



Identification of Potocki–Lupski syndrome in patients with developmental delay and growth failure

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Purpose: Potocki–Lupski syndrome (PTLS), is a recently identified, rare genomic disorder. The patients are affected by infantile hypotonia, poor growth and developmental delay. Facial dysmorphism may not be obvious in some patients. PTLS is associated with microduplication at chromosome 17p11.2. In the current study, three Korean patients are reported with their clinical and genetic features.

Materials and Methods: The clinical findings of each patient were reviewed. Karyotyping and multiplex ligation-dependent probe amplification (MLPA) analyses were done for genetic diagnoses.

Results: All the patients did not have the characteristic dysmorphic features, such as broad forehead, triangular face, asymmetric smile and palpebral fissures. On the other hand, all three patients were affected by variable degree of developmental delay, poor oral intake, failure to thrive, and language development disorders. Chromosome 17p11.2 duplication was identified by conventional karyotyping analysis only in one patient, whereas the other confirmed by MLPA analyses.

Conclusion: Delayed development was mostly commonly observed in our patients without distinct dysmorphic facial features. In this respect, genomic screening in patients with developmental delay would identify more cases with PTLS to understand their long-term clinical courses with the development of adequate psychological and rehabilitation education program.

Key words: Potocki–Lupski syndrome, Chromosome duplication, Developmental disabilities.

Introduction

Potocki–Lupski syndrome (PTLS) (OMIM #610883) is a genetic disorder caused by the genomic duplication at chromosome 17p11.2 [1]. The region includes retinoic acid-induced protein 1 (*RAI1*) gene. Although the role of this gene is elusive, it has been suggested as associated with the psychiatric disorders such as developmental delay, schizophrenia and autism [2].

PTLS patients show the characteristic dysmorphic features

such as microcephaly, prominent forehead, ears and nose, and broad square-shaped face [3]. In addition, most patients have multi-systemic problems including hypotonia in infancy, cardiovascular disorder, hearing impairment and failure to thrive (FTT) due to feeding problem [3,4]. Among these, the neurodevelopmental problems are most commonly observed, including developmental delay, intellectual disability, autism and behavioral problems such as hyperactivity [3,5].

Most PTLS patients have 3.7 Mb duplication at 17p11.2, with

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larger and smaller duplications reported [5]. The heterogeneity of clinical manifestations are associated with the size of the duplicated genome [6].

Here we describe the three Korean patients with PTLs due to a duplication of 17p11.2. The clinical features of our patient will help to understand this rare genetic condition.

Materials and Methods

1. Patient

From June 2014 to December 2018, three Korean patients were diagnosed with PTLs in Asan Medical Center Children's Hospital, Seoul, Korea. We reviewed the clinical and genetic features of each patient, including sex, age at diagnosis, congenital anomalies, growth and development. This study was approved by the Institutional Review Board at the Asan Medical Center (approval number: 2019-0831), and appropriate written informed consent was obtained from the parents of each patient.

2. Genetic testing

Karyotyping was performed using each patient's peripheral blood sample by Giemsa-banded techniques at the level of 550 bands in metaphase. In order to identify the multiple microdeletion of the patients, multiplex ligation-dependent probe amplification (MLPA) analysis were done using two types of SALSA Reference Kit, P064 and P245 (MRC Holland, Amsterdam, The

Netherlands) according to the manufacturer's instructions. This SALSA MLPA probemix P064 Microdeletion Syndromes–1B contains 52 MLPA probes with amplification products, respectively, corresponding to the *RAI1* and *TOM1L2* genes located at the 17p11.2 regions. This SALSA MLPA probemix P245 Microdeletion Syndrome–1A contains 50 MLPA probes with amplification products, respectively, corresponding to the *RAI1*, *DRC3* and *LLGL1* genes located at the 17p11.2 regions. In order to confirm PTLs, the fluorescence in situ hybridization (FISH) was conducted as hybrid probe for *RAI1* locus at 17p11.2 and *PAFAH1B1* (*LIS1*) gene at 17p13.3 in more than 10 metaphase and 200 interphase peripheral leukocytes.

Results

The clinical and genetic findings of each patient are summarized in Table 1.

1. Case 1

The patient was the second baby of non-consanguineous Korean parents. His prenatal period was uneventful. He was born after 39 weeks of gestation with 2,930 g of birth weight (standard deviation [SD] score, -0.7). His height was 49 cm (SD score, -0.3) and head circumference was 31 cm (SD score, -2). At birth, he was hypotonic and tachypneic. Echocardiogram, abdominal and brain ultrasonography were normal. His face was not dysmor-

Table 1. Clinical and genetic findings of patients with Potocki–Lupski syndrome

Variable	Case 1	Case 2	Case 3
Age (at diagnosis)	6 mo	1 yr 2 mo	4 yr 7 mo
Sex	Male	Male	Male
Gestational age	39 weeks	Full term	40 weeks
Birth weight (g)	2,930	No information	2,600
Dysmorphic features	Not dysmorphic, mild camptodactyly	Posteriorly rotated, large ears, micrognathia	Not dysmorphic
Cardiac	No	No evaluation	No evaluation
Gastrointestinal	No	No	No
Seizure	No	No	No
Developmental delay	Yes	Yes	Yes
Endocrinologic	Hyperthyrotropinemia	Not conducted	Not conducted
Hearing & ophthalmologic	Strabismus	No	No
Skeletal	No	No	No
Genitourinary	No	No	No
Results of MLPA analysis	17p11.2 rsa17p11.2(P064)x3	17p11.2 rsa17p11.2(P064)x3	17p11.2 rsa17p11.2(P064)x3
Karyotype	46, XY	46, XY	46, XY, dup(17)(p11.2p11.2)

MLPA, multiplex ligation-dependent probe amplification.

phic except mild camptodactyly. When he visited our clinic at 6 months of age, his weight was 6.3 kg (SD score, -2.1), height was 67.3 cm (SD score, -0.2) and head circumference was 42 cm (SD score, -1.1). Brain magnetic resonance image (MRI) did not show any remarkable abnormality. The thyroid stimulation hormone was mildly elevated in his thyroid function test. At 6 months of age, he was able to control his head, but not able to roll over. His sucking power was weak. At 20 months of age, he was able to stand with support. He had a surgical correction for strabismus at age 2 when he started to walk. At the last visit, he was able to say only 2 words ("mama", "dada") but to understand receptive language at until 3.

Genetic testing was performed to identify the cause of delayed growth and development. His karyotype was 46, XY. 17p11.2 duplication was identified by MLPA analysis (Fig. 1).

2. Case 2

The patient was the first baby of non-consanguineous Korean parents. He was born at full term. Perinatal and postnatal periods were uneventful. At 11 months of age, he was not able to speak meaningful word. Brain MRI study did not demonstrate any remarkable abnormality. The thyroid function test was not performed in our clinic.

When he visited out clinic at 14 months of age, he weight was 8 kg (SD score, -1.9), his height was 76.9 cm (SD score, 0) and head circumference was 45 cm (SD score, -1.0). He was able to crawl but could not walk. He was still unable to say any meaningful word. Mild dysmorphic facial features such as posteriorly rotated, large ear, micrognathia were noted.

His karyotype was 46, XY. MLPA analysis suggested the presence of 17p11.2 duplication, which was confirmed by FISH

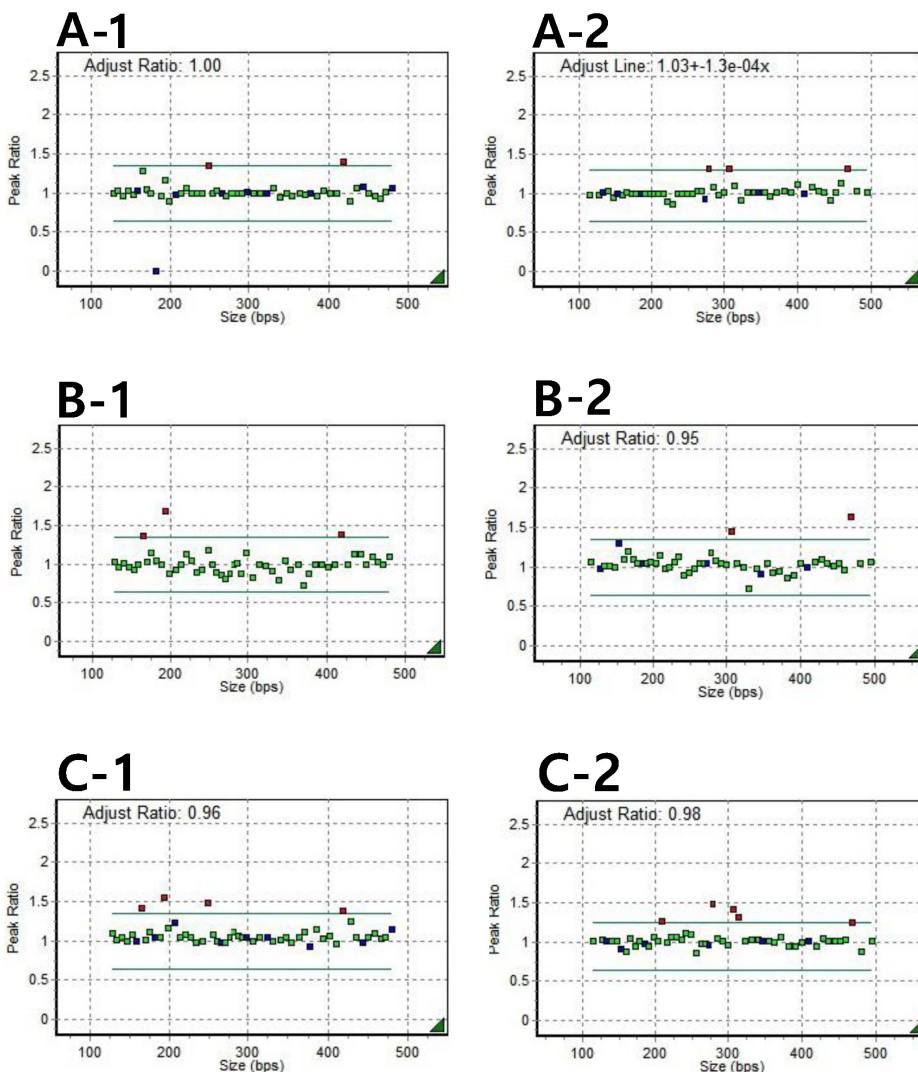


Fig. 1. The results of multiplex ligation-dependent probe amplification (MLPA) analysis. MLPA analyses were done using two types of SALSA Reference Kit, P064 and P245 (MRC Holland) according to the manufacturer's instructions. P064 and P245 contains MLPA probes with amplification products, respectively, corresponding to *RAI1*, *TOM1L2*, *DRC3* and *LLGL1* genes located at the 17p11.2 regions. Green dots indicate normal allele, while red dots are abnormal that is duplicated at 17p11.2. (A) Case 1 patient, (B) case 2 patient, (C) case 3 patient. Each 1, 2: P064, P245 probemix.

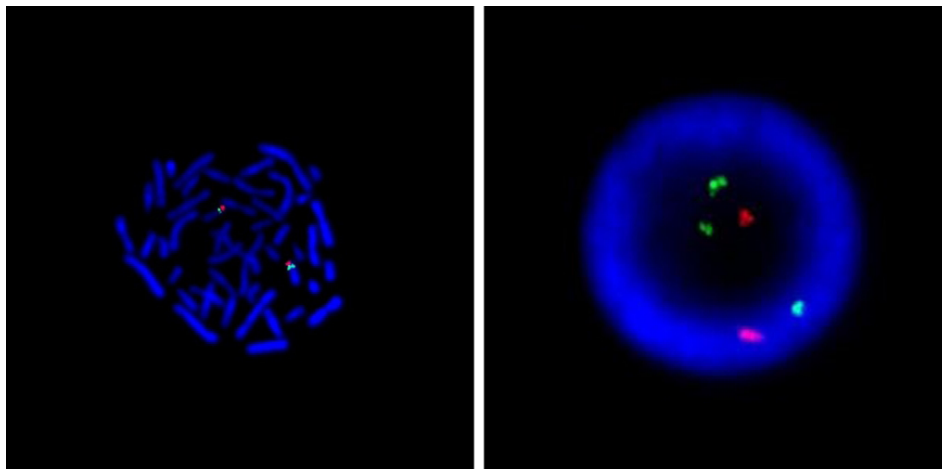


Fig. 2. The fluorescence in situ hybridization was performed with a hybrid probe for *RAI1* locus at 17p11.2 (green) and *PAFAH1B1 (LIS1)* gene at 17p13.3 (red) (Case 2). Two duplication *RAI1* signals (green) were observed in a metaphase cell (left). In interphase cell, duplication *RAI1* signals (green) were more prominently visualized in chromatin before condensed (left). While there are 2 *LIS1* signals as a normal control (red), there is one more *RAI1* signal (left).

analysis showing the duplicated *RAI1* probe (Fig. 2).

3. Case 3

The patient was the first baby of non-consanguineous Korean parents. He was born after 40 gestational weeks via caesarean section with a birth weight of 2,600 g (SD score, -1.7). Facial dysmorphism was not noted nor was a remarkable congenital anomaly. Weaning of breast-milk feeding was delayed. At 18 months of age, he was able to walk alone. At 4 years of age, he is able to speak only a few meaningful words. At 4 year 7 months of age, he weight was 15 kg (SD score, -1.3) and height was 100.3 cm (SD score, -1.3). A Bayley developmental test at 52 months of age demonstrated that her cognitive development was at age 8 months, receptive communication at 6 months, expressive communication at 9 months, fine motor and gross motor development at 16 months and at 15 months, indicating profound global developmental delay. He presented a self-injurious habit of pulling his hair. At 4.8 years of age, he had severe intellectual disability and autism spectrum disorder. At 7 years of age, he can't speak more than 3 words phase. He has trouble interacting with other colleagues because of autism spectrum disorder. He has been taking psychiatric clinic treatment regularly.

His karyotype was 46, XY dup(17)(p11.2p11.2). 17p11.2 duplication was diagnosed by MLPA analysis at the same time.

Discussion

PTLS is a recently reported disorder, with the first genetically confirmed case reported by Brown et al. in 1996 [7]. The incidence of PTLS is thought to be at least 1 in 20,000 individuals. However, fewer than 50 cases have been described in the medi-

Table 2. Frequency of clinical features in three patients compared to those commonly reported in Potocki–Lupski syndrome

Clinical features	Affected frequency in the previous reports (n=58)	Number of patients (n=3)
Dysmorphic features	25 (43.1)	1
Poor feeding in the neonatal period	33 (56.9)	2
Autism	22 (37.9)	1
Failure to thrive	20 (34.5)	3
Developmental delay	52 (89.7)	3
Cardiovascular involvement	12 (20.7)	0
Seizure	5 (8.6)	0

Values are presented as number (%) or number only.

cal literatures.

Most patients with PTLS have been described as showing global developmental delay [4]. All of our patients also had developmental problems including cognitive, motor and language delay. In addition, autism spectrum disorder has been observed in some patients with PTLS (37.9%) [1,4], as in one of our patients (Table 2).

In recent reports, neuroimaging revealed mild brain abnormalities; mild attenuation of corpus callosum and delay in myelination and microcephaly [4,8]. In our patients, brain MRI at 0.5 to 1 year of age did not reveal any structural abnormalities (Table 2).

Seizure (8.6%) has been rarely reported [4], and it was not detected in our case, although longer-term observation is required (Table 2).

Facial dysmorphism such as broad forehead, palpebral fissures, bulbous nasal tip, posterior rotated ear and micrognathia have been reported (43.1%), but our patients did not show easily-noticeable dysmorphism (Table 2). Only one patient had a mild facial anomaly including posteriorly rotated large ear, and mi-

crognathia.

Feeding difficulty is another common manifestation in PTLs patients. This problem leads to FTT and growth failure in 34% to 71% of the patients [1,9]. Oropharyngeal incoordination may contribute to FTT in PTLs patients [9]. In our study, feeding problems were noted in 2 patients. Subsequently, most PTLs patients were consistently small in weight and height, indicating that the intrinsic genetic factors may underline these growth abnormality [9].

PTLs patients have a wide range of congenital multi-organ anomaly, such as cardiovascular anomaly (20.7%), low thyroid stimulation hormone levels (30%), ophthalmic, orthopedic, oropharyngeal, and renal anomalies [4,8]. None of our patients had a cardiac anomaly. One patient had strabismus and hearing loss was not reported in our study.

Duplicated region of chromosome 17p11.2 contains several genes including *SMCR5*, *SREBF1*, and *TOM1L2*. Among these, *RAI1* gene has been suggested as associated with the neurodevelopmental abnormality in PTLs patients. The *RAI1* gene was first isolated in 1995 [10]. *RAI1* is expressed in human hippocampus, cortex and cerebellum, and is suggested to be associated with cognitive and motor nervous function [2]. *RAI1* is a transcription factor but its precise mode of action is unclear. On the other hand, when a subject has a heterozygous deletion at 17p11.2 including the *RAI1* gene, facial dysmorphism, mental retardation and neurobehavioral disorders may develop, known as Smith-Magenis syndrome. Therefore, the *RAI1* gene may have a role in the development of human intellectual and behavioral skills by the gene-dosage effect [2,11].

The common recurrent duplication of PTLs is heterozygous ~3.7 Mb duplication at 17p11.2 (chr17:16,757,111-20,219,651 [hg19]). The size of duplication region might be associated with the clinical severity of the PTLs patients [1].

For the identification of PTLs, karyotyping, FISH, MLPA analysis, and chromosome microarray (CMA) can be performed. In our study, FISH and MLPA performed to diagnosis this syndrome, but microarray is the most sensitive diagnostic tool that can reveal the duplication length [4,12].

The limitation of this study is retrospective observation study on only a small number of patients. The duplication size was not determined since CMA analysis was not performed.

In conclusion, as PTLs is a rare genomic disorder associated with developmental delay but with mild dysmorphism, its clinical suspicion is not easy based on physical examination alone. Although most mutation occurs as a de novo microduplication at 17p11.2 and length of the duplication is 3.7 Mb [4]. Inherited

PTLs is also rarely reported [12]. Universal screening with CMA for patients with delayed development will help to identify more cases, which will help to understand its long term prognosis and provide adequate psychological and rehabilitation education.

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