Taiwanese Journal of Obstetrics & Gynecology 55 (2016) 871–873

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Case Report

Prenatal diagnosis of familial transmission of 17q12 microduplication associated with no apparent phenotypic abnormality

Chih-Ping Chen [a, b, c, d, e, f, *], Chung-Hu Fu [g], Yi-Hui Lin [h], Schu-Rern Chern [b], Peih-Shan Wu [i], Yen-Ni Chen [a], Shin-Wen 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] Hungchi Women and Children's Hospital, Chungli, Taoyuan, Taiwan
[h] Department of Obstetrics and Gynecology, Taipei Medical University-Wan Fang Hospital, Taipei, Taiwan
[i] Gene Biodesign Co. Ltd, Taipei, Taiwan
[j] Department of Bioengineering, Tatung University, Taipei, Taiwan

ARTICLE INFO

Article history:
Accepted 30 August 2016

Keywords:
17q12 duplication
ACACA
HNF1B
LHX1
prenatal diagnosis

ABSTRACT

Objective: We present prenatal diagnosis of familial transmission of 17q12 duplication associated with no apparent phenotypic abnormality.

Case Report: A 36-year-old woman underwent amniocentesis at 17 weeks of gestation because of advanced maternal age. Cytogenetic analysis revealed a karyotype of 46,XY. Array comparative genomic hybridization of uncultured amniocytes revealed a 1.42-Mb duplication of 17q12 or arr 17q12 (34,822,465–36,243,365) × 3 encompassing 12 Online Mendelian Inheritance in Man (OMIM) genes including *LHX1*, *ACACA*, and *HNF1B*. Array comparative genomic hybridization analysis of parental bloods revealed no genomic imbalance in the mother, and a result of arr 17q12 (34,611,377–36,248,889) × 2.9 encompassing 16 OMIM genes, including *LHX1*, *ACACA*, and *HNF1B*, in the 29-year-old phenotypically normal father. Prenatal ultrasound findings were unremarkable. The parents elected to continue the pregnancy. At 37 weeks of gestation, a 2789-g normal male baby was delivered uneventfully. When examined at the age of 7 months, the neonate was as phenotypically normal as his father.

Conclusion: The 17q12 microduplication may present with variable phenotypes including no apparent phenotypic abnormality in familial cases. However, neuropsychiatry assessment and monitoring should be warranted in childhood and through adulthood under such a circumstance.

Introduction

The copy-number variations (CNVs) in 17q12 including 17q12 deletion and reciprocal 17q12 duplication mediated by a nonallelic homologous recombination mechanism are associated with a wide spectrum of phenotypes and considerable variability in expressivity. Chromosome 17q12 deletion syndrome (OMIM 614527) may manifest clinical features such as MODY5 (OMIM 137920) or maturity-onset diabetes of the young type 5 with renal cysts and diabetes, Müllerian aplasia/dysgenesis, autism spectrum disorder, and schizophrenia [1,2]. Chromosome 17q12 duplication syndrome (OMIM 614526) may manifest clinical features such as developmental delay, intellectual abilities, speech and motor delay, epilepsy, eye vision problems, cardiac and renal anomalies, autism spectrum disorder, schizophrenia, and behavioral abnormalities including aggression and self-injury [2,3]. The 17q12 recurrent duplication has reduced penetrance and variable expressivity, and is usually (90%) inherited in an autosomal dominant pattern from a parent who is minimally affected or phenotypically normal [3].

* Corresponding author. Department of Obstetrics and Gynecology, MacKay Memorial Hospital, 92, Section 2, Chung-Shan North Road, Taipei 10449, Taiwan.
E-mail address: cpc_mmh@yahoo.com (C.-P. Chen).

http://dx.doi.org/10.1016/j.tjog.2016.08.004

Here, we present prenatal diagnosis of familial transmission of 17q12 duplication associated with no apparent phenotypic abnormality.

Case report

A 36-year-old primigravid woman underwent amniocentesis at 17 weeks of gestation because of advanced maternal age. Her husband was 29 years old. She and her husband were healthy, and there were no family history of seizures, mental illnesses, and congenital malformations. Cytogenetic analysis of cultured amniocytes revealed a karyotype of 46,XY. Simultaneous array comparative genomic hybridization (aCGH) of uncultured amniocytes using Affimatrix 750K Array (Affimatrix, Santa Clara, CA, USA) revealed a 1.42-Mb duplication of 17q12 or arr 17q12 (34,822,465–36,243,365) × 3, encompassing 12 Online Mendelian Inheritance in Man (OMIM) genes including *ZNHIT3*, *PIGW*, *GGNBP2*, *DHRS11*, *LHX1*, *AATF*, *ACACA*, *TADA2A*, *DUSP14*, *SYNRG*, *DDX52*, and *HNF1B*. An aCGH analysis of parental bloods using CytoChip ISCA (Illumina, San Diego, CA, USA) revealed no genomic imbalance in the mother and a 1.638-Mb duplication of 17q12 or arr 17q12 (34,611,377–36,248,889) × 2.9, encompassing 16 OMIM genes, including *CCL3L1*, *CCL4L1*, *TBC1D3H*, *TBC1D3G*, *ZNHIT3*, *PIGW*, *GGNBP2*, *DHRS11*, *LHX1*, *AATF*, *ACACA*, *TADA2A*, *DUSP14*, *SYNRG*, *DDX52*, and *HNF1B*, in the phenotypically normal father (Figure 1). Prenatal ultrasound findings were unremarkable. The parents elected to continue the pregnancy. At 37 weeks of gestation, a 2789-g normal male baby was delivered uneventfully. When examined at the age of 7 months, the neonate was 8.2 kg (50–75th centile) in weight and 70 cm (85–95th centile) in height, and was as phenotypically normal as his father.

Discussion

The present case represents one of the most challenging issues for genetic counselors in modern genetic counseling of prenatally detected CNVs in not known at-risk pregnancies. With the advent of aCGH, many CNVs with varied clinical phenotypes are unexpectedly detected in pregnancies with normal fetal karyotype, normal fetal ultrasound, and/or normal parents carrying the same CNVs. Since there is difficulty in accurately predicting the phenotype of 17q12 microduplication, interpretation of the results acquired by aCGH from prenatal testing is challenging for genetic counselors, parents, and obstetricians under such a circumstance. Prenatal diagnosis of 17q12 microduplication in a not known at-risk pregnancy is very rare. Li et al [2] previously reported a prenatal diagnosis of a *de novo* 1.56-Mb 17q12 microduplication by aCGH at cord blood sampling at 28 weeks of gestation in a 26-year-old

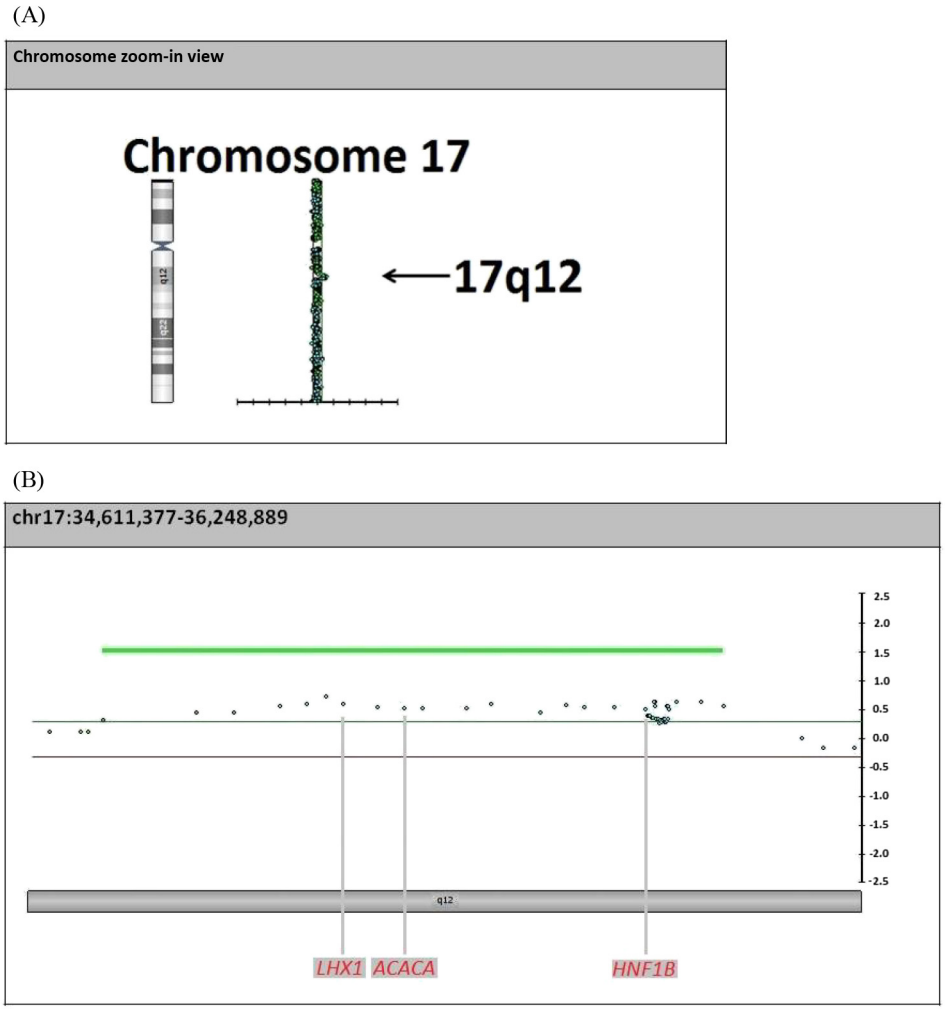

Figure 1. Array comparative genomic hybridization analysis of paternal blood shows a 1.638-Mb duplication of 17q12 encompassing 16 Online Mendelian Inheritance in Man (OMIM) genes including *LHX1*, *ACACA*, and *HNF1B*. (A) Chromosomal 17q12. (B) Chromosomal zoom-in view.

woman with prenatal ultrasound findings of mild ventriculomegaly, microcephaly, and agenesis of the corpus callosum. The pregnancy was subsequently terminated. The present case is an additional case of prenatally detected 17q12 microduplication in a not known at-risk pregnancy. Although the present neonate is phenotypically normal at the time of this writing, detailed neuropsychiatry assessment and monitoring should be warranted in the future.

The present case had a 17q12 microduplication encompassing the genes of *LHX1*, *ACACA*, and *HNF1B*. HNF1B (OMIM 189907) or transcription factor 2 is a transcription factor that belongs to the homeodomain-containing superfamily of transcription factors [4]. *HNF1B* is associated with autosomal dominant non-insulin-dependent diabetes mellitus (OMIM 125853), and autosomal dominant renal cysts and diabetes (OMIM 137920). *LHX1* (OMIM 601999) or *LIM1* belongs to the *LIM*/homeobox gene family, and is essential for head-organizer function, renal system, central nervous system, and female reproductive duct development [5–11]. *ACACA* (OMIM 200350) encodes the α form of acetyl-coenzyme A carboxylase, which is a key regulatory enzyme of fatty acid synthesis [12]. Although the genes of *LHX1*, *ACACA*, and *HNF1B* have been implicated to be associated with 17q12 recurrent duplication syndrome, no single gene has been identified to be responsible for the phenotypes of 17q12 duplication syndrome [3].

In a review of 26 patients from 13 families with 17q12 duplication, Rasmussen et al [13] reported two cases with prenatal chromosomal microarray testing, of which one case was followed up at the age of 9 months with delayed motor milestone and esophageal atresia, and the other case was followed up at the age of 1 month with frontally thinning of the corpus callosum. The most consistent findings of 17q12 duplication among 26 patients reported by Rasmussen et al [13] were learning disability (55%), delayed language development (43%), delayed motor milestones (43%), and a broad range of psychiatric and neurological features (27%). The penetrance of 17q12 recurrent duplication has been estimated to be 21% [14]. Rasmussen et al [13] reported 7/26 (26.9%) asymptomatic carriers with 17q12 duplication in their series and 15/53 (28.3%) asymptomatic carriers with 17q12 duplication in their literature review, indicating that the 17q12 duplication can be benign, and this information should be included in genetic counseling at prenatal diagnosis. Rasmussen et al [13] reported a prevalence of 1.6/1000 chromosomal microarrays in 17q12 duplication, and Moreno-De-Luca et al [15] reported a prevalence of 1.3/1000 chromosomal microarrays in 17q12 duplication. However, such estimated prevalence may be underestimated because some affected individuals are asymptomatic and may not receive any genetic testing.

Recurrent duplications of 17q12 are associated with variable phenotypes [16]. Genetic counseling of 17q12 microduplications remains a challenge for obstetricians as well as parents, genetic counselors, and clinicians [17]. Our report provides evidence that 17q12 microduplication may present variable phenotypes including no apparent phenotypic abnormality in the familial cases. However, neuropsychiatry assessment and monitoring should be warranted in childhood and through adulthood under such a circumstance.

Conflicts of interest

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

Acknowledgments

This work was supported by research grants MOST-103-2314-B-195-010 and MOST-104-2314-B-195-009 from the Ministry of Science and Technology, and MMH-E-105-04 from MacKay Memorial Hospital, Taipei, Taiwan.

References

[1] Chen C-P, Chang S-D, Wang T-H, Wang L-K, Tsai J-D, Liu Y-P, et al. Detection of recurrent transmission of 17q12 microdeletion by array comparative genomic hybridization in a fetus with prenatally diagnosed hydronephrosis, hydroureter and multicystic kidney, and variable clinical spectrum in the family. Taiwan J Obstet Gynecol 2013;52:551–7.

[2] Li R, Fu F, Zhang Y-L, Li D-Z, Liao C. Prenatal diagnosis of 17q12 duplication and deletion syndrome in two fetuses with congenital anomalies. Taiwan J Obstet Gynecol 2014;53:579–82.

[3] Mefford H, Mitchell E, Hodge J. 17q12 recurrent duplication. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, et al, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington; 1993–2016. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26925472. [accessed 02.08.16].

[4] Bach I, Mattei M-G, Cereghini S, Yaniv M. Two members of an HNF1 homeoprotein family are expressed in human liver. Nucl Acids Res 1991;19:3553–9.

[5] Shawlot W, Behringer RR. Requirement for *Lim1* in head-organizer function. Nature 1995;374:425–30.

[6] Bozzi F, Bertuzzi S, Strina D, Giannetto C, Vezzoni P, Villa A. The exon–intron-structure of human *LHX1* gene. Biochem Biophys Res Commun 1996;229:494–7.

[7] Kobayashi A, Shawlot W, Kania A, Behringer RR. Requirement of *Lim1* for female reproductive tract development. Development 2004;131:539–49.

[8] Kobayashi A, Kwan K-M, Carroll TJ, McMahon AP, Mendelsohn CL, Behringer RR. Distinct and sequential tissue-specific activities of the *LIM*-class homeobox gene *Lim1* for tubular morphogenesis during kidney development. Development 2005;132:2809–23.

[9] Tam PPL, Khoo P-L, Wong N, Tsang TE, Behringer RR. Regionalization of cell fates and cell movement in the endoderm of the mouse gastrula and the impact of loss of *Lhx1 (Lim1)* function. Dev Biol 2004;274:171–87.

[10] Pedersen A, Skjong C, Shawlot W. *Lim1* is required for nephric duct extension and ureteric bud morphogenesis. Dev Biol 2005;288:571–81.

[11] Cirio MC, Hui Z, Haldin CE, Cosentino CC, Stuckenholz C, Chen X, et al. *Lhx1* is required for specification of the renal progenitor cell field. PLoS One 2011;6:e18858.

[12] Travers MT, Cambot M, Kennedy HT, Lenoir GM, Barber MC, Joulin V. Asymmetric expression of transcripts derived from the shared promoter between the divergently oriented *ACACA* and *TADA2L* genes. Genomics 2005;85:71–84.

[13] Rasmussen M, Vestergaard EM, Graakjaer J, Petkov Y, Bache I, Fagerberg C, et al. 17q12 deletion and duplication syndrome in Denmark—a clinical cohort of 38 patients and review of the literature. Am J Med Genet A 2016;170:2934–42.

[14] Rosenfeld JA, Coe BP, Eichler EE, Cuckle H, Shaffer LG. Estimates of penetrance for recurrent pathogenic copy-number variations. Genet Med 2013;15:478–81.

[15] Moreno-De-Luca D, SGENE Consortium, Mulle JG, Simons Simplex Collection Genetics Consortium, Kaminsky EB, Sanders SJ, et al. Deletion 17q12 is a recurrent copy number variant that confers high risk of autism and schizophrenia. Am J Hum Genet 2010;87:618–30.

[16] Mitchell E, Douglas A, Kjaegaard S, Callewaert B, Vanlander A, Janssens S, et al. Recurrent duplications of 17q12 associated with variable phenotypes. Am J Med Genet 2015;167A:3038–45.

[17] Bertini V, Orsini A, Bonuccelli A, Cambi F, Del Pistoia M, Vannozzi I, et al. 17q12 microduplications: a challenge for clinicians. Am J Med Genet 2015;167A:674–6.