Partial Trisomy 16p (16p12.2→pter) and Partial Monosomy 22q (22q13.31→qter) Presenting With Fetal Ascites and Ventriculomegaly: Prenatal Diagnosis and Array Comparative Genomic Hybridization Characterization

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SUMMARY

Objective: To present prenatal diagnosis and array comparative genomic hybridization (aCGH) characterization of partial trisomy 16p (16p12.2→pter) and partial monosomy 22q (22q13.31→qter) presenting with fetal ascites and ventriculomegaly in the second trimester.

Case Report: A 31-year-old woman, gravida 2, para 1, was referred to the hospital at 20 weeks of gestation because of fetal ascites. Amniocentesis revealed a derivative chromosome 22. Subsequent parental karyotyping revealed that the father carried a balanced reciprocal translocation between 16p12 and 22q13. Bacterial artificial chromosome-based aCGH using amniocyte DNA demonstrated partial trisomy 16p and partial monosomy 22q [arr cgh 16p13.3p12.2 (CTD-3077J14→RP11-650D5)×3, 22q13.31q13.33 (RP1-111J24→CTD-3035C16)×1]. Oligonucleotide-based aCGH showed a 20.9-Mb duplication of distal 16p and an approximate 3.7-Mb deletion of distal 22q. Level II ultrasound revealed fetal ascites and ventriculomegaly. The pregnancy was terminated and a malformed male fetus was delivered with craniofacial dysmorphism and abnormalities of the digits. The fetal karyotype was 46,*XY*,der(22)t(16;22)(p12.2;q13.31)pat. The paternal karyotype was 46,*XY*,t(16;22)(p12.2;q13.31).

Conclusion: Partial trisomy 16p can be associated with fetal ascites and ventriculomegaly in the second trimester. Prenatal sonographic detection of fetal ascites in association with ventriculomegaly should alert chromosomal abnormalities and prompt cytogenetic investigation, which may lead to the identification of an unexpected parental translocation involving chromosomal segments associated with cerebral and vascular abnormalities. [*Taiwan J Obstet Gynecol* 2010;49(4):506–512]

Key Words: chromosome 16, chromosome 22, fetal ascites, monosomy 22q, trisomy 16p, ventriculomegaly

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Introduction

Partial trisomy 16p is a rare clinical recognizable syndrome characterized by mental retardation, growth retardation, craniofacial abnormalities, abnormally

placed thumbs, finger tapering, simian crease, club hand/foot, hammer toes, urogenital abnormalities, cardiac anomalies, respiratory distress, pulmonary vascular diseases and other vascular anomalies [1–11]. The 22q13.3 deletion syndrome or Phelan-McDermid syndrome (OMIM 606232) is characterized by large or unusual ears, relatively large hands, full brow, dolichocephaly, ptosis, full cheeks, a bulbous nose, a pointed chin, autistic behavior, neonatal hypotonia, global developmental delay, normal or accelerated growth and absent to severely delayed speech [12–16]. A concomitant occurrence of partial trisomy 16p and 22q13.3 deletion is unusual. We previously described the application of array comparative genomic hybridization (aCGH) in prenatal diagnosis of aneuploidy [17,18]. Here, we report prenatal diagnosis and aCGH characterization of partial trisomy 16p (16p12.2→pter) and partial monosomy 22q (22q13.31→qter) in a fetus associated with fetal ascites and ventriculomegaly.

Case Report

A 31-year-old woman, gravida 2, para 1, was referred to the hospital at 20 weeks of gestation because of fetal ascites which had developed 2 weeks prior to referral. She had a 5-year-old, healthy daughter. The woman reported no teratogenic medications, recent viral infections, diabetes mellitus or hypertension. The maternal blood group was O, Rh-positive and the maternal syphilis screen was negative but thalassemia screen was positive. The paternal thalassemia screen was negative. Maternal rubella IgG levels were consistent with past history of a childhood infection of rubella. The parents were non-consanguineous and healthy and there was no family history of congenital malformations. Prenatal sonography at 20 gestational weeks revealed a male fetus with fetal biometry equivalent to 20 weeks, a normal amount of amniotic fluid and fetal ascites. The internal organs were unremarkable. Amniocentesis revealed a derivative chromosome 22, or der(22) (Figure 1). Subsequent parental karyotyping revealed that the father carried a balanced reciprocal translocation between 16p12 and 22q13 (Figure 2). The karyotype of the mother and her daughter were normal. Bacterial artificial chromosome-based aCGH of amniocyte DNA using CMDX bacterial artificial chromosome-based aCGH CA3000 chips (CMDX, Irvine, CA, USA) demonstrated partial trisomy 16p and partial monosomy 22q [arr cgh 16p13.3p12.2 (CTD-3077J14→RP11-650D5)×3, 22q13.31q13.33 (RP1-111J24→CTD-3035C16)×1] (Figure 3). Oligonucleotide-based aCGH using Oligo HD Scan (CMDX, Irvine, CA, USA) showed a 20.9-Mb duplication of distal 16p and an approximate 3.7-Mb deletion of distal 22q (Figure 4). Level II ultrasound revealed fetal ascites and ventriculomegaly (Figure 5). The pregnancy was terminated at 22 gestational weeks. A 436-g male fetus was delivered with dysmorphic features including a round face, hypertelorism, prominent glabella, a bulbous nose, a depressed nasal bridge, full cheeks, anteverted nares, a long philtrum, thin lips, micrognathia, low-set ears, a short neck, finger tapering, malposition of the toes, flexion-deformity of the fingers, bilateral proximally inserted thumbs, a bilateral simian crease, a gap between the first and the second toes, and overlapping fingers (Figures 6 and 7). The external genitalia and anus were normal. Molecular analysis revealed negative findings for parvovirus B19,

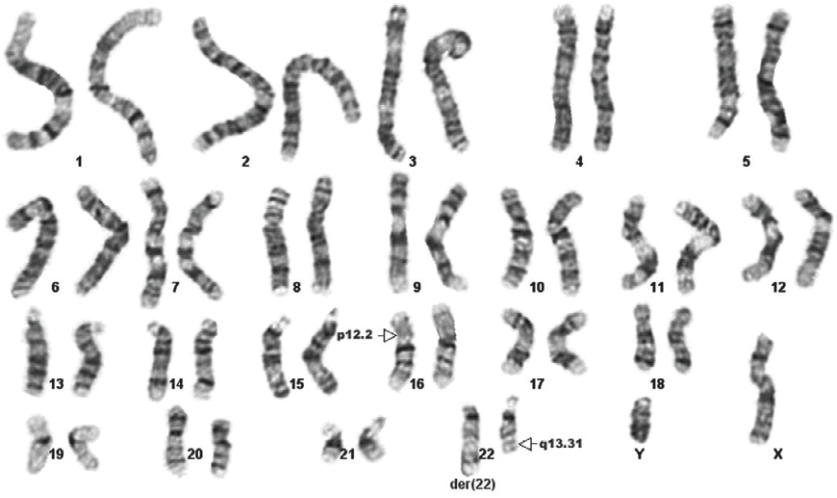

Figure 1. G-banded karyotype of the fetus shows a derivative chromosome 22, or der(22). The karyotype is 46,XY,der(22) t(16;22)(p12.2;q13.31)pat. The arrows indicate the breakpoints on normal chromosomes.

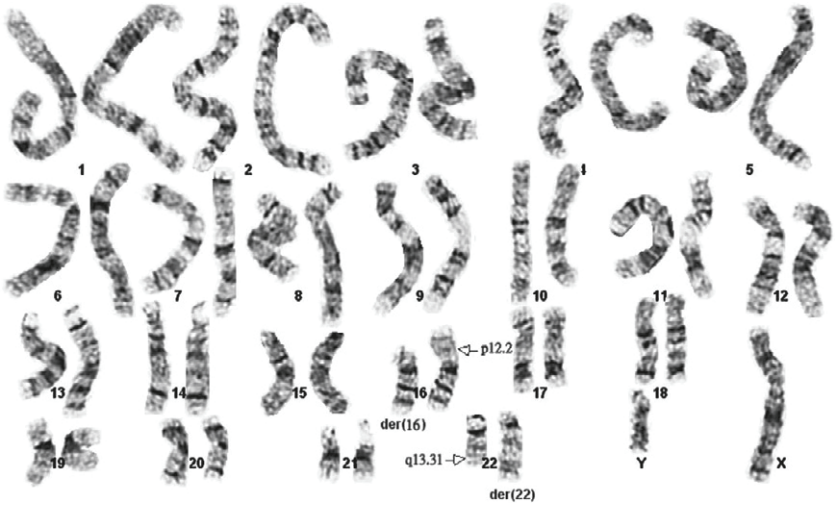

Figure 2. G-banded karyotype of the father shows a der(16) and a der(22). The karyotype is 46,*XY*,t(16;22)(p12.2;q13.31). The arrows indicate the breakpoints on normal chromosomes.

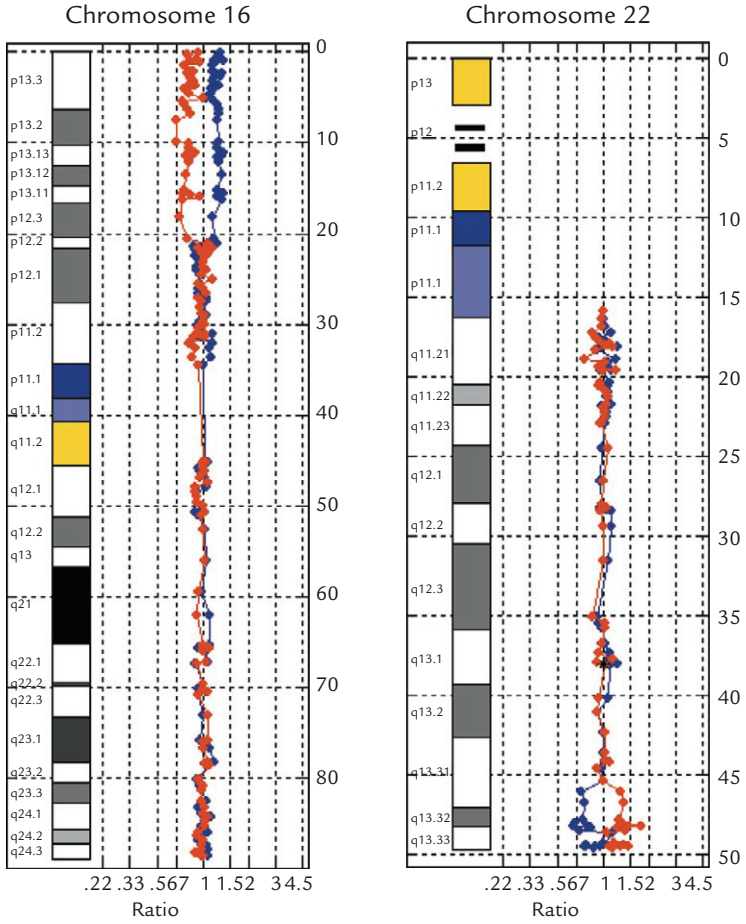

Figure 3. Bacterial artificial chromosome-based array comparative genomic hybridization shows partial trisomy 16p [arr cgh 16p13.3p12.2 (CTD-3077J14→RP11-605D5)×3] and partial monosomy 22q [arr cgh 22q13.31q13.33 (RP1-111J24→CTD-3035C16)×1].

cytomegalovirus, toxoplasma and herpes simplex virus in the cord blood. The karyotype of the father was 46,*XY*,t(16;22)(p12.2;q13.31). The karyotype of the fetus was 46,*XY*,der(22)t(16;22)(p12.2;q13.31)pat.

Discussion

The present case manifested characteristic craniofacial and limb abnormalities associated with partial trisomy

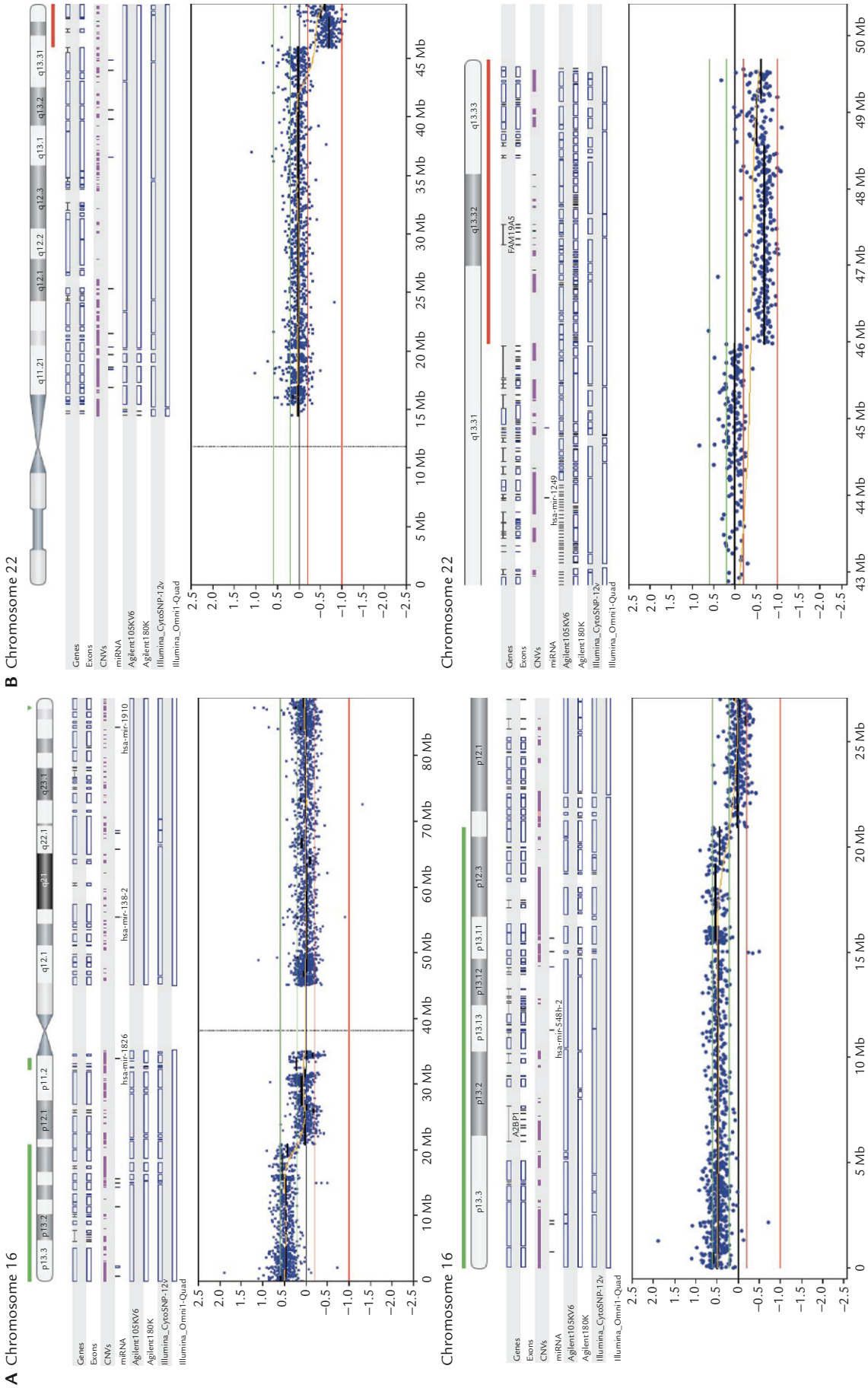

Figure 4. Oligonucleotide-based array comparative genomic hybridization shows (A) a 20.9 Mb duplication in 16p13.3→16p12.2 [arr cgh 16p13.3p12.2 (0-20,935,453)×3] and (B) an approximate 3.7 Mb deletion of 22q13.31→22q13.33 [arr cgh 22q13.31q13.33 (45,981,778-49,691,432)×1].

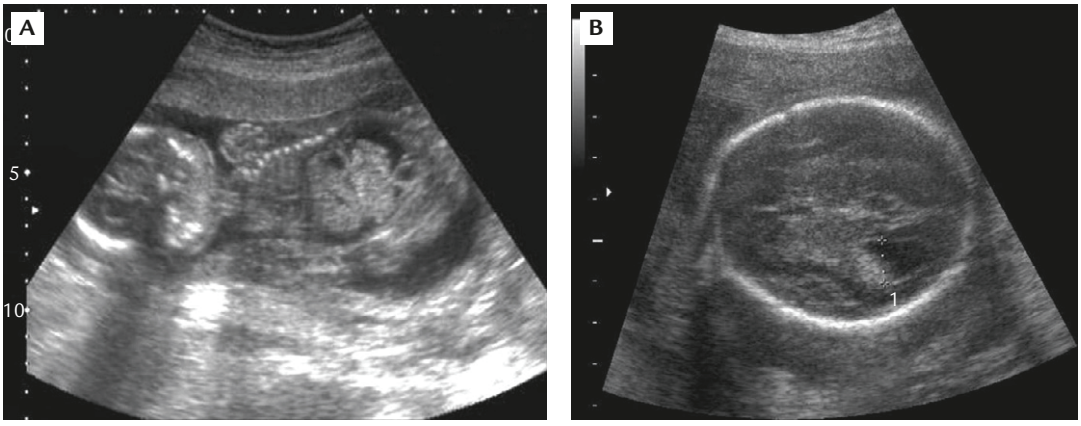

Figure 5. (A) Prenatal ultrasound at 20 gestational weeks shows fetal ascites. (B) Prenatal ultrasound at 22 gestational weeks shows ventriculomegaly.

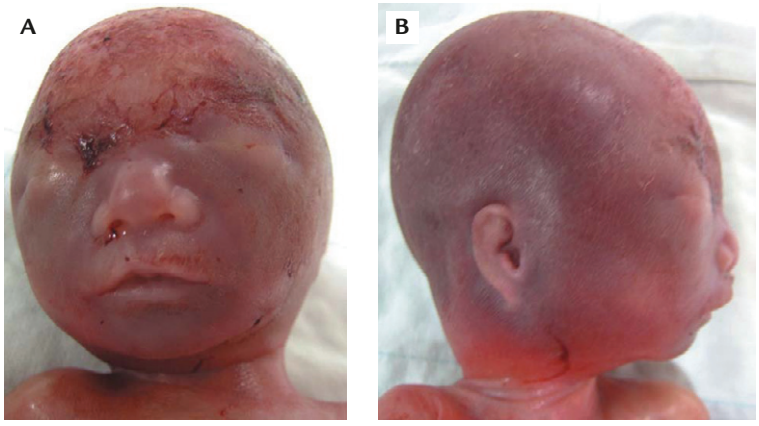

Figure 6. (A) and (B) Craniofacial appearance of the proband shows a round face, hypertelorism, prominent glabella, a bulbous nose, a depressed nasal bridge, full cheeks, anteverted nares, a long philtrum, thin lips, low-set ears and micrognathia.

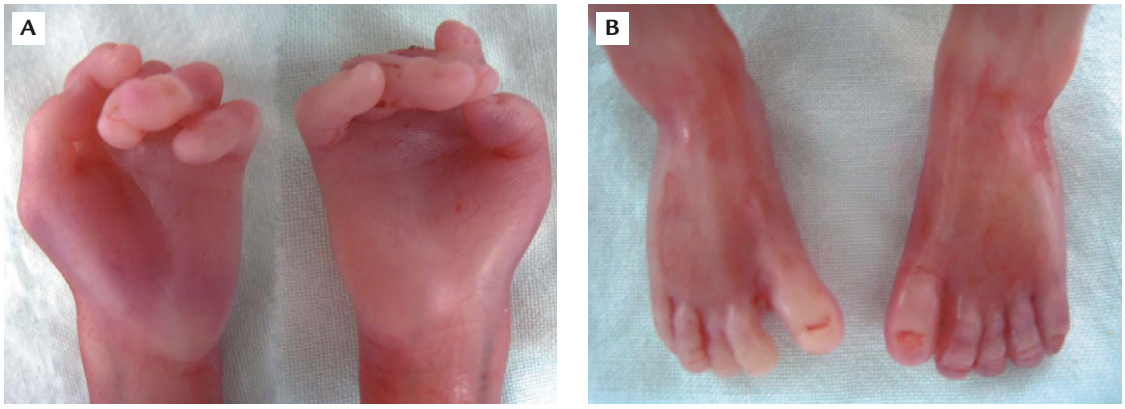

Figure 7. (A) Flexion-deformity of the fingers, finger tapering, simian crease and proximally inserted thumbs of the hands. (B) Malposition of the toes and a gap between the first and the second toes.

16p and 22q13.3 deletion syndrome. This case had chromosome 16p duplication encompassing the critical region of 16p13.1–p13.3 and chromosome 22q deletion encompassing the critical region of 22q13.3. Previous studies have shown that the critical region of partial trisomy 16p is located within 16p13.1-p13.3, and the phenotypic severity does not correlate to the size of the duplicated segment [8]. Haploinsufficiency of the *SHANK3* gene (OMIM 606230) on 22q13.3 has been shown to be a major causative factor in the neurological symptoms of 22q13.3 deletion syndrome, including neonatal hypotonia, developmental delay, absent to severely delayed speech and autistic behavior [19]. The *SHANK3* gene encodes proline-rich synapse-associated

protein 2, which is a structural protein of post-synaptic density.

The present case was associated with fetal ascites. Fetal ascites and hydrops fetalis have been described in fetuses with partial trisomy 16p. Chen et al [6] reported bilateral renal agenesis, oligohydramnios and fetal ascites in a fetus with partial trisomy 16p (16p13.2→pter) and partial trisomy 13q (13q12.3→qter). Martin et al [8] reported non-immune hydrops fetalis and cystic hygroma in a fetus with an approximate 10-Mb terminal 16p duplication. Digilio et al [11] reported the association of partial trisomy 16p (16p13.1-p13.3) with pulmonary vascular disease, pulmonary hypertension, portal cavernoma, vascular ring and vascular disruption, and suggested that this critical region is related to vascular abnormalities.

The present case was also associated with ventriculomegaly. In a review of 11 patients with microduplication of the subtelomeric region of chromosome 16p, Digilio et al [11] found 38% (3/8) of the patients had corpus callosum hypoplasia, and 55% (6/11) of the patients had microcephaly. Digilio et al [11] reported a female infant with a 12-Mb duplication of 16p13.3p13.13, portal hypertension, a portal vein cavernoma with esophageal varices and corpus callosum hypoplasia. Martin et al [8] reported a female infant with severe classical lissencephaly, mild hypogenesis of the rostrum and splenium of the corpus callosum and moderate enlargement of the lateral ventricles and cavum septi pellucidi and an approximate 3.5–4-Mb terminal 16p duplication. Martin et al [8] also reported a female infant with sagittal craniosynostosis, corpus callosum hypoplasia, arachnoid cyst, seizures, mental retardation, a behavior disorder and a 10-Mb terminal 16p duplication. The present case additionally provides evidence that partial trisomy 16p can present fetal ascites and ventriculomegaly in the second trimester.

In conclusion, prenatal sonographic detection of fetal ascites in association with ventriculomegaly should be an indicator for chromosomal abnormalities and prompt cytogenetic investigation, which may lead to the identification of an unexpected parental translocation involving chromosomal segments associated with cerebral and vascular abnormalities. The information acquired through perinatal studies is helpful for both genetic counseling and investigation of subsequent pregnancies.

Acknowledgments

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