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Case Report

Detection of *de novo* del(18)(q22.2) and a familial of 15q13.2-q13.3 microduplication in a fetus with congenital heart defectsChih-Ping Chen^{a, b, c, d, e, f, *}, Chen-Yu Chen^{a, g, h}, Schu-Rern Chern^b, Peih-Shan Wuⁱ, Shin-Wen Chen^a, Fang-Tzu Wu^a, Li-Feng Chen^a, Wayseen Wang^{b, j}^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 Medicine, MacKay Medical College, New Taipei City, Taiwan^h MacKay Junior College of Medicine, Nursing and Management, Taipei, Taiwanⁱ Gene Biodesign Co. Ltd, Taipei, Taiwan^j Department of Bioengineering, Tatung University, Taipei, Taiwan

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ABSTRACT

Objective: We present detection of *de novo* del(18)(q22.2) and a familial 15q13.2-q13.3 microduplication in a fetus with congenital heart defects (CHD).**Case report:** A 27-year-old, primigravid woman was referred for genetic counseling because of fetal CHD. Prenatal ultrasound at 17 weeks of gestation revealed pericardial effusion, cardiomegaly and a large ventricular septal defect. The pregnancy was subsequently terminated at 18 weeks of gestation, and a 192-g female fetus was delivered with facial dysmorphism. Cytogenetic analysis of the umbilical cord revealed a karyotype of 46,XX,del(18)(q22.2). The parental karyotypes were normal. Array comparative genomic hybridization (aCGH) of the placental tissue revealed a 2.08-Mb 15q13.2-q13.3 microduplication encompassing *KLF13* and *CHRNA7*, and a 10.74-Mb 18q22.2-q23 deletion encompassing *NFATC1*. The phenotypically normal father carried the same 2.08-Mb 15q13.2-q13.3 microduplication. Polymorphic DNA marker analysis confirmed a paternal origin of the distal 18q deletion.**Conclusion:** Prenatal diagnosis of CHD should include a complete genetic study of the embryonic tissues, and the acquired information is useful for genetic counseling.© 2019 Taiwan Association of Obstetrics & Gynecology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

The chromosome 18q deletions syndrome [Online Mendelian Inheritance in Man (OMIM) 601808] is a well-recognized chromosomal abnormality with variable deletions ranging from 18q21.2, 18q21.3 or 18q22.2 → 18qter, and has an estimated prevalence of 1:40,000 live births and phenotypic features of growth deficiency, low birth weight, short stature, microcephaly, facial dysmorphisms of mid-facial hypoplasia, prognathism, a carp-shaped mouth, a

protuberant lower lip, dysplastic ears with prominent antihelix and antitragus, abnormal skull, vertebrae, ribs, atretic ear canals, vertical tali, tapered fingers, dimples over limb joints, hypoplasia of the labia or scrotum, a micropenis, cryptorchidism, hypospadias, nystagmus, strabismus, glaucoma, tapetoretinal degeneration, optic atrophy, hypotonia, seizures, deafness, enlarged ventricles, hydrocephalus, porencephaly, holoprosencephaly, cerebellar hypoplasia, decreased white matter, delayed myelination and congenital heart defects (CHD) [1–8].

There is a preferential loss of the paternal alleles in the 18q deletion syndrome [9]. A female preponderance of the 18q deletion has been noted. Cody et al. [8] reported a male: female sex ratio of 12:30 in the 42 individuals with the 18q deletion syndrome. Chen et al. [10] reported direct transmission of del(18)(q22.2) from

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mother to daughter, and both had 18q deletion syndrome including short stature, facial dysmorphism, microcephaly and mental retardation. Chen et al. [10] suggested that identification of affected females with the 18q deletion syndrome should include genetic counseling of possible direct transmission and consideration of birth control or prenatal genetic testing at reproductive age.

We previously reported detection of pure 18q deletion [5–7,10]. Here, we present detection of *de novo* del(18)(q22.2) and a familial 15q13.2-q13.3 microduplication in a fetus with CHD.

Case report

A 27-year-old, primigravid woman was referred for genetic counseling because of fetal CHD. Her husband was 27 years old, and there was no family history of CHD. The woman and her husband were phenotypically normal. Prenatal ultrasound at 17 weeks of gestation revealed pericardial effusion, cardiomegaly and a large ventricular septal defect (VSD). Following counseling, the parents elected to terminate the pregnancy at 18 weeks of gestation, and a 192-g female fetus was delivered with facial dysmorphism including low-set ears, a carp-shaped mouth, mid-face hypoplasia, a large nose and a prominent forehead (Fig. 1). Cytogenetic analysis of the umbilical cord revealed a karyotype of 46,XX,del(18)(q22.2) (Fig. 2). The parental karyotypes were normal. Array comparative genomic hybridization (aCGH) of the placental tissue revealed a result of arr 15q13.2q13.3 (30,819,465–32,899,558) \times 3.0, arr 18q22.2q22.3 (67,274,465–78,012,829) \times 1.0 [GRCh37 (hg19)] (Fig. 3) with a 2.08-Mb 15q13.2-q13.3 microduplication encompassing *KLF13* and *CHRNA7*, and a 10.74-Mb 18q22.2-q23 deletion encompassing *NFATC1*. The phenotypically normal father carried the same 2.08-Mb 15q13.2-q13.3 microduplication (Fig. 4). Polymorphic DNA marker analysis confirmed a paternal origin of the distal 18q deletion (see Fig. 5).

Discussion

The present case had a 10.74-Mb interstitial deletion 18q22.2-q23 and presented CHD on prenatal ultrasound. Prenatal diagnosis of pure 18q deletion syndrome is rare. Casseler et al. [11]

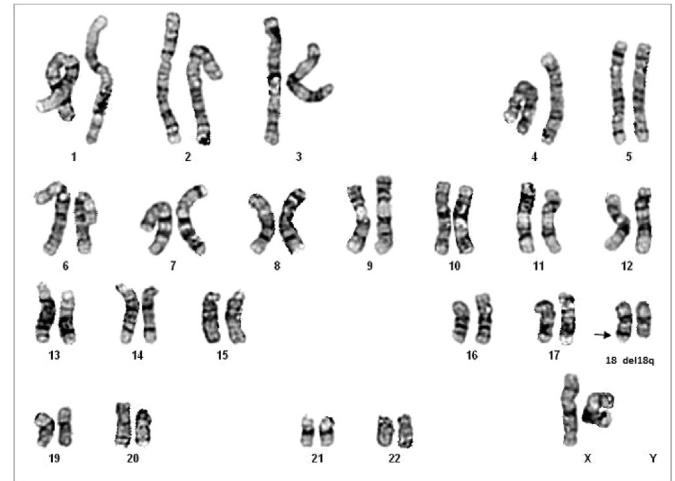


Fig. 2. A karyotype 46,XX,del(18)(q22.2).

reported prenatal diagnosis of 46,XX,del(18)(q21q23) by amniocentesis in a fetus with facial cleft on prenatal ultrasound. Chen et al. [5] reported prenatal diagnosis of 46,XX,del(18)(q22.2) by amniocentesis in a pregnancy with an abnormal maternal serum screening result. The genetic marker analysis revealed a paternal origin of the deletion. Chen et al. [6] reported prenatal diagnosis of mosaicism for 46,XY,del(18)(q21.3) by amniocentesis in a fetus with microcephaly and facial cleft on prenatal ultrasound. Chen et al. [7] reported two cases of 18q deletion syndrome by amniocentesis. The first case had a karyotype of 46,XY,del(18)(q23) with short femurs and clubfoot on prenatal ultrasound. The genetic marker analysis revealed a paternal origin of the deletion. The second case had a karyotype of 46,XX,del(18)(q22.2) with microcephaly, short femurs, fetal ascites, pericardial effusion and a hypoplastic left heart on prenatal ultrasound. The genetic marker analysis revealed a maternal origin of the deletion. Anselem et al. [12] reported prenatal diagnosis of 46,XX,del(18)(q21.2) by amniocentesis in a fetus



Fig. 1. The craniofacial dysmorphism of the fetus at birth.

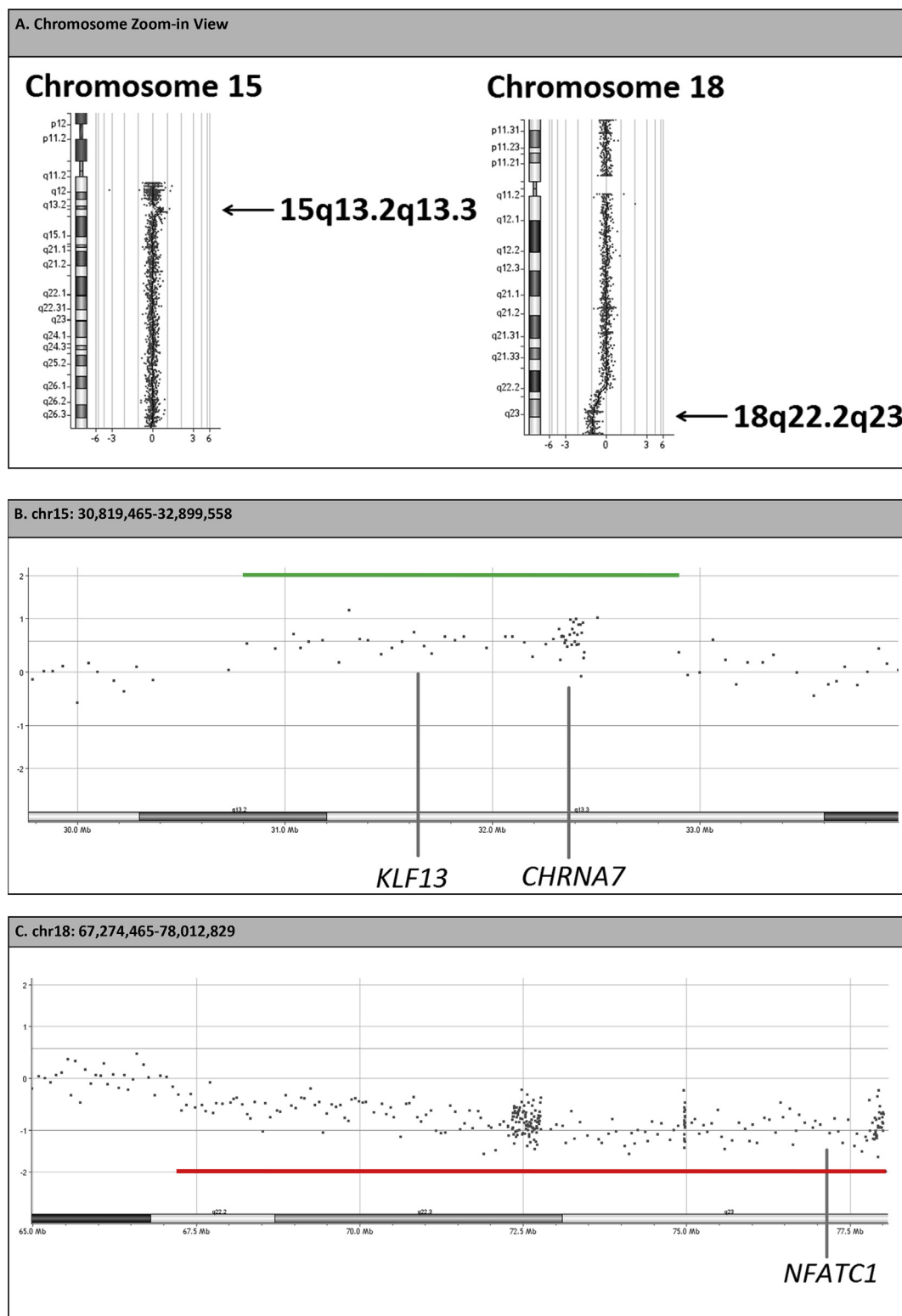


Fig. 3. Array comparative genomic hybridization (aCGH) using SurePrint G3 Unrestricted CGH ISCA v2, 8 × 60 K (Agilent Technologies, Santa Clara, CA, USA) on the DNA extracted from the placenta shows (A) a 15q13.2–q13.3 duplication and an 18q22.2–q22.3 deletion, (B) a 2.08-Mb 15q13.2–q13.3 microduplication encompassing *CHRNA7* and *KLF13*, and (C) a 10.74-Mb 18q22.2–q23 deletion encompassing *NFATC1*.

with partial agenesis of the corpus callosum on prenatal ultrasound.

The present case presented VSD and pericardial effusion on prenatal ultrasound. The reported incidence of CHD in patients with the 18q deletion syndrome ranges from 24% [8] to 36% [13].

van Trier et al. [14] found that the most common cardiac defects associated with the 18q deletion syndrome were pulmonary valve anomalies and atrial septal defects. The present case had haploinsufficiency of *NFATC1* and VSD. *NFATC1* (OMIM 600489) encodes cytoplasmic nuclear factor of activated T cells calcineurin-

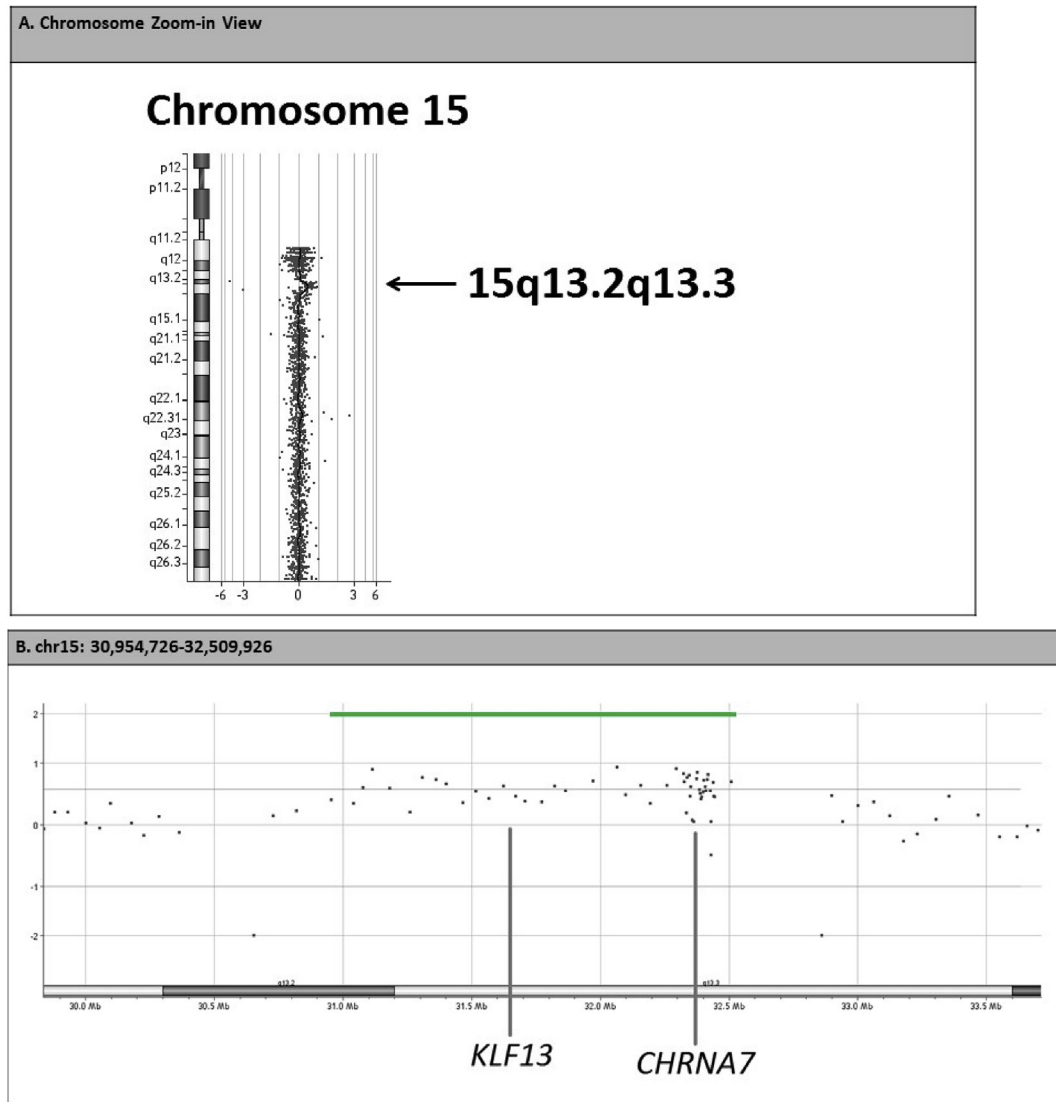


Fig. 4. aCGH using SurePrint G3 Unrestricted CGH ISCA v2, 8 × 60 K (Agilent Technologies, Santa Clara, CA, USA) on the DNA extracted from the paternal blood shows (A) a 15q13.2-q13.3 duplication and (B) a 2.08-Mb 15q13.2-q13.3 microduplication encompassing *CHRNA7* and *KLF13*.

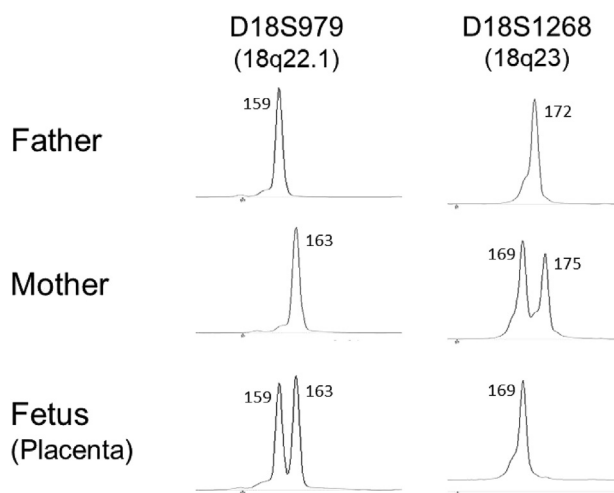


Fig. 5. Polymorphic DNA marker analysis using the informative marker D18S1268 (18q23) shows the placental tissue carries only one allele of 169 bp from the mother and lacks the paternal allele, indicating a paternal origin of the distal 18q deletion.

dependent 1. *NFATC1* is essential for embryonic cardiac valve formation in mice [15–17]. *NFATC1* belongs to the Rel family of transcription factors, which is expressed in the embryonic mice heart and is restricted to endocardium. Yehya et al. [18] reported homozygous mutation of *NFATC1* in patients with VSD and suggested that *NFATC1* is a potential VSD-susceptibility gene. Abdul-Sater et al. [19] reported heterozygous mutations in *NFATC1* in a patient with tricuspid atresia. Shen et al. [20] reported an association of *NFATC1* gene polymorphism and VSD in the Chinese Han population. Li et al. [21] reported a correlation between *NFATC1* gene polymorphism and CHD in children. Ferese et al. [22] reported heterozygous mutations in *NFATC1* in patients with atrioventricular septal defects (AVSD) and suggested that defective *NFATC1* function plays a role in the etiology of isolated and heterotaxy-related AVSD.

The present case had a familial 15q13.2-q13.3 microduplication encompassing *KLF13* and *CHRNA7*. The phenotype of chromosome 15q13.2-q13.3 microdeletion/duplication syndrome includes features of autism spectrum disorder, a variety of neuropsychiatric disorders and cognitive impairment [23,24]. van Bon et al. [24] suggested a highly variable intra- and inter-familial phenotype of

chromosome 15q13.2-q13.3 microdeletion/duplication syndrome. van Bon et al. [24] found that 18% of the 15q13.2-q13.3 deletion patients had CHD and suggested that *KLF13* may contribute CHD. *KLF13* (OMIM 605328) encodes Kruppel-like factor 13, which is a regulator of heart development [25]. *CHRNA7* (OMIM 118511) encodes neuronal nicotinic cholinergic receptor α polypeptide 7 and has a possible association with schizophrenia (SCZD13; OMIM 613025) [26–30], idiopathic generalized epilepsy 7 (EIG7; OMIM 604827) [31–34], and 15q13.3 microdeletion syndrome with mental retardation and seizures (OMIM 612001).

In summary, we present genetic analysis of *de novo* del(18)(q22.2) and a familial 15q13.2-q13.3 microduplication in a fetus with CHD. Our case emphasizes that prenatal diagnosis of CHD should include a genetic study of the embryonic tissues, and the acquired information is useful for genetic counseling.

Conflicts of interest

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

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