen [a], Yu Mei Liu [b], Chien Hong Li [c], Yao Lung Chang [a], Shuenn Dyh Chang [a, *]

[a] Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, Lin-Kou Medical Center, Chang Gung University, Taoyuan, Taiwan
[b] Cytogenetic Laboratory, Department of Obstetrics and Gynecology, Keelung Chang Gung Memorial Hospital, Keelung City, Taiwan
[c] Department of Medicine, Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan

ARTICLE INFO

Article history:
Accepted 20 May 2016

Keywords:
array comparative genomic hybridization
Beckwith–Wiedemann syndrome
karyotyping
short tandem repeat marker

ABSTRACT

Objective: To characterize a prenatally detected chromosomal aberration with molecular cytogenetic approaches and explore its relationship with Beckwith–Wiedemann syndrome (BWS).
Case report: A 33-year-old woman, gravida 2, para 0, was referred to our prenatal clinic at 20+ weeks due to an abnormal amniocentesis karyotyping finding, which showed 46,XY,add(11)(q24.2)dn. The mother conceived through *in vitro* fertilization–intracytoplasmic sperm injection (IVF-ICSI), then embryo transfer. Fetal ultrasound revealed a left-sided congenital diaphragmatic hernia, overgrowth of the fetus, and an enlarged placenta. After genetic counseling and careful deliberation by the family, the pregnancy was subsequently terminated at 22+ weeks of gestation, delivering a fetus weighing 810 g (85^{th} to 90^{th} centile) and a placenta of 325 g (85^{th} to 90^{th} centile). To further delineate the nature of the rearrangement involved in the defective chromosome 11, repeat chromosomal analyses, including array comparative genomic hybridization (aCGH) test and quantitative fluorescence–polymerase chain reaction (QF-PCR) using short tandem repeat (STR) markers, were performed by sampling fetal tissue. The final result confirmed a diagnosis of 46,XY,del(11)(q24.3q25),dup(11)(p14.3p15.5). The abnormal chromosome 11 was inherited from the father and the duplicated segment involved 11p15.5, a critical imprinting region for BWS.
Conclusion: We presented a prenatally detected chromosomal aberration characterized by paternal duplication of chromosome 11p15.5, which strongly related to the phenotypic manifestation of BWS.

Introduction

Beckwith–Wiedemann syndrome (BWS) is an overgrowth malformation disorder; it is a model imprinting abnormality. The molecular basis of BWS is associated with mutations or epigenetic events happening on the genes at the chromosome 11p15.5 critical imprinting region. Loss of methylation at LIT1, causing LIT1 overexpression is the most frequent genetic abnormality in BWS, accounting for 60% of cases. Other mechanisms responsible for BWS occur with lower frequencies, including 20% with 11p15.5 paternal uniparental disomy (UPD), 5% with CDKN1C mutations and 2% to 7% with H19 hypermethylation. The remaining 1% to 2% are reported as cytogenetic abnormalities [1]. According to Brown et al [2] and Krajewska-Walasek et al [3], chromosomal duplication of 11p15.5, if of paternal origin, could bring about the BWS phenotype. They also maintained that functional trisomy of the 11p segment, even though nonimprinted, might contribute to the phenotype as well. Clinical features of patients with duplication of 11p and BWS encompassed overgrowth, macroglossia, abdominal wall defect, visceromegaly, renal anomalies, hemihypertrophy, inguinal hernia, ear anomalies, hypoglycemia, and so on [4].

We herein presented a prenatal diagnosis of an aberrant chromosome 11, the case displaying fetal ultrasound characteristics implicating BWS. By applying array comparative genomic hybridization (aCGH), the exact breakpoints on chromosome 11 were revealed, involving a duplication of the distal segment of the short arm and a deletion of the distal segment of the long arm. Further quantitative fluorescence–polymerase chain reaction (QF-PCR) analysis using a polymorphism short tandem repeat (STR) marker

* Corresponding author. Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, 5 Fu-Hsing Street, Taoyuan, Taiwan.
E-mail address: gene@cgmh.org.tw (S.D. Chang).

http://dx.doi.org/10.1016/j.tjog.2016.05.012

on 11p11.5 was able to pinpoint the abnormal chromosome arising from paternal inheritance.

Case report

A 33-year-old, gravida 2, para 0, pregnant patient visited our prenatal clinic for a second opinion due to an abnormal genetic amniocentesis finding of 46,XY,add(11)(q24.2)dn detected at another hospital. She was then at 20+ weeks' gestation, having conceived via *in vitro* fertilization–intracytoplasmic sperm injection (IVF-ICSI) then embryo transfer due to a male factor. The karyotype that caught attention was an abnormal chromosome 11 with additional genetic materials attached to the end of its long arm at band 11q24.2. According to the patient, she and her partner had had their chromosomes checked and they were all normal. However, a fetal ultrasound examination done at our hospital found a left-sided congenital diaphragmatic hernia (Figure 1), originally unknown to the patient and family, accompanied by an enlarged fetus, enlarged placenta, and mild polyhydramnios. After genetic counseling and over a week of deliberation by the family, the pregnancy was discontinued at 22+ weeks, where a male fetus weighing 810 g and the placenta at 325 g were delivered, both weighing close to the 90th centile for the gestation. There were no other apparent abnormalities detected on the fetus. The family agreed to further investigate the aberrant chromosome 11. Subsequently, by sampling the fetal tissue, repeated conventional karyotyping (Figure 2) and aCGH were performed. The latter using Agilent 8 × 60 K gene chip (Agilent, Santa Clara, CA, USA) featured a resolution of 0.05–0.5 Mb and disclosed arr[hg19] 11p15.5p14.3(196966–250338960) × 3 and arr[hg19] 11q24.3q25(9129510272–134868407) × 1 (Figure 3), indicating a partial trisomy in 11p15.5-14.39 (about 25 Mb) and a deletion in 11q24.3-q25 (about 5.3 Mb). Since the duplicated chromosome 11p segment involved a critical region containing genes for BWS, further QR-PCR analysis using an STR marker specific for 11p15.5 (Amp FISTR Identifier PCR Amplification Kit, Applied Biosystems, Waltham, MA, USA) on the DNA from both parents and the fetus revealed a *de novo* duplication of 11p15.5 and a paternal origin of the duplication (Figure 4).

Discussion

A prenatal diagnosis of a chromosomal aberration with an undetermined nature may give rise to difficulties in genetic counseling not only regarding the present pregnancy but also regarding future pregnancies. The molecular cytogenetics approach using aCGH clearly pinpointed the exact condition and detailed the size of the aberration. The QF-PCR technique further provided insights into the origin of the abnormality, giving a genetic fingerprint of the fetus by amplification of microsatellite markers.

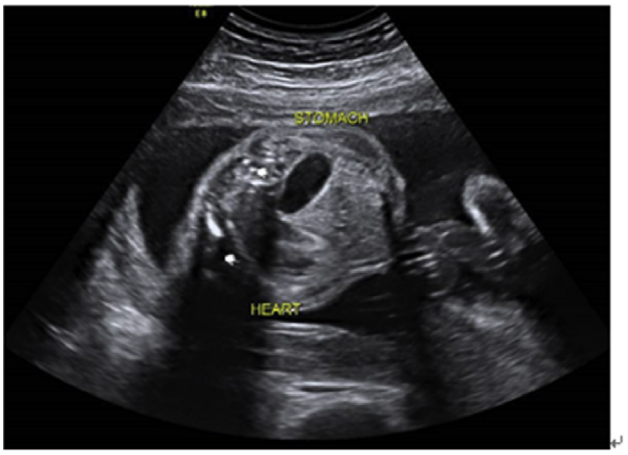

Figure 1. Left-sided congenital diaphragmatic hernia of the fetus.

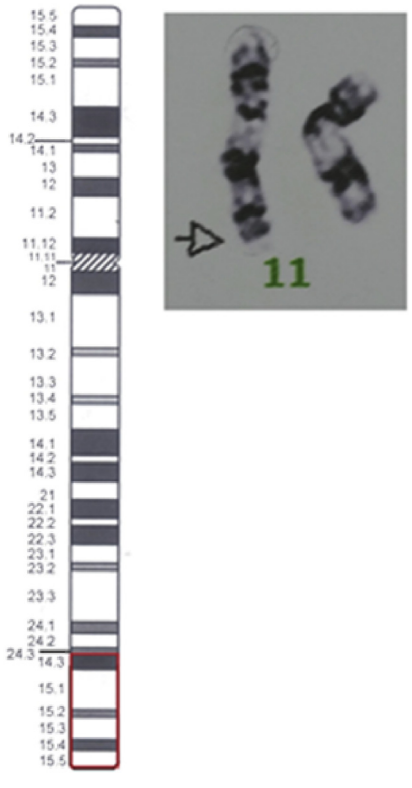

Figure 2. A partial Giemsa-banded karyotype of a pair of chromosomes 12; the arrow pointing to the aberrant chromosome 11 [add(11)(q24.3)dn] and near where the duplication and deletion occurred; the ideogram showing the duplicated segment 11p15.5-14.3 framed in red.

We presented a case of prenatally detected cytogenetic abnormality that was later proven to encompass a paternal duplication of chromosome 11p11.5, indicating a relationship with BWS. BWS is an overgrowth disorder; the majority of cases of which are due to imprinting problems of the genes over the 11p1.5 area, with only a minority of cases (1–2%) caused by cytogenetic abnormalities [1]. A double expression of a paternally inherited 11p15 locus or loci can bring about the BWS phenotype [2,3,5]. Functional trisomy of unimprinted chromosome 11p segments may otherwise contribute to the phenotype [5].

Chen et al described a prenatal diagnosis of BWS characterized by an ultrasound finding of omphalocele at 21 weeks of gestation where a methylation-specific PCR assay confirmed altered methylation status at 11p15.5 with hypomethylation at KvDMR1(IC2) and normal methylation at H19DMR(IC1) [6]. Another report featured a 32-week prenatal BWS case published by Ma et al showing an overgrown fetus (2990 g) accompanied by hepatomegaly, nephromegaly, fetal macroglossia, and a molecular mechanism confirmed with LIT1 hypomethylation using an endonuclease-coupled quantitative PCR method [1]. Reish et al suggested that macrosomia, polyhydramnios, enlarged placenta, and distended abdomen are the constant prenatal findings [7]. Our case was caused by a cytogenetic double dosage of paternal 11p15.5

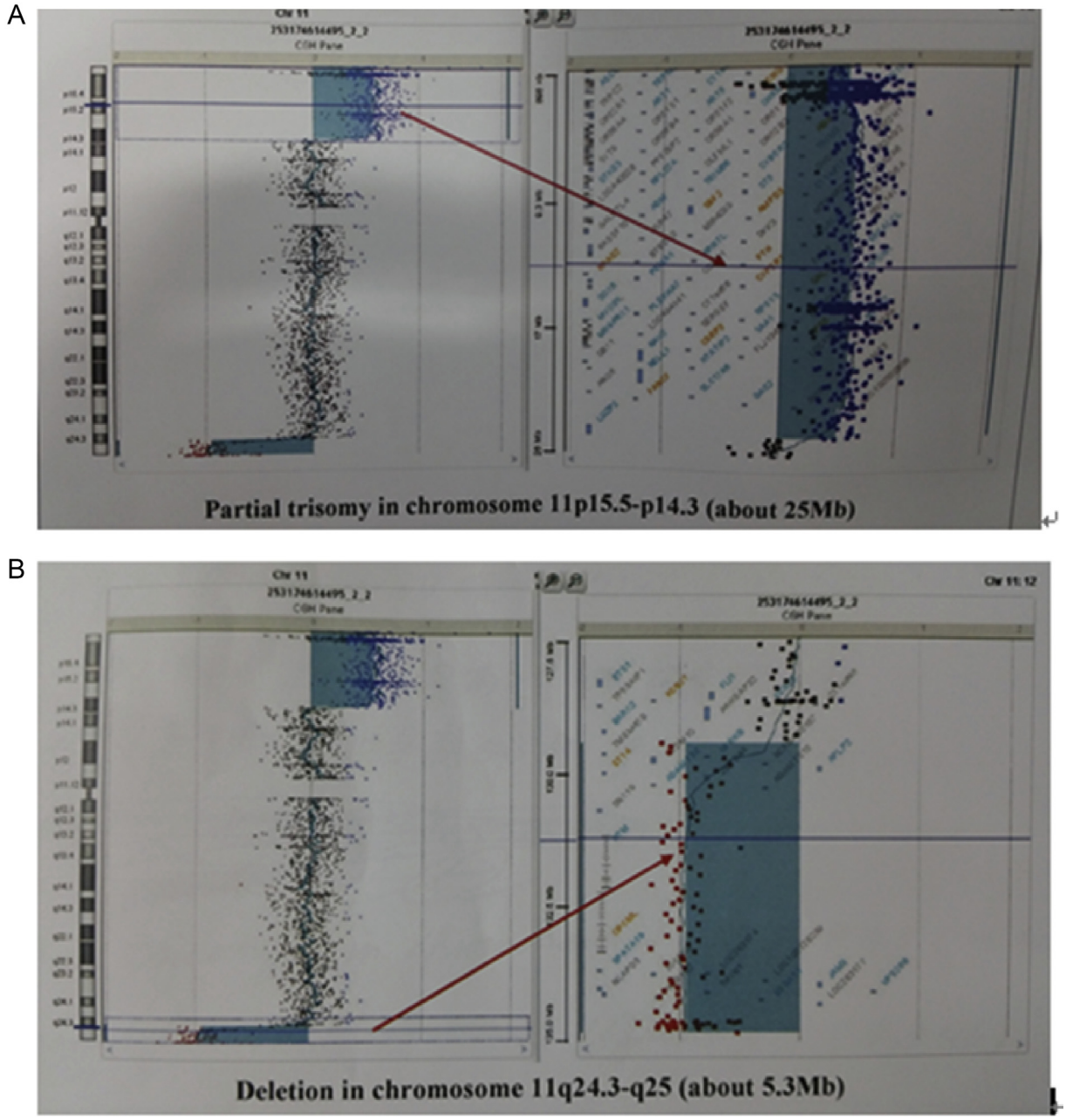

Figure 3. Array comparative genomic hybridization analysis exhibiting (A) a 25-Mb duplication of 11p15.5-14.3 and (B) a 5.3-Mb deletion of 11q24.3-q25.

presented at 20+ weeks with macrosomia, placentomegaly, along with a left-sided congenital diaphragmatic hernia (Table 1). BWS involving the diaphragm was reported showcasing a trisomy 11p 15 where one of the clinical findings was posterior diaphragmatic eventration [8].

Children conceived by IVF-ICSI are at an increased risk of developing BWS [9]. However, in the majority of cases abnormal methylation at the imprinted 11p15.5 critical region is to blame [10]. Different from a molecular imprinting disorder, our case, with a male factor problem and conceived through IVF-ICSI, had a chromosomal abnormality involving the sperm. Abnormalities of meiotic recombination during spermatogenesis may happen like in the situation of pericentric inversion where a crossover within the inversion loop may lead to the production of two complementary chromosomes. One of these has a duplication of the distal segment of the short arm and a deletion of the distal segment of the long arm and the other chromosome has the opposite [11]. Our case had duplication of the distal segment of the short arm of chromosome 11, dup(11)(p14.3pter), and deletion of the distal segment of the long arm, del(11)(q24.3qter).

In conclusion, our case demonstrated that by analyzing ultrasound images, conventional cytogenetic finding, and molecular cytogenetic results, we were able to explore the relationship of a prenatal case with BWS.

Molecular result using a polymorphic DNA marker specific for 11p15.5

Locus designation	Chromosome location	Alleles included in AmpFℓSTR® Identifiler® Allelic Ladder
TH01	11p15.5	4, 5, 6, 7, 8, 9, 9.3, 10, 11, 13.3

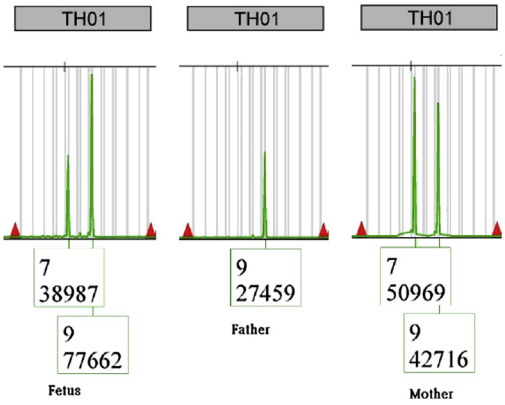

Figure 4. Quantitative fluorescence–polymerase chain reaction short tandem repeat marker analysis.

Table 1
Prenatal ultrasound features of Beckwith–Wiedemann syndrome patients with a duplication of 11p with normal karyotypes.

Prenatal image	No duplication		Duplication 11p15.5
	Hypomethylation KvDMR1(IC2), Chen et al. 21+ weeks	LIT1 hypomethylation, Ma et al. 32 weeks	Our case 20+ weeks
Macrosomia		+	+
Placentomegaly			+
Macroglossia		+	
Hepatomegaly		+	
Nephromegaly		+	
Omphalocele	+		
Congenital diaphragmatic hernia			+

Conflicts of interest

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

References

[1] Ma GC, Chang SD, Chang Y, Chang SP, Yang CW, Lee MJ, et al. Rapid prenatal confirmation of LIT1 hypomethylation using a novel quantitative method (E-Q-PCR) in fetuses with Beckwith–Wiedemann syndrome impressed with ultrasonography. Fertil Steril 2008;90:1279–82.
[2] Brown KW, Gardner A, Williams JC, Mott MG, McDermott A, Maitland NJ. Paternal origin of 11p15 duplications in the Beckwith–Wiedemann syndrome. A new case and review of the literature. Cancer Genet Cytogenet 1992;58:55–70.
[3] Krajewska-Walasek M, Gutkowska A, Mospinek-Krasnopolska M, Chrzanowska K. A new case of Beckwith–Wiedemann syndrome with 11p15 duplication of paternal origin. In: International Symposium on Genomic Imprinting. Florence: University of Florence; 1994. p. 93.
[4] Slavotinek A, Gaunt L, Donnai D. Paternally inherited duplications of 11p15.5 and Beckwith–Wiedemann syndrome. J Med Genet 1997;34:819–26.
[5] Li M, Squire JA, Weksberg R. Molecular genetics of Beckwith–Wiedemann syndrome. Am J Med Genet 1998;79:253–9.
[6] Chen CP, Su YN, Chen SU, Chang TY, Wu PC, Chern SR, et al. Prenatal diagnosis of hypomethylation at KvDMR1 and Beckwith–Wiedemann syndrome in a pregnancy conceived by intracytoplasmic sperm injection and in vitro fertilization and embryo transfer. Taiwan J Obstet Gynecol 2014;53:90–4.
[7] Reish O, Lerer I, Amiel A, Heyman E, Herman A, Dolfin T, et al. Wiedemann–Beckwith syndrome: further prenatal characterization of the condition. Am J Med Genet 2002;107:209–13.
[8] Turleau C, de Grouchy J, Chavin-Colin F, Martelli H, Voyer M, Charlas R. Trisomy 11p15 and Beckwith-Wiedemann syndrome. Hum Genet 1984;67(2):219–21.
[9] Halliday J, Oke K, Breheny S, Algar E. Beckwith–Wiedemann syndrome and IVF: a case-control study. Am J Hum Genet 2004;75:526–8.
[10] Chen CP. Prenatal findings and the genetic diagnosis of fetal overgrowth disorders: Simpson–Golabi–Behmel syndrome, Sotos syndrome, and Beckwith–Wiedemann syndrome. Taiwan J Obstet Gynecol 2012;51:186–91.
[11] Gardner RJM, Sutherland GR, Shaffer LG. Chromosome abnormalities and genetic counseling. Oxford Monographs on Medical Genetics No. 46. New York: Oxford University Press; 2004. p. 142–62.