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Case Report

De novo HDAC8 mutation causes Rett-related disorder with distinctive facial features and multiple congenital anomalies

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Abstract

We present a unique 11-year-old girl showing clinical features of Rett-related disorder with distinctive facial features and multiple congenital anomalies including ocular hypertelorism, arched eyebrows, a broad nose, dental anomalies, congenital heart disease, truncal obesity, and epilepsy. A novel *de novo* mutation in histone deacetylase 8 (*HDAC8*) (c.652G > T, p.Gly218Cys) was confirmed by whole exome sequencing and Sanger sequencing. X-chromosome inactivation analysis on DNA isolated from peripheral blood lymphocytes revealed a completely skewed pattern associated with an inactive maternal allele. Late clinical loss of acquired purposeful hand movements and psychomotor deterioration may be a feature of Rett-related disorder, while distinctive facial features and multiple congenital anomalies are reminiscent of Cornelia de Lange syndrome.

Keywords: Rett-related disorder; HDAC8; *De novo*; Missense mutation; Skewed X-inactivation; Cornelia de Lange syndrome

1. Introduction

Rett syndrome [RTT (MIM #312750)] is a neurodevelopmental disorder that primarily affects females. Approximately 90–95% of typical RTT cases harbor loss-of-function mutations in the X-linked gene, *MECP2*, which encodes methyl-CpG binding protein 2. Recently, high-throughput sequencing identified new mutant genes in Rett-related disorder (RRD): *CDKL5*, *FOXG1*, *TCF4*, *EEF1A2*, *STXBP1*, and *SLC35A2* [1]. MECP2 recruits the SIN3A histone deacetylase (HDAC) complex to chromatin [2]; therefore mutations in genes encoding HDACs may be good candidates for genetically undetermined RRD [3]. Here, we describe for the first time, a *de novo* missense *HDAC8* mutation in a unique girl with RRD with distinctive facial features and multiple congenital anomalies. Clinical aspects of this patient will be discussed.

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2. Patient and methods

2.1. Case report

A Japanese female aged 2 months old was examined at our hospital, because of poor weight gain. She presented with ocular hypertelorism, a broad nose, arched eyebrows, brachydactyly of bilateral fifth fingers (Fig. 1), and atrial septal defect. She gained head control at 4 months, rolling over at 12 months, sitting alone at 14 months, crawling at 18 months and walking alone at 30 months. She could speak a few words at 2 years of age. Thereafter, her verbal and non-verbal communication gradually deteriorated, and autistic behavior and stereotypical hand wringing appeared. She was unable to speak at 4 years. Her purposeful hand movement was completely impaired at 4 years. Her gross and fine motor skills further deteriorated after 6 years. She spent most of her daily life in a wheelchair by 10 years. Brain magnetic resonance imaging (MRI) was normal at 3 years. Her Tanaka-Binet intelligence quotient (IQ) test score was 33 at 10 years of age. Her clinical features fulfilled the four main criteria of the revised diagnostic criteria for RTT, except for extremely early onset in infancy [4]. Therefore, she was diagnosed with RRD.

Giant granules and phagocytosis in white blood cells were not detected by peripheral blood smears. Analysis for natural killer cell activity was normal. Flow cytometry indicated normal expression of T cells (CD3, CD4, and CD8) and B cells (CD19). She did not show any clinical symptoms of recurrent pyogenic infection, albinism, or peripheral neuropathy.

Peripheral blood leukocytes from the patient and her parents were used for DNA extraction. The research protocol was approved by the Ethics Committees of Kurume University School of Medicine and Yokohama City University School of Medicine.

2.2. Sanger sequencing and multiplex ligation-dependent probe amplification

MECP2 was screened in the patient using the Sanger method. Parental samples were also sequenced for candidate variants. Moreover, multiplex ligation-dependent probe amplification (MLPA) was performed to detect exonic deletions/duplications of *MECP2*, *CDKL5*, and *FOXG1*.

2.3. Whole exome sequencing

Genomic DNA was captured using the SureSelect Human All Exon v4 Kit (51 Mb; Agilent Technologies, Santa Clara, CA, USA), and sequenced on an Illumina HiSeq2000 (Illumina, San Diego, CA, USA) with 101 bp

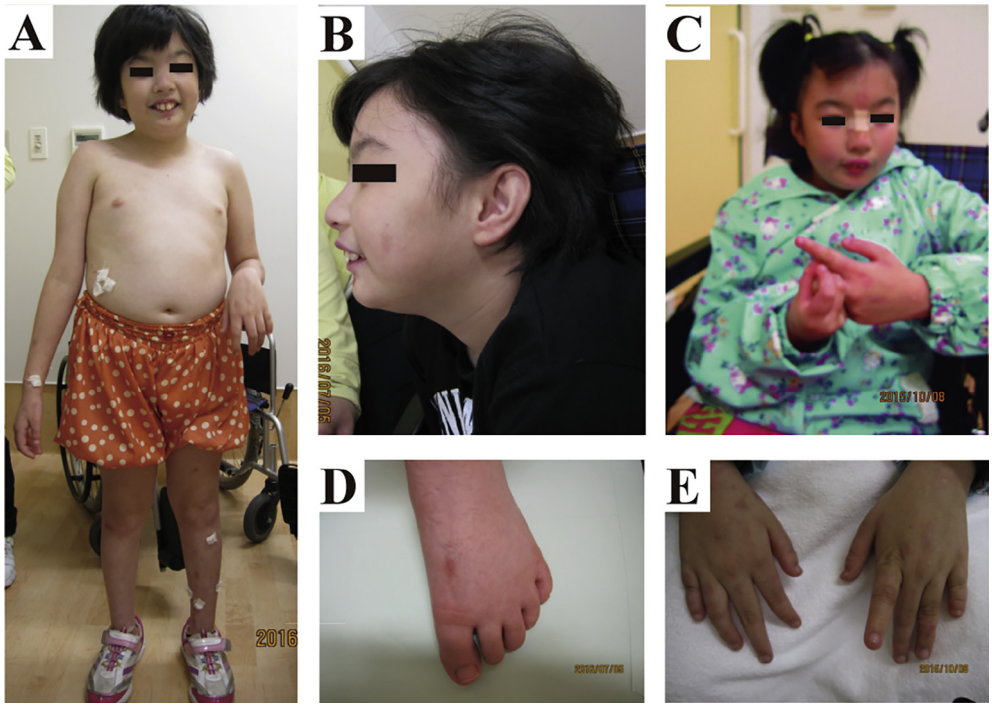

Fig. 1. A–E: Clinical features of the patient. A: Full-length figure: the patient looks happy and gently smiles. She is short in stature, has truncal obesity, arched eyebrows, and a broad nasal tip. B: Left-side facial view: she has retrognathia and arched eyebrows. C: The patient shows stereotypical hand movements and self-mutilation of her face. D: Her left foot is small and feels cold. E: Her hands are small and exhibit brachydactyly of the bilateral fifth fingers.

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