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Mowat-Wilson syndrome in a Moroccan consanguineous family

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Mowat-Wilson syndrome is a mental retardation-multiple congenital anomaly syndrome characterized by a typical facies, developmental delay, epilepsy, and variable congenital malformations, including Hirschsprung disease, urogenital anomalies, congenital heart disease, and agenesis of the corpus callosum. This disorder is sporadic and is caused by heterozygous mutations or deletions of the *ZFHX1B* gene located in the 2q22 region. We report here the first Moroccan patient, born to consanguineous parents, with Mowat-Wilson syndrome, due to a *de novo*, unreported mutation of the *ZFHX1B* gene.

Key words: Dysmorphia, Mowat-Wilson syndrome, severe mental retardation, *ZFHX1B* gene

Introduction

Mowat-Wilson syndrome (MWS) (MIM#235730) is characterized by a typical facies, severe mental retardation, epilepsy, and variable congenital malformations, including Hirschsprung's disease (HSCR), genitourinary abnormalities, congenital heart disease, and agenesis of the corpus callosum.^[1] The majority of the reports in the literature originate from Northern Europe and Australia.^[2] MWS is caused by *de novo* heterozygous mutations or deletions in the zinc finger homeobox 1B gene (*ZFHX1B*) located in the 2q22 region. *ZFHX1B* encodes the Smad-interacting protein-1 (SMADIP1 or SIP1), a transcriptional corepressor involved in the transforming growth factor-beta signaling pathway.^[1] Over 100 mutations have been described in patients with typical features of MWS; these have essentially been truncating mutations (nonsense or frameshift) or large deletions of the *ZFHX1B* gene, suggesting a haploinsufficiency mechanism.^[1]

We present the clinical data and the molecular analysis of a 2½-year-old Moroccan boy with Mowat-Wilson syndrome who was born to consanguineous parents.

Case Report

The patient was the first boy born to healthy consanguineous parents, both 29 years old, with no relevant familial history. The pregnancy and delivery were normal and the child was born at term, with normal weight, length, and head circumference. He had normal passing of meconium in the first 24 h of life, and no history of chronic constipation was reported. In the neonatal period, he developed seizures. Hypotonia and psychomotor and developmental delay were observed. He could hold his head up at 10 months, sit by himself at 24 months, and was not yet walking.

At 2½ years of age he presented with striking dysmorphic features: square-shaped face with a prominent but narrow triangular chin, plagiocephaly, thick eyebrows, sunken eyes, hypertelorism, broad nasal bridge, saddle nose, prominent columella, open mouth, and large uplifted ear lobes [Figure 1]. He had a smiling face, with a happy behavioural phenotype. His head circumference was normal and no genital malformations were observed.

MRI scan of the brain revealed agenesis of the corpus callosum and cerebral hypotrophy. Electroencephalogram (EEG), echocardiography, and genitourinary ultrasound examinations were normal.



Figure 1: Facial phenotype of the patient

Since the patient presented with typical dysmorphic features, severe developmental delay, epilepsy, and agenesis of the corpus callosum we suspected a MWS, and molecular analysis of the *ZFHX1B* gene was performed. This analysis led to the identification of a novel heterozygous nonsense mutation, c.1165A>T (p.Lys389X) in exon 8 of the *ZFHX1B* gene.

At the time of diagnosis, the mother of the patient was 8 months pregnant.

Discussion

Mowat-Wilson syndrome, first clinically delineated by Mowat *et al.* in 1998,^[3] is a rare mental retardation-multiple congenital anomalies syndrome associated with typical facial dysmorphism, including hypertelorism, medially flared and broad eyebrows, enophthalmia, prominent columella, pointed chin, and uplifted earlobes, which typically prompts the clinician to consider the diagnosis.^[2] Patients can present a variety of other anomalies, such as short stature (50%); microcephaly (84%); HSCR (50%); chronic constipation (25%); malformations of the brain, particularly agenesis of the corpus callosum (60%); seizures (75%), with no predilection for any particular seizure type; congenital heart defects (75%); and urogenital anomalies,^[2,4,5] particularly hypospadias (55%).^[2,6] In our patient, suspicion of MWS was based essentially on the dysmorphic features associated with severe mental retardation and seizures. Absence of microcephaly, HSCR, congenital heart defect, and hypospadias did not preclude the diagnosis.

Several differential diagnoses of MWS can be evoked. In patients with mental retardation (MR), microcephaly, and HSCR, born to consanguineous

parents, the Goldberg-Shprintzen syndrome (GOSHS), a rare autosomal recessive disorder, can be suspected if associated with specific dysmorphia.^[4] Severe MR, seizures, ataxia, microcephaly, a prominent jaw, and a happy behaviour phenotype are also features of Angelman syndrome.^[4] Finally, Pitt-Hopkins syndrome can be considered in patients with MR, characteristic facial gestalt, and episodes of hyperventilation.^[7,8]

In MWS, the *ZFHX1B* gene mutations are most often truncating (nonsense, frameshift, or deletions) and no obvious genotype-phenotype correlation has been identified so far. In a few cases, atypical phenotypes have been described with missense or splice mutations of the *ZFHX1B* gene.^[9] Few recurrent mutations (6/100) have been identified.^[1] As this disorder is sporadic, with the mutations occurring *de novo*, the risk of recurrence of MWS is low. However, a case of germline mosaicism has been reported.^[10] As the genetic counseling of MWS is reassuring, it is important to evoke this diagnosis, particularly in consanguineous families. In our case, the mother gave birth to a healthy girl.

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