European Journal of Medical Genetics 58 (2015) 86–94

Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: http://www.elsevier.com/locate/ejmg

Clinical research

A Korean family with KBG syndrome identified by *ANKRD11* mutation, and phenotypic comparison of *ANKRD11* mutation and 16q24.3 microdeletion

Hyo Jeong Kim [a], Eunhae Cho [b], Jong Bum Park [c], Woo Young Im [d], Hyon J. Kim [e,*]

[a] Department of Pediatrics, Konyang University College of Medicine, Daejeon, Republic of Korea
[b] Green Cross Genome, Yongin, Republic of Korea
[c] Department of Rehabilitation Medicine, Konyang University College of Medicine, Daejeon, Republic of Korea
[d] Department of Psychiatry, Konyang University College of Medicine, Daejeon, Republic of Korea
[e] Department of Medical Genetics, Konyang University College of Medicine, 158 Gwanjeodongro, Seogu, Daejeon, Republic of Korea

ARTICLE INFO

Article history:
Received 3 October 2014
Accepted 9 November 2014
Available online 20 November 2014

Keywords:
ANKRD11
16q24.3
KBG syndrome
Developmental delay
Intellectual disability
Short stature
Dysmorphism

ABSTRACT

KBG syndrome is a rare disease characterized by intellectual disability, typical craniofacial dysmorphism, macrodontia of the upper central incisors, short stature, and skeletal anomalies. Recently, *ANKRD11* was identified as a gene that is responsible for the disease. In addition, microdeletion of 16q24.3, including *ANKRD11*, has been reported to result in the KBG syndrome phenotype. Herein, we discuss a Korean family with KBG syndrome, as identified by *ANKRD11* gene mutation. The patients included a nine-month-old boy and his 21-month-old sister who failed to thrive and have delayed development. Chromosomal microarray was performed to identify the underlying genetic cause, but the results showed no abnormalities. However, the mother of the children was found to have features similar to her children. Therefore, we strongly suspected an autosomal-dominant inherited disease and performed whole exome sequencing. A mutation of *ANKRD11* gene was found in all patients, and the frameshift variant c.2395-2398delAAAG was confirmed. Clinical manifestations of the patients were consistent with KBG syndrome. We reviewed all reported cases with confirmed *ANKRD11* mutation or 16q24.3 microdeletion including *ANKRD11*. As a result, we conclude that severe short stature, intellectual disability, and macrodontia are the main characteristics in KBG syndrome related to *ANKRD11* mutation.

1. Introduction

KBG syndrome (OMIM 148050), first described in 1975, is a rare genetic disease characterized by short stature, craniofacial dysmorphism, intellectual disability, macrodontia, and skeletal anomalies [Herrmann et al., 1975]. Loss-of-function mutations in *ANKRD11* was recently reported as a cause of KBG syndrome [Sirmaci et al., 2011]. In addition, microdeletions in chromosome 16q24.3, including *ANKRD11*, was also reported to present a similar phenotype to KBG syndrome [Isrie et al., 2012; Willemsen et al., 2010; Youngs et al., 2011]. In particular, 16q24.3 microdeletion syndrome was described to produce characteristics such as autism spectrum disorder, variable cognitive impairment, facial dysmorphism, and brain abnormalities [Willemsen et al., 2010]. In this study, we aimed to characterize the clinical features of the three Korean familial patients who have an *ANKRD11* mutation via whole exome sequencing and determine if clinical diagnosis of KBG syndrome was appropriate. In addition, we reviewed the previously reported cases with identified *ANKRD11* mutations or microdeletions in chromosome 16q24.3 and then compared the clinical and genetic features of the patients of each group.

2. Patients

The pedigree of the Korean family is shown in Fig. 1.
Clinical findings of the patients are summarized in Table 1.

2.1. Patient 1 (Fig. 1, III-4)

A nine-month-old boy was referred for failure to thrive and delayed development. He was born prematurely at 28 weeks gestation by emergency caesarean section due to fetal distress and

* Corresponding author. Tel.: +82 2 523 9230; fax: +82 2 581 9230.
E-mail address: raredisease@hanmail.net (H.J. Kim).

http://dx.doi.org/10.1016/j.ejmg.2014.11.003
1769-7212/

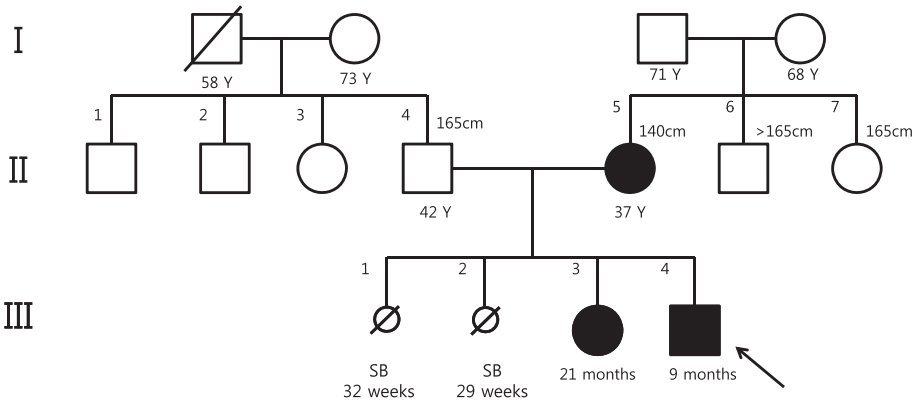

Fig. 1. Pedigree of the family. Patient 1 (III-4), Patient 2 (III-3), and Patient 3 (II-5).

breech presentation. He was the second living child of the family. His birth weight was 500 gm (<3rd percentile), length was 29 cm (<3rd percentile), and head circumference was 21 cm (<3rd percentile). He was intubated and received pulmonary surfactant because he was premature, and he was hospitalized for 4 months in a neonatal intensive care unit (NICU). The patient had complications from being premature such as bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), patent ductus arteriosus (PDA), and intraventricular hemorrhage (IVH) grade I. Before discharge, the PDA was closed and the IVH was resolved. He had no neonatal seizures, and brain magnetic resonance imaging (MRI) scan showed no abnormalities (Fig. 2).

At nine months of age, he was first evaluated at the Medical Genetics Clinic. His growth and development were severely delayed. His weight was 5.6 kg (<3rd percentile, 50th percentile for two-month-olds), height was 63 cm (<3rd percentile, 50th percentile for three-month-olds), and head circumference was 37.7 cm (<3rd percentile, 50th percentile for one-month-olds). He showed dysmorphic features such as brachycephaly, triangular face, long philtrum, tented upper lip, and high-arched palate (Fig. 2). He was hypotonic and could not control his head. However, deep tendon reflexes were preserved, echocardiography was normal, and other congenital anomalies were not found. Chromosomal microarray was done and the result was normal. At 11 months of age, his bone age was 3 months (Fig. 2). No skeletal abnormalities in the ribs, whole spine, hip, or extremities were found (Fig. 2). Electroencephalography (EEG) showed occasional non-specific slowing in both occipital lobes. The Bayley Scale of Infant Development showed that his cognition, language, and motor development were equivalent to the 3- to 4-month level.

Table 1
Clinical findings of the patients with KBG syndrome.

Clinical findings	Patient 1	Patient 2	Patient 3
Sex (M/F)	M	F	F
Age at diagnosis	11 months	23months	37 years
Short stature	+ (<3percentile)	+ (<3percentile)	+ (140 cm)
Craniofacial findings			
Brachycephaly	+	+	+
Triangular face	+	+	+
Wide eyebrows	+	+	+
Mild synophrys	+	+	+
Ptosis	+	+	+
Strabismus	–	–	+
Prominent nasal bridge	–	–	+
Anteverted nostril	+	+	–
Long philtrum	+	+	+
High arched palate	+	+	–
Tented upper lip	+	+	–
Macrodontia	NA (no teeth)	+ (deciduous teeth)	+
Prominent ears	+	+	+
Webbed neck	–	–	+
Skeletal abnormalities			
Scoliosis	–	–	+
Abnormal vertebrae	–	–	+
Clinodactyly	–	–	+
Delayed bone age	+	+	NA
Neurologic findings			
Developmental delay	+	+	
Intellectual disability			+
Seizure	–	–	–
Abnormal EEG	+	+	+
Abnormal brain MRI	–	–	Cerebellar atrophy
Others	Prematurity Inguinal hernia	Prematurity	DM Breast benign mass Spontaneous abortion

NA, not applicable; DM, diabetes mellitus.

2.2. Patient 2 (Fig. 1, III-3)

Patient 2 was Patient 1's older sister. She was 21 months old at the time of her first visit. She was born by emergency caesarean section delivery at 31 weeks gestation because of fetal distress. Her birth weight was 830 gm (<3rd percentile), length was 33 cm (<3rd percentile), and head circumference was 24.1 cm (<3rd percentile). She was treated with surfactant and had ventilator care for 2 weeks. She had ROP, subependymal hemorrhage, and PDA. The PDA was closed before discharge. Abdominal ultrasonography and brain MRI scan showed no abnormalities. She had no neonatal seizures.

At 21 months, her weight was 7.5 kg (<3rd percentile, 50th percentile for 5-month-olds), length was 74 cm (<3rd percentile, 50th percentile for 11-month-olds), and head circumference was 43 cm (<3rd percentile, 50th percentile for 6-month-olds). Furthermore, she could only walk with support, and language development was also delayed; she could only say "momma" and "papa." She also showed brachycephaly, a long triangular face, mild ptosis, long philtrum, high-arched palate, and macrodontia of deciduous teeth (Fig. 3). Chromosomal microarray was normal.

She was re-evaluated at 24 months of age. She could walk 4–5 steps without support. Speech showed no improvement, but she babbled more actively. Her bone age was 18 months (Fig. 3), but no skeletal anomalies were found, including in the ribs, whole spine,