Recurrent Distal 16q Duplication and Terminal 22q Deletion: Prenatal Diagnosis and Genetic Counseling

Chih-Ping Chen[1,2,3,4,5,6]*, Ming-Chao Huang[1], Yi-Ning Su[7], Fuu-Jen Tsai[4,8], Pei-Chen Wu[1], Chen-Chi Lee[1], Dai-Dyi Town[1], Chen-Wen Pan[1], Wayseen Wang[2,9]

Departments of [1]Obstetrics and Gynecology and [2]Medical Research, Mackay Memorial Hospital, [5]Institute of Clinical and Community Health Nursing, and [6]Department of Obstetrics and Gynecology, School of Medicine, National Yang-Ming University, [7]Department of Medical Genetics, National Taiwan University Hospital, and [9]Department of Bioengineering, Tatung University, Taipei; [3]Department of Biotechnology, Asia University, [4]School of Chinese Medicine, College of Chinese Medicine, China Medical University, and [8]Departments of Medical Genetics and Medical Research, China Medical University Hospital, Taichung, Taiwan.

A 36-year-old woman, gravida 4, para 0, was referred for amniocentesis at 18 gestational weeks because of advanced maternal age and an autosomal reciprocal translocation in her second spouse. This was the woman's fourth pregnancy, and she had experienced two preterm deliveries with neonatal death during her previous marriage and one spontaneous abortion following a relationship with her current spouse. Nine years before, the ex-wife of the woman's current spouce gave birth to a growth-restricted malformed baby at term with a karyotype of 46,XX,der(22)t(16;22)(q12.1;q13.3) and an unbalanced reciprocal translocation between 16q and 22q [1]. The baby's chromosomal aberration led to the diagnosis of a 46,XY,t(16;22)(q12.1;q13.3) karyotype in the man. Four years later, the man's ex-wife delivered a malformed baby again with a karyotype of 46,XX, der(22)t(16;22)(q12.1;q13.3) [2]. During this pregnancy, amniocentesis at 18 gestational weeks revealed a karyotype of 46,XX,der(22)t(16;22)(q12.1;q13.3) (Figure 1). Level II ultrasound revealed a singleton with fetal biometry consistent with the gestational age, dolichocephaly, decreased fetal movements and a thickened nuchal fold. The pregnancy was subsequently terminated. At 22 gestational weeks, a 342 g malformed female fetus was delivered with a high forehead, bitemporal narrowing, frontal bossing, dolichocephaly, a prominent nose, hypertelorism, large low-set ears, micrognathia, a short neck with a thickened nuchal fold and clinodactyly (Figure 2). Array comparative genomic hybridization (aCGH) using genomic DNA extracted from the uncultured umbilical cord confirmed a distal 16q duplication and a terminal 22q deletion (Figure 3).

We previously reported the prenatal diagnosis of an inherited unbalanced reciprocal translocation by aCGH using uncultured amniocytes [3]. Our case demonstrates that aCGH can be applied for rapid confirmation of prenatally diagnosed aneuploidy using uncultured postnatal tissues. The present case manifested some of the characteristic features associated with 22q13.3 deletion syndrome and partial trisomy 16q. The 22q13.3 deletion syndrome or Phelan-McDermid syndrome (OMIM 606232) is characterized by long eye lashes, large or unusual ears, relatively large hands, dysplastic toenails, a 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 [4]. The reported abnormal findings of trisomy 16q on prenatal ultrasound include hydrocephalus, intrauterine growth restriction, micrognathia, congenital heart defects, clinodactyly and abnormal external genitalia [5,6]. The present case had haploinsufficiency of the *SHANK3* gene (49,459,936–49,518,507 bp) (NCBI Build 36). Haploinsufficiency of the *SHANK3* gene is a major cause of the neurological symptoms of the 22q13 deletion syndrome [7,8]. The abnormal gene dosage of *SHANK3* is associated with autism spectrum disorders and language and speech disorders [8].

In the present case, the reason for prenatal chromosome analysis was the paternal carrier status, which was primarily ascertained through a previous term aneuploid child. Inherited unbalanced structural chromosomal abnormalities detected at prenatal chromosome analysis

Correspondence to: Dr Chih-Ping Chen, Department of Obstetrics and Gynecology, Mackay Memorial Hospital, 92, Section 2, Chung-Shan North Road, Taipei, Taiwan.
E-mail: cpc_mmh@yahoo.com
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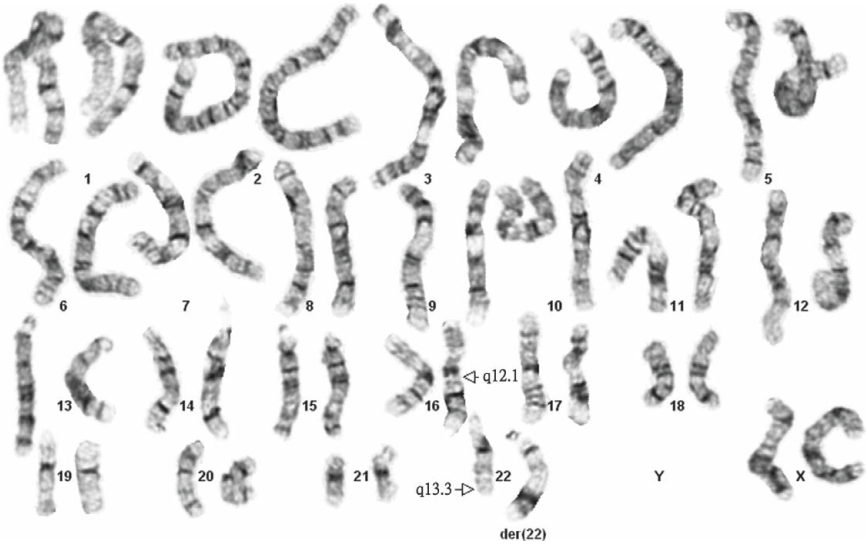

Figure 1. 46,XX,der(22)t(16;22)(q12.1;q13.3) karyotype in the fetus. The arrows indicate the breakpoints.

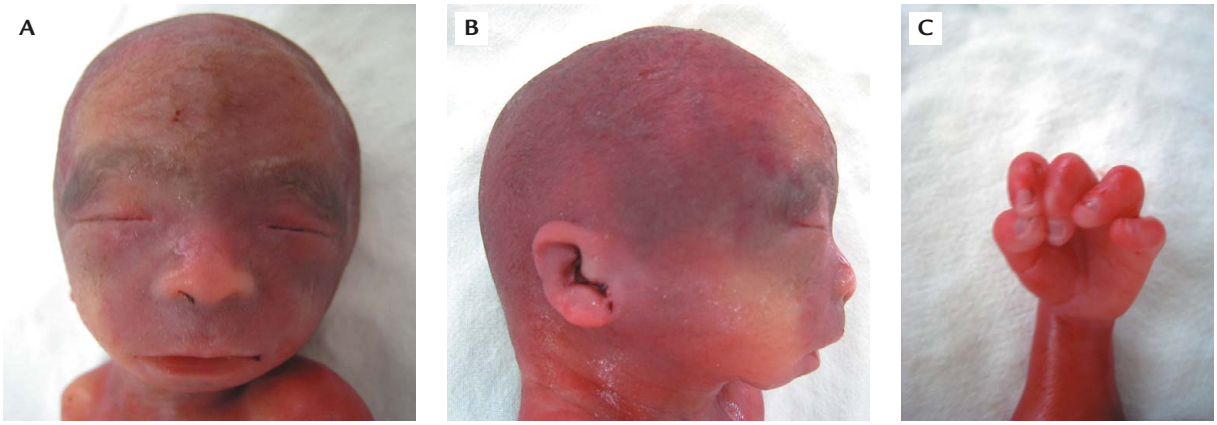

Figure 2. (A) Anterior view and (B) lateral view of a fetus with dolichocephaly, bitemporal narrowing, a short neck, frontal bossing, a prominent nose, hypertelorism, large low-set ears and micrognathia, and (C) clinodactyly.

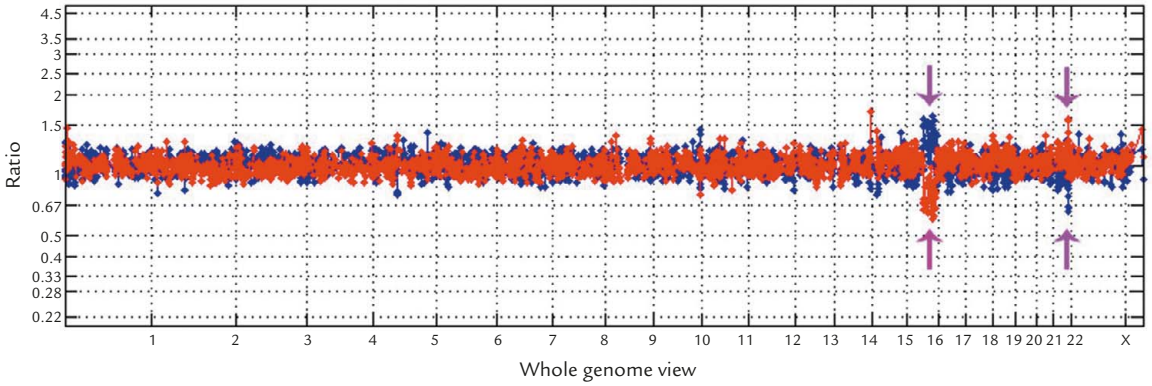

Figure 3. Whole genome view of array comparative genomic hybridization shows a distal 16q duplication (arrows at chromosome 16) and a terminal 22q deletion (arrows at chromosome 22).

are most commonly ascertained through a previous child with an unbalanced karyotype [9]. In a study of 56 inherited unbalanced structural chromosomal abnormalities detected at prenatal chromosome analysis, Franssen et al [9] found that the modes of ascertainment were a previous child with an unbalanced karyotype (48%, 27/56), ultrasound abnormalities (20%, 11/56), advanced maternal age (9%, 5/56), abnormal serum screening (4%, 2/56), abnormal nuchal translucency (4%, 2/56), intracytoplasmic sperm injection (4%, 2/56),

and recurrent miscarriage (2%, 1/56), among others. Structural chromosomal rearrangements in couples are usually identified through recurrent miscarriages, previous aneuploid live birth or stillbirth, and prenatal diagnosis of chromosomal aberrations. Chen et al [10,11] found that 17 of 22 (77.3%) families with prenatal diagnosis of an inherited acrocentric rearrangement by amniocentesis were aware of their carrier status only after the diagnosis of a fetus with a translocation.

Structural chromosomal rearrangements in couples are estimated to be 2.2% after one miscarriage, 4.8% after two miscarriages and 5.2% after three miscarriages compared with 0.7% in the general population [12–14]. In a study of reproductive outcome after chromosome analysis in couples with two or more miscarriages, Franssen et al [15] concluded that the risk (0.4% at prenatal diagnosis and 0.4% at birth) of viable offspring with chromosomal abnormalities was low, and that the chance of having a healthy child (83%) was as high as that of non-carrier couples (84%) despite a higher risk of a subsequent miscarriage. Nonetheless, carrier couples ascertained through a previous aneuploid child are at a higher risk of having unbalanced viable offspring than those ascertained through miscarriages [15–18]. Boué and Gallano [16] reported a 20.8% risk of unbalanced fetuses at prenatal diagnosis when the translocation was ascertained through an aneuploid infant, compared with a risk of 4.9% when the ascertainment was through other means. Daniel et al [17] reported a 20–25% risk of unbalanced pregnancy in carriers of 2:2 segregating reciprocal translocations ascertained by previous term unbalanced offspring irrespective of carrier parents. Barišić et al [18] reported a 31.6% risk of an unbalanced fetal karyotype at prenatal diagnosis when the translocation was determined through an aneuploid infant, compared with a risk of 11.8% when the ascertainment was through spontaneous abortions. Therefore, for carrier couples whose carrier status is determined through a previous aneuploid child, preimplantation genetic diagnosis by fluorescence *in situ* hybridization [19] or by whole genome amplification [20,21] may be an alternative to prenatal diagnosis in cases where there are multiple failed attempts to achieve a successful pregnancy.

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