Taiwanese Journal of Obstetrics & Gynecology 60 (2021) 161–164

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Case Report

Prenatal diagnosis of familial 2p15 microduplication associated with pulmonary artery stenosis, single umbilical artery and left foot postaxial polydactyly on fetal ultrasound

Chih-Ping Chen [a, b, c, d, e, f, *], Schu-Rern Chern [b], Peih-Shan Wu [g], Shin-Wen Chen [a], Fang-Tzu Wu [a], Wayseen Wang [b]

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

ARTICLE INFO

Article history:
Accepted 30 September 2020

Keywords:
2p15 duplication
Polydactyly
Prenatal diagnosis
Pulmonary artery stenosis

ABSTRACT

Objective: We present prenatal diagnosis of familial 2p15 microduplication associated with pulmonary artery stenosis, single umbilical artery and left foot postaxial polydactyly on fetal ultrasound.

Case report: A 34-year-old woman underwent amniocentesis at 17 weeks of gestation because of advanced maternal age. Amniocentesis revealed the karyotype of 46,XX. Prenatal ultrasound examination at 21 weeks of gestation showed pulmonary artery stenosis, single umbilical artery and left foot postaxial polydactyly. Repeat amniocentesis was performed at 22 weeks of gestation and array comparative genomic hybridization (aCGH) analysis on the DNAs extracted from amniocytes revealed the result of arr 2p15 (61, 495, 220–62,885,679) × 3.0 [GRCh37 (hg19)] with a 1.391-Mb 2p15 duplication encompassing seven Online Mendelian Inheritance in Man (OMIM) genes of *USP34*, *XPO1*, *FAM161A*, *CCT4*, *COMMD1*, *B3GNT2* and *TMEM17*. aCGH analysis on the DNAs extracted from parental bloods confirmed a familial transmission from a normal carrier mother who had no phenotypic abnormality. A 3270-g female baby was delivered at term with mild pulmonary artery stenosis and left foot postaxial polydactyly. The infant had normal physical and psychomotor development when follow-up at age of one year.

Conclusion: Prenatal diagnosis of fetal structural abnormalities should include aCGH analysis in addition to conventional cytogenetic analysis.

Introduction

Chromosome 2p16.1-p15 deletion syndrome [Online Mendelian Inheritance in Man (OMIM) 612,513] is a neurodevelopmental disorder with variable degrees of intellectual disability, delayed psychomotor development, craniofacial dysmorphism and autistic features, and has the shortest region of microdeletion including two genes of *USP34* and *XPO1* [1,2]. Bagheri et al. [3] suggested that four genes of *XPO1*, *USP34*, *BCL11A* and *REL* are candidate genes responsible for 2p16.1-p15 deletion syndrome. Chromosome 2p16.1-p15 microduplication has been observed in patients with phenotypic abnormalities milder than those with chromosome 2p16.1-p15 microdeletion [4,5]. Here, we present prenatal diagnosis of familial transmission of 2p15 microduplication in a fetus with pulmonary artery stenosis, single umbilical artery and left foot postaxial polydactyly inherited from an asymptomatic mother carrier.

Case report

A 34-year-old, gravida 3, para 1, woman underwent amniocentesis at 17 weeks of gestation because of advanced maternal

* Corresponding author. Department of Obstetrics and Gynecology, MacKay Memorial Hospital, 92, Section 2, Chung-Shan North Road, Taipei 104215, 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.2020.11.025

age. Her husband was 34 years old, and there was no congenital malformation in the family. Amniocentesis revealed the karyotype of 46,XX. Prenatal ultrasound examination at 21 weeks of gestation showed pulmonary artery stenosis, single umbilical artery and left foot postaxial polydactyly (Fig. 1). Repeat amniocentesis was performed at 22 weeks of gestation and array comparative genomic hybridization (aCGH) analysis on the DNAs extracted from amniocytes revealed the result of arr 2p15 (61, 495, 220–62,885,679) × 3.0 [GRCh37 (hg19)] with a 1.391-Mb 2p15 duplication encompassing seven OMIM genes of *USP34*, *XPO1*, *FAM161A*, *CCT4*, *COMMD1*, *B3GNT2* and *TMEM17* (Fig. 2). aCGH analysis on the DNAs extracted from parental bloods confirmed a familial transmission from a normal carrier mother who had no phenotypic abnormality. A 3270-g female baby was delivered at term with mild pulmonary artery stenosis and left foot postaxial polydactyly. The infant had normal physical and psychomotor development when follow-up at age of one year.

Discussion

Clinical reports concerning the 2q15 microduplication are rare. Minouni-Bloch et al. [4] suggested the 2p16.1-p15 microduplication has a milder cognitive effect and no effect on other body system. Minouni-Bloch et al. [4] first reported a 3-year-old boy with a *de novo* 1.655-Mb 2p16.1-p15 duplication involving 10 genes of *BCL11A*, *PAPOLG*, *REL*, *PUS10*, *PEX13*, *KIAA1841*, *C2orf74*, *AHSA2*, *USP34* and *XPO1*, mild global developmental delay and mild dysmorphism. Pavone et al. [5] reported a 12-year-old boy with a *de novo* 1.73-Mb 2p16.1-p15 microduplication encompassing *BCL11A*, *PAPOLG*, *REL*, *PUS10*, *PEX13*, *KIAA1841*, *C2orf74*, *AHSA2*, *USP34* and *XPO1*, moderate neurodevelopmental delay, epileptic seizures, behavioral disturbances and minor dysmorphic features. Our case had the duplication of *USP34* and *XPO1* overlapping with the cases reported by Mimouni-Bloch et al. [4] and Pavone et al. [5] but without neuropsychiatric disorders.

According to the DECIPHER database v10.1 [6], at least six cases with a 2p15 microduplication similar to our case have been described. #256542 had a *de novo* 487.41-kb 2p15 duplication (61, 297, 652–61,785,065) with facial dysmorphism, hypotonia, abnormal upper respiratory tract, patent ductus arteriosus, feeding difficulties and intellectual disability. #261432 had a 161.71-kb 2p15 duplication (61, 246, 790–61,408,495) inherited from a normal parent with no phenotypic abnormalities. #281239 had a *de novo* 904.83-kb 2p15 duplication (61, 406, 990–62,311,815) with no phenotypic abnormalities. #290412 had a 145.48-kb 2p15 duplication (61, 246, 086–61,391,564) with clinodactyly of the fifth toe, developmental regression, hirsutism, hypertrichosis and intellectual disability. #299941 had a 1.07-Mb 2p15 duplication (61, 804, 054–62,869,158) inherited from the mother and abnormality of the cerebral ventricles. #366385 had a 1.42-Mkb 2p15 duplication (61, 025, 143–62,445,156) with intellectual disability. Our case had novel findings of pulmonary artery stenosis and foot polydactyly, and added to the list of the literature.

The peculiar aspect of the present case is the involvement of *USP34*, *XPO1* and *FAM161A*. *USP34* (OMIM 615295) is a ubiquitin-specific protease that regulates axin stability and Wnt/β-catenin signaling [7]. *XPO1* (OMIM 602559) is a nuclear protein essential for proliferation and chromosome region maintenance [8,9]. Fannemel et al. [1] reported haploinsufficiency of *XPO1* and *USP34* by a *de novo* 230-kb 2p15 microdeletion in a patient with mild intellectual disability and craniofacial dysmorphism. *FAM161A* (OMIM 602559) encodes member A of family with sequence similarity 161, which is associated with autosomal recessive retinitis pigmentosa 28 (OMIM 606068) [10].

In summary, we present prenatal diagnosis of familial 2p15 microduplication associated with pulmonary artery stenosis, single umbilical artery and left foot postaxial polydactyly on fetal

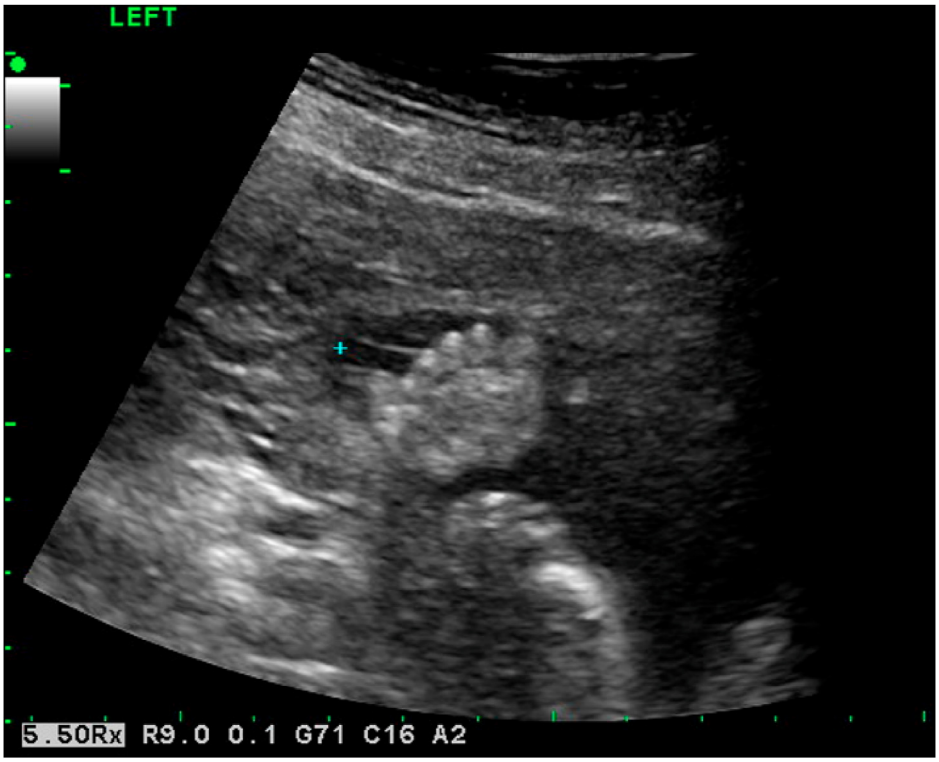

Fig. 1. Left foot postaxial polydactyly on prenatal ultrasound at 21 weeks of gestation.

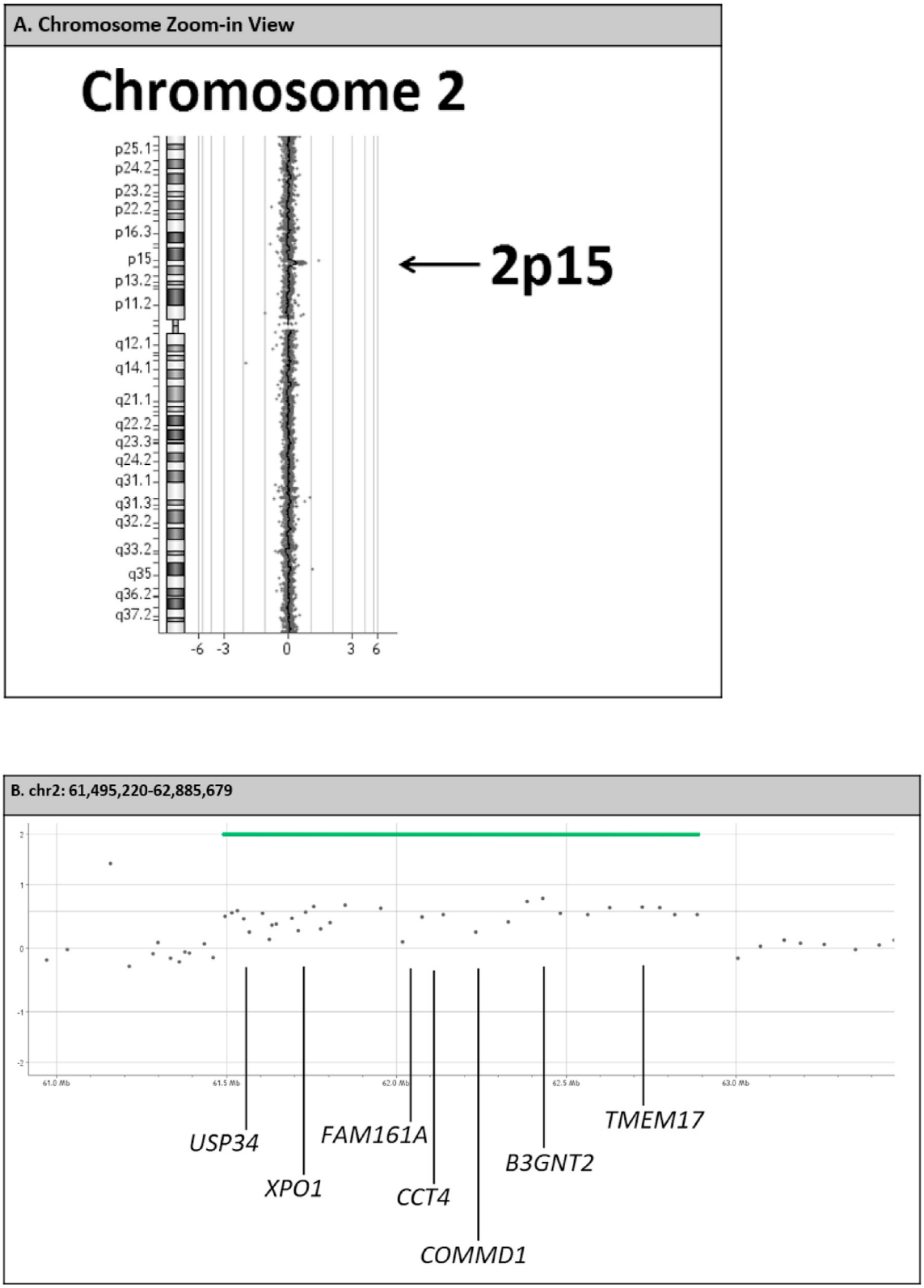

Fig. 2. (A) and (B) Array comparative genomic hybridization analysis on the DNA extracted from cultured amniocytes using SurePrint G3 Unrestricted CGH ISCA v2, 8 × 60K (Agilent Technologies, CA, USA) shows a 1.391-Mb 2p15 duplication including the genes of *USP34*, *XPO1*, *FAM161A*, *CCT4*, *COMMD1*, *B3GNT2* and *TMEM17*.

ultrasound. Prenatal diagnosis of fetal structural abnormalities should include aCGH analysis in addition to conventional cytogenetic analysis.

Declaration of competing 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, Taiwan, andMMH-E-109-04 from Mackay Memorial Hospital, Taipei, Taiwan.

References

[1] Fannemel M, Barøy T, Holmgren A, Rødningen OK, Haugsand TM, Hansen B, et al. Haploinsufficiency of *XPO1* and *USP34* by a *de novo* 230 kb deletion in 2p15, in a patient with mild intellectual disability and cranio-facial dysmorphisms. Eur J Med Genet 2014;57:513–9.

[2] Shimojima K, Okamoto N, Yamamoto T. Characteristics of 2p15-p16.1 microdeletion syndrome: review and description of two additional patients. Congenit Anom (Kyoto) 2015;55:125–32.

[3] Bagheri H, Badduke C, Qiao Y, Colnaghi R, Abramowicz I, Alcantara D, et al. Identifying candidate genes for 2p15p16.1 microdeletion syndrome using clinical, genomic, and functional analysis. JCI Insight 2016;1:e85461.

[4] Mimouni-Bloch A, Yeshaya J, Kahana S, Maya I, Basel-Vanagaite L. A *de-novo* interstitial microduplication involving 2p16.1-p15 and mirroring 2p16.1-p15 microdeletion syndrome: clinical and molecular analysis. Eur J Paediatr Neurol 2015;19:711–5.

[5] Pavone P, Falsaperla R, Rizzo R, Praticò AD, Ruggieri M. Chromosome 2p15-p16.1 microduplication in a boy with congenital anomalies: is it a distinctive syndrome? Eur J Med Genet 2019;62:47–54.

[6] DECIPHER database: database of chromosomal imbalance and phenotype in humans using ensembl resources. Available at: http://decipher.sanger.ac.uk/ [Accessed 2020 Aug 14].

[7] Lui TTH, Lacroix C, Ahmed SM, Goldenberg SJ, Leach CA, Daulat AM, et al. The ubiquitin-specific protease USP34 regulates axin stability and Wnt/β-catenin signaling. Mol Cell Biol 2011;31:2053–65.

[8] Stade K, Ford CS, Guthrie C, Weis K. Exportin 1 (Crm1p) is an essential nuclear export factor. Cell 1997;90:1041–50.

[9] Ullman KS, Powers MA, Forbes DJ. Nuclear export receptors: from importin to exportin. Cell 1997;90:967–70.

[10] Bandah-Rozenfeld D, Mizrahi-Meissonnier L, Farhy C, Obolensky A, Chowers I, Pe'er J, et al. Homozygosity mapping reveals null mutations in *FAM161A* as a cause of autosomal-recessive retinitis pigmentosa. Am J Hum Genet 2010;87:382–91.