Case Report

Mowat-Wilson Syndrome: The First Clinical and Molecular Report of an Indonesian Patient

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Mowat-Wilson syndrome (OMIM 235730) is a genetic condition characterized by moderate-to-severe intellectual disability, a recognizable facial phenotype, and multiple congenital anomalies. The striking facial phenotype in addition to other features such as severely impaired speech, hypotonia, microcephaly, short stature, seizures, corpus callosum agenesis, congenital heart defects, hypospadias, and Hirschsprung disease are particularly important clues for the initial clinical diagnosis. All molecularly confirmed cases with typical MWS have a heterozygous loss-of-function mutation in the zinc finger E-box protein 2 (ZEB2) gene, also called SIP1 (Smad-interacting protein 1) and ZFHX1B [2]. To date, about 200 molecularly proven MWS cases with over 100 different ZEB2 mutations have been reported [3].

The facial features are the most important diagnostic clue for the initial clinical diagnosis and provide a hallmark for ZEB2 mutation analysis [4]. Establishing a molecular diagnosis is important for the patients and their families as it allows reliable genetic counseling for their families and a better clinical management of the patients. Here, we report the first Indonesian patient with molecularly confirmed MWS.

1. Introduction

Mowat-Wilson syndrome (MWS; OMIM 235730) is a rare genetic condition described by Mowat et al. in 1998, who reported a series of six children with intellectual disability (ID), striking facial features, and variable multiple congenital anomalies (MCA) [1]. All molecularly confirmed cases with typical MWS have a heterozygous loss-of-function mutation in the zinc finger E-box protein 2 (ZEB2) gene, also called SIP1 (Smad-interacting protein 1) and ZFHX1B [2]. To date, about 200 molecularly proven MWS cases with over 100 different ZEB2 mutations have been reported [3].

The patient was a nineteen-year-old male with severe ID. He was the third son of nonconsanguineous, healthy, Javanese parents and family history was unremarkable. The patient was born at term after an uneventful pregnancy with a weight of 3200 g (25th centile) and length 50 cm (50th centile). He showed hypotonia and delayed developmental milestones. He started to sit at 20 months of age. At two years of age, he developed recurrent generalized seizures and was commenced on valproic acid, which brought his epilepsy under control. He started to walk at four years of age and spoke his first words at the age of five years. He had recurrent otitis media. Speech consisted of only a few words and he often communicated using sign language. He showed happy behavior with frequent smiling. In addition, he showed repetitive hand movements. On physical examination, his weight was 45 kg (<3rd centile), height 161 cm (<3rd centile), and head circumference 53 cm (<3rd centile).

2. Case Presentation

The patient was a nineteen-year-old male with severe ID. He was the third son of nonconsanguineous, healthy, Javanese parents and family history was unremarkable. The patient was born at term after an uneventful pregnancy with a weight of 3200 g (25th centile) and length 50 cm (50th centile). He showed hypotonia and delayed developmental milestones. He started to sit at 20 months of age. At two years of age, he developed recurrent generalized seizures and was commenced on valproic acid, which brought his epilepsy under control. He started to walk at four years of age and spoke his first words at the age of five years. He had recurrent otitis media. Speech consisted of only a few words and he often communicated using sign language. He showed happy behavior with frequent smiling. In addition, he showed repetitive hand movements. On physical examination, his weight was 45 kg (<3rd centile), height 161 cm (<3rd centile), and head circumference 53 cm (<3rd centile).
Facial dysmorphisms included a long face, deep-set eyes, large eyebrows with medial flaring, hypertelorism, strabismus, saddle nose with prominent rounded nasal tip, prominent columella, low-set and posteriorly rotated ears, prominent and triangular pointed chin, small mouth, full lips, and prognathia noted.

The individual was part of a larger series of 527 Indonesian individuals with ID from schools and institutions, whose conventional karyotyping, FMR1 gene analysis, and subtelomeric MLPA were normal [5]. Based on the clinical features, MWS was suspected. Therefore, molecular analysis of the ZEB2 gene was warranted. Sanger sequencing of all coding exons and surrounding splice sites of the ZEB2 gene was performed as described below. The genomic DNA reference sequence was NM_014795.2. PCR of exon eight was performed using primers CTTTACTTGGTTTCCCACC (forward) and GGGGCTTGTCATTCCTT (reverse). One hundred nanograms of DNA solution (1 µL) were added into PCR mixture, which contained 7.6 µL of 360 PCR master mix (Applied Biosystem), 0.5 µL of primers working solution, and 6 µL of H2O. Amplification was performed using PCR System 9700 (Applied Biosystem) with the following protocol. PCR was initiated by 10’ denaturation at 95°C, followed by 35 PCR cycles (30’ 95°C, 30’ 60°C, 60’ 72°C) and 7’ final elongation at 72°C. The result was analyzed on ABI 3730 analyzer (Applied Biosystem). Sequence result was compared to published reference sequence (rs148709333) using SEQPilot software version 3.2.1.0 (JSI medical system). In exon eight, a nonsense mutation has been detected, changing a TAC codon (coding for a tyrosine) into a TAG stop-codon; c.1965C>G (p.Tyr652X) (nomenclature according to the HGVS guidelines; http://www.hgvs.org/mutnomen/) (Figure 2). To our knowledge, this mutation has not been reported before.

3. Discussion

This is the first report of an Indonesian individual with MWS confirmed by molecular genetic testing. Although nonsense
Conflicts of Interests

The authors have no conflict of interests to declare.

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