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MECP2 duplication syndrome initially misdiagnosed as cerebral palsy: a case report

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Abstract

Mutations in the X-linked methyl-CpG-binding protein 2 (*MECP2*) gene were first described as a cause of Rett syndrome. *MECP2* duplication can cause intellectual disability, developmental delay, severe feeding difficulties, and recurrent infections. Here, we report a Korean family with *MECP2* duplication syndrome, which was previously misdiagnosed as cerebral palsy. A man in his early 30 s visited our clinic with intellectual disability, speech impairment, epilepsy, and progressive spasticity. He had been previously misdiagnosed with cerebral palsy, and had received orthopedic surgeries such as musculotendinous lengthening and derotational osteotomy. After the surgeries, he received comprehensive rehabilitation. Upon carefully checking his family history, we noted that his younger brother had similar symptoms. Next-generation sequencing revealed whole exon duplication in *MECP2* in both the patient and his brother; their mother also had this genetic mutation but was asymptomatic. Early diagnosis is essential for improving the success of *MECP2* duplication syndrome treatment. Individuals with *MECP2* duplication syndrome should be referred to specialists to manage multidisciplinary symptoms and to regularly check for complications that are common in this syndrome.

Keywords

MECP2 duplication syndrome, next-generation sequencing, neurodevelopmental disorder, Rett syndrome, cerebral palsy, differential diagnosis

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Introduction

Cerebral palsy (CP) is a disorder that affects muscle tone, posture, balance, movement, and daily activities; it is caused by damage to the immature and developing brain.[1] As a clinically heterogeneous disorder, CP is often associated with epilepsy, intellectual disability, motor impairment, visual and hearing impairments, and musculoskeletal problems.[2] However, primarily as a result of advancements in metabolic and genetic research, a growing group of metabolic and genetic disorders have been diagnosed in patients presenting symptoms and signs similar to those of CP.[2] For example, a systematic review has identified at least 54 treatable inborn errors of metabolism that are reported to mimic CP.[3] Furthermore, whole-exome sequencing has revealed genetic mutations and potentially disease-causing candidate gene variants in patients with CP.[4,5] Importantly, some neurometabolic disorders have disease-specific treatments that can markedly improve symptoms and developmental outcomes. A genetic diagnosis can also improve the quality of life of patients' families, regardless of treatment options, and genetic counseling can help to prevent or inform the possibility of disease occurrence in future siblings. Thus, given the potential for a treatable metabolic or genetic etiology, along with a more accurate diagnosis and genetic counseling, it is important to be very attentive when determining etiology in patients with symptoms resembling those of CP.

Here, we report the first case of Korean siblings with methyl-CpG-binding protein 2 (*MECP2*) duplication syndrome, which was initially misdiagnosed as CP. The siblings inherited the duplicated gene from their asymptomatic mother. Their clinical features and genetic characteristics are presented in this report.

Case report

The patient, a man in his early 30 s, was born at 40 weeks of gestation weighing 3.3 kg, with no perinatal history. From early childhood, he showed signs of delayed development, speech impairment, intellectual disability, and equinus gait pattern; he was initially diagnosed with CP. He started sitting independently at 1 year of age and walked independently at 3 years of age. Equinus gait pattern began at 7 years of age and the spasticity of both lower extremities began to develop around 12 years of age. Until his late 20 s, he was able to walk alone. However, with worsening spasticity and weakness of both lower extremities, it became impossible for him to walk independently (Table 1).

Table 1. Clinical features of subjects with *MECP2* duplication.

Characteristics	Patient	Patient's brother	Patient's mother
MECP2 mutation (whole exon duplication)	+	+	+
Intellectual disability	+	+	−
Developmental motor delay	+	+	−
Developmental speech delay	+	+	−
Autistic features	+	+	−
Progressive spasticity	+	+	−
Seizures	+	+	−
Recurrent infection	−	+	−
Dysphagia	−	+	−

MECP2, methyl-CpG-binding protein 2.

Convulsions occurred at around 3 years of age and he started taking anticonvulsant medications. Electroencephalogram showed generalized fast polyspike wave pattern. However, because the frequency of seizures increased to five to six times a day, a vagus nerve stimulation device was implanted at 30 years of age.

The patient received orthopedic surgeries, including bilateral heel cord and hamstring lengthening, at 18 years of age. Two years later, he also underwent bilateral femur extension, supramalleolar derotational osteotomy, and internal fixation. After the surgery, he received comprehensive rehabilitation including physical, occupational, speech, and cognitive therapies.

On manual muscle testing, both upper extremities had grade 4 and lower extremities had grade 3. Hyperactive patellar tendon reflexes and ankle jerks were noted on both sides. Bilateral Babinski signs and ankle clonus were also present. The patient was able to stand unaided for approximately 10 to 15 s and indoor ambulation was possible. He was also able to perform simple self-care activities, bathing, feeding, and dressing under repetitive cues, but he was often unable to continue such tasks because of cognitive impairment. The patient was able to handle a spoon when feeding, but often needed help. On the modified Ashworth scale, his upper extremities scored G1 and his lower extremities scored G2. On the Functional Independence Measure, he scored 49. On the Korean Wechsler Adult Intelligence Scale-IV, his intelligence quotient was below 45. In brain magnetic resonance imaging, a focal volume decrease in the splenium of the corpus callosum and several nonspecific T2 hyperintense lesions in the white matter were noted (Figure 1).

Family history revealed that his younger brother was born at 40 weeks of gestation with a birth weight of 2.8 kg and neonatal

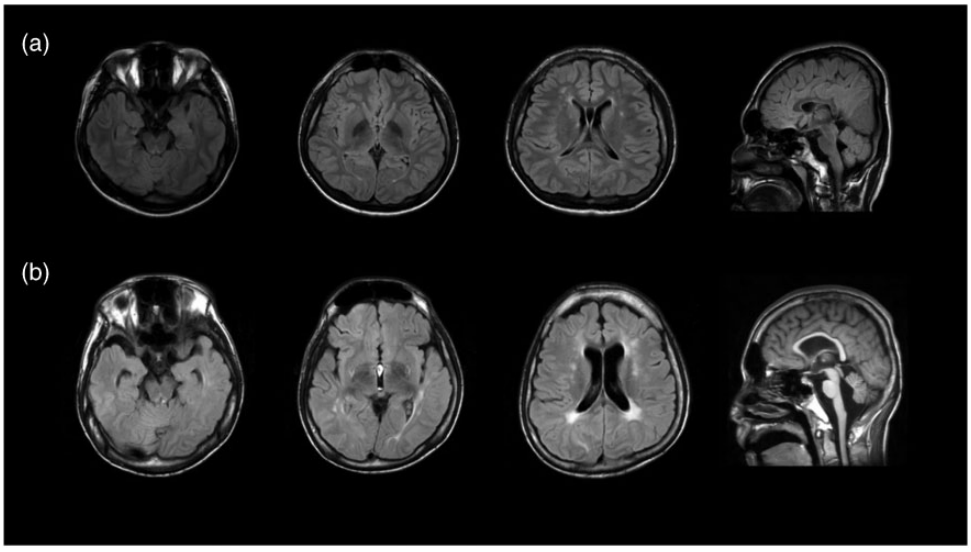

Figure 1. Brain MRI findings of the siblings. (a) MRI of the patient showing a focal volume decrease in the splenium of the corpus callosum as well as several non-specific T2 hyperintense lesions in the white matter and (b) MRI of the patient's brother showing multiple T2 hyperintensities in the periventricular and deep white matter.
MRI, magnetic resonance image.

jaundice. This brother also exhibited severe developmental delay and was initially diagnosed with CP. He developed normally until 1 year of age, but his functional level worsened thereafter. He began walking with two-hand support at 5 years of age and started to walk with ankle-foot orthosis at 8 years of age. At 19 years of age, he was unable to sit alone and began to use a wheelchair, with functional decline. He was unable to walk or speak any meaningful words and had intellectual disability. He also had recurrent respiratory tract infections and was hospitalized several times with severe pneumonia (Table 1).

The brother was diagnosed with status epilepticus and started to take antiepileptic drugs at 1 year of age. Electroencephalogram showed bilateral bursts or continuous discharges of sharp and/or slow waves of 2 to 4 Hz. Despite continuous changes in the type and dose of anticonvulsants, seizures were not controlled and a vagus nerve stimulation device was implanted.

Similar to the original patient, the brother also received orthopedic surgeries such as bilateral peroneus brevis lengthening, calcaneus lengthening osteotomy, bone allograft, and percutaneous pinning at 19 years of age because of an abnormal gait pattern and leg length discrepancy. After the surgery, he received comprehensive rehabilitation, such as physical and occupational therapies.

Because of severe intellectual disability, the brother required maximal assistance to perform simple tasks of personal hygiene, bathing, feeding, and dressing. On the modified Ashworth scale, his upper extremities scored G1 and his lower extremities scored G2. On the Korean Wechsler Adult Intelligence Scale-IV, his intelligence quotient was below 25. At 21 years of age, tracheostomy was performed because of uncontrolled seizures, desaturation, and tachypnea. One year later, percutaneous endoscopic gastrostomy was performed to treat dysphagia and poor oral intake. Even after the procedures, the brother was unable to sit or stand independently and was completely dependent in all daily activities. He died at 24 years of age of sudden cardiac arrest.

We conducted next-generation sequencing (NGS) to identify the cause of epilepsy and delayed development in the brothers. In both the patient and his brother, NGS of 172 genes was performed and massive parallel sequencing was conducted using the MiSeq System (Illumina, San Diego, CA, USA). Quality control, sequence analysis, and copy number analysis were performed using our custom analysis pipeline. GRCh37 (hg19) was used as the reference sequence for mapping and variant calling. The following databases were used for analysis and variant annotation: Online Mendelian Inheritance in Man (OMIM), Human Gene Mutation Database, ClinVar, Single Nucleotide Polymorphism Database, 1000 Genomes Project, Exome Aggregation Consortium, Exome Sequencing Project, and Korean Reference Genome Database. For variant classification, the standards and guidelines established by the American College of Medical Genetics were followed. The NGS results revealed whole exon duplication in *MECP2* (OMIM 300005), leading to *MECP2* duplication syndrome (OMIM 300260), in both brothers. The breakpoint of the duplication position was located between 153297646 and 153298018 bp (Figure 2). When genetic testing was performed on the asymptomatic mother, the same genetic mutation as that of the brothers was confirmed (Figure 3).

All patient details have been de-identified so that the identity of the patient and his family may not be ascertained in any way. The patient and his parents provided verbal informed consent. The reporting of this study conforms to CARE guidelines (for CAse REports).[6] Because the study reports findings from the general medical treatment of the family, no further ethical approval was required.

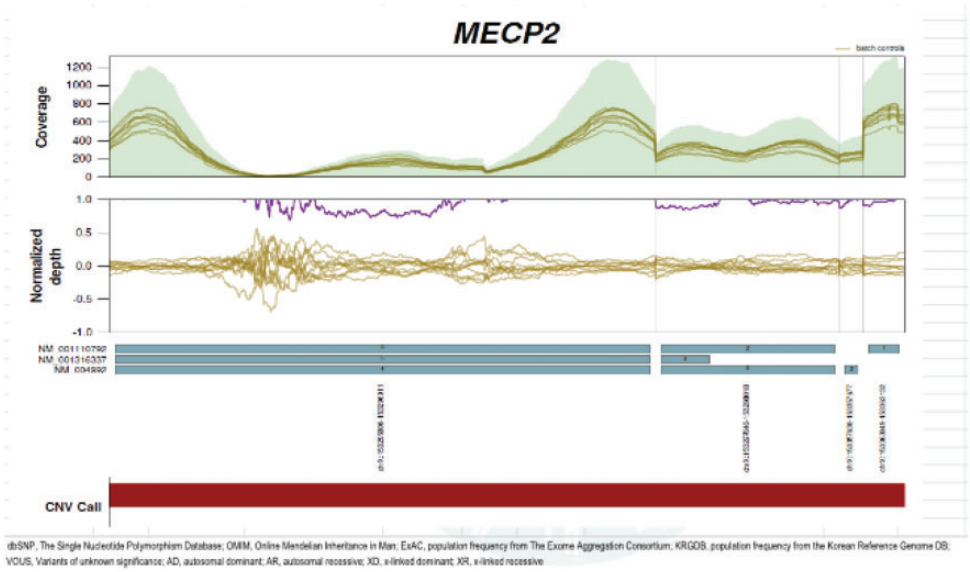

Figure 2. Results of the *MECP2* mutation in the patient. NGS of 172 genes was performed, revealing a whole exon duplication in *MECP2*.
NGS, next-generation sequencing; *MECP2*, methyl-CpG-binding protein 2.

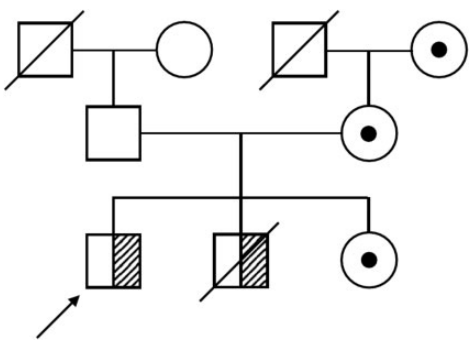

Figure 3. Pedigree structure of the patient's family. Genetic testing indicated that the patient, his brother, and his asymptomatic mother had the same *MECP2* duplication. The patient remains alive; his brother died of cardiac arrest at the age of 24. The patient is undergoing rehabilitation treatment in our hospitals.
MECP2, methyl-CpG-binding protein 2.

Discussion

Mutations in *MECP2* were first described as a cause of Rett syndrome, which is a neurodevelopmental disorder that is characterized by a period of normal psychomotor development during the first 6 months of life. By the age of 3 to 4 years, neurodevelopmental regression occurs—including the loss of previously acquired skills, purposeful use of hands, speech, and gait pattern—and autistic behavior develops.[7,8]

The *MECP2* gene is located on chromosome X (Xq28) and acts as a regulator of transcription.[7] The MECP2 protein has functions in synaptic transmission and neuronal maturation. In the mature brain, MECP2 binds to methylated cytosine in the non-CG context with high affinity, thus influencing the level of brain-derived neurotrophic factor, which is also linked to the pathophysiology of Rett syndrome.[8] There is an important correlation between the number of *MECP2* copies and clinical severity; triplication of the *MECP2* region results in a more serious phenotype.[9] Furthermore, duplications involving *MECP2*—and the corresponding increase in MECP2 protein expression—can cause

intellectual disability, developmental delay, feeding difficulties, epilepsy, and recurrent infections. In affected male patients, *MECP2* duplication syndrome, caused by a gain-of-function mutation of *MECP2*, has 100% penetrance.

There are few epidemiological studies on *MECP2* duplication syndrome; an Australian study estimated the birth prevalence to be 1/150,000 live births.[10] Because *MECP2* duplication syndrome is a rare disease, it is likely to be confused with CP. However, *MECP2* duplication syndrome should be included in the differential diagnosis when an infant boy presents with developmental delay, intellectual disability, speech and cognitive impairments, progressive spasticity in the lower limbs, and recurrent infections.[11] Its accurate diagnosis is important because many therapies are currently under development. For example, antisense oligonucleotides are being developed that pharmacologically target neurotrophic pathways or influence MECP2 protein stability; deep brain stimulation is another potential therapy.[12] Regardless of treatment methods, early diagnosis is essential to improve treatment of *MECP2* duplication syndrome.

The importance of NGS in the early identification of genetic causes of neurological and neurodevelopmental disorders in children has been previously emphasized.[13] For example, NGS-based approaches have led to the identification of new causal and estimated genes of epilepsy, enabling us to better understand its underlying pathophysiological mechanisms.[13,14] The development of NGS-based techniques have also provided important advances in the diagnosis and optimization of clinical management in people with epilepsy.[14] In the differential diagnosis of *MECP2*-related disorders, we should also consider neurodevelopmental conditions mimicking CP, such as *MFSD2A*-related disorder,[15] and complex epileptic encephalopathies, such as *EEF1A2*-related disorder.[16]

Here, we have reported the first case of Korean siblings with *MECP2* duplication syndrome. They inherited the duplicated gene from their asymptomatic mother and were initially misdiagnosed with CP. Clinical features as a result of *MECP2* mutations in male patients include intellectual disability, developmental motor delay, developmental speech delay, autistic features, progressive spasticity, seizures with or without recurrent infection, and dysphagia (Table 1). Individuals with *MECP2* duplication syndrome should be referred to specialists in neurology, physical and rehabilitation medicine, psychology, gastroenterology, immunology, ophthalmology, and genetics, both to manage multidisciplinary symptoms and to regularly monitor the development of syndrome-associated complications. Patients should receive physical, occupational, speech, and behavioral therapies to maximize function and minimize the risk of regression.

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Author contributions

S-JL and K-MK contributed to data acquisition and collection. T-YK, S-JL, and S-RC designed the study, performed data interpretation, and wrote and finally approved the manuscript.

Data Availability statement

The results, table, and figures of this case report are available from the authors, on request.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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