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# Severe neurodevelopmental disorder caused by an *MEF2C* nonsense mutation

**nonsense mutation**

Short title: Neurodevelopmental disorder due to MCHS

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Myocyte-specific enhancer factor 2C (MEF2C) is a transcriptional factor that has critical roles in the neurogenesis and synaptogenesis of early neuroprogenitors.[1,2] Haploinsufficiency of *MEF2C* (5q14.3) causes intellectual disability (ID), global developmental delay, epilepsy, and absence of speech without distinctive facial features (MIM#613443).[3] Some patients have cerebral manifestations, including enlarged ventricles, white matter abnormalities, and corpus callosum deficiencies identified by magnetic resonance imaging. This disorder is called *MEF2C* haploinsufficiency syndrome (MCHS), which may occur due to a whole-gene deletion of *MEF2C*, including a chromosome 5q14.3 deletion or an autosomal dominant intragenic pathogenic mutation; however, MCHS due to a point mutation is very rare.

A two-year-old girl was referred to our department for severe developmental delay. Her gestational age was 38 weeks and 5 days; body weight, 2.35 kg (-1.47 standard deviations [SD]); height, 46.5 cm (-1.08 SD); and head circumference, 32.5 cm (-0.49 SD). She was the firstborn child, had no significant family history, and her parents were healthy and non-consanguineous. Strabismus was observed at 4 months of age. She did not have any abnormal facial features. At 2 years of age, she was hypotonic, and could not sit alone or walk by herself. She had no cardiac disease. At 5 years of age, her height was 102.5 cm (-1.90 SD); body weight, 13.32 kg (-3.03 SD);

and head circumstance, 48.5 cm. She has had five episodes of febrile seizures since when she was 1 year of age. She had non-febrile right-sided facial twitching at 5 years of age, and her electroencephalogram showed polyspikes and waves in the frontal to parietal lobe (Fig.1a). Her brain was normal at 4 years of age as determined by magnetic resonance imaging. She was diagnosed with focal epilepsy, and levetiracetam was initiated at 5 years of age; however, she still could not stand alone or speak significant words. There was no dysmorphic feature and abnormal involuntary movements. Stereotyped movement was not observed. Her karyotype was 46,XX, and array comparative genomic hybridization did not show any abnormalities.

Comprehensive genetic analysis using next-generation sequencing (NGS) was performed to confirm the molecular diagnosis. Written informed consent was obtained from her parents. All procedures were approved by the Institutional Review Boards (IRB) of Kobe University School of Medicine (IRB approval #86) and Hyogo Prefectural Kobe Children's Hospital (IRB approval #28-2). The study was performed in accordance with the Declaration of Helsinki. NGS was performed with the TruSight One sequencing panel (Illumina, San Diego, CA, USA). We identified an heterozygous nonsense variant in *MEF2C* (NM_001193350.1: c.7A>T, p.Arg3Ter; Fig. 1b), which was not present in her parents. This variant was not reported in various databases;

72 therefore, we considered *MEF2C* as the causative gene.

73 The MEF2 family is essential for neuronal development, including synaptic
74 connections. The expression of MEF2C is dominant in the brain cortex in mice.[4] Here,
75 the patient showed severe developmental delay, and the mutation was located in the
76 MADS domain of *MEF2C* (exon 1). Recently, five patients with a point mutation in
77 *MEF2C* have been reported. Patients with a mutation near the N-terminus of MEF2C
78 might have more severe ID than those with a mutation more downstream.[2] Although all
79 previously reported patients had severe ID, two patients with downstream nonsense
80 mutations did not show any electroencephalogram abnormalities and could walk
81 independently, unlike other patients. However, generally the nonsense variants will
82 induce nonsense-mediated mRNA decay, but the precise genotype-phenotype
83 correlation is still unclear in patients with MCHS.

84 The primary treatment for MCHS is supportive care. Most patients with MCHS
85 develop febrile and non-febrile seizures; therefore, medical practitioners need to be
86 aware of the onset of epilepsy. Furthermore, these patients may have congenital heart
87 disorders, such as double outlet right ventricle, ventricular septal defect, and dilated
88 cardiomyopathy.[2] Because dilated cardiomyopathy may develop after childhood, long-
89 term follow-up of neurological and cardiac symptoms is necessary. Unfortunately, there

are currently no treatments for MCHS. Nitrosynapsin, an N-methyl-D-aspartate-type glutamate receptor antagonist, has been reported to be effective in murine models of MCHS and may be useful for patients in the future.[5] Our patient had non-syndromic ID diagnosed by NGS; therefore, we believe that accurate genetic diagnosis is useful for patients with non-syndromic ID including MCHS.

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**Disclosures**

No conflict of interest.

**Author contributions**

N.M. designed the study, wrote the manuscript, and performed the genetic analysis and genetic counseling for the family. Y.I., S.T., and A.M. evaluated the patient and collected and interpreted the data. K.I. reviewed the manuscript, discussed the results, and gave final approval. All authors have read and approved the final manuscript.

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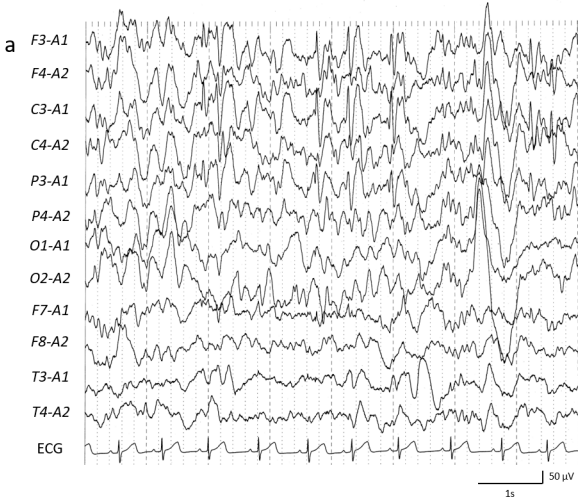
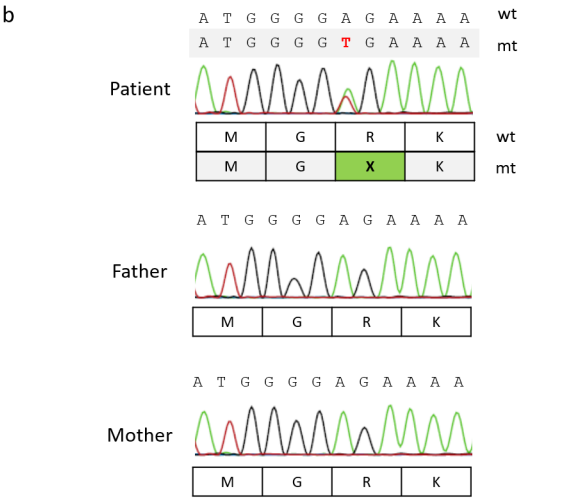
**Figure Legend**

Fig. 1 (a) Electroencephalogram of the 5-year-old patient showing polyspikes in the left frontal to parietal regions. (b) Sanger sequencing of *MEF2C* for the patient and her parents. Abbreviations: mt, mutant; wt, wild type.


a
F3-A1
F4-A2
C3-A1
C4-A2
P3-A1
P4-A2
O1-A1
O2-A2
F7-A1
F8-A2
T3-A1
T4-A2
ECG
50 µV
1s


b
A T G G G G A G A A A A
wt
A T G G G G T G A A A A
mt
Patient
M G R K
wt
M G X K
mt
A T G G G G A G A A A A
Father
M G R K
A T G G G G A G A A A A
Mother
M G R K