JIG Journal of Interdisciplinary Genomics

Journal of Interdisciplinary Genomics 2019;1(1):10-13

eISSN 2671-6771

First Korean Case of 16p11.2 Duplication Syndrome Diagnosed by Chromosomal Microarray Analysis

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A 10-year and 5 month-old girl with developmental delay, intellectual disability, attention deficit hyperactivity disorder, poor weight gain, and microcephaly was transferred to our pediatric clinic for genetic evaluation. Her height was within the 5-10th percentile, and her weight was under the 3rd percentile. On the social maturity scale, her developmental status was scored as 3 years 9 months for social age, and the social quotient was 35.98. A chromosomal microarray analysis was performed and the microduplication at chromosome 16p was observed: arr[GRCh37] 16p11.2 (29580020_30190029)×3. Currently, the patient is diagnosed with Grade 2 intellectual disability and is attending a computerized cognitive rehabilitation class twice weekly. In addition, nutritional support and growth follow up are also ensured in the Pediatric Gastrointestinal and Endocrinology clinic.

Key words: 16p11.2 microduplication, 16p11.2 copy number variations, Chromosomal microarray

CASE REPORT

Received: March 30, 2019
Revised: April 5, 2019
Accepted: April 12, 2019
Published: April 30, 2019

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INTRODUCTION

Both deletion and duplication of chromosome 16p11.2 have been associated with developmental delay, intellectual disability, and several psychiatric disorders [1]. Thus, early genetic diagnosis and intervention in these patients are important. However, no case of copy number variations (CNVs) in 16p11.2 has been reported from Korea yet. Here, we report the first Korean case of 16p11.2 duplication syndrome having classical characteristic features as confirmed by chromosomal microarray analysis (CMA).

CASE DESCRIPTION

A 10-year and 5 month-old-girl was transferred to our pediatric clinic. She had visited several medical centers since she was a toddler with complaints of language delay, poor weight gain, attention deficit-hyperactivity disorder (ADHD), and delayed walking. Her face showed epicanthal folds, broad nose, wide mouth, micrognathia, and prominent ears. Her parents were healthy and she had no sibling. At 6 years of age, magnetic resonance imaging of her brain and karyotype using peripheral blood were performed and the results showed no abnormal finding. She was investigated for Williams syndrome due to the morphologic features and learning disability: there was no abnormality in 7q11.23 by fluorescence in situ hybridization. The workup for periodic hypokalemic paralysis due to motor delay and symptoms of falling down on her legs; there was no mutation in *CACNA1S* and *SCN4A* genes by DNA sequencing. The screening for lysosomal storage

disease including Pompe disease using dried blood spot considering muscle weakness associated with myopathy; the enzyme levels were in all normal range.

At 7 years and 4 months of age, she undertook a language problem-solving ability test in our Pediatric Neurology Clinic and Department of Rehabilitation. The language problem-solving score was found to be 5 (< 1st percentile). The acceptance vocabulary equivalent age was estimated to be 3 years and 6 months by Peabody Picture Vocabulary Test (< 1st percentile). The accuracy of the consonants and vowels by Urimal test of Articulation and Phonology was 65.11% and 100%, respectively. The nerve conduction velocity and electromyography showed normal electrophysiological findings at 7 years and 4 months of age. The electroencephalography showed normal waking pattern at the age of 8 years and 2 months.

At 10 years and 5 months of age, during the time of visiting our genetics clinic, her height was within the 5-10th percentile and her weight was under the 3rd percentile (Fig. 1A). Her head circumference (HC) was within the 5-10th percentile (based on a 7-year-old girl's standard). The radiological findings suggested scoliosis of the thoracic spine (Fig. 1B). On the social maturity scale, her developmental status was scored as 3 years and 9 months for social age, and the social quotient was 35.98. She had poor performance in learning self-help skills due to poor cognitive and motor development. She had difficulty in performing most of her daily activities, which were all performed under the direction and assistance of her parents. It was difficult for her to write her own name because of the lack of visual perception. There was a delay in providing her training for age-appropriate social skills and adaptation behaviors.

Based on her symptoms and signs, CMA (Affymetrix Cytoscan 750K array, Genome build: Hg 19) was performed and was found to be arr 16p11.2 (29580020_30190029)×3 (Fig. 2). Accordingly, the patient was diagnosed with 16p.11.2 duplication syndrome. Her microarray showed a gain of 610 kb at the 16p11.2 site. We provided genetic counseling to her family. A prenatal genetic test will be necessary for her parents in subsequent pregnancies to rule out the possibility of gonadal mosaicism. Currently, the patient is diagnosed with Grade 2 intellectual disability and she is attending a computerized cognitive rehabilitation class twice weekly. Her visual perception is improving, although memory is further deteriorating and she needs repeated learning.

A nutritional evaluation revealed that she was having moderate malnutrition. The general nutritional requirement at her age is 1,600-1,900 kcal/day, but her oral intake was only 800-1,300 kcal/day. As a result, she consulted nutritionists and her mother was counseled for providing her additional nutritional

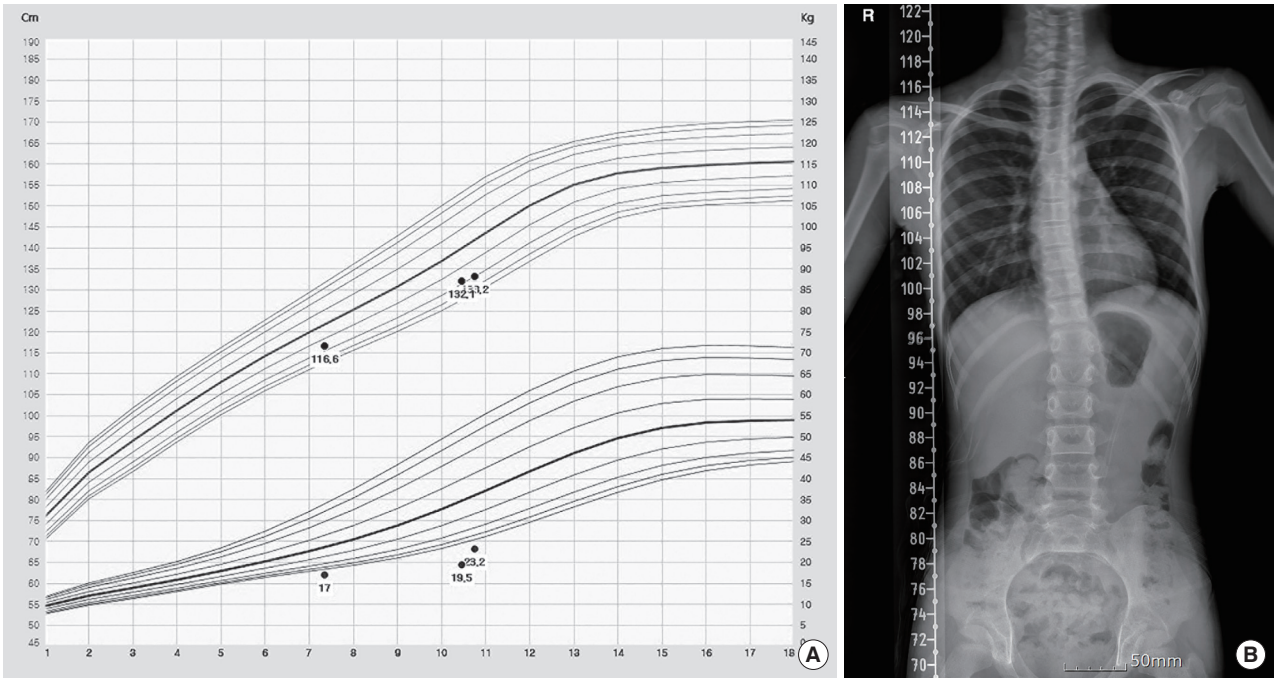

Fig. 1. The growth curve (A) and X-ray findings (B) of a 10-year-old Korean girl with 16p11.2 duplication syndrome. Her height was within the 5-10th percentile (upper curve) and her weight was under the 3rd percentile (lower curve) showing poor weight gain and failure to thrive (A). The radiological findings suggested right thoracolumbar scoliosis with an apex at T12 and a Cobb angle of 6° (B).

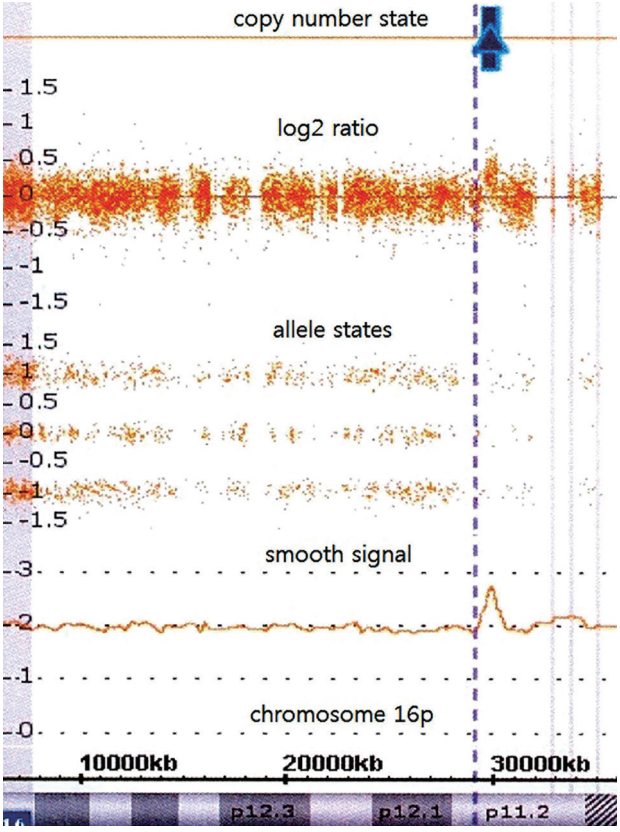

Fig. 2. The chromosomal microarray analysis (Affymetrix Cytoscan 750K array, Genome build: Hg19) of a 10-year-old Korean girl with 16p11.2 duplication syndrome. The patient's microarray showed a gain of 610kb at the 16p11.2 site: arr[GRCh37] 16p11.2 (29580020_30190029)×3.

supplements. During the endocrinological evaluation, there was no abnormal finding in the laboratory test results including insulin-like growth factor-1, insulin-like growth factor binding protein-3, thyroid-stimulating hormone, free thyroxine 4, adrenocorticotropic hormone, cortisol, luteinizing hormone, follicle stimulating hormone, estradiol, 25-hydroxyvitamin D, and parathyroid hormone levels. Her bone age was estimated to be 10.5 years, which was normal. This study was approved by the institutional review board of Keimyung University Dongsan Hospital (Approval No. 2019-04-005).

DISCUSSION

Recurrent 16p11.2 deletions or duplications (approximately 600 kb, chr16; 29.6–30.2 mb-HG19) are risk factors for neurodevelopmental and psychiatric problems [2, 3]. CNVs in 16p11.2 are known to occur in a frequency of 1-3 per 10,000 [4]. About 70% of the 16p11.2 deletions occur *de novo*, while around 70% of the 16p11.2 duplications are familial [5]. The parents of this patient were symptom-free and did not undertake any special investigations. However, a prenatal genetic test to rule out the possibility of gonadal mosaicism will be necessary for her parents for subsequent pregnancies.

Language delay and cognitive impairment are the most common clinical characteristics of 16p11.2 CNVs [6]. In addition, motor delay, seizures, behavioral problems (especially ADHD), congenital anomalies, and autism are frequently observed symptoms in CNVs [6]. The patients with 16p11.2 duplication have a higher frequency of ADHD [1, 7]. The 16p11.2 duplication carriers have a higher frequency of psychiatric disorders and ADHD than the normal controls and the 16p11.2 deletion carriers [1]. The frequency of ASD was similar between the duplication carriers and the deletion carriers [1, 8]. The patient had typical features of 16p11.2 duplication syndrome including language delay, intellectual impairment, and ADHD. However, she does not have any sign of ASD. She is friendly with people, has good eye contact, and maintains a good relationship with her mother.

Interestingly, 16p11.2 deletion and duplication have opposite patterns of HC and body mass index (BMI) [6]. The 16p11.2 deletion is associated with large HC and risk of obesity, while 16p11.2 duplication is associated with small HC and low BMI [6]. Several studies provided evidence supporting the linkage between small HC with schizophrenia and large HC with ASD [9-12]. There are several genes in the site of 16p11.2. Among them, *KCTD13* is suggested as a major driver of head size phenotypes in 16p11.2 CNVs through the regulation of neurogenesis by the animal data [13]; 1) only one gene (*KCTD13*) of the 16p11.2 site showed microcephaly in the overexpression test in vivo; 2) the reciprocal suppression of this locus resulted the mirrored phenotype, macrocephaly; 3) a neurogenic defects were established by the functional analyses [13]. Potassium channel tetramerization domain containing 13 encoded by *KCTD13* interacts with the proliferating cell nuclear antigen, thus might be involved in cell cycle regulation during neurogenesis [14]. This patient also had a small HC without ASD. Although it was difficult to compare her HC directly to normal control due to lack of data on normal HC for Korean children of ≥7 years, she also showed a relatively small HC as compared to her peers. Although she is still young and does not present the symptoms of schizophrenia yet, it is necessary to take appropriate psychiatric measures as there is a possibility that she may develop schizophrenia later.

CONFLICT OF INTEREST

There are no potential conflicts of interest relevant to this article.

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