Taiwanese Journal of Obstetrics & Gynecology 56 (2017) 93–97

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Case Report

Familial transmission of recurrent 15q11.2 (BP1-BP2) microdeletion encompassing *NIPA1*, *NIPA2*, *CYFIP1*, and *TUBGCP5* associated with phenotypic variability in developmental, speech, and motor delay

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ARTICLE INFO

Article history:
Accepted 7 December 2016

Keywords:
15q11.2 (BP1-BP2) deletion
CYFIP1
NIPA1
NIPA2
TUBGCP5

ABSTRACT

Objective: We present recurrent 15q11.2 (BP1-BP2) microdeletion encompassing *NIPA1*, *NIPA2*, *CYFIP1*, and *TUBGCP5* in a family with phenotypic variability in developmental, speech, and motor delay.
Case Report: A 32-year-old woman underwent amniocentesis at 17 weeks of gestation because of an abnormal maternal serum screening result of Down syndrome risk of 1/226. Her husband was 31 years old. She and her husband were phenotypically normal, and there was no family history of mental disorders and congenital malformations. Amniocentesis revealed a karyotype of 46,XX. Prenatal ultrasound findings were unremarkable. A 2492-g female baby was delivered at 37 weeks of gestation uneventfully. During the subsequent pregnancy, the same woman at the age of 35 years underwent amniocentesis at 18 weeks of gestation because of advanced maternal age, which revealed a karyotype of 46,XY. Prenatal ultrasound findings were unremarkable. A 2780-g male baby was delivered at 37 weeks of gestation uneventfully. About 3 years after the birth of this boy, array comparative genomic hybridization of the family revealed 15q11.2 microdeletion encompassing *NIPA1*, *NIPA2*, *CYFIP1*, and *TUBGCP5* in the two siblings, who displayed developmental, speech, and motor delay, and in their phenotypically normal father.
Conclusion: Recurrent phenotypic abnormality in the family with normal karyotype at amniocentesis should include a differential diagnosis of familial pathogenic copy-number variations.

Introduction

Chromosome 15q11.2 (BP1-BP2) deletion syndrome (OMIM 615656) is caused by a 15q11.2 microdeletion spanning the nonimprinted region between breakpoint 1 (BP1) and breakpoint 2 (BP2) of Prader-Willi (PWS)/Angelman syndrome (AS) critical region and containing four nonimprinted genes of *NIPA1* (OMIM 608145), *NIPA2* (OMIM 608146), *CYFIP1* (OMIM 606322), and *TUBGCP5* (OMIM 608147), all of which are expressed in the central nervous system and may play roles in brain development and function [1–4]. Chromosome 15q11.2 (BP1-BP2) deletion syndrome may present psychomotor developmental and speech delay, autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder, and seizures [2,3,5–11].

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http://dx.doi.org/10.1016/j.tjog.2016.12.002

Chromosome 15q11.2 (BP1-BP2) deletion is inherited in an autosomal dominant pattern and is associated with incomplete penetrance and phenotypic variability [3,6,12].

Prenatal diagnosis of chromosome 15q11.2 (BP1-BP2) deletion syndrome in not known at-risk pregnancy is very unusual, because this syndrome is not frequently associated with major structural abnormalities on fetal ultrasound, and conventional cytogenetic analysis has difficulty in detecting such a microdeletion. Vanlerberghe et al [12] reported prenatal diagnosis of 15q11.2 (BP1-BP2) microdeletion with abnormal ultrasound findings in three fetuses; two were inherited from the asymptomatic fathers, and one was inherited from the mother. In their report, the first fetus manifested intrauterine growth restriction, aortic coarctation, perithalamic echogenicity, large cavum, and ischemic lesion of thalamocaudesillon, the second fetus manifested intrauterine growth restriction, microcephaly, vermis agenesis, bilateral cleft lip and palate, and clubfeet, and the third fetus manifested pachygyria and microcephaly.

Here, we present familial transmission of recurrent 15q11.2 (BP1-BP2) microdeletion associated with phenotypic variability in developmental, speech, and motor delay.

Case Report

A 32-year-old, gravida 2, para 1 woman underwent amniocentesis at 17 weeks of gestation because of an abnormal maternal serum screening result of Down syndrome risk of 1/226. Her husband was 31 years old. She and her husband were phenotypically normal, and there was no family history of psychiatric and behavior disorders, seizures, and congenital malformations. Two years previously, her first pregnancy resulted in an intrauterine fetal death at 37 weeks of gestation. During the second pregnancy, prenatal ultrasound findings were unremarkable, and the amniocentesis revealed a karyotype of 46,XX. The second pregnancy resulted in a 2492-g female baby delivered uneventfully at 37 weeks of gestation. During the subsequent pregnancy, the same woman at the age of 35 years underwent amniocentesis at 18 weeks of gestation because of advanced maternal age, which revealed a karyotype of 46,XY. Prenatal ultrasound findings were unremarkable. The third pregnancy resulted in a 2780-g male baby delivered uneventfully at 37 weeks of gestation. About 3 years after the birth of this boy, array comparative genomic hybridization (aCGH) of the family revealed

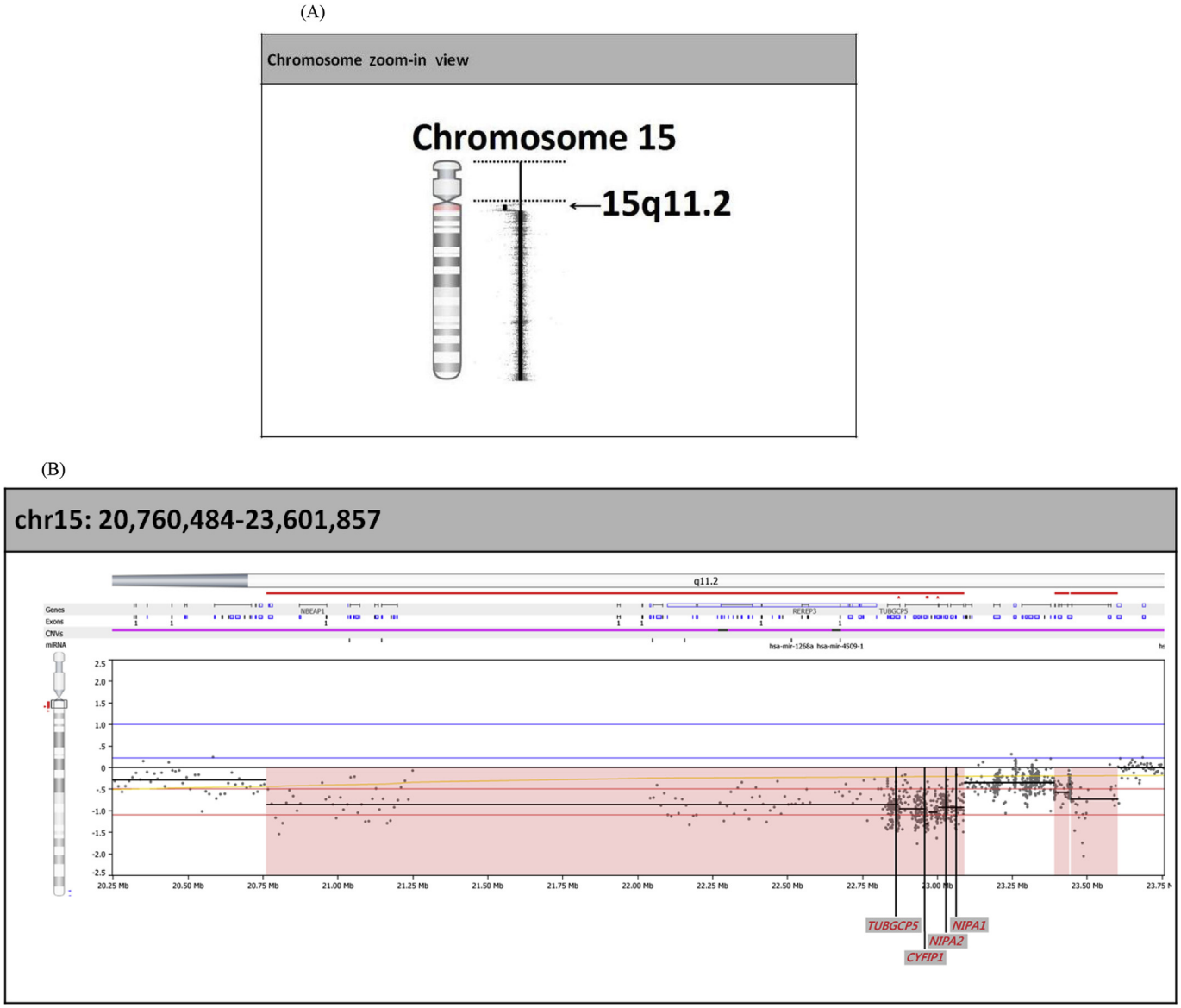


Figure 1. Array comparative genomic hybridization (aCGH) analysis of the elder daughter's peripheral blood reveals a 2.84-Mb deletion of 15q11.2 encompassing *NIPA1*, *NIPA2*, *CYFIP1*, and *TUBGCP5*. (A) Chromosome zoom-in view and (B) chromosome 15.

15q11.2 microdeletion in the two sibs and their phenotypically normal father.

At the time of aCGH testing, the elder daughter was 5.5 years old and had a body weight of 16.5 kg (1^{st}–3^{rd} centile), a body height of 107 cm (3^{rd}–15^{th} centile) and a head circumference of 47.6 cm (<3^{rd} centile). She manifested developmental, speech, and motor delay, tension tremor, and unstable gait, but no facial dysmorphism, no seizures, no cognitive disorders, and no congenital heart defects. Electroencephalography (EEG) revealed high voltage background rhythms without definite epileptiform discharge suggesting encephalopathy. The aCGH result of the girl's peripheral blood was arr 15q11.2 (20,760,484–23,601,857) × 1.1 with a 2.84-Mb deletion of 15q11.2 encompassing six OMIM genes of *POTEB*, *NIPA1*, *NIPA2*, *CYFIP1*, *TUBGCP5*, and *MKRN3* (Figure 1).

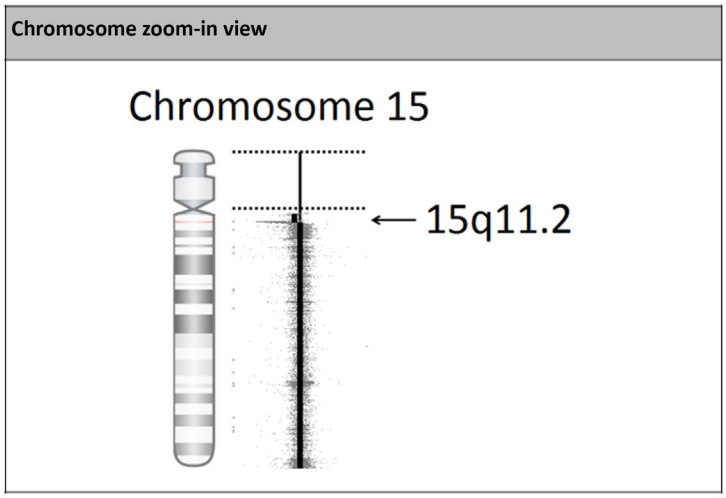
At the time of aCGH testing, the younger son was 3 years old and had a body weight of 12.5 kg (5^{th}–15^{th} centile), a body height of 95 cm (25^{th}–50^{th} centile) and a head circumference of 46.4 cm (<3^{rd} centile). He manifested developmental, speech, and motor delay more severe than his sister, borderline cognitive function, tension tremor, ataxic gait, irritable mood, myoclonus, but no congenital heart defects and no facial dysmorphism. EEG showed focal epileptogenicity. The aCGH result of the boy's peripheral blood was arr 15q11.2 (22,748,697–23,188,522) × 1.0 with a 0.44-Mb deletion of 15q11.2 encompassing four OMIM genes of *NIPA1*, *NIPA2*, *CYFIP1*, and *TUBGCP5* (Figure 2).

The peripheral blood of the phenotypically normal father was found to have an aCGH result of arr 15q11.2 (20,540,770–23,601,857) × 1.0 with a 3.06-Mb deletion of 15q11.2 encompassing seven OMIM genes of *NBEAP1*, *POTEB*, *NIPA1*, *NIPA2*, *CYFIP1*, *TUBGCP5*, and *MKRN3* (Figure 3).

Discussion

The proximal region of 15q contains low copy repeats of which mispairing may result in recurrent duplications and deletions of this region including deletion of BP1-BP3 (type 1 deletion of PWS/

(A)



(B)

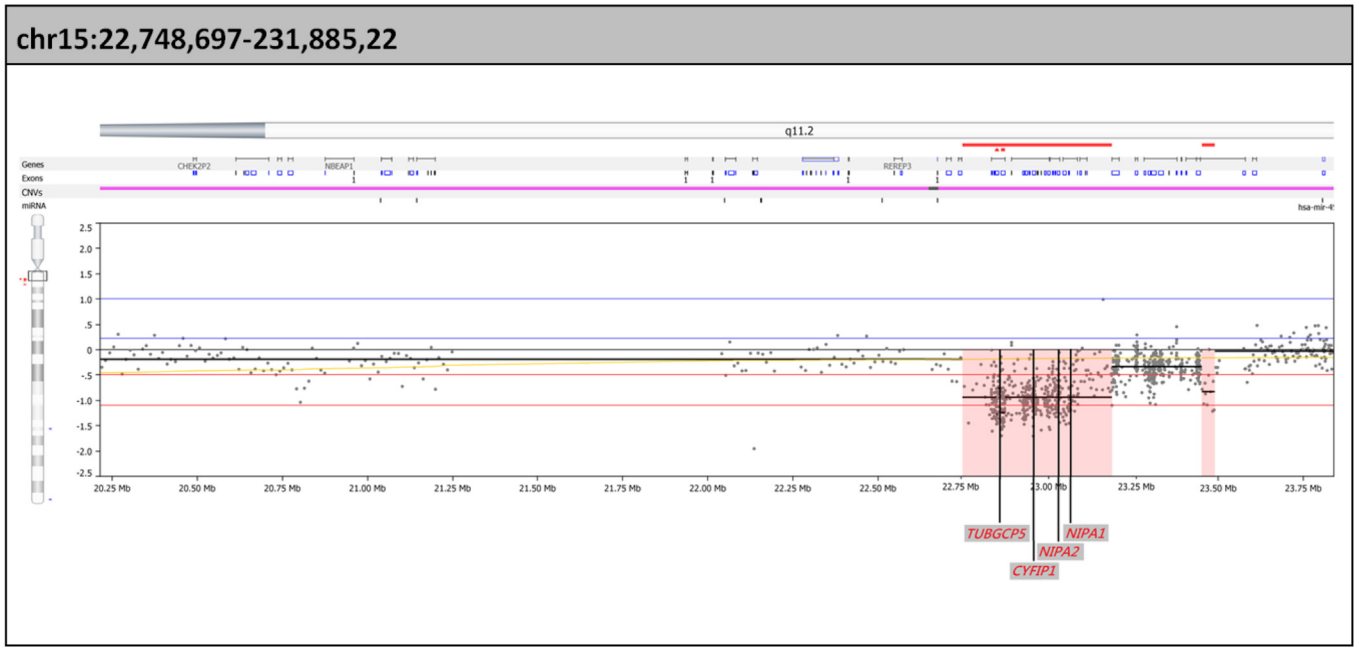


Figure 2. aCGH analysis of the younger son's peripheral blood reveals a 0.44-Mb deletion of 15q11.2 encompassing *NIPA1*, *NIPA2*, *CYFIP1*, and *TUBGCP5*. (A) Chromosome zoom-in view and (B) chromosome 15.

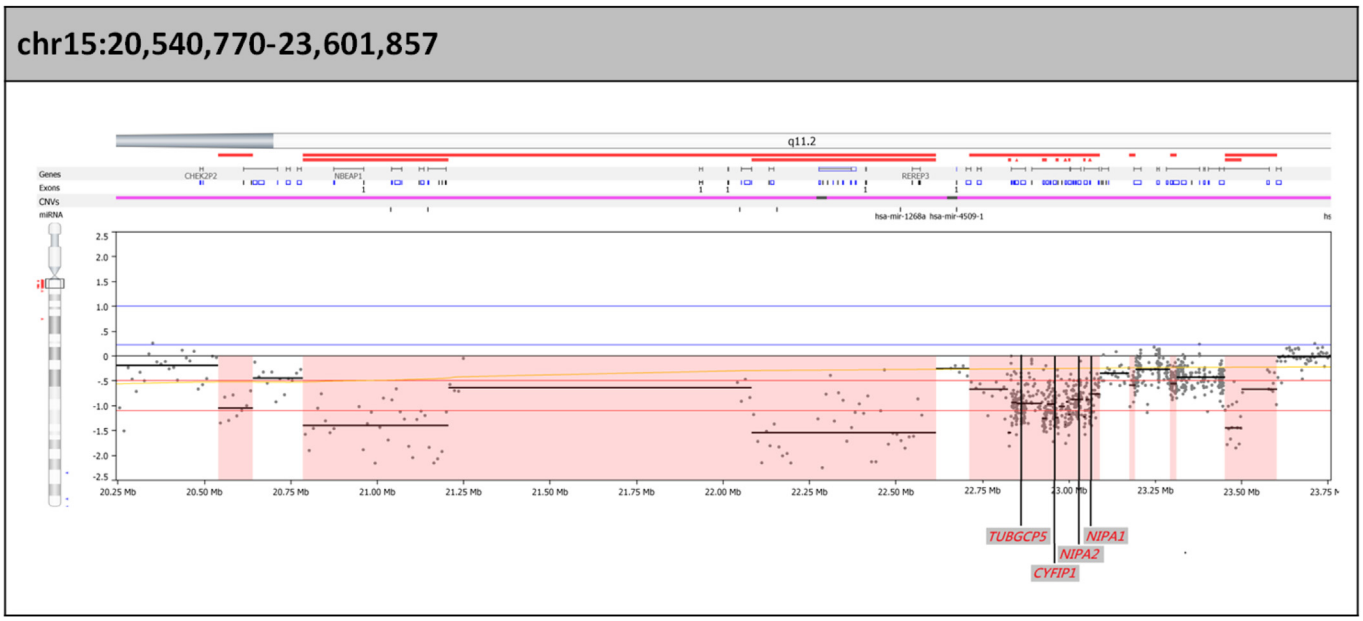


Figure 3. Array comparative genomic hybridization analysis of the father's peripheral blood reveals a 3.06-Mb deletion of 15q11.2 encompassing *NIPA1*, *NIPA2*, *CYFIP1*, and *TUBGCP5*.

AS) and deletion of BP2-BP3 (type 2 deletion of PWS/AS) causing PWS/AS, deletion of BP1-BP2 causing 15q11.2 (BP1-BP2) deletion syndrome, and parent-of-origin specific 15q proximal duplication associated with ASD.

Murthy et al [5] first reported 15q11.2 (BP1-BP2) deletion spanning *NIPA1*, *NIPA2*, *CYFIP1*, and *TUBGCP5* in a 3.5-year-old boy with cleft palate, motor delay, speech delay, ADHD, and hypotonia. The deletion was inherited from his father with less severe features. Doornbos et al [6] additionally reported nine patients of 15q11.2 (BP1-BP2) deletion spanning *NIPA1*, *NIPA2*, *CYFIP1*, and *TUBGCP5* with common features of motor delay, speech delay, dysmorphism, and behavior problems of ADHD, ASD, and obsessive-compulsive behavior. In their report, seven cases were inherited from a normal or mildly affected parent. de Kovel et al [7] identified 15q11.2 microdeletion in 1% of idiopathic generalized epilepsy patients compared with 0.2% in controls and suggested that 15q11.2 microdeletion predisposes to idiopathic generalized epilepsy. Stefansson et al [11,13] reported that recurrent 15q11.2 microdeletion is associated with schizophrenia. Burnside et al [8] reviewed 56 patients with 15q11.2 (BP1-BP2) microdeletion and found 59% with developmental delay, 36% with motor delay, and among the patients older than 1 year of age, 90% with speech delay, 67% with behavioral and neurological disorders such as ataxia, dyspraxia, hypotonia, tantrums, obsessive-compulsive disorder, and abnormal magnetic resonance imaging, and EEG findings, and 25% with seizures, and suggested that BP1-BP2 copy-number variations may increase susceptibility to neuropsychiatric or neurodevelopmental disorders. von der Lippe et al [9] reported seven patients from six families with 15q11.2 (BP1-BP2) microdeletion, and all patients had some degree of learning difficulties, delayed development, and/or behavioral problems but without common dysmorphic features and congenital malformations. The deletion was inherited from a mildly affected parent in all six cases tested. Cafferkey et al [14] reported a prevalence of 0.57% (83/14605) for 15q11.2 (BP1-BP2) deletion in the population referred for diagnostic cytogenetic testing, and found the associated phenotypic features including generalized developmental delay [84.4% (65/77)], motor delay [37.6% (29/77)], speech delay [48.1% (37/77)], ASD/autistic features [26% (19/73)], behavioral problems [47.9% (35/73)], dysmorphism [33.7% (28/83)], and epilepsy/seizures [15.6% (13/83)]. Vanlerberghe et al [12] reported a prevalence of 0.8% (80/9852) for 15q11.2 (BP1-BP2) microdeletion in the population with aCGH investigation and found that out of 52 patients, 68.3% had developmental delay, 85.4% had speech impairment, 63.4% had psychological problems such as ADHD, ASD, or obsessive-compulsive disorder, 18.7% had seizures, and 17.3% had congenital heart defects. In their study of 34 families with 15q11.2 (BP1-BP2) microdeletion patients, Vanlerberghe et al [12] found that 18.8% occurred *de novo*, and 81.2% were inherited from one of the parents, and there were incomplete penetrance and variable expressivity. Hashemi et al [15] reported a prevalence of 0.76% (55/7221) for 15q11.2 (BP1-BP2) microdeletion in the pediatric population undergoing chromosomal microarray and found that out of 35 patients, 91.4% had developmental delay, 20% had ASD, 37.1% had behavior problems including ADHD, 42.9% had dysmorphic features, 17.1% had epilepsy/seizures, and 84.3% were inherited from a parent. Cox and Butler [3] in a review of 200 individuals with 15q11.2 (BP1-BP2) microdeletion categorized the following clinical features: developmental delay (73%), speech delay (67%), dysmorphic ears (46%), palatal anomalies (46%), writing difficulty (60%), reading difficulty (57%), memory problem (60%), verbal IQ scores <75 (50%), unspecified general behavioral disorders (55%), abnormal brain imaging (43%), seizures/epilepsy (26%), ASD (27%), ADHD (35%), schizophrenia/paranoid psychosis (20%), and motor delay (42%), and suggested that 15q11.2 (BP1-BP2) microdeletion is associated with neuropsychiatric and behavioral disturbance, dysmorphic features, and an apparent incomplete penetrance and variable expressivity.

In summary, we present familial transmission of recurrent 15q11.2 (BP1-BP2) microdeletion associated with phenotypic variability in developmental, speech, and motor delay. Our presentation emphasized that recurrent phenotypic abnormality in a family with normal karyotype at amniocentesis should include a differential diagnosis of familial pathogenic copy-number variations.

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.

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