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Clinical and submicroscopic findings of two prenatal cases with inv dup del (8p) syndrome

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ABSTRACT

Chromosome 8p inverted duplication deletion syndrome [inv dup del(8p)] is a rare disease characterized by intellectual disability, congenital heart defects, central nervous system abnormalities, and dysmorphic features. To date, the chromosomal alterations have been presented at the molecular level in only a small number of prenatal cases. Here, we report two prenatal cases, one with increased nuchal translucency, cerebellar vermis agenesis, a solitary interhemispheric cyst, and ventricular septal defect (VSD) and the other with VSD and discordance between right and left heart ventricles. Conventional cytogenetic, fluorescence in situ hybridization (FISH), and array comparative genomic hybridization (array CGH) analyses revealed that both cases had inv dup del(8p). This presented as a deletion larger than 6.5 megabases (Mb) distal to the 8p23 (8p23.1–pter) region, followed by an intermediate intact segment, and then an inverted duplicated proximal segment of approximately 30 MB, from 8p23.1 to 8p11.1 in the first fetus and from 8p23.1 to 8p11.21 in the second. The *GATA4* gene has now been implicated in the cardiac defects associated with deletions of 8p23.1. Although both fetuses had VSD, *GATA4* was located in the intact region, whereas the *NRG1* gene, which is necessary for heart development, was duplicated in our cases. We suggest that duplication of the *NRG1* gene could be responsible for the cardiac findings in our cases, but further studies are necessary to confirm this hypothesis.

1. Introduction

The chromosome 8p inverted duplication deletion [inv dup del(8p)] is a complex chromosomal rearrangement with an estimated prevalence of 1/10,000–1/30,000 in live births [Floridia et al., 1996]. In childhood, this chromosomal alteration often clinically manifests as intellectual disability, hypotonia, central nervous system anomalies (like agenesis of corpus callosum), variable skeletal anomalies, congenital heart defects, and dysmorphic features [Guo et al., 1995; de Die-Smulders et al., 1995; Devriendt et al., 1999].

Various mechanisms have been proposed to explain the origin of inv dup del(8p). The most common process involves the formation of a dicentric chromosome 8 [dic(8)] in meiosis I, followed by breakage of the dic(8) either during meiotic division or during the early stages of embryonic development to produce the inv dup del(8p) [Yu et al., 2010]. This altered region is prone to genomic rearrangements due to the presence of the two olfactory receptor gene clusters, REPD (REPeat in Distal 8p23.1) and REPP (REPeat in Proximal 8p23.1), that flank an ~5 Mb region of 8p23.1 [Yu et al., 2010]. The final formation of this rearrangement almost always ends with a distal deletion, which is followed by an intermediate intact segment, and then a proximal inverted duplication of various extensions.

Only a limited number of studies have addressed the submicroscopic chromosomal changes and the clinical presentation in the prenatal period for this deletion syndrome [Macmillin et al., 2000; Chen et al., 2016; Akkurt et al., 2017]. We present two new prenatal cases to contribute additional data to the literature.

Abbreviations: ARHGEF10, Rho guanine nucleotide exchange factor 10; Array CGH, Array comparative genomic hybridization; ASD, Atrial septal defect; CCA, Corpus callosum abnormality; CVA, Cerebellar vermis agenesis; dic(8), Dicentric chromosome 8; FISH, Fluorescence in situ hybridization; GATA4, GATA binding protein 4; Hg19, Human genome 19; Inv dup del(8p), Inverted duplication deletion 8p; ISCA, International Standards for Cytogenomic Arrays; Mb, Megabase; NRG1, Neuregulin 1; OMIM, Online Mendelian Inheritance in Man; ORDRs, Olfactory receptor gene clusters or defensin repeats; PDA, Patent ductus arteriosus; REPD, Repeat in distal; REPP, Repeat in proximal; RVH, Right ventricle hypertrophy; SOX7, SRY-box 7; THAP1, THAP domain containing 1; VSD, Ventricular septal defect

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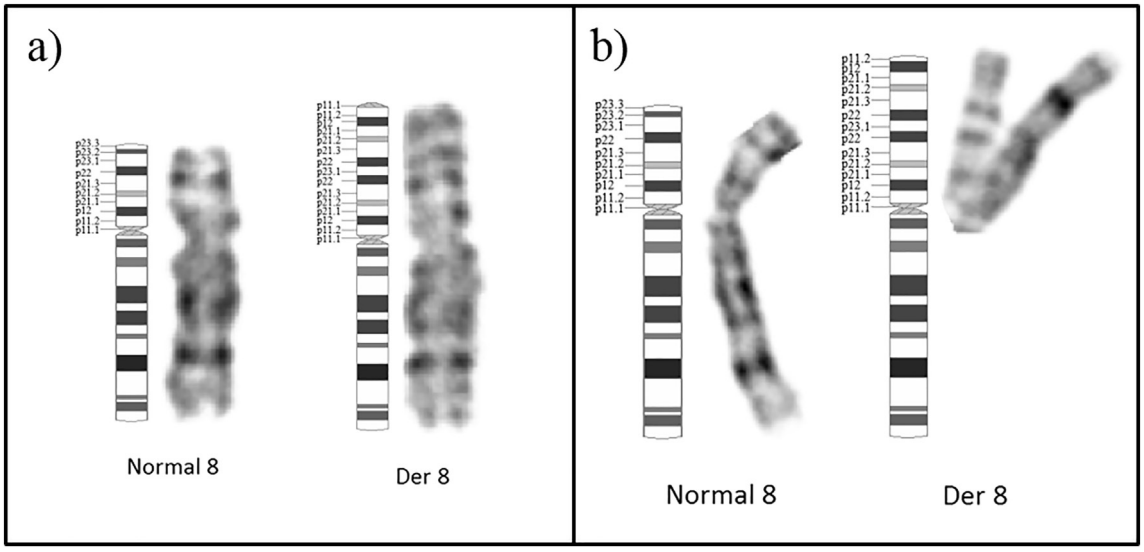

Fig. 1. Conventional cytogenetic analyses of both fetuses show an addition material of unknown origin on the short arm of the chromosome 8. Fig. 1a belongs to fetus 1. Fig. 1b belongs to fetus 2.

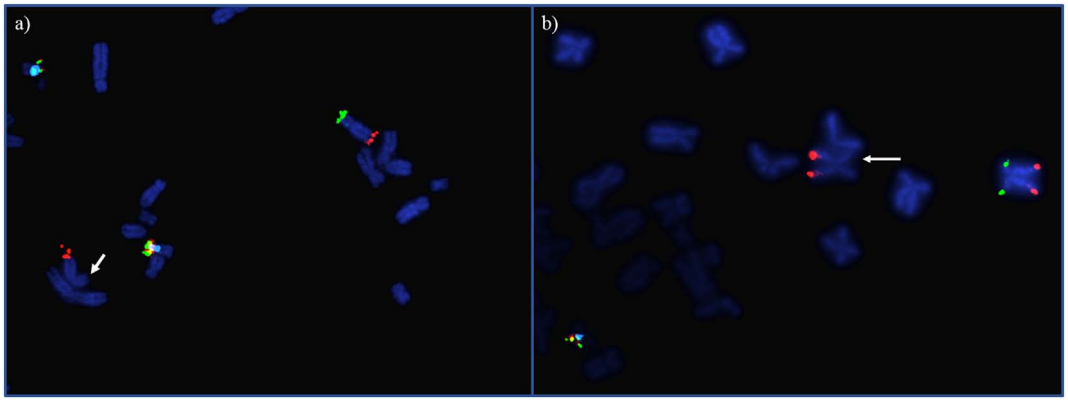

Fig. 2. FISH technique was ended with the deletion of 8pter. Arrows are indicating the deleted segments. Fig. 2a belongs to fetus 1. Fig. 2b belongs to fetus 2.

2. Material and methods

2.1. Clinical description

Fetus 1, which was the second pregnancy of a 39-year-old woman, was referred for genetic counselling at 11th gestational week because of an increased nuchal translucency measurement in fetal ultrasound. Chorionic villus sampling was performed at the 12th gestational week for both conventional and molecular cytogenetic analyses. Cerebellar vermis agenesis, interhemispheric cyst, and ventricular septal defect (VSD) were observed at the level II ultrasound and fetal echocardiography at 18th week of gestation. The corpus callosum could not be visualized clearly.

Fetus 2 was the third pregnancy of another 39-year-old woman. Because of the advanced maternal age and parental anxiety, amniocentesis was performed at the 16th week of gestation to evaluate the karyotype of the fetus. VSD of both outlet and muscular types and discordancy between the right and left heart were observed at level II ultrasound and fetal echocardiography at the 19th gestational week.

Based on the abnormal results of the genetic analyses and the abnormal ultrasound and fetal echocardiography findings, both pregnancies were terminated at the request of the families at the 18th and 20th gestational weeks for fetus 1 and fetus 2, respectively.

2.2. Conventional cytogenetic analysis

Routine cytogenetic analysis using G-banding techniques were performed after cultivation of the chorionic villus sample of fetus 1, amniotic fluid of fetus 2, fibroblast materials from both terminated fetuses, and parental blood samples. Three long-term primary cell cultures were obtained from each fetal tissue. Twenty metaphase plaques were analyzed for each specimen.

2.3. FISH

Fluorescence staining was performed using probes specific to the terminal region of the short arm of chromosome 8s (8pter) and control probes indicating the long arm of the same chromosome. At least five metaphases were analyzed for each case.

2.4. Chromosomal microarray

DNA was extracted after cultivation of the chorionic villus and amniotic fluid materials. Whole-genome array comparative genomic hybridization (array CGH) was performed using the Agilent Human Genome G3 SurePrint 8x60K ISCA Oligonucleotide Microarray. Data were analyzed using Agilent CytoGenomics software.