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The First Korean Case Report of Siblings with 12q24.22q24.33 Duplication

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Live-born cases of partial trisomy 12q are rare, and only a few fetuses with this unbalanced translocation have survived to term. To our knowledge, only about 40 patients have been reported as having 12q duplication, and among them are no Korean reports. Here, we report the first Korean case of siblings with a 12q24.22q24.33 duplication. An 11-year-old boy visited our clinic for short stature. He was born small for his gestational age and had distinctive facial features, a history of surgery for anorectal malformation, psychomotor delay, intellectual disabilities, and attention-deficit/hyperactivity disorder (ADHD). He had an older sister with similar clinical features. The chromosomal microarray of the patient and his sister showed identical results: a 16.2 Mb duplication of 12q24.22q24.33. They had an identical cutoff point, but their symptoms were not. Symptoms common to both included growth retardation, psychomotor delay, intellectual disability, ADHD, and small for their gestational age.

Keywords: Attention deficit disorder with hyperactivity, Fetal growth retardation, Intellectual disability, Microarray analysis, Trisomy 12q

Introduction

Live births with 12q partial trisomy are very rare [1]. Hobolth et al. [2] reported partial trisomy 12 in a mentally retarded boy and balanced translocation (12;21) in his mother. The boy had hypertelorism, a broad nasal bridge, low-set and poorly lobulated ears, and a prominent xiphoid process. Since the publication of this first report, only approximately 40 patients with 12q duplication have been documented in other countries [3]; to date, no such cases have been reported in Korea.

Here, we report a long-term follow-up (11, 16 years) of 12q24.22q24.33 duplication in Korean siblings with similar clinical features, including developmental delays and short stature; a balanced t(11;12)(q25;q24.2) translocation was found in one of the parents.

Case report

An 11-year-old Korean boy visited our pediatric outpatient clinic because of his short stature. He was the second child of young, healthy, non-consanguineous parents. He was born at a gestational age of 33 weeks and 3 days, weighing 1.56 kg (3rd-10th percentile) through cesarean section chosen based on a previous maternal cesarean section. His Apgar scores were 4 and 7 at 1 and 5 minutes, respectively. He was admitted to the neonatal intensive care unit for pre-

mature birth and low birth weight. The patient had a single umbilical artery. Echocardiography performed 29 days after birth showed a secundum atrial septal defect (ASD) measuring 5 to 7 mm, which spontaneously closed before follow-up examination at 8 months of age. Brain magnetic resonance imaging (MRI) performed at the age of 29 days showed no abnormal findings, except for mild molding of the occipital bone. At the age of 2 months, he was diagnosed with an imperforate anus based on the chief complaint of frequent painful defecation and underwent an anoplasty at the pediatric surgery department. He presented with global developmental delay, and a brain MRI performed at age 4 showed no abnormalities. He received speech therapy, occupational and physical therapy. When he was 9 years, he was diagnosed with attention-deficit/ hyperactivity disorder (ADHD) and adjustment disorder and started taking methylphenidate, which was effective. He was diagnosed with intellectual disability at the age of 10 (IQ: 46, moderate mental retardation). Upon presentation to our clinic, his height and weight were 133.5 cm (1st-3rd percentile, -1.90 standard deviation score [SDS]) and 27.6 kg (1st-3rd percentile, -1.94 SDS), respectively. Upon physical examination, his facial features showed hypertelorism, epicanthus, a broad and flat nasal bridge, prominent antihelix, down-turned mouth, and micrognathia.

In the history taking, the parents of the patient had a history of 3 spontaneous abortions (Fig. 1). There was no family history of intellectual disability or congenital malformation, except for the patient's older sister (16 years old). She had similar clinical features, presenting with low birth weight, growth delays, global developmental delay, intellectual disability, distinctive facial features resembling those of her younger brothers, and congenital heart disease. She was born at 36 weeks and 6 days of gestation, weighing 2.14 kg (3rd-10th percentile) through cesarean section due to fetal distress. She was diagnosed with a ventricular septal defect (VSD, 8 mm), ASD (4 mm), and patent ductus arteriosus (PDA) when she was 5 days old and underwent total corrective surgery at 3 months of age. She also presented with global developmental delay and was diagnosed with intellectual disability at the age of 14 (IQ: 51, mild mental retardation). Upon presentation to our clinic, her height and weight were 151.4 cm (3rd-5th percentile, -1.69 SDS) and 37.9 kg (< 1st percentile, -2.71 SDS), respectively. She had characteristic facial features like her younger brother, including hypertelorism, epicanthus, a broad and flat nasal bridge, prominent antihelix, down-turned mouth, and micrognathia. Additionally, she was on medication for ADHD, similar to her brother. She had a history of both genu valgum surgery, idiopathic scoliosis, and spina bifida.

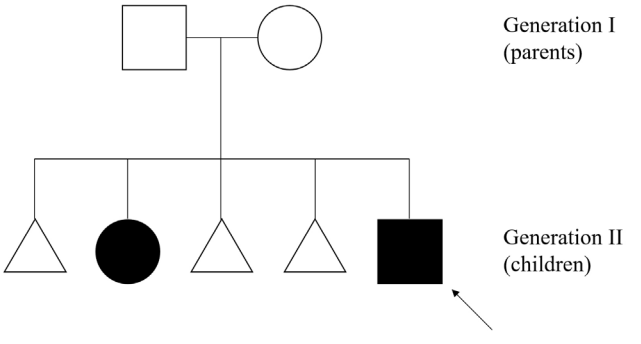

Fig. 1. A pedigree of the family of the siblings with 12q24.22q24.33 duplication. Circles indicate females, squares indicate males, and triangles indicate a miscarriage. The affected individuals are denoted as solid symbols. The arrow indicates the proband (II:5).

The partial karyogram and chromosomal microarray results are shown in Fig. 2. The proband's karyotype was 46,XY-,der(11)t(11;12)(q25;q24.2) and the karyotype of his sister was 46,XX,der(11)t(11;12)(q25;q24.2). The karyotype of one of the parents showed a balanced translocation t(11;12)(q25;q24.2). We use the phrase "one of the parents" because they refused to know which of them had a balance translocation (Fig. 2A). The chromosomal microarray of the proband and his older sister showed identical results: 11q25(134,513,530_134,938,470)×1,12q24.22q24.33(117,533,207_133,777,902)×3 (Fig. 2B). The deleted 11q25 region included no genes, but the duplicated 12q24.22q24.33 region included up to 100 genes.

Discussion

We described the first Korean cases of 12q24.22q24.33 duplication. Previously reported clinical features of 12q duplication include craniofacial dysmorphia, growth retardation, brain malformations, abnormalities of the extremities, skeletal and thoracic malformations, cardiovascular defects, anogenital abnormalities, psychomotor delays, and intellectual disabilities [3]. There are several reports of 12q duplication, but pure 12q duplications are rare [3,4]. In many cases, 12q duplications result from balanced translocations in the parents, where a segment of chromosome 12 is exchanged with another chromosome. These translocations often involve the partial deletion of other chromosomes, making it challenging to determine the exact contribution of the 12q duplication to the clinical features observed in individuals. Our cases were also

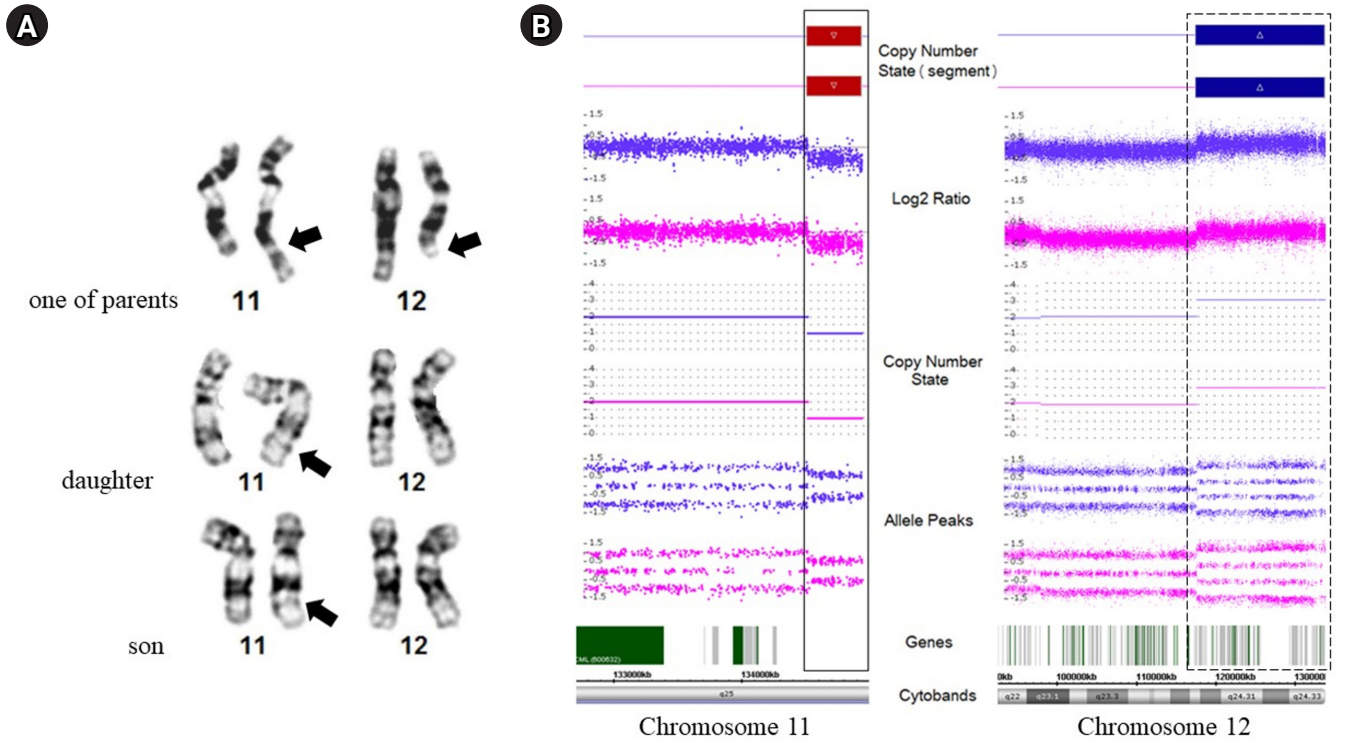

Fig. 2. (A) Partial karyogram of one of the parents, daughter, and son. The parent's karyogram shows balanced translocation t(11;12)(q25;q24.2). The daughter and son had the same der(11)t(11;12)(q25;q24.2) chromosome, originating from the parent, and a normal chromosome 12. Arrows indicate breakpoints. (B) Results of the chromosomal microarray analysis. The daughter and son exhibited the same 425 Kb microdeletion in the 11q25 terminal region (solid box), as well as a 16.2 Mb duplication in the 12q24.22q24.33 region (dashed box). The deleted 11q25 region included no genes, but the duplicated 12q24.22q24.33 region included up to 100 genes.

accompanied by 11p deletion, but since the deleted region did not contain any genes, the clinical features of our case can be considered purely due to the 12q duplication. Therefore, the 16.2 Mb duplication of the 12q24.22q24.33 region in our patients provides valuable insight into the specific manifestations of this genetic condition.

To better understand the phenotypic characteristics observed in our cases, we conducted a review of five previously published cases of pure 12q duplications that contained overlapping segments with the 12q24.22q24.33 region (Table 1) [2,4-7]. Among the 7 cases, 4 cases were de novo duplications, while 3 cases had a parental origin. All the cases exhibited developmental delays as a common feature. The majority of cases (6 cases) had ear malformations. In 6 cases, abnormalities in the extremities or skeletal findings were observed, although the specific findings varied. Additionally, a significant number of cases showed growth delays (5 cases) and attention deficit disorder (5 cases). More than half of the cases (4 cases) presented with hypertelorism, down-turned mouth, and cardiac anomalies. Hearing loss was observed in one case but was not a universally shared symptom.

As in the previous seven cases, phenotypes can appear differently even with the same chromosomal abnormality or genetic mutation [8]. In our case, the proband and his older sister had the exactly same duplicated region generated by unbalanced segregation from same parent's balanced translocation, but their symptoms were not exactly the same. Common symptoms included growth retardation, psychomotor delays, intellectual disabilities, ADHD, and small for gestational their age. However, the proband had ASD, which closed spontaneously, whereas his older sister had to undergo heart surgery for VSD, ASD, and PDA. In addition, anorectal malformation was only observed in the proband, and skeletal deformities were only observed in the older sister.

The understanding of the 12q duplication syndrome remains challenging. The lack of well-defined cases characterized by molecular techniques adds to the complexity of studying this syndrome. To establish a clearer relationship between the duplicated region and the resulting phenotype, it is crucial to gather more cases with detailed molecular cytogenetic

Table 1. Clinical findings of 12q duplication: the present cases and previously reported cases with overlapping duplicated segments including 12q24.22q24.33 in pure 12q duplication

	Sex	Age at the report (yr)	Duplication	Origin	IUGR	Craniofacial dysmorphism	Neck/ thorax	Brain anomalies	Cardiac anomalies	Extremities/ skeletal findings	Genito-urinary/GI/renal findings	Neurologic/ Behavior problems	Developmental delay	Growth retardation	Hearing problems
Present cases	F	16	12q24.22q24.33	One of parents	Yes	Hypertelorism, epicanthus, broad and flat nasal bridge, prominent antihelix, down-turned mouth, micrognathia	Normal	Not done	VSD PDA	Genu valgum surgery, idiopathic scoliosis and spina bifida	NM	ADHD ID	Yes	Yes	No
	M	11	12q24.22q24.33	One of parents	Yes	Hypertelorism, epicanthus, broad and flat nasal bridge, prominent antihelix, down-turned mouth, micrognathia	Normal	Normal	ASD (spontaneously closed)	NM	Imperforated anus	ADHD ID	Yes	Yes	No
Ieshima et al. (1984) [5]	F	1	12q24.2→qter	De novo	No	Brachycephaly, left exotropia, hypertelorism, long eyelashes, flat nasal bridge, small nose with hypoplastic nasal tip, downward corners of the mouth, mild micrognathia and poorly lobulated ears	Short neck, widely spaced nipples	Mild dilation of third and lateral ventricles, cortical atrophy.	Small VSD	Mild brachydactyly, hypoplastic nails Big and broad thumbs and the first toes	NM	NM	Yes	Yes	NM
Ireland et al. (2004) [6]	M	30	12q24.31→qter	De novo	No	Intermittent right congenital ptosis, strabismus, flattening in the temporal areas, mild retrognathia	NM	NM	Normal	Deep sacral dimple, scoliosis, kyphosis, recurrent right patella subluxation	NM	Attention deficit disorder	Yes	No	Normal
Cappellacci et al. (2006) [4]	M	8	12q22q24.33	De novo	No	Macrocephaly, flat occiput, long palpebral fissures, long eyelashes, protruding nasal root, anteverted nostrils, large, asymmetric, and simple ears, thin lips, high-arched palate, mild prognathism, malar hypoplasia,	NM	Dandy-Walker malformation	Normal	Short stubby hands, femoral fibrous chondrodysplasia	GI : normal	ADHD	Yes	No	NM
Ruiter et al. (2006) [7]	F	9	12q24.21q24.23	De novo	Yes	Epicanthic folds, hypertelorism, arched eyebrows, low set ears, short philtrum, open mouth appearance, full lips, irregular position of the lower teeth, broad gums and a flat palate with a normal uvula	NM	Slight cerebral atrophy (at the age of 1 year) Normal (at the age of 7 years)	NM	Positional clubfeet, clinodactyly of the fifth fingers, distal brachydactyly, short toenails	Inguinal hernia (spontaneous remission)	Aggression, hypertonia, ataxia, progressive spasticity, spastic tetraplegia	Yes	Yes	Deafness of right side, impaired hearing of left side
Plaza-Benhumea et al. (2022) [3]	F	5	12q24.21q24.33	Maternal	No	Down-turned mouth, low set ears	Short neck	NM	PDA with interventricular communication	Single Palmar creases, sacral dimple	Genital hypoplasia	Seizures	Yes	Yes	NM

F, female; M, male; IUGR, intrauterine growth retardation; GI, gastrointestinal; VSD, ventricular septal defect; PDA, patent ductus arteriosus; NM, not mentioned; ADHD, attention-deficit/hyperactivity disorder; ID, intellectual disability; ASD, atrial septal defect.

characterizations and thorough clinical descriptions. Furthermore, conducting long-term clinical follow-up studies is essential to assess the developmental trajectory of individuals with 12q duplication syndrome. These studies should focus on the overall clinical course of the affected individuals. In conclusion, advancing our knowledge of 12q duplication syndrome requires a multidisciplinary approach involving molecular cytogenetics, clinical genetics, and long-term follow-up assessments. By combining comprehensive genetic characterization with detailed clinical observations, we can strive to unravel the complexities of this rare chromosomal disorder and provide better care and support for affected individuals.

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None.

Ethics approval

This retrospective analysis was approved by the Institutional Review Board (IRB) of Keimyung University Dongsan Hospital (IRB No. 2023-01-062), which waived the requirement for obtaining informed consent from the patient.

Conflict of interest

The authors have nothing to disclose.

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