

Mowat-Wilson syndrome: the first two Malaysian cases

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ABSTRACT

Mowat-Wilson syndrome (MWS) is a recently delineated mental retardation; a multiple congenital anomaly syndrome characterised by a typical facial gestalt, Hirschsprung disease or severe constipation, genitourinary anomaly, congenital heart defects, agenesis of corpus callosum and eye defects. Some cases also present with epilepsy, growth retardation with microcephaly and speech impairment. MWS was first described in 1998 by Mowat et al, and approximately 180 cases have been reported as of August 2008. The syndrome occurs as a result of heterozygous mutations or deletions in the zinc finger E-box-binding homeobox 2 gene, *ZEB2*, previously called *ZFHX1B* (*SIP1*). Most cases reported so far were sporadic occurrences; however, rare cases of sibling recurrence have been cited. The facial phenotype is particularly important for the initial clinical diagnosis and provides the hallmark, warranting *ZEB2* mutational analysis even in the absence of Hirschsprung disease. We present the first two molecularly confirmed Malaysian MWS patients, one of whom has a novel mutation.

Keywords: congenital anomaly syndrome, Hirschsprung disease, mental retardation, Mowat-Wilson syndrome, *ZEB2* gene

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INTRODUCTION

Mowat-Wilson syndrome (MWS) (MIM#235730) is a congenital syndrome caused by *de novo* heterozygous mutations or deletions of the transcriptional repressor *ZFHX1B* gene.^(1,2) It was first described in 1998 by Mowat et al, who also identified a locus at chromosome 2q21-q23.⁽³⁾ *ZFHX1B* is classified as a trans-dev gene (genes involved in the regulation of transcription and/or development) and encodes Smad-interacting protein-1 (SMADIP1 or SIP1), a transcriptional corepressor involved in the transforming growth factor-beta signaling pathway.⁽⁴⁾ The gene is highly evolutionarily conserved and is widely expressed in embryological development.

The prevalence of MWS is currently unknown, but it is likely that the syndrome is under-diagnosed, particularly in patients without Hirschsprung disease (HSCR).⁽⁵⁾ To date, approximately 180 cases with 100 different *ZEB2* mutations have been reported,⁽⁶⁾ predominantly in Europe, Australia and the United States.⁽⁷⁾ Patients with clinically typical MWS almost always have whole gene deletions or truncating mutations (nonsense or frameshift) of *ZFHX1B*, suggesting that haploinsufficiency is the basis of MWS pathology. No obvious genotype-phenotype correlation could be identified so far, but atypical phenotypes have reported missense or splice mutations in the *ZFHX1B* gene.⁽⁴⁾ The majority of the cases reported are sporadic in occurrence, with low recurrence risk; however, a few cases of sibling recurrence have been observed.^(6,8-10) MWS is characterised by the following: (1) distinctive facial features (ocular hypertelorism, medially flared broad eyebrows, prominent columella, prominent or pointed chin and uplifted ear lobes with central depression, described as resembling “orechietta pasta” or reds blood corpuscles)⁽⁶⁾ and additional suggestive facial features, including telecanthus, posteriorly rotated ears and a full or everted lower lip;^(3,8) (2) structural anomalies, including HSCR, genitourinary anomalies (particularly hypospadias in males), agenesis or hypogenesis of the corpus callosum, congenital heart defects (including abnormalities of the pulmonary arteries and/or valves) and ophthalmological anomalies (microphthalmia, Axenfeld anomaly);^(4,7) (3) functional abnormalities, including moderate to severe mental retardation in all patients, severe speech impairment,^(3,6) epilepsy,^(3,7) growth retardation, microcephaly and chronic constipation with or without HSCR.^(6,7)

CASE REPORT I

A five-year-four-month-old Chinese girl, born at term with a birth weight of 2.9 kg via an uneventful spontaneous vaginal delivery to a healthy, 20-year-old parity two mother of a non-consanguineous marriage, was the second of two children. Antenatally, the mother had no history of exposure to any potentially teratogenic medications or environmental toxins. She experienced good foetal movements throughout an uncomplicated pregnancy, and her first pregnancy was similarly uneventful.

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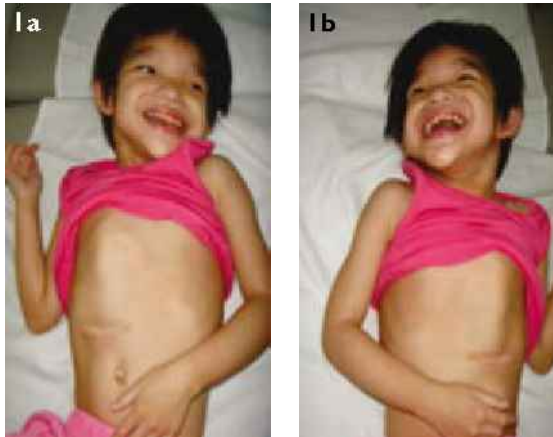


Fig. 1a & b Photographs of the four-year-old child show a happy demeanor, open-mouthed expression, a pointed chin, elevated ear lobes and a surgical abdominal scar.

The patient had severe constipation during the neonatal period and was diagnosed with HSCR, for which a colostomy was performed. She also had a cardiac murmur, and a 2D echocardiogram revealed a small patent ductus arteriosus (PDA) and an atrial septal defect (ASD). The PDA then closed spontaneously. At one-and-a-half years of age, she developed afebrile seizures and was commenced on carbamazepine, which brought her epilepsy under control. It was then that the patient was observed to be hypotonic, globally delayed and dysmorphic, and she was subsequently referred to our Clinical Genetics Unit. Her growth parameters, including head circumference (42 cm, 2 standard deviations [SD]), were below the 3rd percentile. She had sparse, coarse hair, medially flared thick eyebrows, hypertelorism, a saddle nose, epicanthic folds, a pair of prominent simple ears with uplifted ear lobes, long tapered fingers and a prominent pointed chin (Fig. 1). At two years of age, the patient only managed to roll over and grasp objects momentarily, but was unable to sit up, reach out or vocalise. At five years old, she remained severely delayed and was totally dependent on her caretaker for daily activities.

The investigations, including karyotyping, electroencephalogram (EEG), methylation polymerase chain reaction (PCR) for Angelman syndrome, were all normal. Magnetic resonance (MR) imaging of the brain, however, showed a thinned corpus callosum. Molecular analysis of the *ZXHX1B* gene by direct sequencing (Applied Biosystems SeqScape software, Paris, France) and semi-quantitative multiplex fluorescent PCR (QMF-PCR) analysis (QIAGEN Multiplex PCR kit, Paris, France) of the *ZFH1B* gene were performed, and the results revealed a *de novo* splice site mutation c.916+5G>T (NM_014795.2) (Fig. 3).



Fig. 2 Photographs of the child at eight years of age show (a) a triangular face, broad forehead, hypertelorism, medially flared thick eyebrows and a prominent pointed chin; and (b) a low-set ear with uplifted ear lobe and overfolded helices.

CASE REPORT 2

A ten-year-nine-month-old Chinese girl, born 11 days post due date to a healthy, 29-year-old parity four mother of a non-consanguineous marriage, via spontaneous vaginal delivery, was the eldest of four siblings. Her birth weight was 2.78 kg (10th percentile), length 48 cm (25th percentile) and head circumference 31 cm (−3 SD). The mother had her regular antenatal reviews at a government health clinic and an uneventful pregnancy.

Dysmorphism and a cardiac murmur were detected soon after birth. Echocardiogram revealed a PDA and ventricular septal defect (VSD). The patient had afebrile seizures at five years of age, which was controlled with carbamazepine and clonazepam. EEG showed a left centroparietal focus. She had chronic constipation from the age of approximately seven years, which was conservatively managed by her treating physician. No rectal biopsy had been performed. The patient was referred to our Clinical Genetics Unit at eight years of age for an assessment of her global developmental delay. She was significantly restricted in her abilities to carry out most daily activities and had significant speech delay. Her weight was 17.5 kg (< 3rd percentile), height

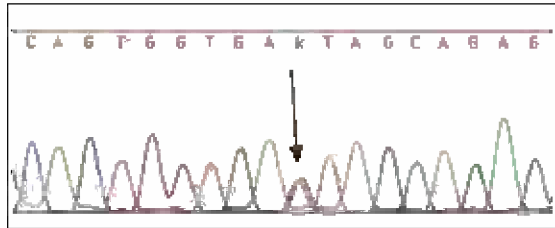


Fig. 3 Electropherogram shows the sequence of the exon 7-intron 7 junction of the *ZFH1B* gene in Case 2. The arrows indicate the heterozygous G -> T mutation at position +5 of the intron 7 following the exon 7 (c.916+5G>T).

112.5 cm (<3rd percentile) and head circumference 47.5 cm (−2 SD). She had a triangular face, broad forehead, hypertelorism, medially flared thick eyebrows, a prominent pointed chin, a short philtrum, low-set ears with uplifted ear lobes and overfolded helices (Fig 2).

The investigations included karyotyping, FISH 22 q11, genitourinary ultrasonography, audiometry, methylation PCR for Angelman syndrome and brain MR imaging, which were found to be normal. Analysis of the *ZXHX1B* gene showed a *de novo* deletion that removed Exons 3–10 of the gene.

DISCUSSION

Mowat-Wilson syndrome is characterised by typical facial features, moderate-to-severe mental retardation, epilepsy and variable congenital malformations, including HSCR, genital anomalies (particularly hypospadias in males), congenital heart disease, agenesis of the corpus callosum and eye defects. The facial phenotype is particularly important for the initial clinical diagnosis and provides the hallmark that warrants a *ZEB2* mutational analysis, even in the absence of HSCR.⁽¹¹⁾ This was the case in these two patients. Furthermore, the facial phenotype has been reported to evolve over time and become more recognisable in older individuals.^(4,12) The nasal tip typically lengthens and becomes more depressed, while the collumela becomes more pronounced, resulting in the appearance of a short philtrum. The face tends to elongate and the jaw becomes more prominent. The eyebrow may become heavier with an increased medial flare. This progression was demonstrated in Case 2.

Other major associated features, such as mental retardation, microcephaly, epilepsy and congenital heart disease, were also present in both our patients. We also found severe speech delay, in particular, expressive language delay, to be a useful clinical clue in conjunction with other symptoms. Microcephaly can be present from birth, as seen in Case 2. In both cases, epilepsy was not difficult to control, as was the experience of most other reported cases.⁽¹³⁾ Case 1 had biopsy-proven

HSCR; whereas Case 2 had chronic constipation that did not warrant a biopsy. MWS was initially described as a syndromic form of HSCR; however, only 46% of the larger series of mutation-positive cases had HSCR, suggesting that it is not an obligatory feature and that the diagnosis should not be dismissed in the absence of HSCR.⁽⁴⁾

MWS is caused by mutation in the zinc finger E-box-binding homeobox 2 gene (*ZFH1B*). Approximately 180 cases have thus been reported, with 100 different *ZEB2* mutations.⁽³⁾ In all of these patients, heterozygous mutations of the zinc finger E-box-binding homeobox 2 gene (*ZEB2*) were detected. The *ZEB2* gene spans approximately 70 Kb, consists of ten exons and nine introns, and encodes for SIP1 (Smad interacting protein 1, SMADIP1).⁽¹⁾ SIP1 is a zinc finger/homeodomain transcriptional repressor and consists of 1,214 amino acids.⁽¹⁴⁾ *ZEB2* mRNA is detected in nearly all human tissues.⁽¹⁵⁾ Clinical features suggest that the *ZEB2* gene is involved in the development of neural crest-derived cells (enteric nervous system, craniofacial mesoectoderm), central nervous system, heart septation (PDA, VSD and ASD) and midline development.⁽¹¹⁾ The spectrum of *ZFH1B* mutations include nonsense or frameshift mutations (81%), intermediate and large deletions (17%) or large-scale rearrangement (2%).⁽¹⁶⁻¹⁸⁾ No obvious genotype-phenotype correlations have been described, except for several individuals with large deletions (> 5 Mb) who were more severely affected.⁽¹⁷⁾ Case 1 had a splice site mutation which was not reported before, while Case 2 had a deletion similar to one previously reported in a Japanese patient.⁽¹⁷⁾ A small number of patients with rare mutations (inframe, missense and splice site mutations) may show an atypical clinical picture.⁽¹¹⁾

MWS is usually the result of a *de novo* dominant mutation in the *ZFH1B* gene, with a low recurrence risk for siblings. However, genetic counselling for these families should include the consideration of recent reports which demonstrated possible germline mosaicism^(5,19) and somatic mosaicism.⁽⁶⁾ A 1%–2% recurrence risk in siblings may be an appropriate estimation.^(6,9) However, the risk is higher in a balanced familial translocation. Karyotype and gene analysis should be offered to the parents of an affected child, and prenatal diagnosis may be possible in these cases. There is scarce data concerning specific prenatal markers suitable during pregnancy. Wilson et al reported an increased nuchal translucency in two patients.⁽¹²⁾ Paying particular attention to the facial features (dysplastic ears) at ultrasonography or during the foetopathological examination may help in the diagnosis of MWS in

foetuses with agenesis of the corpus callosum.

MWS is a relatively new clinical entity and may be an under-diagnosed syndrome. Therefore, it is recommended that MWS should be considered in individuals with a characteristic facial phenotype and mental retardation, with or without epilepsy, and with other associated structural anomalies, such as HSCR or chronic constipation, congenital heart disease and agenesis or hypogenesis of the corpus callosum.

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