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CASE REPORTS IN DIVERSE POPULATIONS

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MBD5-related intellectual disability in a Vietnamese child

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Abstract

The disruption of *methyl-binding domain protein 5* (*MBD5*) gene has been determined as a significant cause of a group of disorders known as MBD5-associated neurodevelopmental disorder. Here, we report a novel pathogenic mutation, NM_001378120.1 (MBD5): c.217-1G>C, occurring at the acceptor splicing site of intron 6 of the *MBD5* gene identified in a Vietnamese child with intellectual disability, autistic-like behaviors, and seizure. Phenotypic manifestations in this patient are highlighted with neurodevelopmental impairments whereas his facial dysmorphism is unremarkable. Our finding has enriched the understanding of the spectrum of *MBD5* variants, a critical database for diagnosis, genetic counseling, and management of the patients with neurological diseases.

KEYWORDS
c.217-1G>C, intellectual disability, *MBD5* gene, seizure, splicing site mutation

1 | INTRODUCTION

Neurodevelopmental delay is a severe health condition which mainly impairs the cognition, behavior, and social communication of the affected individuals. Recently, *Methyl-CpG-binding domain protein 5 (MBD5)* gene (OMIM: 611472) has been determined as a critical gene responsible for a group of neurodevelopmental disorders known as *MBD5*-associated neurodevelopmental disorder (MAND). The disruption of *MBD5* gene function has been reported to cause intellectual disabilty, autistic-like behaviors, epilepsy, and other facial dysmorphic features (Mullegama & Elsea, 2016; Verhoeven et al., 2019).

MBD5 gene, a member of *MBD* family genes, locates at 2q23.1 region. This gene covers 495,961 bp in length, contains 15 exons including five noncoding exons (exon 1–exon 5) followed by 10 coding exons (exon 6–exon 15; Laget et al., 2010). There are growing evidences which suggest that *MBD5* gene may play a pivotal role in cerebral function as it is mainly expressed in the brain as well as in epigenetic reprogramming after fertilization (Bonnet et al., 2013; Laget et al., 2010). Therefore, the malfunction of this gene may cause neurological diseases. Up to date, more than 40 different variants of *MBD5* gene have been identified as pathogenic or likely pathogenic to patients with neurodevelopmental delay (ClinVar database). Here for the first time, we report a novel mutation of the *MBD5* gene as a pathogenic factor which is identified in a Vietnamese male child with intellectual disability, seizure, and autistic-like behaviors.

2 | CASE REPORT

The patient is an 8-year-old son of a healthy non-consanguineous couple. He was born full-term via vaginal delivery without complications from her mother's second gravida. His birth weight was 3,300 g and neonatal adaptation was normal. According to his mother, he developed normally during his first year. However, later he was unable to achieve the key developmental milestones including motor skill delay by until 19 months of age and speech delay by until 24 months of age. Simultaneously, he first experienced an episode of seizure at 19 months of age which was recurrent at uncountable times during the following years. He was diagnosed developmental delay and recurrent nonfebrile seizures. He was indicated anti-epilepsy treatment and kept monitored every 3 months. Neuropsychiatric examination revealed autistic-like behaviors and short attention span. He has been attached to physical therapy and special intervention therapy till now.

At the latest visit, clinical examination showed that his physical growth was in normal range as his height (131 cm) and weight (33 kg) were between the 50th and 85th percentile and between the 85th and 97th percentile, respectively. His facial features were not specific

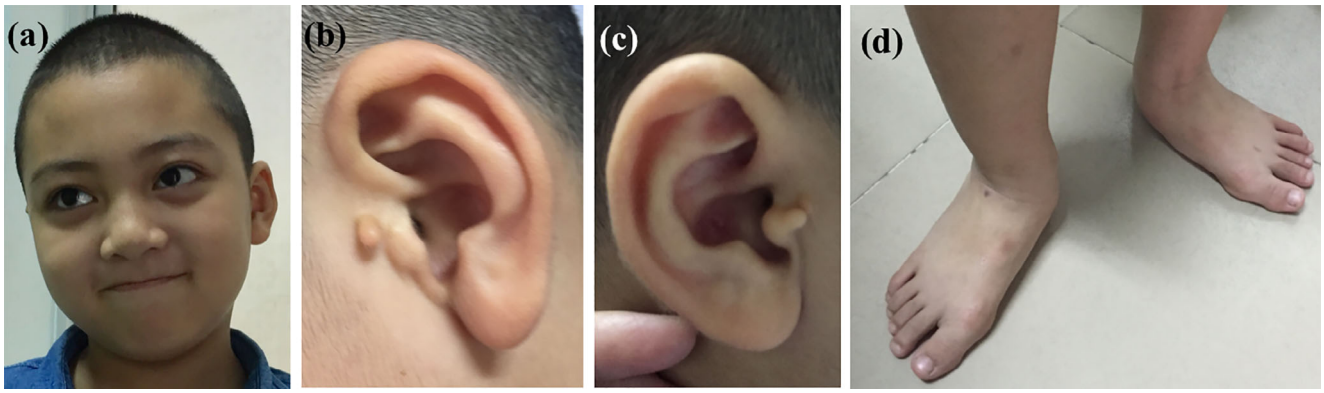

FIGURE 1 Clinical presentation of the patient. All photos and clinical information were obtained written consent for publication. (a) The patient presented broad forehead, prominent nasal bridge; (b) and (c) Pre-auricular skin tags on both ears; (d) Flat feet [Color figure can be viewed at wileyonlinelibrary.com]

with broad forehead, prominent nasal bridge (Figure 1a) and pre-auricular skin tags on both ears (Figure 1b,c). Examination of patellar tendon and triceps reflexes revealed decreased. He walked in a wide-based gait with flat feet (Figure 1d). Currently, he is wearing orthotic shoes. Seizure has been absent for more than 1 year. He also presents severe intellectual disability with the IQ score of 57 (Universal Non-verbal Intelligence Test). No other symptoms were observed. Familial medical history reported no specific findings regarding to genetic conditions or neuropathological disorders. He has one elder healthy sister.

Written informed consent was obtained from the parents of the patient in accordance with the Institutional Review Board of Hue University of Medicine and Pharmacy. By next-generation sequencing (NextSeq, Illumina, San Diego, CA) and subsequent Sanger sequencing using our own-designed primers (Table S1), a novel mutation of the *MBD5* gene was detected, NM_001378120.1(MBD5): c.217-1G>C. This novel mutation was already submitted to ClinVar database (SCV001372471.1).

3 | DISCUSSION

The clinical manifestations of this patient are in line with those frequently observed in MAND including severe intellectual disability, seizure, autistic symptoms, and motor delay (Bonnet et al., 2013; Mullegama & Elsea, 2016 ; Talkowski et al., 2011). His physical features were unremarkable with broad forehead, prominent nasal bridge and pre-auricular skin tags on both ears. He also presented hand/foot abnormality with wide-based walking gait and flat feet. These symptoms were also reported in the literature, yet less common (Mullegama & Elsea, 2016; Talkowski et al., 2011). However, he did not experience dementia which is common presented in patients with 2q31.1 deletion encompassing complete or partial *MBD5* gene (Mullegama & Elsea, 2016; Talkowski et al., 2011). Bonnet et al. presented five cases with neurodevelopment disorders due to *MBD5* functional disruption. Noticeably, none of them was found with sleep disturbance (Bonnet et al., 2013). Moreover, the patient in this report responded well to anti-epilepsy therapy and no recurrence was observed during the last 1 year whereas there was a few cases reported with treatment-resistant epilepsy (Verhoeven et al., 2019).

By next generation sequencing, we identified a novel heterozygous c.217-1G>C mutation of *MBD5* gene, resulting to the disruption of the acceptor splice site at the boundary intron 6– exon 7 (Figure S1a). The mutation was further confirmed by Sanger sequencing (Figure S1b). In silico tools were applied for prediction of consequence of that mutation on its splice site. Both MutationTaster and MaxEntScan predict the aberrant RNA splicing which likely results in an absent or disrupted protein product.

Since the first discovery by Talkowski et al unveiling *MBD5* gene as the critical region causing abnormal phenotype in patients with 2q23.1 deletions (Talkowski et al., 2011), *MBD5* has become a target gene in searching for the genetic cause in patients with neurodevelopment impairments and autistic spectrum disorders. Recently, there are more than 40 pathogenic and likely pathogenic variants in this gene published in dbSNP and ClinVar databases. However, no report was found regarding c.217-1G>C mutation of the *MBD5* gene. Interestingly, most of known variants of *MBD5* gene are missense followed by nonsense or frameshift mutations whereas our novel mutation occurring on the acceptor splice site of intron 6 which is among few splice site mutations reported (Bonnet et al., 2013; Mullegama & Elsea, 2016). A brief summary of these pathogenic mutants were presented in Table S2.

In conclusion, we identified a novel *MBD5* gene mutation (NM_001378120.1: c.217-1G>C) in a patient with intellectual disability, autistic-like behaviors, and seizure. The abnormal genetic finding in combination with abnormal phenotype suggesting this variant as a pathogenic mutation. Our finding has enriched the understanding of the spectrum of *MBD5* variants which might be a critical database for diagnosis, genetic counseling and management of the patients with neurodevelopmental disorders.

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CONFLICT OF INTEREST

The author declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Thanh Nha Uyen Le and Thi Minh Thi Ha performed Universal Nonverbal Intelligence Test, clinical evaluation, collected medical history details, and wrote the draft. Thanh Nha Uyen Le designed primers for Sanger sequencing. Thi Minh Thi Ha evaluated the Next-Generation sequencing and Sanger sequencing data, revised the draft, and supervised the study. All authors read and approved the final version of the article.

DATA AVAILABILITY STATEMENT

This novel mutation was already submitted to ClinVar database (SCV001372471.1) https://www.ncbi.nlm.nih.gov/clinvar/variation/973733/.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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