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Taiwanese Journal of Obstetrics & Gynecology 51 (2012) 260–265

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Case Report

Prenatal diagnosis of microdeletion 16p13.11 combination with partial monosomy of 2q37.1-qter and partial trisomy of 7p15.3-pter in a fetus with bilateral ventriculomegaly, agenesis of corpus callosum, and polydactyly

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Accepted 21 March 2012

Abstract

Objective: To present a prenatal diagnosis of microdeletion 16p13.11 with partial monosomy of 2q37.1-qter and partial trisomy of 7p15.3-pter in a fetus with bilateral ventriculomegaly, agenesis of corpus callosum, and polydactyly.
Case Report: A 41-year-old well-being Taiwanese, nulligravida woman received amniocentesis at a gestational age of 18 weeks for advanced maternal age. The fetus' karyotype showed 46,XY,der(2)t(2;7)(q36.2;p15.1). Both parents also received cytogenetic examinations and the mother's karyotype revealed 46,XX,t(2;7)(2q36.2;p15.1). High-resolution ultrasound showed the fetus had bilateral ventriculomegaly, agenesis of corpus callosum, and polydactyly of the right hand. After the termination of this pregnancy, the whole genome oligonucleotide-base array comparative genomic hybridization (CGH) by using fetal skin cells demonstrated a 8.44-Mb deletion at 2q37.1 (234602276-243041305), a 22.8-Mb duplication (65558-22869338) at 7p15.3, and an additional 1.32-Mb deletion (14968855-16292235) at 16p13.11.
Conclusion: Array CGH is a useful tool not only to discover the genomic imbalance at the breakpoints as well as to detect unexpectedly complex rearrangements in other chromosomes. Our case also provided evidence that genomic aberration at chromosome 16p13.11 involves in the formation of polydactyly.

Keywords: agenesis of corpus callosum; microdeletion 16p13.11; polydactyly; ventriculomegaly

Introduction

Amniocentesis can detect inherited or *de novo* reciprocal translocations. Parents may be aware of their carrier status only after amniocentesis was performed. Jacobs and colleagues [1] found a prevalence of 0.218% for unbalanced structural rearrangements and a prevalence of 0.017% for unbalanced reciprocal translocations at prenatal diagnosis. The reciprocal translocations (products), which have gained or lost genetic materials, are called unbalanced reciprocal translocation. Most unbalanced translocations would produce such enormous genetic imbalance that the conceptus would be lost very early in pregnancy or even fail to implant. Chen and colleagues [2] reported in Taiwan that most unbalanced reciprocal translocations detected at amniocentesis were ascertained through abnormal ultrasound findings (44.8%, 13/29), and more than 80% of the fetus with unbalanced reciprocal translocations were associated with clinical abnormalities. Hillman and colleagues [3] reported an increasing of diagnostic yield up to 5.2% (95% confidence interval: 1.9–13.9) for genomic imbalance by array comparative

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1028-4559/$ - see front matter
doi:10.1016/j.tjog.2012.04.017

genomic hybridization (CGH) more than conventional karyotyping when the referral indication was a structural malformation on ultrasound [3]. Here, we report a fetus with bilateral ventriculomegaly, agenesis of corpus callosum, and polydactyly of the right hand in prenatal ultrasound at gestational 20 weeks; the fetus had inherited unbalanced reciprocal translocation involving in chromosome 2q37.1 and 7p15.3 from the mother and also had an additional microdeletion of 16p13.11 identified by high-resolution array CGH.

Case report

A 41-year-old well-being Taiwanese, gravida 1, para 0 woman received a regular prenatal survey and received amniocentesis at 16 weeks of gestation because of her advanced maternal age. She and her husband denied any personal or family history of birth defect or abnormality and denied consanguinity. The fetal karyotype showed 46,XY,der(2)t(2;7)(q36.2;p15.1; Fig. 1A). Parents received further investigation and the mother's karyotype revealed 46,XX,t(2;7)(q36.2;p15.1; Fig. 1B). After abnormal karyotype revealed, high-resolution ultrasound showed bilateral ventriculomegaly, agenesis of corpus callosum (tear-drop sign) and polydactyly of right hand (Fig. 2A to C). The fetus revealed normal development: the estimated body weight was 406 g (50th percentile), biparietal diameter was 54 mm (90th percentile), femoral length was 34 mm (90th percentile), and abdominal circumference was 160 mm^2 [90th percentile]. Fetal magnetic resonance imaging performed at the same week showed similar results (Fig. 2D). After genetic counseling with parents, the termination of pregnancy was performed at 21 weeks of gestation. The appearance of the abortus revealed polydactyly over the right hand, a thin upper lip with a thick lower lip, and large anterior fontanelle (Fig. 3A to C). The parents refused autopsy of the fetus; thus, a central nervous system condition could not be confirmed. Further investigation of the abnormality was suggested and oral informed consent was obtained from the parents. Cultured fetal skin cell showed the same karyotype.

Fluorescent in situ hybridization (FISH) studies on the cultured fetal skin cells indicated the breakpoint on chromosome 2 is at 2q37.1 with a physical position of 235.24-235.44 Mb and the breakpoint on chromosome 7 is at 7p15.3 with a physical position 22.80-22.96 Mb (Fig. 4A and B). Oligonucleotide-based (oligo) aCGH (SurePrint H3 Human CGH Microarray Kit 4x180k; Agilent Technologies, Santa Clara, CA, USA) using culture fetal skin cell demonstrated a 8.44-Mb deletion at 2q37.1-qter (234602276-243041305), a 22.8-Mb duplication (65558-22869338) at 7p15.3-pter, and an additional 1.32-Mb interstitial deletion (14968855-16292235) at 16p13.11 (Fig. 4C and D).

Discussion

The present case of apparently unbalanced reciprocal translocations identified by conventional karyotype had multiple abnormalities, including bilateral ventriculomegaly, agenesis of corpus callosum (tear-drop sign), and polydactyly of the right hand. Array CGH helped to identify additional change of genomic changes at 16p13.11. Application of array CGH in the prenatal or postnatal setting to help detection of copy number variations, such as microdeletion and microduplication, is increasing [4]. Chen and coauthors [5] reported that array CGH had found an additional microduplication 2p12 in a case with balanced reciprocal translocation, 46,XY,t(3;11)(q14;q23). Chen and team [5] also described a fetus at 18 weeks' gestation with facial dysmorphism and hypospadias, and amniocentesis revealed a karyotype of 46,XY,del(4p16.1), and further array CGH analysis revealed a 6.5-Mb deletion at 4p16.3-p16.1, a 1.2-Mb microduplication at 8p22-p21.3, and a 1.1-Mb microduplication at 10p15.3 [6]. Therefore, precise definitions of simple or complex apparently balanced or imbalanced reciprocal translocations should include genome-wide aneuploidy diagnosis such as array CGH to find any subtle chromosome imbalance that may have occurred in other chromosomes.

Chromosome 16p13.11 recently has been reported as a region of recurrent microdeletion/duplication [7]. Microdeletion of 16p13.11 has been reported with multiple congenital

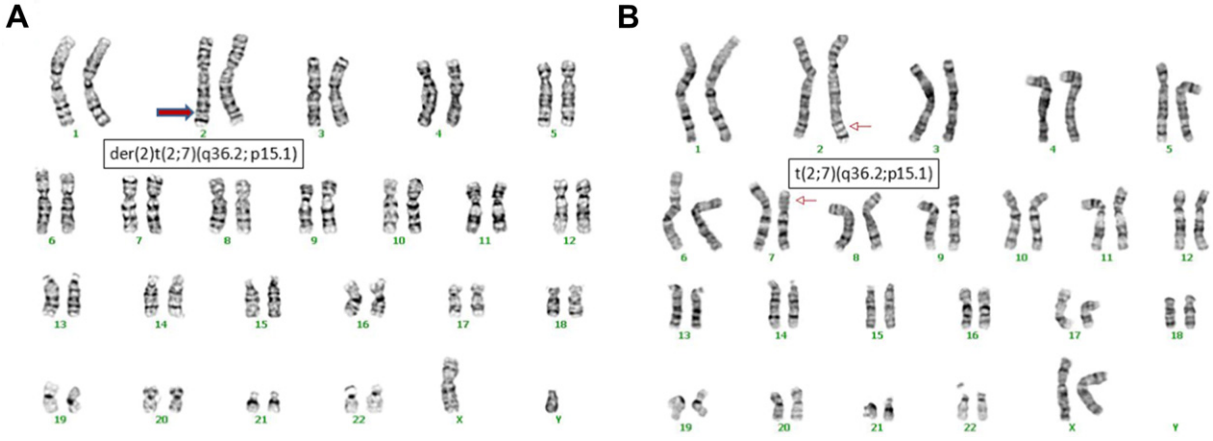

Fig. 1. (A) Fetal karyotype; (B) maternal karyotype.

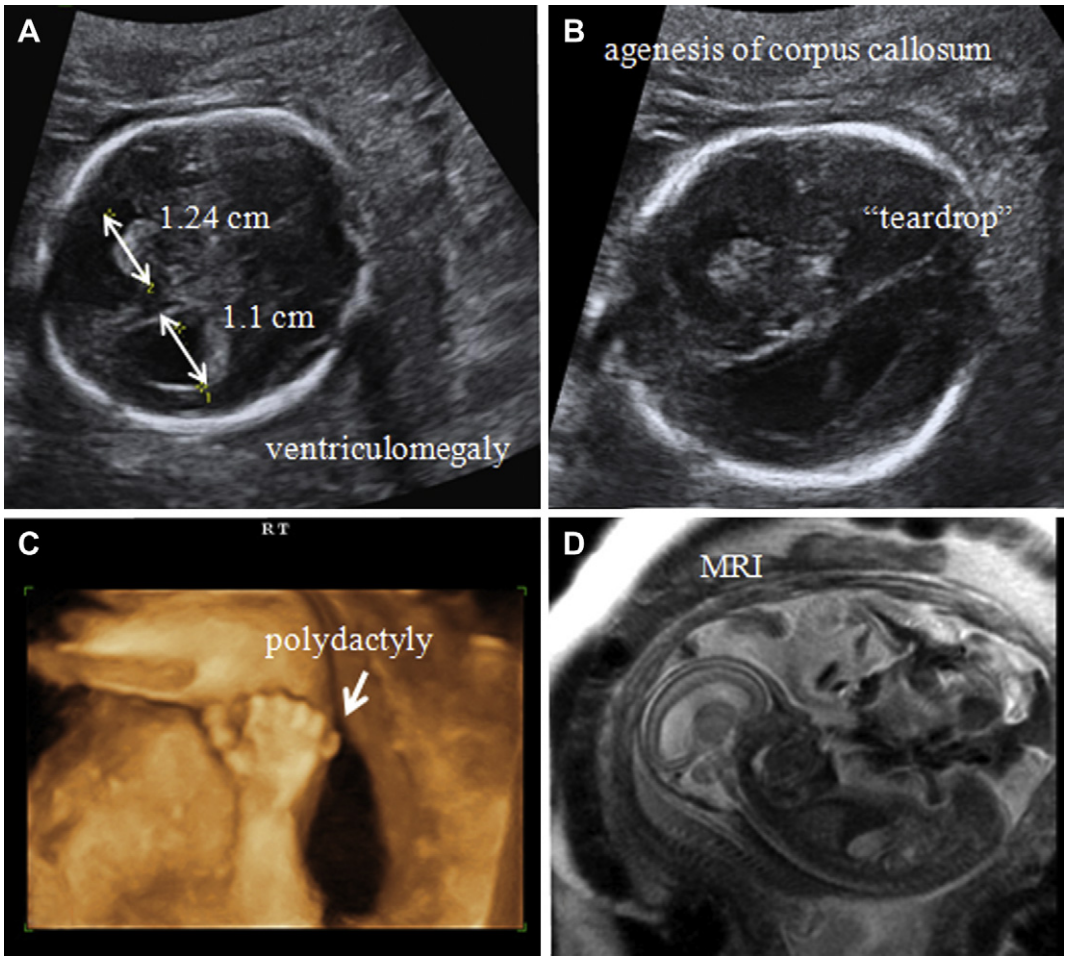

Fig. 2. Ultrasound showed ventriculomegaly, agenesis of corpus callosum and polydactyly(A–C). Magnetic Resonance Imagin presented ventriculomegaly (D).

abnormalities, including moderate to severe mental retardation, schizophrenia, developmental delay, and idiopathic generalized epilepsy. The present case had a 1.32-Mb microdeletion in 16p13.11 [arr cgh 16p13.11(14968655-19292381)x1] encompassing the genes NDE1,MYH11,ABCC6. NDE1 [Online Mendelian Inheritance in Man (OMIM) 609449], which is strongly expressed in the brain, can causes lissencephaly-4 (LIS4; OMIM 614019), which is an autosomal recessive neurodevelopment disorder characterized by lissencephaly, severe brain atrophy, and extreme microcephaly [7]. Hannes and others [8] also described a 21 weeks' fetus with deletion of 16p13.11 who had posthemorrhagic hydrocephalus with marked ventriculomegaly, cortical thinning, hypoplastic falx cerebri, cleft lip on right, two preauricular skin tags on right, and cleft T1 and T3 vertebral bodies. Haploinsufficiency of this gene in the present case apparently caused severe consequences for brain development, such as ventriculomegaly and agenesis of corpus callosum. MYH11 (OMIM 160745), or MYOSIN, HEAVY

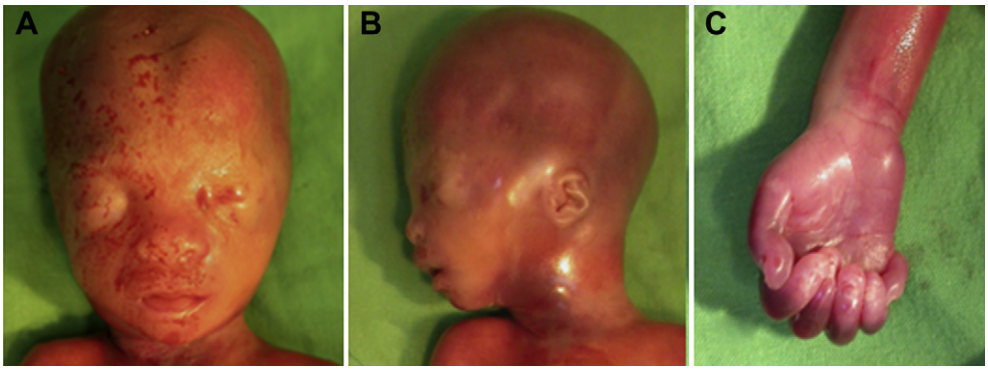

Fig. 3. (A) Anterior view: thin upper lip with thick lower lip and large anterior fontanelle; (B) lateral view; (C) polydactyly of right hand.

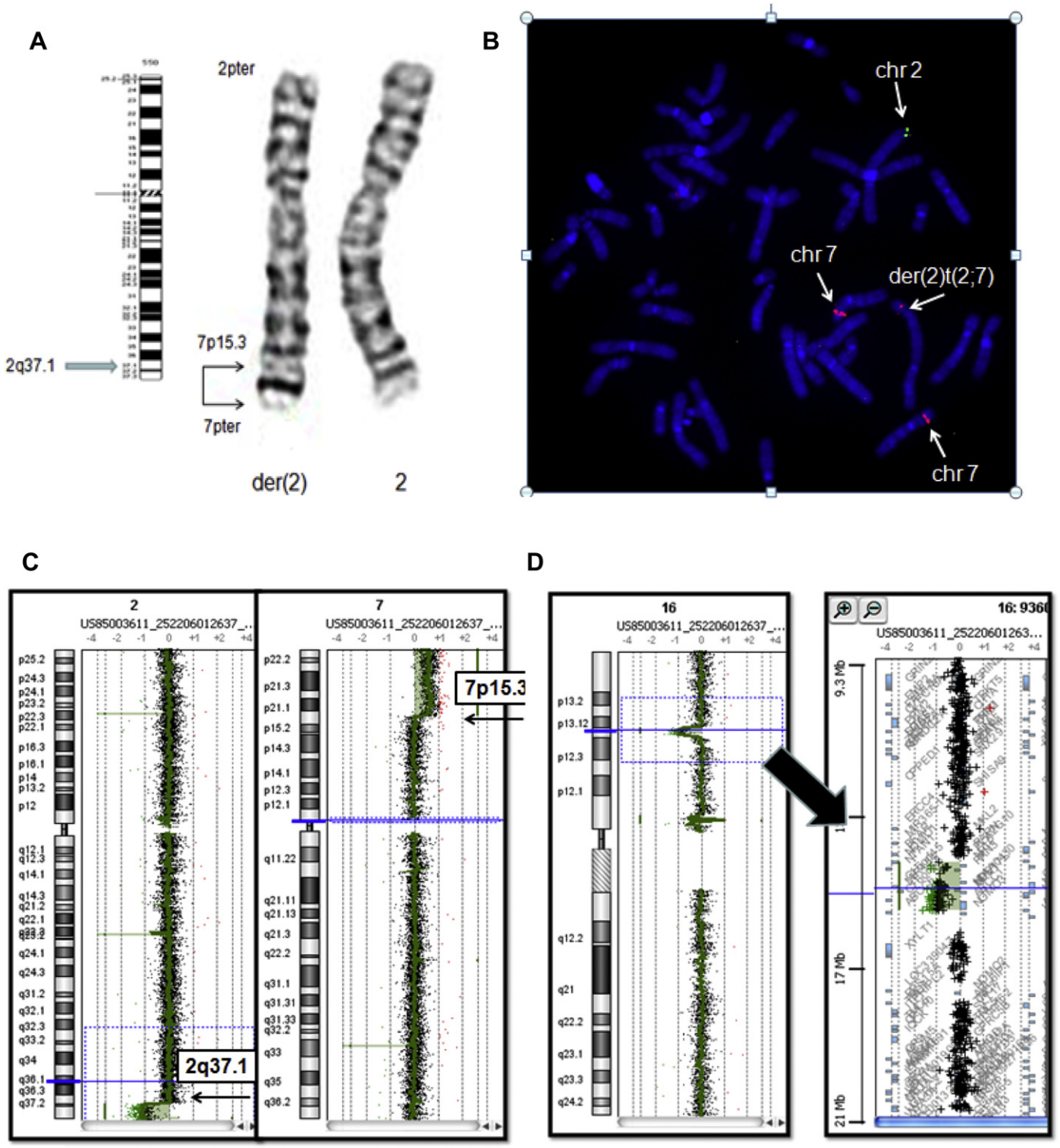

Fig. 4. (A) G-banded chromosome 2 and der(2)t(2;7)(q37.1; p15.3); (B) Fluorescent in situ hybridization metaphase from amniotic fluid cells: der(2)t(2;7) with gain signal of 7p telomere probe (RP11-160l16; red) and loss signal of 2q telomere robe (RP11-21K1; green); array-CGH analysis; (C) a 8.44-Mb deletion (234602276-243041305) on the chromosome 2q37.1, a 22.8-Mb duplication (65358-22869338) on the chromosome 7p15.3; (D) 1.32-Mb deletion (14968855-16292235) at 16p13.11.

CHAIN 11 participates thoracic aortic aneurysm, and/or aortic dissection with patent ductus arteriosus (OMIM 132900). ABCC6 (OMIM 603234) belongs to the multidrug resistance-associated protein (MRP) subfamily of adenosine triphosphate (ATP)-binding cassette (ABC) transmembrane transporters and are involved in cancer drug resistance. *ABCC6* gene not only cause a heritable connective tissue disorder, pseudoxanthoma elasticum (OMIM 264800), which is characterized by calcification of elastic fibers in skin, arteries, and retina, but it also cause generalized arterial calcification of infancy-2 (GACI2),

which is a severe autosomal recessive disorder characterized by calcification of the internal elastic lamina of muscular arteries and stenosis due to myointimal proliferation (OMIM 614473). Haploinsufficiency of these two genes may be suggestive to survey any consequences for cardiovascular structure in the present case. The skeletal features such as polydactyly observed in the present case have been reported in microduplication of 16p13.11 but was rarely associated with microdeletion of 16p13.11. Nagamani and colleagues [7] reported on three patients with duplication of 16p13.11 with skeletal features, such as polydactyly or syndactyly. Balasubramanian and colleagues [9] reported a 3-year-old boy with the 16p13.11 microdeletion syndrome who had bilateral flexion deformity of 3/4 fingers at 4 months of age. There are no genes in this interval with a known role in musculoskeletal development. Nagamani and others [7] suggested the reason for the observed cardiac or skeletal features may be due to the involvement of regulatory elements, including two known microRNAs (hsa-mir 1972 and hsa-mir 484), epistatic influences, or interactions with other gene modifiers. Further investigation is needed.

Deletion of 2q37.1-qter is also relative common and reported as a syndrome with defined abnormality. Ronan and coauthors [10] reported seven patients found in 11688 cases (0.06%) with 2q terminal deletion, and most individuals with the 2q37 deletion syndrome have a *de novo* chromosome deletion. In approximately 5% of published cases, probands have inherited the deletion from a parent who is a balanced translocation carrier as well as our case [10]. The major abnormality in previous reported cases with deletion of 2q37.1 included several organs, such as cardiac, tracheal, gastrointestinal, genital-urinary, central nervous system, and skeletal systems [11–16]. Falk and others [14] reported patients with deletion of 2q37 who also suffered from mild-moderate mental retardation, autism, behavior disorders, seizures, and a pattern of findings described as an Albright hereditary osteodystrophy-like phenotype (AHO). Lehman and others [15] described a female infant who survived 5 hours and 30 minutes and was delivered at 33 weeks' gestation who carried an isolated deletion of 2q37.1-2q37.2. The autopsy of this infant showed the olfactory bulbs and tracts, corpus callosum and septum pellucidum were absent. The prenatal central nervous system findings, such as agenesis of corpus callosum in the present case, was similar to what Lehman had reported. Two genes, diacylglycerol kinase, delta (DGKD) and serotonin receptor 2b (HTR2B), are mapped at 2q37.1 and one gene, holoprosencephaly 6 (HPE6) is mapped at 2q37. These genes had been reported to be involved in central nervous system development and function [15,17]. Casas and others [18] described hemidiaphragmatic hernia in a patient with deletion breakpoint at 2q37.1. Masumoto and coauthors [11] reported patent ductus arteriosus, tracheomalacia, and gastroesophageal reflux with hiatus hernia in a newborn girl with terminal deletion of the long arm of chromosome 2 at 2q37.1. The present case had deletions at 2q37.1 but no kind of hernia was found in the prenatal ultrasound.

Prenatal diagnosis of trisomy of 7p is uncommon and the manifestations include characteristic craniofacial phenotype of dolichocephaly or brachycephaly, large fontanelles, large low-set malformed ears, hypertelorism, down-slanting palpebral fissures, a high or prominent forehead, a broad or prominent nasal bridge, micrognathia, and a high arch palate [19–28]. The critical region for these phenotypes was restricted as 7p15.3-pter by Reish [28]. Kozma and others [27] found hydrocephalus in seven cases (19%), other central nervous system anomalies in 13 cases (35%), cardiac anomalies in 16 cases (43%), and foot deformities in 18 cases (49%). Ozgun and colleagues [29] reported prenatal diagnosis of partial trisomy 7p (7p15.3-pter) and partial monosomy 9p (9p24-pter) in a fetus with corpus callosum agenesis, an enlarged left kidney, single umbilical artery, hypertelorism, a depressed nasal bridge, frontal bossing, irregular maxillary alveolar composition, club feet, flexion deformity of the upper extremities, and Epstein anomaly. Chen and coworkers [24,30] reported two cases with Dandy-Walker variant, one in a boy with partial trisomy 7p (7p21.2-pter) and partial monosomy 12q (12q24.33-qter) and the other in a fetus with partial trisomy 7p (7p15.3-p22.3) and partial monosomy 13q (13q33.3-q34). These previous cases were suggestive that partial trisomy 7p (7p15.3-pter) also contributed to the central nervous system phenotypes in the present case. The other particular manifestations for this region include the abnormal skull development with large, gaping anterior fontanel and diastasis of the cranial sutures [19,21,23,31]. Chen and colleagues [25] reported an infant who was delivered at 34 weeks following unsuccessful tocolytic treatment and also manifested a sloping forehead, trigonocephaly, a large anterior fontanelle, prominent sutures, and the karyotype of the proband was designated as 46,XX.ish der(9)t(7;9)(p15.1;p22). Megarbane and colleagues [32] suggested triple dosage of the *TWIST* gene (OMIM #601622, Saethre-Chotzen syndrome, 7p21) that manifested the delayed closure of a large fontanelle. Large anterior fontanelle was also observed in the present case.

In summary, microdeletion of 16p13.11 is a quiet novel microdeletion/duplication syndrome, which detected after array CGH, was widely approached. Case that combination of this microdeletion with partial monosomy of 2q37.1-qter and partial trisomy of 7p15.3-pter was not reported before our case. The present case provided evidence that microdeletion of 16p13.11, which may be, like the microduplication of 16p13.11, associated with polydactyly.

Acknowledgments

This study was supported partially by grants from the National Sciences Counsel in Taiwan (NSC 99-2314-B-039-003-MY2 and 100-2311-B-040-001) and the Yen Tjing Ling Medical Foundation (CI-100-34).

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