Case report

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Diagnostic exome sequencing을 통한 KBG 증후군의 조기 진단

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Early Diagnosis of KBG Syndrome Using Diagnostic Exome Sequencing

KBG syndrome is a rare neurodevelopmental disorder characterized by intellectual disability, skeletal anomalies, short stature, craniofacial dysmorphism, and macrodontia. *ANKRD11* gene mutation and 16q24.3 microdeletion have been reported to cause KBG syndrome. Here, we report two patients with *ANKRD11* mutations who initially presented with neurologic symptoms such as developmental delay and seizures. Patient 1 was a 23-month-old boy who presented with a global developmental delay. Language delay was the most dominant feature. He had hypertelorism, hearing impairment, and behavior problems characterized as hyperactivity. A c.1903_1907delAAACA (p.Lys635GlnfsTer26) mutation in *ANKRD11* was identified with diagnostic exome sequencing. Patient 2 was a 14-month-old boy with developmental delay and seizure. He also had atrial septum defect, and ventricular septal defect. Generalized tonic seizures began at the age of 8 months. Electroencephalography showed generalized sharp and slow wave pattern. Seizures did not respond to antiepileptic drugs. A loss of function mutation c.5350_5351delTC (p.ser1784HisfsTer12) in *ANKRD11* was identified with diagnostic exome sequencing. In both cases, characteristic features of KBG syndrome such as short stature or macrodontia, were absent, and they visited the hospital due to neurological symptoms. These findings suggest that more patients with mild phenotypes of KBG syndrome are being recognized with advances in diagnostic exome sequencing genetic technologies.

Key Words: Developmental disabilities, *ANKRD11* protein, KBG syndrome

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Introduction

KBG syndrome (OMIM 148050) is a rare neurodevelopmental disorder, that typically presents with characteristic dysmorphisms[1)]. Clinical characteristics include distinctive craniofacial findings and skeletal anomalies[2)]. Previous studies have recommended diagnostic criteria of KBG syndrome focusing on these morphological abnormalities[3,4)]. A patient can be diagnosed with KBG syndrome if they meet 4 or more of the following 8 major criteria: macrodontia of the upper central incisors, characteristic facial appearance, hand anomalies, neurological involvement, delayed bone age (2 standard deviations below the mean), costovertebral anomalies, postnatal short stature, and presence of a first-degree

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relative with KBG syndrome[4]. The causative gene, *ANKRD11*, was discovered through whole-exome sequencing in 2011[5]. More diverse phenotypes are being reported in patients with *ANKRD11* gene mutations and KBG syndrome. It is estimated that KBG syndrome is under-diagnosed and that recent advances in massive parallel sequencing will increase early detection of the milder forms of KBG syndrome.

Here, we report two patients who had milder or atypical forms of KBG syndrome. Both were diagnosed with diagnostic exome sequencing when they were younger than 24 months.

Case Reports

1. Patient 1

A 23-month-old boy was referred to our hospital because of developmental delay. He was born at 38 weeks of gestation by cesarean section and his birth weight was 2,700 g (10–25th percentile). He was an only child of non-consanguineous, average intelligence Korean parents. His mother was 40 years old and his father was 38 years old at his conception.

The patient showed developmental delay from his early life. He could not control his head until he was 5 months old and he could not sit when he was 9 months old. When he visited the clinic at the age of 23 months, he could only stand with assistance, not by himself. He could not yet speak his first word at the age of 23 months.

On physical examination, his height (87 cm, 50–75th percentile) and head circumference (49 cm, 50–75th percentile) were measured to be adequate for his age. He had dysmorphic features such as a prominent forehead, prominent ears, and hypertelorism, but no macrodontia. He had no skeletal abnormalities nor hand abnormalities (Fig. 1). He had mild hearing impairment, but no other congenital anomalies.

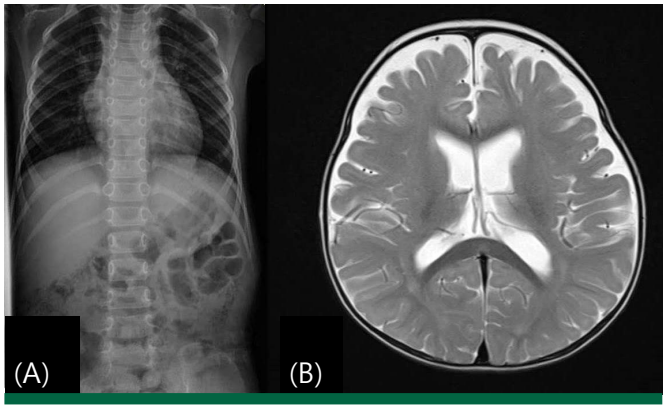

Fig. 1. X-ray and brain magnetic resonance imaging (MRI) finding for Patient 1. (A) No skeletal abnormalities of chest cavity and spine. (B) Normal T2 weighted axial MRI at 11 months of age.

Brain magnetic resonance imaging (MRI) did not reveal any abnormal findings (Fig. 1). Chromosomal microarray and multiplex ligation dependent probe amplification (MLPA) test for Miller-Dieker syndrome (17p), Prader-Willi/Angelman syndrome, DiGeorge syndrome(22q11), Williams syndrome were negative. Diagnostic exome sequencing was performed and a likely pathogenic mutation c.1903_1907delAAACA (p.Lys635GInfsTer26) causing loss of function in the *ANKRD11* gene was identified.

During his follow-up visits, he began to speak. At the age of 30 months, he spoke his first word, and at the age of 40 months, he spoke his first sentence. The Bayley Scales of Infant Development test conducted at 31 months showed his mental developmental index to be 52, and psychomotor developmental index to be below 50. At the age of 50 months, his height was 104.4 cm, 50–75th percentile.

2. Patient 2

A 14-month-old boy was referred to our hospital because of developmental delay and epilepsy. He was born at 39 weeks of gestation following a normal pregnancy and birth weight was 4,160 g (>90th percentile).

He showed global developmental delay and clinical seizures from his early life. His motor development was significantly delayed, and he could sit only with assistance. His eye contact and social smiling was also poor. On physical examination, he had dysmorphisms, such as a round head and round nose. His height was 80.5 cm (75th–90th percentile), weight was 10.3 kg (25th–50th percentile), and head circumference was 46.2 cm (25–50th percentile) at 14 months of age. He had an atrial septal defect and ventricular septal defect.

He had several seizure attacks presenting as vacant staring and head falling, beginning at 7 months of age, and his seizures are not well controlled by multiple antiepileptic drugs. Electroencephalography showed inconsistent slowing, generalized polyspikes and generalized spikes and slow waves. His brain MRI was grossly normal (Fig. 2A).

No abnormality was shown in a chromosome study and comparative genomic hybridization (CGH) array. A loss of function mutation c.5350_5351delTC (p.ser1784HisfsTer12) in *ANKRD11* was detected when we performed diagnostic exome sequencing.

During his follow up visits, at the 28 months of age, he continued to have daily seizures despite the use of sodium valproate, topiramate, vigabatrin and clobazam. His electroencephalography (EEG) began to show frontally dominant slow-

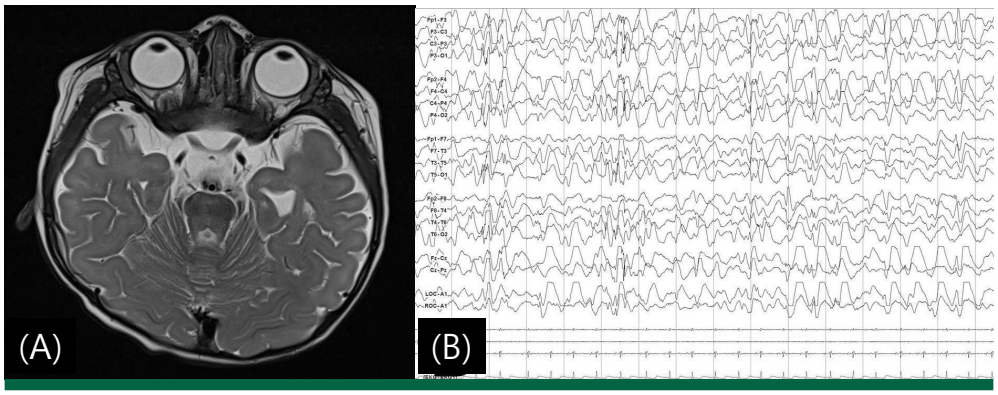

Fig. 2. Brain MRI and electroencephalography finding for Patient 2. (A) Normal T2 weighted axial MRI at 8 months of age. (B) EEG showing inconsistent slowing on both frontal areas and frequent generalized polyspikes.

spike wave discharges which were characteristics of Lennox-Gastaut syndrome (Fig. 2B). He then began to develop myoclonic-tonic-clonic seizures. However, after he developed myoclonic-tonic-clonic seizures, a high dose prednisolone of 40 mg was prescribed for 2 weeks, and he became seizure free for 1 month. His height was 94.2 cm (75–90th percentile) at the age of 28 months.

Discussion

ANKRD11 is a member of the ankyrin repeat-containing cofactors family. *ANKRD11* interacts with p160 nuclear receptor co-activators and inhibits ligand-dependent transcriptional activation of target genes by nuclear receptors[6]. We reviewed two cases of KBG syndrome confirmed by *ANKRD11* gene mutation.

KBG syndrome affects various systems such as cardiology, otolaryngology, ophthalmology, dentistry, endocrinology, and neurology. The degree of disabilities and abnormalities differ among individuals. A previous study reported a wide range of neurodevelopment levels among patients with *ANKRD11* mutations[7]. Some patients had normal intellectual function, while others were unable to live without assistance[8]. Likewise, the two patients in our cases showed different levels of delayed development. The patient with more severe delayed development had seizures and abnormal EEG findings.

According to previous reports, seizures are present in approximately 28–30% of patients with KBG syndrome, and EEG abnormalities are reported in 50–100% of patients[4,7]. However, there are few reports of seizure types or EEG findings in patients with KBG syndrome. One of our patients had seizures, and the other patient had no seizures. The patient with seizures had myoclonic-tonic seizures and electroencephalography showed inconsistent slowing, generalized polyspikes and generalized spike and slow waves. The development of this patient was more delayed, which may have been due to his seizures. This patient's seizures had not been well controlled. Despite treatment with multiple antiepileptic drugs (sodium valproate, topiramate, and clobazam), he had several episode of seizures almost daily. Based on previous studies that high dose prednisolone was helpful in seizure control in drug resistance epilepsy[9,10], we performed a high dose prednisolone trial in this patient. After taking a high dose of prednisolone for 2 weeks, he became seizure free. Further investigation is needed to confirm whether these responses are persistent in patients with *ANKRD11* mutation-positive KBG syndrome.

In our cases, characteristic abnormalities such as macrodontia or small height were absent. The main presenting symptoms were neurological symptoms, such as seizures and developmental delay. Both could not be diagnosed as KBG syndrome according to the clinical diagnostic criteria because both had mild symptoms and were lacking the major characteristics of KBG syndrome. These two patients could be molecularly diagnosed because diagnostic exome sequencing identified *ANKRD11* mutations.

We found two patients with *ANKRD11* gene mutations who manifested with neurologic symptoms. With advances in genetic technologies, more patients who harbor *ANKRD11* will be identified.

요약

KBG 증후군은 특징적인 얼굴 기형 및 발달 장애, 저 신장 등을 보이는 희귀한 질환이며, *ANKRD11*유전자의 변이가 KBG 증후군을 일으킨다고 알려져 있다. 그 임상 양상의 스펙트럼은 넓은 편이며, 발달 장애와 신경학적 이상의 경우 개인마다 다양한 정도로 보고되고 있

다. 본 증례의 환자들 역시 서로 다른 정도의 발달 장애를 보였으며, 그 중 더 심한 정도의 발달 장애를 가진 환자에서는 뇌전증이 동반되었다. 기존의 KBG증후군의 진단 기준에서 macrodontia는 매우 중요한 요소였으며, 대부분의 KBG 증후군 환자에서 나타난다고 보고되었다. 본 증례의 환자들은 발달장애를 보여 시행한 diagnostic exome sequencing을 통해 *ANKRD11* 유전자 이상을 확인하였지만 macrodontia는 관찰되지 않았다. 이는 KBG 증후군이 현재까지 밝혀진 것 보다 더 흔할 수 있으며, 특징적인 얼굴 기형이 없는 경우에도 발달장애가 있는 환자들에서는 더욱 적극적인 유전자 검사를 시행하여 KBG 증후군을 진단 할 필요가 있음을 시사한다.

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