Diagnostic exome sequencing identifies a heterozygous MBD5 frameshift mutation in a family with intellectual disability and epilepsy

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ABSTRACT

Methyl-CpG-binding domain 5 (MBD5)-associated neurodevelopmental disorder caused by 2q23.1 or MBD5-specific mutation has been recently identified as a genetic disorder associated with autism spectrum disorders. Phenotypic features of 2q23.1 deletion or disruption of MBD5 gene include severe intellectual disability, seizure, significant speech impairment, sleep disturbance, and autistic-like behavioural problems. Here we report a 7-year-old girl with intellectual disability and epilepsy without previous clinical diagnosis. Diagnostic exome sequencing identified a novel frameshift mutation c.254_255delGA (p.Arg85Asnfs*6) in the MBD5 gene of the proband and her father. The proband’s father with normal intelligence showed subclinical manifestations observed in subsequent investigations. Clinical manifestations, disease course, and molecular findings of the involvement of MBD5 gene in this family suggest an unusual MBD5-related neurodevelopmental disorder. Moreover, this report demonstrates the critical role of next-generation sequencing technique in characterizing such a rare disorder with variable or no clinical manifestation and providing opportunity to develop effective preventive measures such as pre-implantation genetic diagnosis.

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1. Introduction

Methyl-CpG-binding domain 5 (MBD5) associated neurodevelopmental disorder (MAND) includes deletion, duplication, and mutation of MBD5 (MIM: 156200). This neurodevelopmental disorder has been recently identified as a genetic disorder associated with autism spectrum disorders (Mullegama and Elsea, 2016). MAND is caused by deletion in the chromosomal region 2q23.1 or gene specific deletions in MBD5 (MIM: 611472). MBD5 has two known isoforms (Laget et al., 2010) thought to have a role in epigenetic modification (Cukier et al., 2012; Ladha, 2012). In addition, it has been shown that MBD5/Mbd5 can regulate gene expression, suggesting that it might act as a transcription factor (Mullegama et al., 2015b). Phenotypic features of 2q23.1 deletion or disruption of the MBD5 gene include severe intellectual disability, seizure, significant speech impairment, sleep disturbance, and autistic-like behavioural problem (Chung et al., 2011; Mullegama et al., 2015a; Noh and Graham, 2012).

Clinical features of MBD5 haploinsufficiency are apparent in all individuals with de novo inactivation of one MBD5 allele. However, both phenotypic heterogeneity and variable expressivity have been observed. Typically, deletion of 2q23.1 (up to 90%) is de novo. In some instances, an MBD5 pathogenic deletion (up to 5%) or MBD5 sequence variant (up to 5%) is inherited from a parent who is mildly affected. In some instances, probands have inherited the variant (small MBD5 deletion, duplication, or missense variant) from a mildly affected parent in an autosomal dominant manner, suggesting that incomplete penetrance and/or variable expression...
might be associated with this condition (Hodge et al., 2014; Mullegama and Elsea, 2016; Mullegama et al., 2014).

In this report, we describe a Korean case of familial MAND involving a father and his daughter with intellectual disability (ID) and epilepsy. They both have a novel intragenic frameshift mutation in MBD5.

2. Clinical report

2.1. The proband

The proband (Fig. 1A, individual III-1) is the only child of non-consanguineous parents. The pregnancy was uneventful. Vaginal delivery was induced at 38 weeks of gestation. Birth weight was 3200 g. In infancy, parents reported feeding difficulty with trouble swallowing. She had poor head control. She could not hold objects either. Early development was characterized by a delay in achieving gross motor, fine motor, social-cognitive, and language milestones. She first rolled at 6 months and sat independently at 12 months. She crawled at 18 months, stood at 20 months, and walked with a walker at 25 months. She was able to walk independently at 34 months. She spoke only single words until after age of 4. She was able to use a few words at 8 years of age.

At 13 months of age, she started to have complex febrile seizures. She experienced an unprovoked generalized tonic-clonic seizure at age of 3.5 years which turned out to be intractable epilepsy. Treatment with valproic acid was initiated. Up to date, she has been taking multiple AEDs, including topiramate, valproic acid, levetiracetam, and phenobarbital. Under medication, her epilepsy has been well controlled, with generally two seizures a year. Brain magnetic resonance imaging (MRI) and MR spectroscopy showed normal myelination pattern without any obvious abnormality. Electroencephalography revealed generalized polyspike and waves. Her visual and auditory evoked potentials were normal. Results of metabolic laboratory studies were all within normal limits, including plasma amino acids, urine organic acids, thyroid function tests, lactate/pyruvate, blood gases, urine oligosaccharides and mucopolysaccharides, and carnitine profile. Echocardiogram and abdominal sonogram revealed no structural abnormality.

She gradually developed problematic behaviour, including attention deficit and hyperactivity. At 5 years of age, she became aggressive. She would hit her parents and throw objects. She displayed repetitive behaviours, including tooth grinding, chewing objects, hand flapping, and autistic behaviour. She was hyperactive. Her social communication was very limited. She showed self-stimulatory behaviour. Bed wetting was present up to the day of presentation. Her coordination was poor. She could not tolerate changes in her routine. She needed assistance with feeding, dressing, and carrying out activities required for personal hygiene. Her gait was slightly wide-based. She did not require the use of other aids for ambulation. Her ears, hands, and feet were normal in shape and size. Muscle tone, muscle bulk, and deep tendon reflexes were normal. An assessment at 7 years of age confirmed a diagnosis of autism spectrum disorder. She has been taking risperidone. Her intellectual quotient (IQ) was estimated at 48, indicating severe ID. Her weight, head circumference, and height were all within normal ranges (50th percentile) at age 7. She had a dysmorphic face, including a broad forehead, open mouth, widely spaced teeth, hypertelorism (inner intercanthal distance, 41 mm; interpupillary distance, 67 mm; both > 2SD), downturned corners of the mouth, broad nasal root, and deep nasal bridge (Fig. 1B). She had mild scoliosis, kyphosis, and pes valgus in radiologic findings (Fig. 2).

Fig. 1. (A) Pedigree analysis of a Korean familial MAND with a novel intragenic frameshift mutation in MBD5. Proband (indicated by arrow) and affected family members revealed the same mutation in heterozygous state. The gray symbol indicates clinically-affected individuals without DNA studies. The black symbol indicates clinically affected individuals with MBD5 mutation. (B) Clinical photography of the proband and her father. The proband had a round face, broad forehead, open mouth, hypertelorism, and slightly upturned nose with a broad tip. Her father showed a normal face without facial dysmorphism. (C) Heterozygous frameshift mutation of the MBD5 gene confirmed by Sanger sequencing. The proband and her father carried a novel frameshift mutation c.254_255delGA (p.Arg85Asnfs*6).
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