

Research Letter

Prenatal diagnosis and array comparative genomic hybridization characterization of a *de novo* interstitial deletion of chromosome 20p

Chih-Ping Chen^{a,b,c,d,e,f,*}, Yi-Ning Su^g, Schu-Rern Chern^b, Fuu-Jen Tsai^{d,h}, Pei-Chen Wu^a,
Chen-Chi Lee^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, National Yang-Ming University, Taipei, Taiwan

^g Department of Medical Genetics, National Taiwan University Hospital, Taipei, Taiwan

^h Departments of Medical Genetics, and Medical Research, China Medical University Hospital, Taichung, Taiwan

ⁱ Department of Bioengineering, Tatung University, Taipei, Taiwan

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A 35-year-old, gravida 7 para 3, woman was referred to Mackay Memorial Hospital at 21 gestational weeks for confirmation of a *de novo* interstitial deletion of chromosome 20p in a fetus. She had experienced three spontaneous abortions and had three healthy children. The woman and her husband were healthy, and there was no family history of congenital malformations. Detailed high-resolution ultrasound revealed a singleton fetus consistent with 21 gestational weeks and no gross abnormalities. Repeat amniocentesis was performed at 21 gestational weeks and 40 mL of amniotic fluid was aspirated. Array-based comparative genomic hybridization (aCGH) was performed using uncultured amniocytes from 20 mL, whereas the remaining 20 mL was used for conventional cytogenetic analysis. Conventional cytogenetic analysis revealed an interstitial deletion at 20p (Fig. 1). The parental karyotypes were normal. Oligonucleotide-based aCGH demonstrated partial monosomy 20p [arr cgh 20p12.1p11.21 (13,345,494–25,407,784 bp)×1] with a deletion of 12.1 Mb at chromosome 20p (Fig. 2). The karyotype was 46,XX,del(20)(p11.21p12.1) *de novo*. The parents opted to terminate the pregnancy. A 536-g fetus with facial dysmorphism, hypertelorism, a flat nasal bridge, micrognathia, and low-set ears was delivered at 23 gestational weeks

(Fig. 3). The parental origin of the proximal deletion of 20p in the fetus was investigated by quantitative fluorescent polymerase chain reaction using polymorphic DNA markers. The deletion was of paternal origin (Fig. 4).

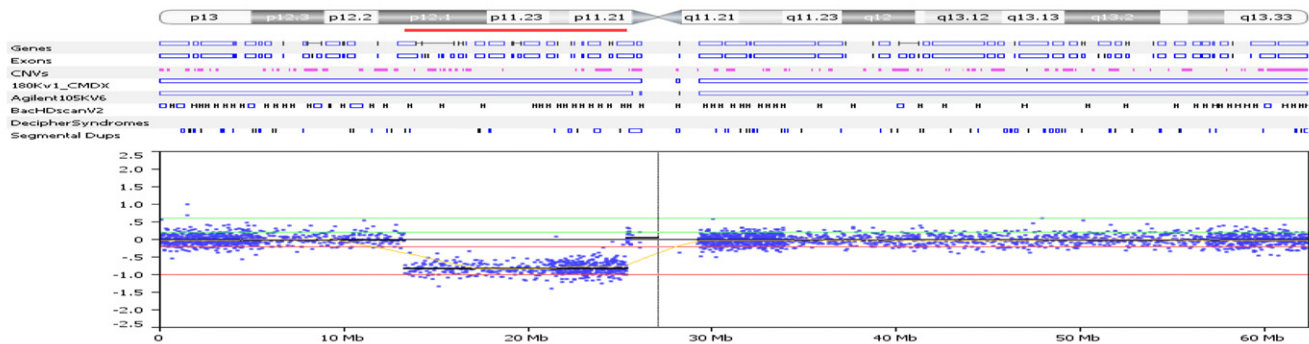
We have presented the diagnosis and molecular characterization of a *de novo* interstitial deletion of chromosome 20p in a second-trimester fetus. Prenatal diagnosis of partial monosomy 20p (20p11.21→p12.1) has not been described previously. The present case had minor facial dysmorphism but no sonographically recognizable structural defects. By using quantitative fluorescent polymerase chain reaction, we demonstrated the paternal origin of the deletion. By using aCGH, we demonstrated that the interstitial deletion of 20p encompassed a 12.1-Mb region (13,345,494–25,407,784 bp) proximal to the Alagille syndrome related gene, *JAG1* (10,566,334–10,602,590 bp). Alagille syndrome is an autosomal dominant disorder characterized by bile duct paucity and three of the following five major clinical features:



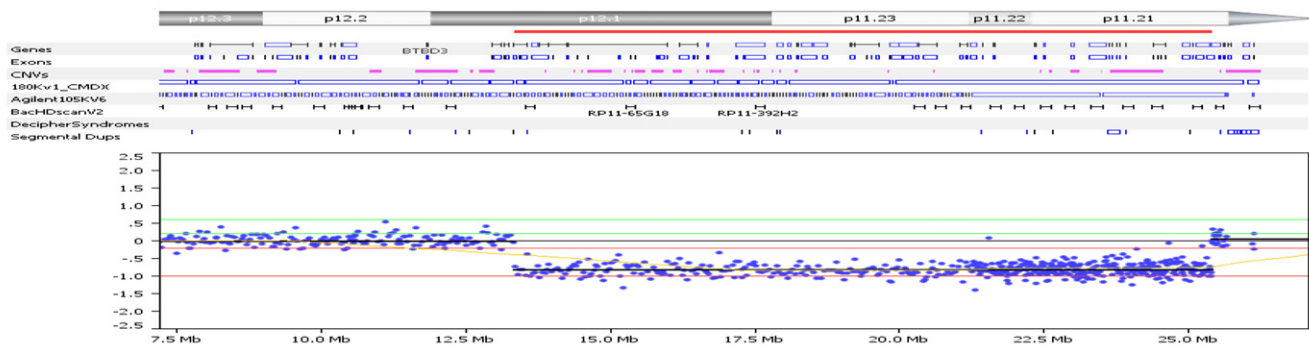
Fig. 1. Partial karyotype shows del(20)(p11.21p12.1). Arrows indicate the breakpoints.

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

Chromosome 20



Zoom-in



Whole genome View

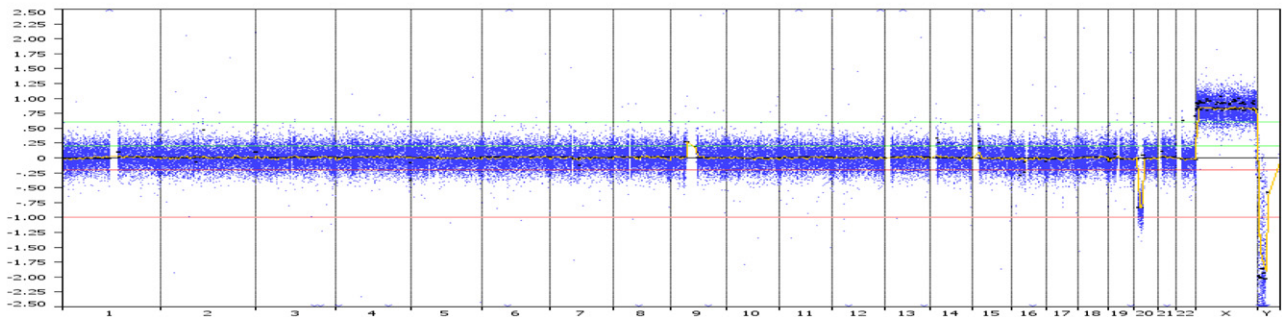


Fig. 2. Oligonucleotide-based array-based comparative genomic hybridization analysis using Oligo HD Scan shows a 12.1-Mb deletion in 20p11.21→p12.1 [arr cgh 20p11.21p12.1 (13,345,494–25,407,784 bp)×1].

cholestasis, cardiac defects (most commonly stenosis of the peripheral pulmonary artery), skeletal abnormalities (most commonly butterfly vertebrae), ophthalmologic abnormalities (most commonly posterior embryotoxon), and characteristic facial features (Spinner et al [1]). Alagille syndrome 1 (ALGS1) (OMIM 118450) is caused by mutations in the *JAG1* gene (OMIM 601920) at 20p12 and Alagille syndrome 2 (ALGS2) (OMIM 610205) is caused by mutations in the *NOTCH2* gene (OMIM 600275) at 1p13-p11. About 7% of the patients with Alagille syndrome are caused by a microdeletion of 20p12 with a deletion of the entire *JAG1* gene [1]. Prenatal sonographic findings of Alagille syndrome include severe

pulmonary stenosis and severe intra-uterine growth restriction [2], and the absence of gallbladder in association with angulation of the fetal spine and tetralogy of Fallot [3].

Constitutional deletions of proximal 20p involving 20p11.21, p11.22, p11.23 and/or p12.1 have been reported to be associated with phenotypic abnormalities. Michaelis et al [4] described a 9-year- and 10-month-old boy with an interstitial deletion of 20p11.22-p11.23, Hirschsprung disease, autism, and facial dysmorphism. Garcia-Heras et al [5] reported a 3-year- and 6-month-old girl with an interstitial deletion of 20p11.1-p12, panhypopituitarism, craniofacial dysmorphism, a semi-bifid scrotum, a small phallus, and wide separation



Fig. 3. The fetus at birth.

between the first and second toes. Kamath et al [6] reported a patient with a karyotype of 46,XY,del(20)(p11.22p11.23) *de novo* and an 8.68-Mb interstitial deletion (13,566,382–22,251,261 bp). The patient manifested cognitive delay, autistic features, hearing loss, short segment Hirschsprung disease, and fourth cranial nerve palsy but no Alagille syndrome. Kamath et al [6] additionally reported a patient

with a karyotype of 46,XY,del(20)(p11.1p12.2) *de novo* and an 11.96-Mb interstitial deletion (14,300,641–26,257,244 bp). The patient manifested cognitive delay, autistic features, hearing loss, an empty sella on computed tomography scan, and growth hormone deficiency but no Alagille syndrome. The present case had a large 12.1-Mb deletion that started from the region proximal to the *JAG1* gene and, as expected, manifested

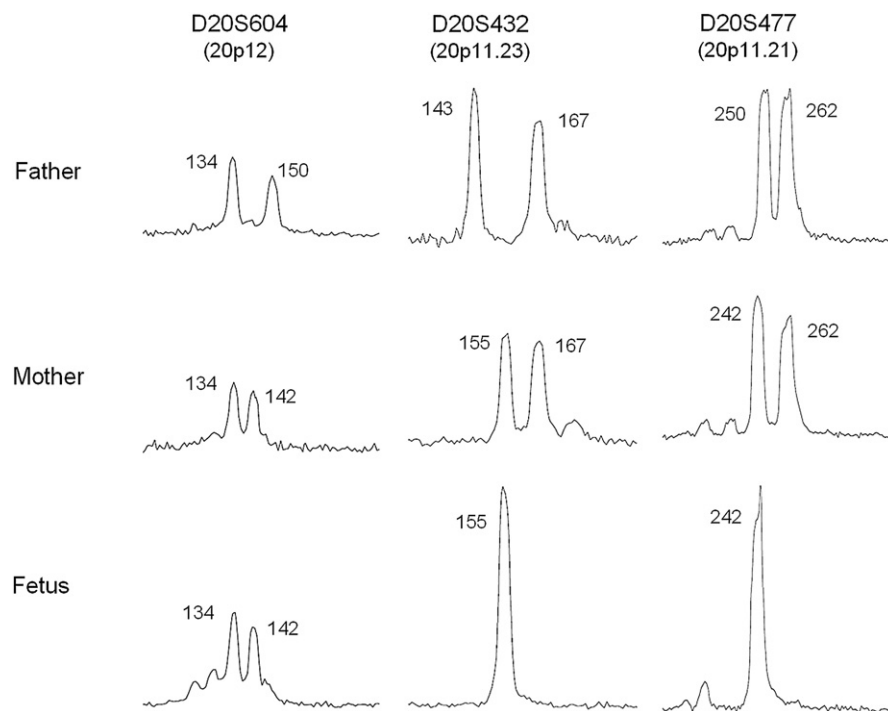


Fig. 4. Representative electrophoretograms of quantitative fluorescent polymerase chain reaction assays using polymorphic DNA markers of D20S604 (20p12) (12,536,112–12,536,366), D20S432 (20p11.23) (19,794,164–19,794,322), and D20S477 (20p11.21) (22,374,886–22,375,136). The marker D20S604 is outside the deleted region and shows two peaks of equal fluorescent activity from two different parental alleles in the fetal tissue. The markers D20S432 and D20S477 are within the deleted region and show only one peak of fluorescent activity from the maternal allele in the fetal tissue indicating a paternal origin of the deletion.

no Alagille syndrome. We previously reported the use of aCGH as a powerful tool for the diagnosis of interstitial deletions [7,8]. In this report, we further demonstrate that aCGH can provide accurate high-resolution definition of genomic abnormalities.

Acknowledgments

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