Available online at www.sciencedirect.com

SciVerse ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology 52 (2013) 273–277

www.tjog-online.com

Case Report

Rapid detection of *de novo* P253R mutation in *FGFR2* using uncultured amniocytes in a pregnancy affected by polyhydramnios, Blake's pouch cyst, and Apert syndrome

Chih-Ping Chen [a,b,c,d,e,f,g,*], Yi-Ning Su [h], Tung-Yao Chang [i], Schu-Rern Chern [b], Chen-Yu Chen [a], Jun-Wei Su [a,j], Wayseen Wang [b,k]

[a] *Department of Obstetrics and Gynecology, Mackay Memorial Hospital, Taipei, Taiwan*
[b] *Department of Medical Research, Mackay Memorial Hospital, Taipei, Taiwan*
[c] *Department of Medicine, Mackay Medical College, New Taipei City, Taiwan*
[d] *Department of Biotechnology, Asia University, Taichung, Taiwan*
[e] *School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan*
[f] *Institute of Clinical and Community Health Nursing, National Yang-Ming University, Taipei, Taiwan*
[g] *Department of Obstetrics and Gynecology, School of Medicine, National Yang-Ming University, Taipei, Taiwan*
[h] *Department of Obstetrics and Gynecology, School of Medicine, Taipei Medical University, Taipei, Taiwan*
[i] *Taiji Fetal Medicine Center, Taipei, Taiwan*
[j] *Department of Obstetrics and Gynecology, China Medical University Hospital, Taichung, Taiwan*
[k] *Department of Bioengineering, Tatung University, Taipei, Taiwan*

Accepted 22 January 2013

Abstract

Objective: To present prenatal ultrasound and molecular genetic diagnosis of Apert syndrome.
Case Report: A 30-year-old, gravida 3, para 2 woman was referred for genetic counseling at 32 weeks of gestation because of polyhydramnios and craniofacial and digital abnormalities in the fetus. She had undergone amniocentesis at 18 weeks of gestation because of maternal anxiety. Results of amniocentesis revealed a karyotype of 46,XX. A prenatal ultrasound at 32 weeks of gestation revealed a female fetus with a fetal biometry equivalent to 32 weeks, polyhydramnios with an increased amniotic fluid index of 26.1 cm, frontal bossing, midface hypoplasia, hypertelorism, Blake's pouch cyst with an apparent posterior fossa cyst in communication with the fourth ventricle on axial images, digital fusion, and bilateral syndactyly of the hands and feet. A DNA testing for the *FGFR2* gene was immediately performed using uncultured amniocytes obtained by repeated amniocentesis, which revealed a heterozygous c.758C>G, CCT>CGT transversion leading to a p.Pro253Arg (P253R) mutation in the *FGFR2* gene. Subsequently, a diagnosis of Apert syndrome was made. Molecular analysis of the *FGFR2* gene in the parents did not reveal such a mutation. The fetus postnatally manifested frontal bossing, midface hypoplasia, and bilateral syndactyly of the hands (mitten hands) and feet.
Conclusion: Prenatal diagnosis of polyhydramnios, frontal bossing, and midface hypoplasia associated with brain and digital abnormalities should include a differential diagnosis of Apert syndrome. A molecular analysis of *FGFR2* using uncultured amniocytes is useful for rapid confirmation of Apert syndrome at prenatal diagnosis.

Keywords: Apert syndrome; Blake's pouch cyst; *FGFR2*; P253R; prenatal diagnosis

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

1028-4559/$ - see front matter
http://dx.doi.org/10.1016/j.tjog.2013.04.022

Introduction

Apert syndrome [Online Mendelian Inheritance in Man (OMIM): #101200] is characterized by acrocephaly, craniosynostosis, midface hypoplasia, and syndactyly of the hands and feet with the bony structures exhibiting a tendency to fuse. The disorder is caused by mutations in the fibroblast growth factor receptor 2 (*FGFR2*) gene (OMIM: 176943), which is located at 10q26.13. Most cases (98%) of Apert syndrome are sporadic, and only a few are inherited in an autosomal dominant pattern [1]. The S252W (p.Ser252Trp, c.755C>G, TCG>TGG) and P253R (p.Pro253Arg, c.758C>G, CCT>CGT) mutations account for over 98% of the cases with Apert syndrome with approximately two-thirds of the cases being caused by the S252W mutation and the remaining one-third of the cases being caused by the P253R mutation [2–5]. Here, we report our experience of a rapid detection of *de novo* P253R mutation in the *FGFR2* gene using uncultured amniocytes in a pregnancy affected by polyhydramnios, Blake's pouch cyst, and Apert syndrome.

Case report

A 30-year-old, gravida 3, para 2 woman was referred for genetic counseling at 32 weeks of gestation because of polyhydramnios and craniofacial and digital abnormalities in the fetus. Her husband was 31 years old. She and her husband were both healthy and unrelated, and there was no family history of congenital malformations. She had undergone amniocentesis at 18 weeks of gestation because of maternal anxiety. Amniocentesis revealed a karyotype of 46,XX. A prenatal ultrasound at 32 weeks of gestation revealed a female fetus with a fetal biometry equivalent to 32 weeks, polyhydramnios with an increased amniotic fluid index of 26.1 cm, frontal bossing, midface hypoplasia, hypertelorism, Blake's pouch cyst with an apparent posterior fossa cyst in communication with the fourth ventricle on axial images, digital fusion, and bilateral syndactyly of the hands and feet (Fig. 1). A DNA testing for the *FGFR2* gene was immediately performed using uncultured amniocytes obtained by repeated amniocentesis, which revealed a heterozygous c.758C>G, CCT>CGT transversion leading to a p.Pro253Arg (P253R) mutation in the *FGFR2* gene (Fig. 2). Subsequently, a diagnosis of Apert syndrome was made. However, a molecular analysis of the *FGFR2* gene in the parents did not reveal such a mutation. The woman decided to discontinue the pregnancy, and a 2372-g female baby was delivered with frontal bossing, midface hypoplasia, and bilateral syndactyly of the hands (mitten hands) and feet (Fig. 3).

Discussion

The peculiar aspect of this case is the association of the P253R mutation in the *FGFR2* gene with severe syndactyly of the hands and feet, polyhydramnios, and Blake's pouch cyst. A genotype–phenotype analysis in Apert syndrome has suggested two recurrent mutations of S252W and P253R on the severity of craniofacial abnormalities and syndactyly, respectively [6,7]. Slaney et al [6] found that syndactyly in the hands and feet were more severe in patients with the P253R mutation, whereas cleft palate was significantly more frequent in patients with the S252W mutation. von Gernet et al [7] found higher frequency of profound midface retrusion and severe malocclusion in patients with the S252W mutation and higher frequency of profound severity of syndactyly in patients with the P253R mutation.

Polyhydramnios may develop in the third trimester in pregnancies with Apert syndrome [8,9]. Chen et al [9] previously reported polyhydramnios in a pregnancy affected with the S252W mutation, in addition to upper airway obstruction and gastroesophageal reflux. The present case shows that a fetus affected by the P253R mutation and a Blake's pouch cyst may also develop polyhydramnios in the third trimester. The Blake's pouch is an inferior protrusion of the fourth ventricle into the retrocerebellar subarachnoid space resulting from a finger-like expansion of the posterior membranous area [10]. Paladini et al [11] proposed that the diagnostic criteria of a Blake's pouch cyst should include (1) normal anatomy and size of the vermis; (2) mild/moderate anticlockwise rotation of the vermis; and (3) normal size of the cisterna magna. Paladini et al [11] found that a Blake's pouch cyst in the fetus is associated with an apparently increased risk of congenital heart disease and trisomy 21.

Polyhydramnios associated with Apert syndrome has been suggested to be caused by decreased fetal swallowing related to abnormalities in the central nervous system (CNS) [12]. The present case was associated with posterior fossa anomaly. The CNS anomalies associated with Apert syndrome have been well documented [13–21]. For example, Ferreira et al [17] reported brain anomalies in cases with Apert syndrome including ventriculomegaly (48.5%), hydrocephalus (9%), gyral abnormalities, and other anomalies (e.g., agenesis or hypogenesis of the corpus callosum, posterior fossa anomalies) (21%). Quintero-Rivera et al [19] reported brain anomalies in 30 cases with Apert syndrome including nonprogressive ventriculomegaly (76%), hydrocephalus (13%), completely absent septum pellucidum (17%), partially absent septum pellucidum (23%), deficiency of septal leaflets (10%), agenesis of the corpus callosum (7%), deficiency of the corpus callosum (3%), and thinning of the corpus callosum (13%).

Using the sophisticated sonographic observations of syndactyly, midface hypoplasia, and abnormal cranial shape, prenatal sonographic diagnosis of Apert syndrome can be achieved in the second trimester [21–23]. However, as presented in this case, most prenatally detected cases of Apert syndrome were reported in the third trimester because the craniofacial and digital abnormalities and polyhydramnios associated with Apert syndrome are more obvious only in the late stages of gestation upon performing a prenatal ultrasound [24]. Recently, a noninvasive prenatal diagnosis of Apert syndrome using fetal DNA from maternal plasma by