



Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Case Report

Detection of a familial 21q22.3 microduplication in a fetus associated with congenital heart defects

Chih-Ping Chen^{a, b, c, d, e, f, *}, Chen-Yu Chen^{a, g}, Schu-Rern Chern^b, Peih-Shan Wu^h, Shin-Wen Chen^a, Tzu-Yun Chuang^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 Medicine, MacKay Medical College, New Taipei City, Taiwan^h Gene Biodesign Co. Ltd, Taipei, Taiwanⁱ Department of Bioengineering, Tatung University, Taipei, Taiwan

ARTICLE INFO

Article history:

Accepted 11 July 2019

Keywords:

21q22.3 microduplication

Congenital heart defects

Prenatal diagnosis

ABSTRACT

Objective: We present a familial 21q22.3 microduplication in a fetus associated with prenatally detected congenital heart defects (CHD).**Case report:** A 38-year-old woman underwent amniocentesis at 22 weeks of gestation because of sonographic findings of double outlet of right ventricle, ventricular septal defect and transposition of great artery in the fetus. Her husband was 42 years old, and there was no CHD and congenital malformation in the family. Cytogenetic analysis revealed a karyotype of 46,XY in the fetus. Simultaneous array comparative genomic hybridization (aCGH) analysis using uncultured amniocytes revealed a 0.56-Mb microduplication of 21q22.3 or arr 21q22.3 (47,482,210-48,043,704)×3.0 [GRCh37 (hg19)] encompassing nine Online Mendelian Inheritance in Man (OMIM) genes of *FTCD*, *SPATC1L*, *LSS*, *MCM3AP*, *YBEY*, *PCNT*, *DIP2A*, *S100B* and *PRMT2*. aCGH analysis of the parental bloods revealed that the phenotypically normal father carried the same microduplication. The parents decided to continue the pregnancy, and a 3168-g male baby was delivered at term without Down syndrome phenotype except CHD. Mutational analysis of the *CRELD1* gene on the DNA extracted from the cord blood showed no mutation in *CRELD1*. Postnatal molecular cytogenetic analysis of the cord blood confirmed the prenatal diagnosis. The infant underwent a successful heart surgery to correct the CHD and was doing well without psychomotor or developmental delay at six months of age.**Conclusion:** Prenatal diagnosis of 21q22.3 microduplication associated with CHD should include a differential diagnosis of Down syndrome.© 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 Down syndrome critical regions (DSCRs) include DSCR3 [Online Mendelian Inheritance in Man (OMIM) 605298] at 21q22.13, DSCR6 (OMIM 609892) at 21q22.13, DSCR4 (OMIM

604829) at 21q22.13, DSCR8 (OMIM 613396) at 21q22.13, DSCR2 (OMIM 605296) at 21q22.2 and Down syndrome chromosome region (OMIM 190685) at 21q22.3. Prenatal diagnosis of chromosome 21q22.3 microduplication associated with congenital heart defects (CHD) raises concerns of Down syndrome phenotype. Here, we present a familial 21q22.3 microduplication in a fetus associated with CHD but without other Down syndrome phenotype.

* 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).

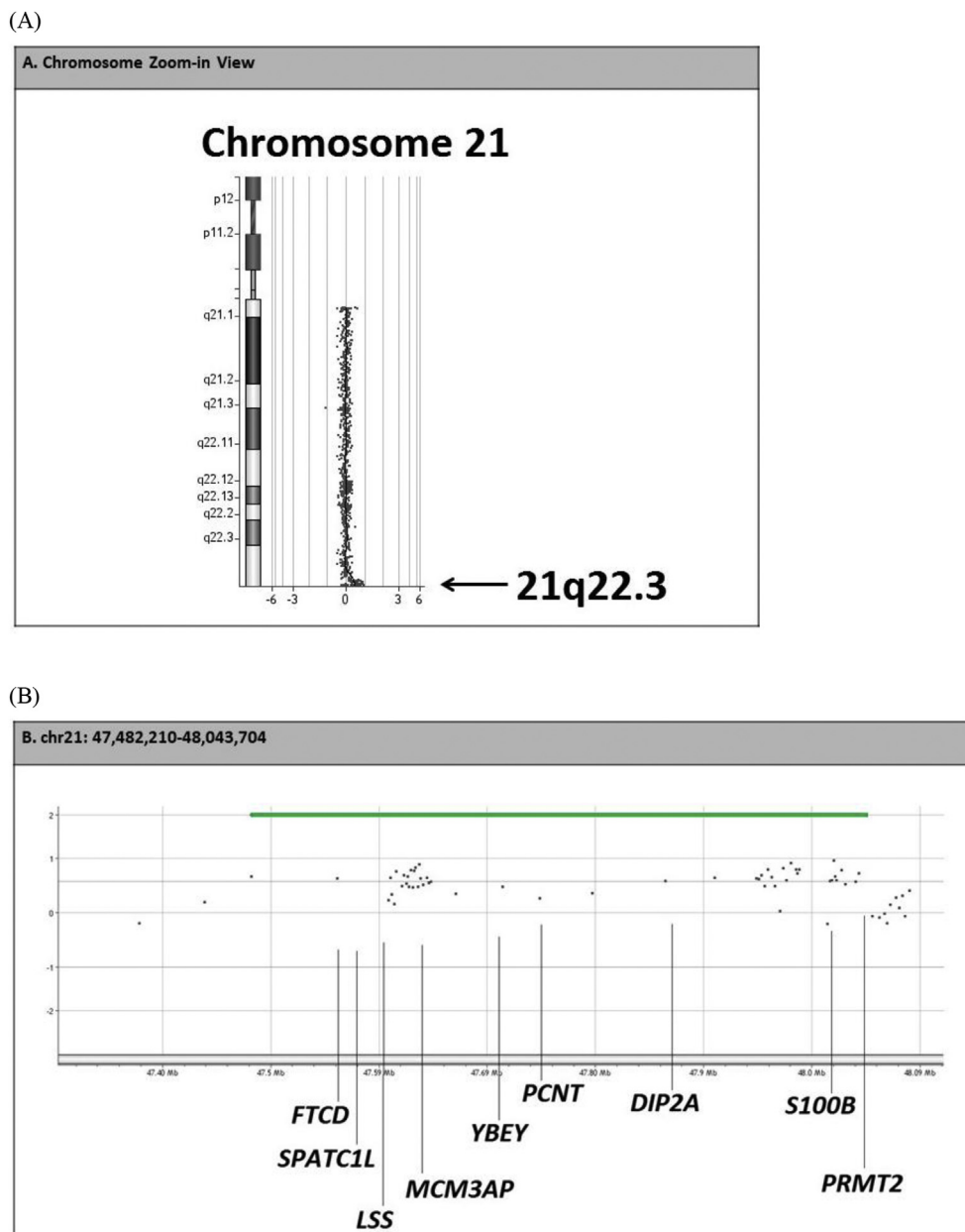


Fig. 1. Array comparative genomic hybridization analysis of the DNA extracted from the cord blood using SurePrint G3 Unrestricted CGH ISCA v2, 8×60K (Agilent Technologies, Santa Clara, CA, USA) shows a 0.56-Mb microduplication of 21q22.3 or arr 21q22.3 (47,482,210-48,043,704)×3.0 [GRCh37 (hg19)] encompassing nine Online Mendelian Inheritance in Man (OMIM) genes of *FTCD*, *SPATC1L*, *LSS*, *MCM3AP*, *YBEY*, *PCNT*, *DIP2A*, *S100B* and *PRMT2*. (A) and (B) Chromosome zoom-in views.

Case report

A 38-year-old, gravida 2, para 1, woman was referred for genetic amniocentesis at 22 weeks of gestation because of abnormal sonographic findings of double outlet of right ventricle (DORV), ventricular septal defect (VSD) and transposition of great artery in the fetus. Her husband was 42 years old. The couple had a 3-year-old healthy daughter, and there was no CHD and congenital malformation in the family. Cytogenetic analysis revealed a karyotype of 46,XY in the fetus. Array comparative genomic hybridization (aCGH) analysis using SurePrint G3 Human CGH ISCA (Agilent Technologies, Santa Clara, CA, USA) on the DNAs extracted from uncultured amniocytes and amniotic fluid revealed a result of arr [GRCh37 (hg19)] 21q22.3 (47,482,210-48,043,704)×3, (X,Y)×1. The

0.56-Mb microduplication of 21q22.3 encompassed nine Online Mendelian Inheritance in Man (OMIM) genes of *FTCD*, *SPATC1L*, *LSS*, *MCM3AP*, *YBEY*, *PCNT*, *DIP2A*, *S100B* and *PRMT2*. aCGH analysis on the DNAs extracted from the parental bloods revealed that the phenotypically normal father carried the same microduplication. The parents decided to continue the pregnancy, and a 3168-g male baby was delivered at term without Down syndrome phenotype except CHD. Postnatal molecular cytogenetic analysis of the cord blood confirmed the prenatal diagnosis (Figs. 1 and 2). Mutational analysis of the *CRELD1* gene on the DNA extracted from the cord blood showed no mutation in *CRELD1*. The infant postnatally underwent a successful heart surgery to correct the CHD and was doing well without psychomotor or developmental delay at six months of age.

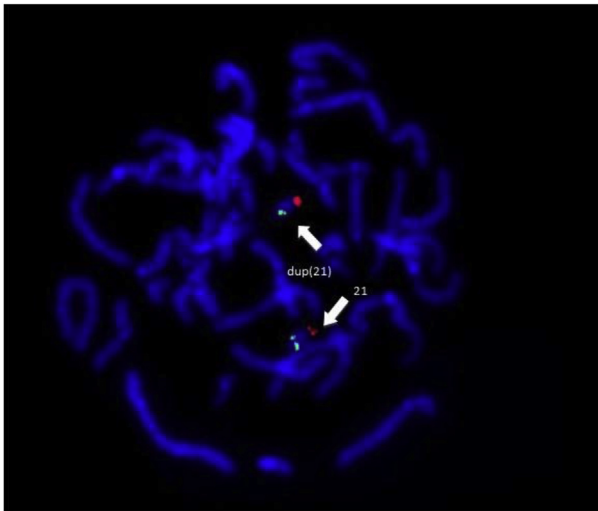


Fig. 2. Metaphase fluorescence *in situ* hybridization (FISH) analysis on the blood lymphocytes using the bacterial artificial chromosome (BAC) probes of RP11-47B13 [21q11.2 (14,376,516–14,569,218) (hg19), dye: fluorescein isothiocyanate (FITC, spectrum green)] and RP11-1115G12 [21q22.3 (47,678,489–47,838,268) (hg19), dye: Texas Red, spectrum red] shows duplicated red signals on the abnormal chromosome 21 [dup(21)] with 21q22.3 microduplication. dup = duplication.

Discussion

The present case carried a 21q22.3 microduplication distal to the DSCR at 21q22.3 (GRCh38: 21: 41,200,000–46,709,983) and presented no Down syndrome dysmorphism except CHD. The 0.56-Mb microduplication of 21q22.3 in the present case involves nine OMIM genes of *FTCD*, *SPATC1L*, *LSS*, *MCM3AP*, *YBEY*, *PCNT*, *DIP2A*, *S100B* and *PRMT2*. The carrier father was phenotypically normal. *FTCD* (OMIM 606806) encodes formiminotransferase cyclo-deaminase, and mutations of *FTCD* is associated with autosomal receive glutamate formiminotransferase deficiency (OMIM 229100) [1]. *SPATC1L* (OMIM 612412) encodes a male germ cell-specific protein which is associated with the maintenance of sperm head-tail attachment during spermiogenesis [2]. *LSS* (OMIM 600909) encodes lanosterol synthase, and mutations of *LSS* are associated with autosomal recessive cataract (OMIM 616509) [3] and hypotrichosis (OMIM 618275) [4]. *MCM3AP* (OMIM 603294) encodes minichromosome maintenance 3-associated protein, and mutations of *MCM3AP* are associated with autosomal recessive peripheral neuropathy with or without impaired intellectual disability (OMIM 618124) [5]. *YBEY* (OMIM 617461) is an *E. coli* homolog. *PCNT* (OMIM 605925) encodes pericentrin, and mutations of *PCNT* are associated with autosomal recessive microcephalic osteodysplastic primordial dwarfism type II (OMIM 210720) [6]. *DIP2A* (OMIM 607711) encodes disco-interacting protein 2 homolog A of *Drosophila*. *S100B* (OMIM 176990) encodes S100 calcium-binding protein- β , and is a neurotrophic factor and a neuronal survival protein during central nervous system development [7]. *PRMT2* (OMIM 601961) encodes protein arginine methyltransferase 2 which is important in posttranslational methylation of arginine residues [8].

The present case was associated with DORV, VSD and transposition of great artery. Trisomy 21 is the most common chromosomal abnormality associated with atrioventricular septal defect (AVSD). In a study of 39 patients with Down syndrome and complete AVSD, Maslen et al. [9] found that two patients had heterozygosity for missense mutations in the *CRELD1* gene (OMIM 607170; 3p25.3), and suggested that *CRELD1* may contribute to the pathogenesis of AVSD in trisomy 21. In a study of 141 cases with Down syndrome and complete AVSD, and 141 cases with Down syndrome but no AVSD, Ackerman et al. [10] found that 20% of the cases of Down syndrome and complete AVSD had mutations in the six VEGF-A pathway genes including *COL6A1*, *COL6A2*, *CRELD1*, *FBLN2*, *FRZB* and *GATA5*, comparing with 3% of controls. Ackerman et al. [10] suggested that the VEGF-A pathway genes contribute to the genetic causes of AVSD in Down syndrome.

In conclusion, prenatal diagnosis of 21q22.3 microduplication associated with CHD should include a differential diagnosis of Down syndrome.

Conflicts of interest

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

Acknowledgements

This work was supported by research grants MOST-107-2314-B-195-005 from the Ministry of Science and Technology, and MMH-E-107-04 and MMH-E-108-04 from MacKay Memorial Hospital, Taipei, Taiwan.

References

- [1] Hilton JF, Christensen KE, Watkins D, Raby BA, Renaud Y, de la Luna S, et al. The molecular basis of glutamate formiminotransferase deficiency. *Hum Mutat* 2003;22:67–73.
- [2] Kim J, Kwon JT, Jeong J, Kim J, Hong SH, Kim J, et al. *SPATC1L* maintains the integrity of the sperm head-tail junction. *EMBO Rep* 2018;19:e45991.
- [3] Zhao L, Chen X-J, Zhu J, Xi Y-B, Yang X, Hu L-D, et al. Lanosterol reverses protein aggregation in cataracts. *Nature* 2015;523:607–11.
- [4] Romano M-T, Tafazzoli A, Mattern M, Sivalingam S, Wolf S, Rupp A, et al. Biallelic mutations in *LSS*, encoding lanosterol synthase, cause autosomal-recessive hypotrichosis simplex. *Am J Hum Genet* 2018;103:777–85.
- [5] Schuurs-Hoeijmakers JHM, Vulto-van Silfhout AT, Vissers LELM, van de Vondervoort IIGM, van Bon BW, de Ligt J, et al. Identification of pathogenic gene variants in small families with intellectually disabled siblings by exome sequencing. *J Med Genet* 2013;50:802–11.
- [6] Griffith E, Walker S, Martin C-A, Vagnarelli P, Stiff T, Vernay B, et al. Mutations in pericentrin cause Seckel syndrome with defective ATR-dependent DNA damage signaling. *Nat Genet* 2008;40:232–6.
- [7] Wainwright MS, Craft JM, Griffin WST, Marks A, Pineda J, Padgett KR, et al. Increased susceptibility of S100B transgenic mice to perinatal hypoxia-ischemia. *Ann Neurol* 2004;56:61–7.
- [8] Katsanis N, Yaspo M-L, Fisher EMC. Identification and mapping of a novel human gene, *HRMT1L1*, homologous to the rat protein arginine N-methyltransferase 1 (*PRMT1*) gene. *Mamm Genome* 1997;8:526–9.
- [9] Maslen CL, Babcock D, Robinson SW, Bean LJH, Dooley KJ, Willour VL, et al. *CRELD1* mutations contribute to the occurrence of cardiac atrioventricular septal defects in Down syndrome. *Am J Med Genet* 2006;140A:2501–5.
- [10] Ackerman C, Locke AE, Feingold E, Reshey B, Espana K, Thusberg J, et al. An excess of deleterious variants in VEGF-A pathway genes in Down-syndrome-associated atrioventricular septal defects. *Am J Hum Genet* 2012;91:646–59.