Taiwanese Journal of Obstetrics & Gynecology 56 (2017) 843–846

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Case Report

Prenatal diagnosis of an 8q22.2-q23.3 deletion associated with bilateral cleft lip and palate and intrauterine growth restriction on fetal ultrasound

Chih-Ping Chen [a, b, c, d, e, f, *], Tung-Yao Chang [g], Fang-Yu Hung [h], Schu-Rern Chern [b], Peih-Shan Wu [i], Shin-Wen Chen [a], Shih-Ting Lai [a], Tzu-Yun Chuang [a], Chen-Chi Lee [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] Taiji Fetal Medicine Center, Taipei, Taiwan
[h] Department of Obstetrics and Gynecology, Hsinchu MacKay Memorial Hospital, Hsinchu, Taiwan
[i] Gene Biodesign Co. Ltd., Taipei, Taiwan
[j] Department of Bioengineering, Tatung University, Taipei, Taiwan

ARTICLE INFO

Article history:
Accepted 17 October 2017

Keywords:
8q22.2-q23.3 deletion
Cleft lip and palate
Intrauterine growth restriction
Prenatal diagnosis
Ultrasound

ABSTRACT

Objective: We present prenatal diagnosis of an interstitial 8q22.2-q23.3 deletion associated with bilateral cleft lip and palate and intrauterine growth restriction (IUGR) on fetal ultrasound.
Case report: A 29-year-old, primigravid woman underwent elective amniocentesis at 17 weeks of gestation because of anxiety. Amniocentesis revealed a karyotype of 46, XX. However, level II ultrasound at 21 weeks of gestation revealed a fetus with IUGR and bilateral cleft lip and palate. Repeat amniocentesis was performed at 21 weeks of gestation, and array comparative genomic hybridization using uncultured amniocytes revealed a 13.5-Mb interstitial deletion of 8q22.2-q23.3 encompassing 37 Online Mendelian Inheritance of in Man (OMIM) genes including *SPAG1*, *GRHL2*, *NCALD*, *RRM2B* and *ZFPM2*. Polymorphic DNA marker analysis determined a paternal origin of the deletion. The pregnancy was subsequently terminated, and a malformed fetus was delivered with a depressed nose and bilateral cleft lip and palate.
Conclusion: Prenatal diagnosis of facial cleft with IUGR should raise a suspicion of subtle chromosome deletions.

Introduction

Patients with a chromosome 8q22.2-q22.3 deletion may present a well-described syndrome characterized by similar facial phenotype of blepharophimosis, telecanthus, epicanthus, flat malar region, thin upper lip vermillion, poor facial movement, moderate to severe developmental delay, absent speech, microcephaly, seizures, postnatal short stature, and congenital diaphragmatic hernia if *ZFPM2* gene at 8q23.1 is also deleted [1–3]. Patients with 8q23.3 deletion encompassing *TRPS1* gene at 8q23.3 may present trichorhinophalangeal syndrome (TRPS) type II [4,5]. Patients with del(8)(q22q23) or del(8)(q22q24.1) involving haploinsufficiency of *ZFPM2* gene at 8q23.1 has been reported to be associated with congenital diaphragmatic hernia [1,6].

Prenatal diagnosis of an interstitial deletion of 8q22.2-q23.3 has not previously been reported. Here, we present prenatal diagnosis of an interstitial 8q22.2-q23.3 deletion associated with bilateral cleft lip and palate and intrauterine growth restriction (IUGR) on fetal ultrasound.

* 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).

https://doi.org/10.1016/j.tjog.2017.10.026

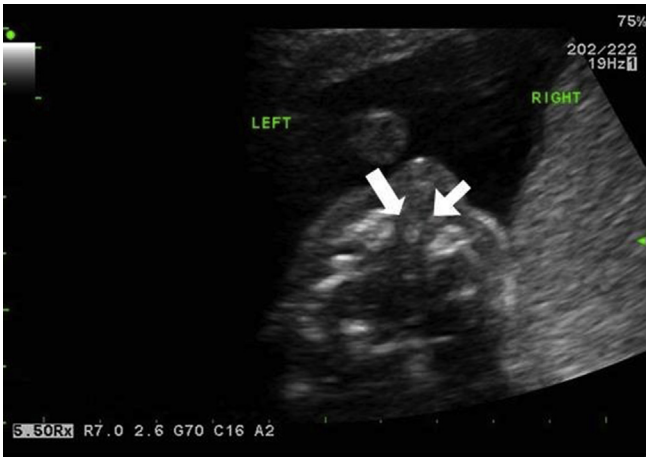

Fig. 1. Prenatal ultrasound at 21 weeks of gestation shows bilateral cleft lip and palate (arrows).

Case report

A 29-year-old, primigravid woman underwent elective amniocentesis at 17 weeks of gestation because of anxiety. Her husband was 36 years old, and there was no family history of congenital malformations. Amniocentesis revealed a karyotype of 46, XX in cultured amniocytes. However, level II ultrasound at 21 weeks of gestation revealed a fetus with IUGR and bilateral cleft lip and palate (Fig. 1). The biparietal diameter (BPD) was 4.68 cm (reference range: 4.87–5.77 cm), the head circumference (HC) was 16.58 cm (reference range: 17.97–20.84 cm), the abdominal circumference (AC) was 13.67 cm (reference range: 13.37–19.47 cm), the femur length (FL) was 2.97 cm (reference range: 3.21–4.01 cm), the HC/AC ratio was 1.21 (reference range: 1.05–1.26), and the HC/FL ratio was 5.58 (reference range: 4.83–5.70). Repeat amniocentesis was performed at 21 weeks of gestation, and array comparative genomic hybridization on uncultured amniocytes using SurePrint G3 Unrestricted CGH ISCA v2, 8 × 60 K Array (Agilent Technologies, Santa

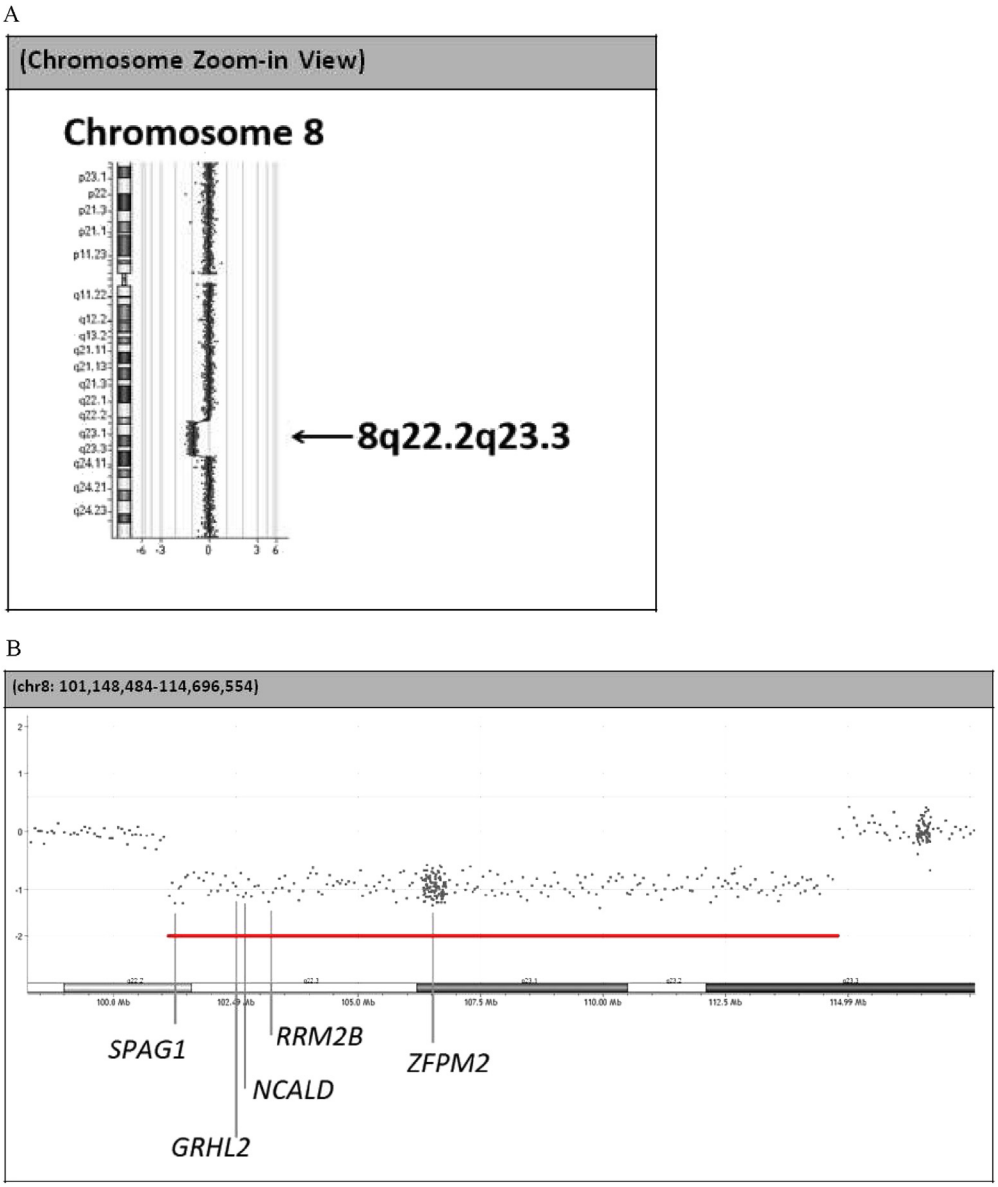

Fig. 2. Array comparative genomic hybridization on uncultured amniocytes shows a 13.5-Mb deletion at chromosome bands 8q22.2-q23.3 encompassing the genes of *SPAG1*, *GRHL2*, *NCALD*, *RRM2B* and *ZFPM2*. (A) and (B) Zoom-in views.

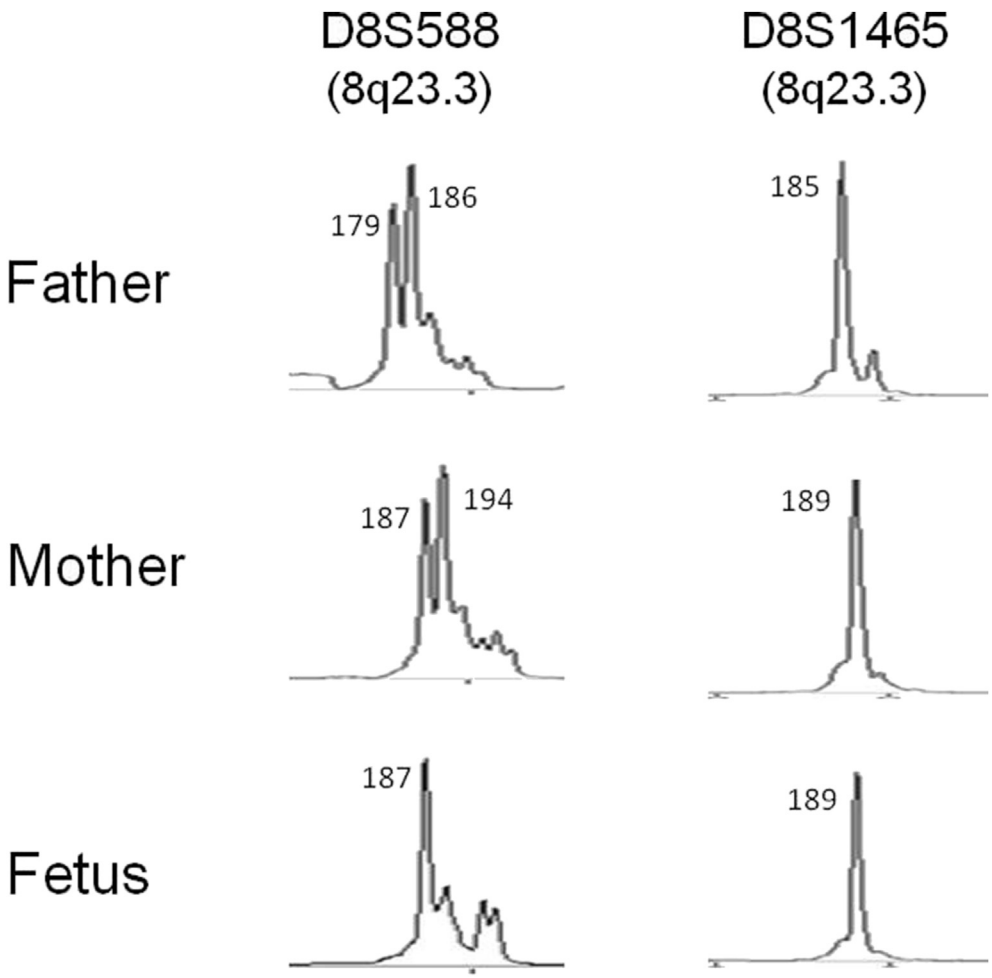

Fig. 3. Polymorphic DNA marker analysis by quantitative fluorescent polymerase chain reaction assays using the short tandem repeat (STR) markers of D8S588 (8q23.3) and D8S1465 (8q23.3) shows that in the markers D8S588 and D8S1465, the fetus inherits only one maternal allele, indicating a paternal origin of the deletion.

Clara, CA, USA) revealed a 13.5-Mb interstitial deletion of 8q22.2-q23.3 or arr 8q22.2q23.3 (101,148,484–114,696,554) × 1.0 [GRCh37 (hg19)] encompassing 37 Online Mendelian Inheritance of in Man (OMIM) genes including *SPAG1*, *GRHL2*, *NCALD*, *RRM2B* and *ZFPM2* (Fig. 2). Polymorphic DNA marker analysis revealed a paternal origin of the deletion (Fig. 3). The pregnancy was subsequently terminated at 23 weeks of gestation, and a 400-g malformed fetus was delivered with a body length of 26 cm, a depressed nose and bilateral cleft lip and palate.

Discussion

The present case had a 13.5-Mb deletion of 8q22.2-q23.3 or arr 8q22.2q23.3 (101,148,484–114,696,554) × 1.0 [GRCh37 (hg19)] and manifested cleft lip and palate and IUGR on fetal ultrasound. According to the seven reported cases with 8q22.2-q23.3 deletions, none presented the phenotype of cleft lip and palate [1–3]. According to the 17 reported cases in DECIPHER database [GRCh37 (hg19)] [7] with overlapping deletions of 8q22.2, 8q22.3, 8q23.1, 8q23.2 and 8q23.3 comparing with the present case, none of the 17 cases manifested the phenotype of facial cleft. A review of the phenotype–genotype correlation of 8q22.2-q23.3 deletion in DECIPHER database shows the following results. DECIPHER # 820 [8q22.2 and 8q22.3 deletions (101209915–106131366)] had aggressive behavior, cryptorchidism, hiatus hernia, hyperactivity, hypospadias, intellectual disability, microcephaly, patent ductus arteriosus and pyloric stenosis; # 2846 [8q22.2 and 8q22.3 deletions (101209915–104530991)] had absence seizures; # 300718 [8q22.3 deletion (104988349–105914699)] had cognitive impairment; # 288167 [8q22.3 and 8q23.1 deletions (104354056–107504649)] had cryptorchidism and micropenis; # 289647 [8q22.3 and 8q23.1 deletions (105865204–106925621)] had intellectual disability and obesity; # 288463 [8q23.1 deletion (107485945–107713453)] had global developmental delay; # 269278 [8q23.1 deletion (107192976–107441101)] had facial hypotonia, malar flattening, moderate global developmental delay and obesity; # 288146 [8q23.1 deletion (107485945–107713453)] had behavioral abnormality; # 288152 [8q23.1 deletion (107485945–107713453)] had autism and inappropriate behavior; # 279251 [8q23.2 deletion (110827754–111263050)] had autism and seizures; # 290162 [8q23.2 deletion (110827754–111263050)] had autism and global developmental delay; # 4438 [8q23.2 and 8q23.3 deletions (111231630–112475547)] had abnormality of the pinna, blepharophimosis, flexion contracture, hypertelorism, intellectual disability, low-set ears, narrow mouth and short stature; # 255962 [8q23.3 deletion (113762201–113950082)] had intellectual disability and recurrent infections; # 259448 [8q23.3 deletion (113394362–113655487)] had anxiety, intellectual disability, mild, obesity, short 2nd toe, short phalanx of fingers and short philtrum; # 287987 [8q23.3 deletion (112009082–112275531)] had abnormal facial shape and depressed nasal bridge; # 289972 [8q23.3 deletion (112579802–112709410)] had autism and

intellectual disability; and # 290446 [8q23.3 deletion (114115629–114318725)] had intellectual disability.

The present case had haploinsufficiency of *SPAG1*, *GRHL2*, *NCALD*, *RRM2B* and *ZFPM2*. *SPAG1* (OMIM 603395) is associated with autosomal recessive primary ciliary dyskinesia (OMIM 615505). *GRHL2* (OMIM 608576) is associated with autosomal dominant deafness (OMIM 608641) and autosomal recessive ectodermal dysplasia/short stature syndrome (OMIM 616029). *NCALD* (OMIM 606722) plays an important role in the regulation of the neuronal signal transduction process [8]. *RRM2B* (OMIM 604712) is associated with autosomal dominant progressive external ophthalmoplegia with mitochondrial DNA deletions (OMIM 613077) and autosomal recessive mitochondrial DNA depletion syndromes 8A and 8B (OMIM 612075). Haploinsufficiency of *NCALD* and *RRM2B* has been suggested to be responsible for the intellectual disability and epilepsy in 8q22.2-q22.3 deletion syndrome [2]. Of interest is the haploinsufficiency of *ZFPM2* (OMIM 603693) in the present case. *ZFPM2* encodes zinc finger protein multitype 2 and acts as a GATA transcription factor which is expressed in mouse embryonic heart, neuroepithelium and urogenital ridge and in the heart, brain and testes of the adult mice [9]. Deletions and mutations of *ZFPM2* are associated with autosomal dominant tetralogy of Fallot (OMIM 187500) and double-outlet right ventricle (OMIM 217095) [10], congenital diaphragmatic hernia (OMIM 610187) [11] and autosomal dominant 46, XY sex reversal-9 (SRXY9; OMIM 616067) [12]. The present case had haploinsufficiency of *ZFPM2* but presented neither congenital diaphragmatic hernia nor congenital heart defects.

In summary, we present a novel phenotype of bilateral cleft lip and palate and IUGR associated with an 8q22.2-q23.3 deletion. We suggest that prenatal diagnosis of facial cleft with IUGR should raise a suspicion of subtle chromosome deletions.

Conflicts of interest

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

Acknowledgements

This work was supported by research grants MOST-105-2314-B-195-012 from the Ministry of Science and Technology and MMH-E-106-04 from Mackay Memorial Hospital, Taipei, Taiwan.

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