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Research Letter

Prenatal diagnosis of chromosome 8p23.1 microdeletion by array comparative genomic hybridization using uncultured amniocytes in a pregnancy associated with fetal partial corpus callosum agenesis and schizencephaly

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Dear Editor

We previously reported a *de novo* 0.7-Mb deletion in sub-band 8p23.1 extending from 7,227,000 to 7,916,187 (NCBI 36/hg 18) overlapping the telomeric β-defensin gene cluster, but outside the 8p23.1 deletion critical region, in a fetus with congenital diaphragmatic hernia (CDH) and additional abnormalities [1]. Herein, we additionally report a fetus with the copy number variable β-defensin gene cluster on 8p23.1 and partial corpus callosum agenesis and schizencephaly. To our knowledge, such a case has not previously been described.

A 29-year-old, gravida 5, para 2, Taiwanese woman was referred for genetic counseling at 24 weeks of gestation because of fetal chromosome aberration and fetal brain abnormalities. This was the fifth pregnancy of the woman. She had one 3-year-old healthy child and had delivered a baby with chromosome 1p32-p31 deletion syndrome, ventriculomegaly, and corpus callosum hypogenesis. The parents had normal karyotypes. During this pregnancy, at 16 weeks of gestation, the woman underwent amniocentesis which revealed a karyotype of 45,X[4]/46,XY[31]. Prenatal ultrasound at 22 weeks of gestation revealed the absence of a septum pellucidum, partial agenesis of the corpus callosum, and wide splaying of the anterior horn of the lateral ventricles. Fetal magnetic resonance imaging examination showed partial corpus callosum agenesis with only the presence of the genu, and schizencephaly at the right occipital lobe. Repeated amniocentesis was performed at 24 weeks of gestation. Cytogenetic analysis of the cultured amniocytes revealed a karyotype of 45,X[6]/46,XY[9]. Array comparative genomic hybridization (aCGH) analysis by NimbleGen ISCA Plus Cytogenetic Array (Roche NimbleGen, Madison, WI, USA) using uncultured amniocytes revealed a 0.57-Mb 8p23.1 microdeletion or arr 8p23.1 (7,235,388-7,809,256) × 1.3 (Build GRCh37, Feb 2009, hg19) encompassing 44 genes including 14 OMIM genes of *FAM90A15P*, *FAM90A3P*, *FAM90A13P*, *FAM90A5P*, *FAM90A20P*, *DEFB103B*, *SPAG11B*, *FAM90A7P*, *FAM90A14P*, *FAM90A18P*, *FAM90A8P*, *FAM90A19P*, *FAM90A9P*, and *FAM90A10P*. The parents did not have such a deletion. The parents decided to terminate the pregnancy, and a fetus was delivered with no abnormalities in gross appearance.

The β-defensin gene cluster on the chromosome band of 8p23.1 has been shown to be one of the most prominent examples of functional-relevant copy number variation (CNV), and various studies have demonstrated that multisite variants and CNV of the defensin-encoding genes are associated with increased risk for various diseases including cancer and inflammatory diseases [2–6].

The present case has CNV on the β-defensin gene cluster at 8p23.1, but without the involvement of the 8p23.1 deletion syndrome critical genes such as *GATA4*, *NEIL2*, *SOX7*, and *TNKS*. The 8p23.1 deletion syndrome includes congenital heart defects,

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microcephaly, mental retardation, CDH, psychomotor developmental delay, and behavior problems [7–12]. *GATA4*, *NEIL2*, and *SOX7* have been associated with congenital heart defects and CDH [12–19]. Haploinsufficiency of either *GATA4* or *SOX7* has been shown to contribute to the development of CDH in individuals with 8p23.1 deletions [20]. *TNKS* has also been proposed as a novel candidate for the Cornelia de Lange syndrome [21].

The peculiar aspect of this case is the concomitant occurrence of fetal partial corpus callosum agenesis, schizencephaly, and partial deletion of *DEFB103* and *SPAG11* on chromosome 8 β-defensin gene cluster. There is increasing evidence that abnormal defensin expression due to CNV of the β-defensin gene cluster of *DEFB107*, *DEFB106*, *DEFB105*, *DEFB104*, *DEFB103*, *DEFB4*, and *SPAG11B* is related to infectious diseases, sperm dysfunction, and infertility in males [22,23]. β-Defensins are a family of multifunctional peptides important for immunity, defense against pathogens, reproduction, and pigmentation [24,25].

A worldwide analysis of β-defensin CNV has found an unusually high frequency of high-*DEFB103*-expressing copies in East Asia [24]. A clinical report of central nervous system abnormalities associated with CNV on the β-defensin gene cluster at 8p23.1 has not previously been presented. The correlation of partial deletion of *DEFB103* with fetal brain abnormalities in this Taiwanese case is unclear and will require more case studies for confirmation.

In the present case, the conventional cytogenetic analysis of cultured amniocytes revealed mosaicism for 45,X and 46,XY, whereas, aCGH analysis on uncultured amniocytes revealed microdeletion of 8p23.1. The aCGH analysis has the advantage of detecting microdeletion syndrome in fetuses with a normal karyotype by conventional cytogenetic analysis [26,27]. Central nervous system abnormality is not the clinical phenotype of mosaic Turner syndrome. We think that aCGH provides the advantage of better understanding of the nature of microdeletion of 8p23.1 and genotype-phenotype correlation in this case.

Conflict of interest

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

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