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Research Letter

Prenatal diagnosis of mosaic ring chromosome 15 with abnormal maternal serum Down syndrome screening and Dandy-Walker malformation

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Ring chromosome 15 is an uncommon chromosomal abnormality which results from the loss of the distal ends of both the p and q chromosome arms, followed by fusion of the broken ends. In most cases, subjects are usually diagnosed postnatally with a variable phenotype. Second-trimester Down syndrome screening has been widely used for decades, but the correlation between the level of maternal serum human chorionic gonadotropin (MShCG) and chromosome 15 abnormalities has never been assessed. In addition, Dandy-Walker malformation (DWM) has also never been reported in the cases of ring chromosome 15 or monosomy 15. Here, we first present the prenatal diagnosis of mosaic ring chromosome 15 characterized by abnormal serum maternal Down screening and DWM.

A 33-year-old female, gravida 1, para 0, presented with uneventful antenatal examination except for an elevated free MShCG level of 2.115 multiples of the median (MoM) and a calculated Down syndrome risk of 1/142 at 16 weeks of gestation. Amniocentesis revealed 46,XX,r(15)(p13q26)[16]/45,XX,-15[9] (Fig. 1A). The following ultrasound at 19 weeks of gestation showed a posterior cranial fossa cyst along with hypoplasia of the cerebellum (Fig. 1B) and hydrops fetalis. The cyst appeared to be posterior ballooning of the fourth ventricle accompanied by a small rudimentary superior vermis and bilateral hemispheres of the cerebellum, as shown on later fetal magnetic resonance imaging (MRI; Fig. 1C,D), indicating DWM. The parental karyotypes were normal. After counseling, the pregnancy was terminated at 20 weeks of gestation. A female fetus was delivered with low-set ears, and no intrauterine growth restriction (IUGR) was found. Chromosome analysis of umbilical cord blood revealed the karyotype of 46,XX,r(15)(p13q26)[111]/45,XX,-15[7], which confirmed the diagnosis of mosaic ring chromosome 15.

There are only four reports of ring chromosome 15 prenatally diagnosed [1–4] (Table 1). These diagnoses were confirmed by cytogenetic analyses after amniocentesis. Fluorescence *in situ* hybridization (FISH) or array-comparative genomic hybridization (CGH) demonstrated the deletions on the distal q arm of chromosome 15. Three cases were detected based on abnormal findings during ultrasonography [1–3], and another one was found inadvertently [4]. Precise genotype–phenotype correlation was undetermined, and variable phenotypes were noted. One fetus showed no significant finding on gross examination except for IUGR [1]. In another case described by Glass et al [2], the fetus presented with a single umbilical artery, IUGR, a large incomplete atrioventricular canal, atrial septal defect, and distinctive facial features at birth. In another case reported by Hatem et al [3], the fetus had IUGR, congenital diaphragmatic hernia, and polycystic kidneys. In the fourth case, the fetus had no pathologic sonographic finding, but facial abnormalities, limb defects, and congenital diaphragmatic hernia were found after termination [4]. Unlike the previously reported cases, neither facial dysmorphism nor IUGR was found in the presenting case. In addition, loss of the unstable ring chromosome may form uniparental disomy (UPD) via monosomy rescue. Maternal UPD 15 is found in 25% of cases with Prader-Willi syndrome, and 1–3% of patients with Angelman syndrome have paternal

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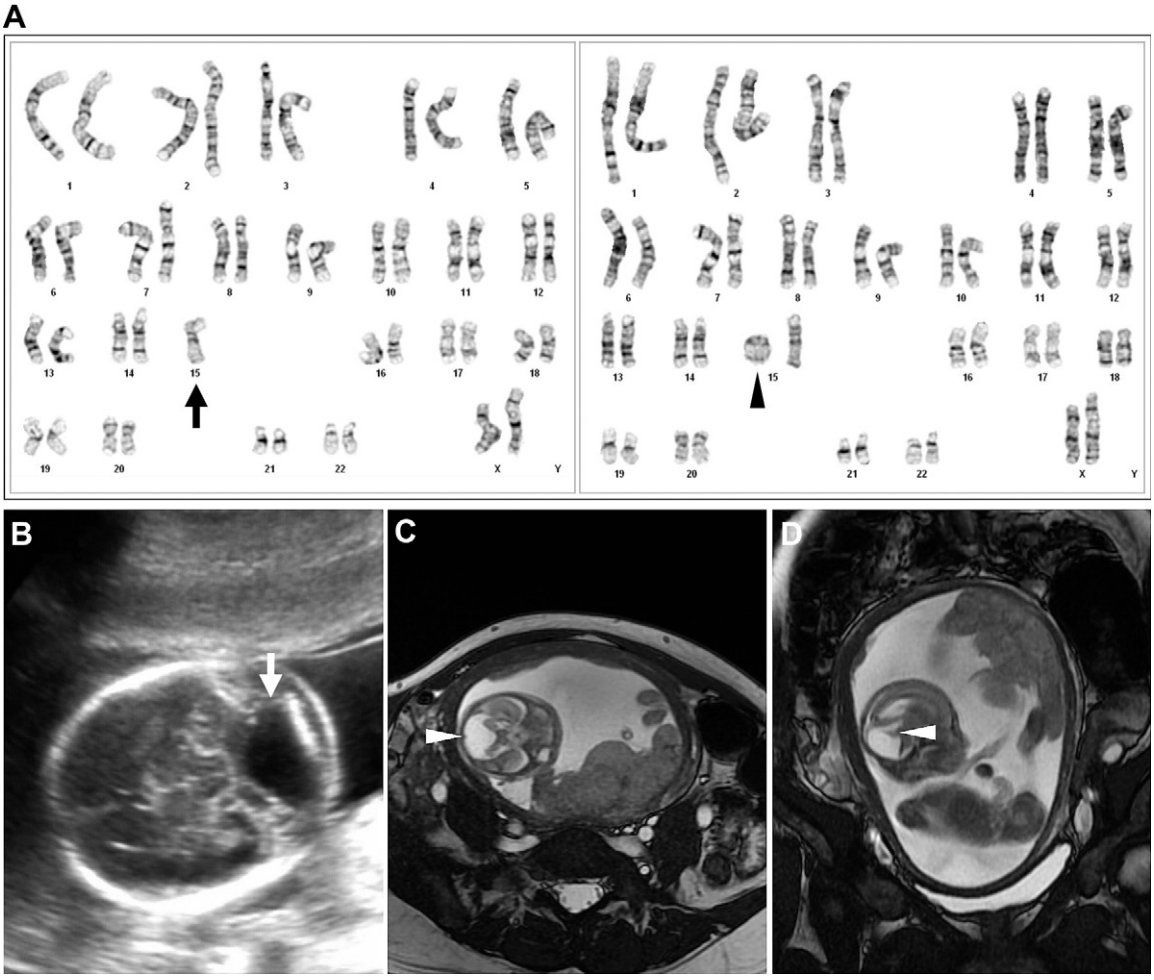

Fig. 1. (A) Karyotype: monosomy 15 (arrow) and ring chromosome 15 (arrowhead). (B) Transabdominal sonography shows a posterior fossa cyst (arrow). (C) MRI (axial plane) of fetal head reveals a hypoplastic cerebellum lying anteriorly and laterally of a markedly dilated fourth ventricle (arrowhead). (D) MRI (sagittal plane) of the fetal head discloses a small rudimentary superior vermis (arrowhead). The inferior vermis was not formed. MRI = magnetic resonance imaging.

Table 1
Cases of ring chromosome 15 diagnosed prenatally.

Author	Maternal age (years)	Associated anomalies	Outcome
Liu et al [1]	27	IUGR	TOP
Glass et al [2]	34	IUGR Oligohydramnios Single umbilical artery Facial dysmorphism ASD Limb anomalies	Delivery
Hatem et al [3]	27	IUGR Oligohydramnios Facial dysmorphism CDH Polycystic kidneys	TOP
Manolakos et al [4]	36	Facial dysmorphism Dolichocephaly CDH Limb anomalies	TOP
Present case	33	DWM Hydrops fetalis Low-set ears	TOP

ASD = atrial septal defect; CDH = congenital diaphragmatic hernia; DWM = Dandy-Walker malformation; IUGR = intrauterine growth restriction; TOP = termination of pregnancy.

UPD 15 [5]. However, without molecular analyses, the extent of euchromatic loss in the ring chromosome could not be evaluated, and the level of mosaicism for ring chromosome, monosomy or other possible chromosomal abnormalities with undetermined origin might contribute to the phenotype.

Abnormal maternal serum Down syndrome screening with an elevated level of MShCG is an important predictor of fetal aneuploidy and placental dysfunction, resulting in an increased risk for IUGR. In addition, confined placental mosaicism (CPM) for chromosomes 2, 9, 13, 15, and 16 has been reported associated with MShCG of $>$ 2.0 MoM, and it has also been viewed as a cause of IUGR [6]. Although IUGR is a common finding in cases of ring chromosome 15, including three prenatally-diagnosed cases, neither elevation of MShCG nor CPM has been identified. We first describe the association of mosaic ring chromosome 15 with abnormal maternal serum Down syndrome screening and high MShCG level. Careful fetal ultrasound is necessary for women with elevated MShCG, especially those with fetal growth restriction, and karyotype analysis of the placenta should be considered to exclude CPM.

DWM is characterized by complete or partial agenesis of the cerebellar vermis, cystic dilatation of the fourth ventricle,

large posterior fossa cyst, and elevated tentorium. It has been associated with various types of chromosomal abnormalities, but it has never been noted in the cases of ring chromosome 15 or monosomy 15. There were two reports of cerebellar anomaly associated with chromosome 15 abnormalities in the literature. One with distal trisomy 15q had DWM, facial dysmorphism, agenesis of the corpus callosum, and multiple limb anomalies [7], and the other with Prader-Willi syndrome had a right cerebellar hypoplasia [8]. Some critical regions or genes regions contributing to DWM have been reported, including certain region in the short arm of chromosome 9 and the *FOXC1* gene at 6p25 [9,10]. However, those on chromosome 15 responsible for the central nervous system malformation including DWM have not been well assessed. To our knowledge, our report is the first of DWM proved to be associated with mosaic ring chromosome 15. The correlation between mosaic ring chromosome 15 and DWM needs to be verified.

We report a case of prenatally diagnosed mosaic ring chromosome 15 associated with DWM and abnormal Down syndrome screening. No reliable serum markers aid in early detection of this abnormality. Advances in fetal ultrasound and MRI along with cytogenetic analysis enable obstetricians to identify such fetuses earlier than ever, and molecular techniques provide more and better information about genotype−phenotype correlation. Accurate diagnoses are essential not only for the management of a current pregnancy, but also for prenatal counseling in subsequent pregnancies.

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