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Case Report

Molecular genetic characterization of a prenatally detected *de novo* interstitial deletion of chromosome 20p (20p12-p13) encompassing *JAG1* and a literature review of prenatal diagnosis of Alagille syndrome

Chih-Ping Chen [a, b, c, d, e, f, *], Chang-Sheng Yin [g], Liang-Kai Wang [a], Schu-Rern Chern [b], Shin-Wen Chen [a], Shih-Ting Lai [a], Peih-Shan Wu [h], Wen-Lin Chen [a], Wayseen Wang [b, i]

[a] *Department of Obstetrics and Gynecology, MacKay Memorial Hospital, Taipei, Taiwan*
[b] *Department of Medical Research, MacKay Memorial Hospital, Taipei, Taiwan*
[c] *Department of Biotechnology, Asia University, Taichung, Taiwan*
[d] *School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan*
[e] *Institute of Clinical and Community Health Nursing, National Yang-Ming University, Taipei, Taiwan*
[f] *Department of Obstetrics and Gynecology, School of Medicine, National Yang-Ming University, Taipei, Taiwan*
[g] *Department of Obstetrics and Gynecology, Kang-Ning General Hospital, Taipei, Taiwan*
[h] *Gene Biodesign Co. Ltd, Taipei, Taiwan*
[i] *Department of Bioengineering, Tatung University, Taipei, Taiwan*

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ABSTRACT

Objective: We present prenatal diagnosis and molecular genetic characterization of a *de novo* interstitial deletion of chromosome 20p (20p12-p13) and a literature review of prenatal diagnosis of Alagille syndrome (ALGS).

Case report: A 33-year-old woman underwent amniocentesis at 17 weeks of gestation because of an abnormal result of combined first-trimester screening. Her husband was 35 years old, and there was no family history of congenital malformations. Amniocentesis revealed a karyotype of 46,XY,del(20)(p12p13), and array comparative genomic hybridization analysis on uncultured amniocytes revealed a 3.749-Mb deletion at 20p13-p12.3 and a 1.84-Mb deletion at 20p12.2 encompassing the gene of *JAG1*. The parental karyotypes were normal. Prenatal ultrasound findings were unremarkable. The fetus postnatally manifested characteristic facial features of ALGS. Postnatal molecular cytogenetic analysis of fetal tissues confirmed the prenatal diagnosis. Polymorphic DNA marker analysis revealed a paternal origin of the deletion.

Conclusion: A *de novo* interstitial 20p deletion can be caused by a paternal effect. Pregnancy with a fetus affected with ALGS may be associated with an abnormal result of combined first-trimester screening and manifest no detectable ultrasound abnormalities.

Introduction

Alagille syndrome (ALGS) is an autosomal dominant disorder that has an estimated frequency of 1:30,000–1:50,000 live births [1]. ALGS is characterized by bile duct paucity, cholestasis, cardiac defects (primarily pulmonary stenosis and tetralogy of Fallot), skeletal abnormalities (primarily hemivertebra and butterfly vertebra), ophthalmologic abnormalities (primarily posterior embryotoxon) and characteristic facial features of broad forehead, deep-set eyes, pointed chin, and occasional renal and central nervous system abnormalities [1,2]. More than 89% of individuals with ALGS are associated with *JAG1* pathogenic variants, and about 1–2% of individuals with ALGS are associated with *NOTCH2* pathogenic variants [1]. ALGS1 [Online Mendelian Inheritance in Man (OMIM) 118450] is caused by mutations or deletions in the *JAG1* gene (OMIM 601920) at 20p12.2, and ALGS2 (OMIM 610205) is caused by mutations or deletions in the *NOTCH2* gene (OMIM 600275) at 1p12. 20p12.2 microdeletion with a deletion of entire *JAG1* gene has been observed in 7% of the affected patients with

* Corresponding author. Department of Obstetrics and Gynecology, MacKay Memorial Hospital, 92, Section 2, Chung-Shan North Road, Taipei 10449, Taiwan. Fax: +886 2 25433642, +886 2 25232448.
E-mail address: cpc_mmh@yahoo.com (C.-P. Chen).

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ALGS [1]. Krantz et al. [3] reported detectable aberrations of 20p12 in 3.6% (2/56) patients with ALGS and molecular deletions in 6.7% (3/45) patients with ALGS. Here, we present our experience of prenatal diagnosis of ALGS1 associated with a *de novo* interstitial deletion of chromosome 20p (20p12.1→p13) encompassing *JAG1*.

Case report

A 33-year-old, primigravid woman was referred to the hospital at 20 weeks of gestation for genetic counseling of a *de novo* interstitial deletion of chromosome 20p [del(20)(p12p13)] in the fetus. Her husband was 35 years old, and there was no family history of congenital malformations. The woman underwent amniocentesis at 17 weeks of gestation because of an abnormal result of combined first-trimester screening which revealed a trisomy 18 risk of 1/211 calculated from a maternal serum pregnancy-associated plasma protein (PAPP-A) level of 1.7 μg/mL [0.25 multiples of the median (MoM)], a maternal serum free β-human choriogonadotropin (β-hCG) level of 9 ng/mL (0.18 MoM), and a nuchal translucency thickness of 1.2 mm (0.97 MoM). Amniocentesis revealed a karyotype of 46,XY,del(20)(p12p13), and array comparative genomic hybridization (aCGH) analysis on uncultured amniocytes using CytoOneArray (Phalanx Biotech Group, Hsinchu, Taiwan) revealed a result of arr 20p13p12.3 (3,944,227–7,692,830) × 1, arr 20p12.2 (10,030,794–11,871,009) × 1, indicating a 3.749-Mb deletion at 20p13-p12.3 and a 1.84-Mb deletion at 20p12.2 encompassing ALGS1 critical gene of *JAG1*. The parental karyotypes were normal. Prenatal ultrasound findings were unremarkable except for an echogenic cardiac focus. After genetic counseling of the consequence of ALGS1, the woman elected to terminate the pregnancy, and a 412-g male fetus was delivered at 22 weeks of gestation. The fetus postnatally manifested broad forehead and pointed chin. Cytogenetic analysis of the cord blood revealed a karyotype of 46,XY,del(20)(p12.1p13). Postnatal aCGH analysis of the DNA extracted from the umbilical cord using CytoChip ISCA Array (Illumina, San Diego, CA, USA) revealed a result of arr 20p13p12.3 (3,998,163–8,315,292) × 1.0, arr 20p12.2p12.1 (9,849,125–12,111,266) × 1.0 with a 4.317-Mb deletion at 20p13-p12.3 encompassing 19 OMIM genes and a 2.262-Mb deletion at 20p12.2-p12.1 encompassing 5 OMIM genes including *JAG1* (Fig. 1). Polymorphic DNA marker analysis using the DNAs extracted from the umbilical cord and the parental bloods revealed a paternal origin of the deletion (Fig. 2).

Discussion

The present case was associated with a *de novo* interstitial deletion of 20p12.1→p13 encompassing *JAG1*, which is located at

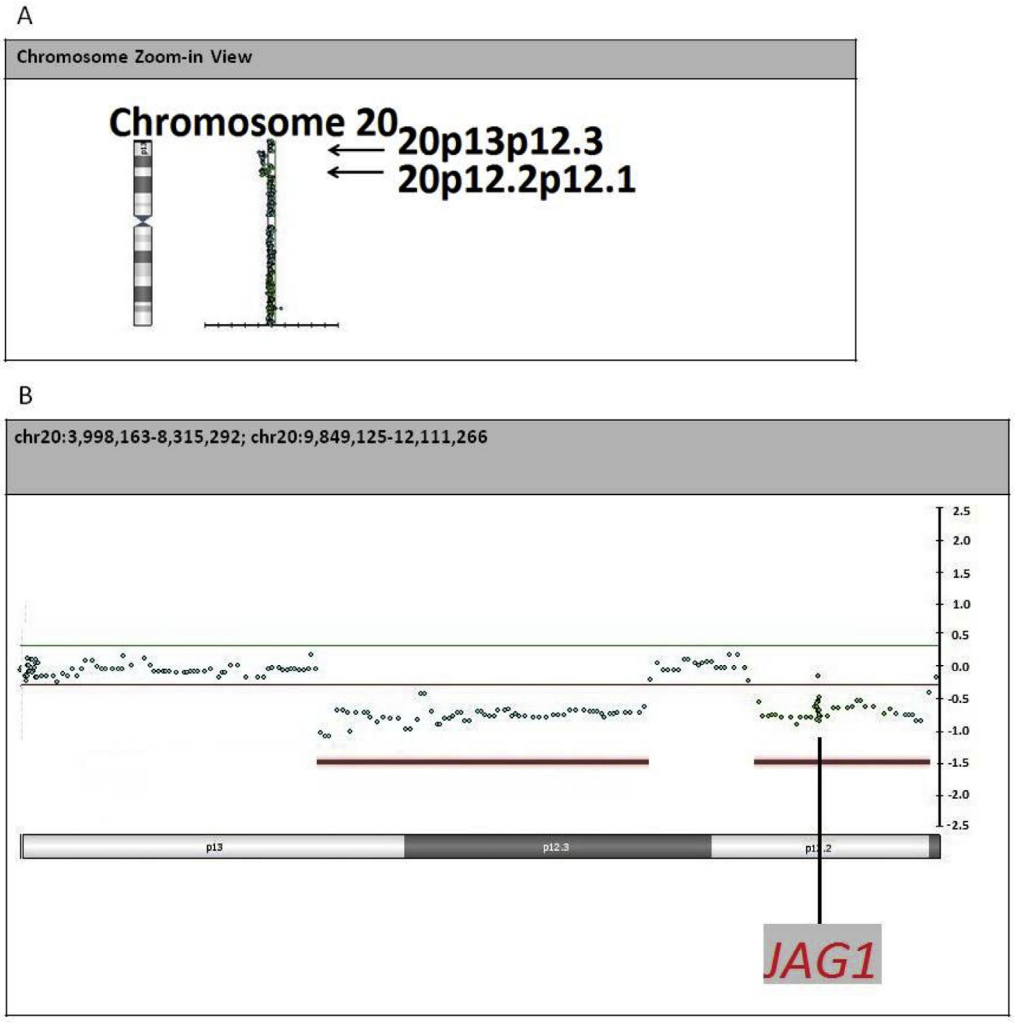

Fig. 1. (A) and (B). Array comparative genomic hybridization analysis on umbilical cord using CytoChip ISCA Array shows a 4.317-Mb deletion at 20p13-p12.3 and a 2.262-Mb deletion at 20p12.2-p12.1 encompassing the gene of *JAG1*.

20p12.2. JAG1 is a ligand of the Notch receptor, and their bindings triggers a cascade of proteolytic cleavage and plays roles in cell differentiation and morphogenesis [4]. Mutations or deletions of the *JAG1* gene are associated with the autosomal dominant disorders of ALGS1 and tetralogy of Fallot (OMIM 187500). We previously reported prenatal diagnosis of *de novo* 46,XX,del(20)(p11.21p12.1) in a fetus because of an advanced maternal age and a paternal origin of the deletion [5]. In this presentation, we additionally report prenatal diagnosis of *de novo* 46,XY,del(20)(p12p13) in a fetus because of an abnormal result of combined first-trimester screening and a paternal origin of the deletion. Both cases provide evidence that *de novo* interstitial deletions of chromosome 20p can be caused by a paternal effect rather than a maternal effect. We suggest that polymorphic DNA marker analysis is useful in determining the parental origin of a *de novo* chromosome aberration, and the information acquired is important for genetic counseling.

The present case shows that fetuses with ALGS may manifest no detectable structural abnormalities on prenatal ultrasound. Ultrasound abnormalities have been previously observed in fetuses with ALGS. The reported prenatal ultrasound findings associated with ALGS include intrauterine growth restriction (IUGR), oligohydramnios, hemivertebrae, butterfly vertebrae, single umbilical artery, prominent chin, ascites, polyhydramnios, kyphoscoliosis, tetralogy of Fallot, non-visualized gallbladder, pulmonary stenosis, prominent stomach and unilateral multicystic kidney [6–13]. Blanc et al. [6] reported prenatal ascites associated with ALGS. Martin et al. [7] reported unilateral multicystic kidney on second-trimester ultrasound in two fetuses affected with ALGS. Quiros-Tejeira et al. [8] suggested that growth failure in patients with ALGS begins in the prenatal period, and thus IUGR may be an indicator of ALGS. Albayram et al. [9] reported prenatal ultrasound findings of pulmonary stenosis, prominent stomach and IUGR in a fetus with ALGS inherited from the mother. Ghidini et al. [10] reported prenatal ultrasound findings of thoracic hemivertebrae, kyphoscoliosis, tetralogy of Fallot and non-visualized gallbladder in a second-trimester fetus with ALGS. Antsaklis et al. [11] reported prenatal ultrasound findings of IUGR, ascites and polyhydramnios in a second-trimester fetus with ALGS inherited from the mother. Wax et al. [12] reported prenatal ultrasound findings of hemivertebrae, butterfly vertebrae, two-vessel cord and prominent chin in a second-trimester fetus with ALGS and a familial history of *JAG1* mutation. Izumi et al. [13] reported oligohydramnios and IUGR in one of the monozygotic twins with ALGS inherited from a maternal missense mutation in *JAG1*.

ALGS is inherited in an autosomal dominant manner. Therefore, offspring of an individual affected with ALGS will have a 50% chance of inheriting the mutation of *JAG1* or *NOTCH2*, or the 20p12.2 microdeletion from the affected parent. Prenatal diagnosis of ALGS by molecular or cytogenetic analysis in at-risk pregnancy can be achieved by preimplantation genetic diagnosis, chorionic villus sampling and amniocentesis [14,15].

In summary, we present prenatal diagnosis and molecular genetic characterization of a *de novo* interstitial deletion of chromosome 20p (20p12.1-p13) encompassing *JAG1*. We also make a complete literature review of prenatal diagnosis of ALGS. Our case shows that a *de novo* interstitial 20p deletion can be caused by a paternal effect. Pregnancy with a fetus affected with ALGS may be associated with an abnormal result of combined first-trimester screening and manifest no detectable ultrasound abnormalities.

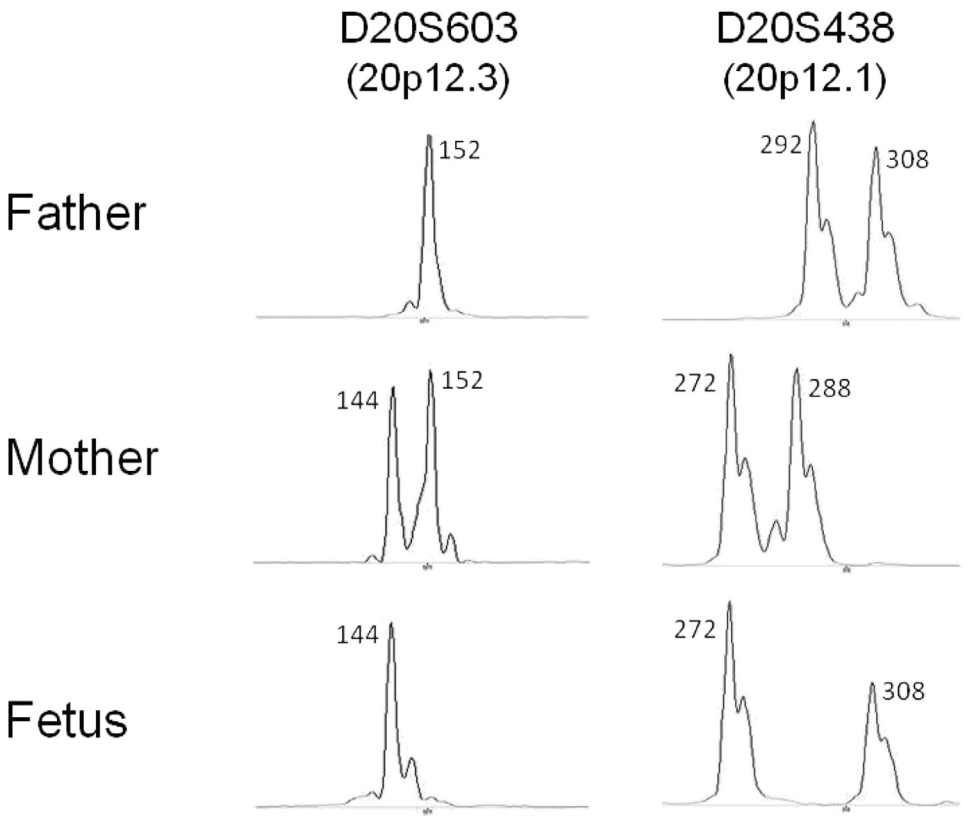

Fig. 2. Representative electrophoretograms of quantitative fluorescent polymerase chain reaction assays using the informative markers D20S603 (20p12.3) and D20S438 (20p12.1). The marker D20S438 is outside the deleted region and shows two peaks of equal fluorescent activity from two different parental alleles in the umbilical cord. The marker D20S603 is within the deleted region and shows only one peak of fluorescent activity from the maternal allele in the umbilical cord, indicating a paternal origin of the deletion in the fetus.

Conflicts of interest

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

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