증 례

14q32.33 Deletion Identified by array-CGH in a 5-year old-girl with Seizure

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Deletions of 14q including band 14q32.33 are uncommon. Patients with terminal deletions of chromosome 14 usually share a number of clinical features. By molecular techniques (array comparative genomic hybridization (CGH) and fluorescence in situ hybridization (FISH), we identified a young girl with 0.3 Mb terminal 14q32.33 deletion. Review of the nine cases with pure terminal 14q32.3 deletions described to date documented that our observation is the smallest terminal 14q deletion ever reported. The phenotype of our patient is much less severe than the phenotypes of the patients reported previously. We report our experience in examining the clinical, behavioral, and cognitive findings in a 5-year-old girl studied with chromosomal microarray hybridization and reviewed previously reported patients with 14q32 deletions.

Key Words: 14q32.33 deletion, Fluorescence in situ hybridization, Array comparative genomic hybridization

Introduction

Terminal deletions of the 14q32.3 sub-band of the long arm of chromosome 14 are rare[1)]. The common clinical features shared by a significant number of patients with 14qter deletions include microcephaly, high forehead with lateral hypertrichosis, broad nasal bridge, long and broad philtrum, high arched palate, epicanthic folds, single palmar crease, hypotonia, and mild to moderate mental retardation and developmental delay[1, 2)]. The phenotypic variation may occur as a result of a slightly different deletion breakpoint. Due to the limited number of cases reported, it was not possible to assign specific features to specific regions of terminal 14q[3)]. Here, we report on a girl with a small sub-telomeric deletion of the long arm of chromosome 14q32.33 (smaller than previously described) and compare her phenotype with previously reported patients with similar 14q deletions, due to either a linear deletion or a ring chromosome 14.

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Case report

The proband, a Korean 5-year old-girl, is the second child of healthy unrelated parents. The girl was delivered at 38 weeks after an uneventful pregnancy. Familial

history is negative for mental retardation and congenital malformations. The mother was 32 years old at conception and the father was 33 years old. Birth height, weight, and head circumference were 42 cm (<3th percentile), 2,200 g (<3th percentile), and 30 cm (<3th percentile), respectively. She has a 7 year-old healthy sister. During the neonatal period, she showed mild hypotonia. Initial development was considered to be normal, but from 12 months of age onward delay in motor milestones gradually became clear. She could stand at 14 months and walk unsupported at 18 months. She was first admitted to a general pediatric ward at 18 months of age because of febrile seizure. At the age 5 year, she was referred because of the recurrent afebrile seizure and mental retardation. On physical examination; height was 107 cm (10-25th percentile), weight was 16.4 kg (5-10th percentile), and head circumference was 45 cm (<3th percentile). Subtle facial dysmorphic features included high forehead, narrow bifrontal diameter, and short bulbous nose with anteverted nares (Fig. 1). Ophthalmological examination showed strabismus and myopia. Liver and spleen were not enlarged. Right inguinal hernias were surgically corrected at age 18 months. Hands, feet, and genitalia were normal. No pathological reflexes were identified and muscle strength of her upper and lower extremities were within normal range. Heart and abdominal sonographic examinations were normal. Magnetic resonance imaging of the brain showed normal findings, and hearing tests were normal. EEG revealed moderately abnormal findings with frequent focal epileptiform discharges over the right occipital and left temporooccipital regions synchronously or independently during sleep. She has an IQ of 56. She liked excessive touching and hugging and showed hyperactivity. Standard chromosomes analysis was normal, 46, XX.

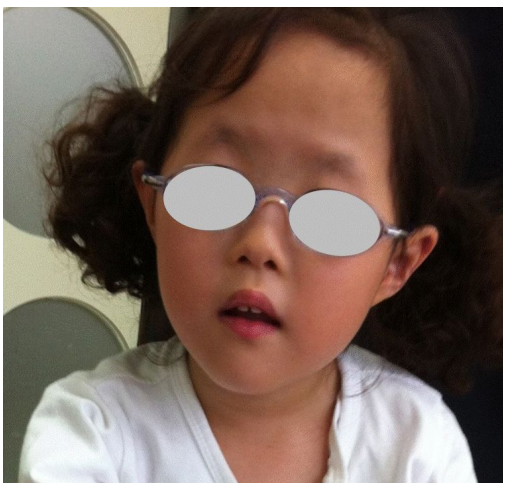

Fig. 1. We obtained formal permission to publish this facial photograph from the parents. Frontal facial views of our patient with the 14q32.33 deletion at 5 years-8months of age show a high forehead, narrow bifrontal diameter, and short bulbous nose with anteverted nares.

Molecular cytogenetic analysis and results

We performed whole genome array CGH using CGH array slides containing 1440 clones with 356 cell growth related genes from BAC libraries and simultaneously performed FISH to confirm abnormal array CGH results. Array CGH showed about a 0.3 Mb deletion on chromosome 14q32.33qter [arr 14q32.33qter (104,687,477-104,976,687)×1] (Fig. 2). In order to confirm the deletion where the terminal segment of chromosome 14q32.33→qter, FISH with a 14q32.33 region specific probe was performed according to the manufacturer's instructions (Macrogen). We confirmed a deletion on 14q32.33 region by FISH analysis [46,XX, ish del(14)(q32.33)(WI-6905-)] (Fig. 3).

DISCUSSION

The focus of our report was to describe an additional patient with a deletion involving the 14q32 band and to review the literature. A purely distal 14q32 deletion was reported in less than 15 published cases[4], and only 12 of them were confirmed by molecular cytogenetics. Nine patients bearing 14q32.3 terminal deletion have been reported to date. Deletions involving exclusively band 14q32.3 have thus far been observed in the rare terminal deletions of 14q and in carriers of a ring

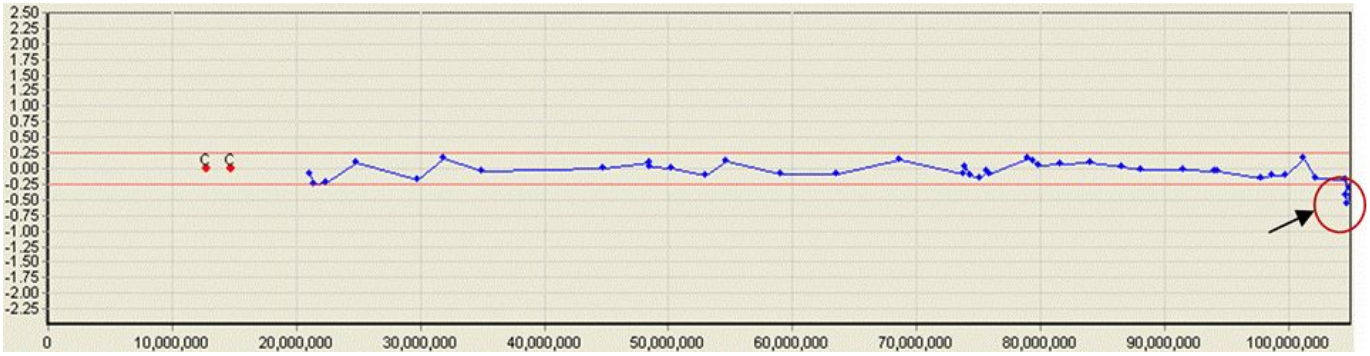

Fig. 2. Array CGH showing a deletion on the long arm of chromosome 14 (14q32.3 region). The arrow indicates a deletion at chromosome 14q32.33→qter.

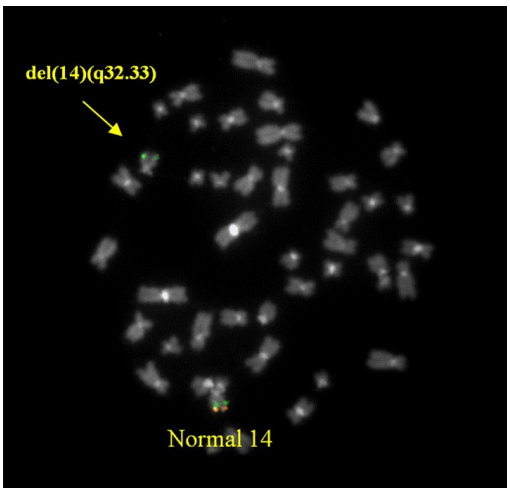

Fig. 3. FISH with 14q32.1 (green color) and 14q32.33 (yellow color) region probes; the arrow indicates a deletion of the probe (WI-6905-) in a del(14)(q32.33) chromosome.

chromosome 14[4, 5]. Major clinical features are mental retardation and dysmorphism[1]. Major congenital malformations are relatively uncommon in terminal 14q deletion patients, except for congenital heart defects[3]. The following list of commonly observed physical anomalies reported in patients with the 14q32.3 deletion; broad philtrum (6/6), broad and flat nasal bridge (5/6), telecanthus (6/8), hypotonia (5/8), high-arched palate (6/8), thin upper lip (4/5), blepharophimosis (5/6), pointed chin (3/7), malformed helices (3/5), small mouth (3/6), and strabismus (3/6). This suggests that genes involved in the clinical features classically reported in 14q32.3 deletions could be located on the telomeric 1-1.6 Mb of the 14q32.33 terminal sub-band of chromosome 14[1]. Our patient did not display all abnormalities that are commonly found in the terminal deletion cases including broad and long philtrum, high arched palate, telecanthus, blepharophimosis, and thin upper lip. Our patient has a terminal deletion (0.3 Mb) shorter than those previously published. This phenotypic variation may be the result of a slightly different deletion breakpoint. The general phenotype of cases with terminal 14q deletion due to ring chromosome is similar or less severely affected than that of cases with linear chromosome deletions of similar size[3]. Specifically, growth retardation is less frequently associated with ring chromosome 14 cases[3]. Seizures and retinitis pigmentosa are not found in patients with linear terminal 14q deletions, but only in 14qter deletions due to ring chromosomes[3, 6]. Interestingly, our patient has a seizure disorder, and it is not commonly found in other reported cases. The literature review reveals only one case report of seizure of the patients with 14q32.3 deletion. These findings should contribute to delineate the emerging phenotype in terminal 14q32.3 deletion but further data will be necessary. The clinical features including cognitive and behavioral findings of the twelve terminal 14q32 deletion cases and of this case are listed in Table 1. Considering that our patient's major clinical feature is mental retardation and seizure, we focused our attention on neurologically implicated genes in terminal 14q32.33 deletion. In this region, two genes *BX248748* and *MTA1* have a putative role in neurolo-

Table 1. Summary of Clinical Features and Developmental/cognitive, Neurological, and Behavioral Findings

	Hreidarsson et al. (1983)[8]	Masada et al. (1989)[9]	Telford et al. (1990)[10]	Wang et al. (1992)[11]	Wintle et al. (1995)[12]	Ortigas et al. (1997)[6]	van Karnebeek et al. (2002)[3]	Schlade-Bartusiak et al. (2005)[13]	Schlade-Bartusiak et al. (2009)[2]	Zollino et al. (2009)[14]	Zollino et al. (2009)[14]	Youngs et al. (2011)[7]	Our patient
Age	12-year	1-day	26-month	3- year	3-month	3-year	9-month	6-month	14-day	4-year	33-year	18-year	5-year
Sex	M	M	F	F	F	F	F	F	M	F	F	F	F
14q distal breakpoint	qter	qter	qter	qter	qter	qter	qter	qter	qter	qter	qter	q32.3	qter
14q proximal breakpoint	q32.3	q32.11	q32.3	q32.2	q32.3	q32.3	q32.31	q32.32	q32.32	q32.31	q32.2	q32.32	Q32.33
Intrauterine growth	+	+	+	-	-	-	-	NR	NR	NR	NR	NR	+
microcephaly	-	-	-	-	-	+	+	-	+	NR	-	+	+
Strabismus	-	-	-	-	NR	+	+	NR	-	NR	+	+	+
Blepharophimosis	-	-	+	+	NR	+	+	NR	+	NR	NR	+	NR
Ptosis	-	-	+	-	+	-	+	NR	-	NR	NR	+	-
Telecanthus	-	+	+	+	+	+	+	+	-	NR	NR	+	-
Broad nasal bridge	+	+	+	+	NR	+	+	NR	-	NR	NR	+	-
Philtrum abnormalities	+	+	+	+	NR	NR	+	+	+	NR	NR	+	-
Small mouth	-	+	+	-	NR	-	-	NR	+	NR	NR	+	-
Thin upper lip	NR	NR	-	NR	NR	+	+	NR	+	NR	NR	+	-
Highly-arched palate	+	+	+	+	+	+	-	+	-	NR	NR	+	-
Pointed chin	+	+	-	+	NR	+	-	-	-	NR	NR	+	-
Malformed helices	+	-	-	+	NR	NR	+	NR	+	NR	NR	-	-
Developmental delay	+	NA	+	+	+	+	+	+	+	NR	+	+	+
Walked	NR	NA	NR	NR	NR	2year	NR	NR	NA	NR	NR	24month	13month
First words	NR	NA	NR	NR	NR	3year	NR	NR	NA	NR	NR	4year	30month
Hypotonia	-	+	+	+	+	-	+	+	-	NR	+	+	+
Seizure	-	+	-	-	-	-	-	NR	+	NR	NR	-	+
Hearing loss	NR	NR	+	NR	NR	NR	NR	NR	+	NR	NR	+	-
Behavioral	NR	NA	NR	NR	NA	NR	NR	NA	NA	NR	Compulsive; hyperactivity	PDDNOS; ADHD; OCD; GAD; aggression	hyperactivity

Abbreviations: ADHD, attention-deficit hyperactivity disorder; CHD, congenital heart disease; F, female; GAD, generalized anxiety disorder; HL, hearing loss; M, male; NA, not applicable; NR, not reported; OCD, obsessive-compulsive disorder; PPDD-NOS, pervasive developmental disorder-not otherwise specified.

gical development[1]. Regulation of genes proximal to the deletion such as *JAG2, AKT1,* and *CKB* may also be associated[1]. Considering these reports, several candidate genes could be involved in the development of the mental retardation and seizures observed in our patient. But molecular genetic and functional studies are required to elucidate the contribution of each gene to a specific phenotype. High resolution techniques, such as chromosome microarray hybridization, allows for a more precise description of location, size, and genes involved in a specific chromosome region, and are helpful to characterize the genetic locus for genotype-phenotype correlations[7]. Thus, the natural history and genetic background need to be further investigated in order to provide appropriate management and genetic counseling.

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국문초록

14q32.33을 포함한 14번 염색체 장완 결실은 드문 질환이다. 14번 염색체의 말단 결실은 여러 임상증상을 공통적으로 보일 수 있으나 결실 절단부 (breakpoint)에 따라 표현형이 다양하게 발생할 수 있다. 저자들은 경련을 동반한 5세 여아에서 array comparative genomic hybridization (array-CGH)와 fluorescence in situ hybridization (FISH) 방법을 이용하여 이전 보고에 비해 가장 작은 14q32.33부위의 0.33 Mb 크기의 말단 결실과 심하지 않은 표현형을 보이는 1례를 경험 하였기에 문헌고찰과 함께 보고하는 바이다.

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