



HAL
open science

Mowat-Wilson syndrome in a Moroccan consanguineous family

Ilham Ratbi, Chafai Siham Elalaoui, Florence Dastot-Le Moal, Michel Goossens, Irina Giurgea, Abdelaziz Sefiani, Chafaisiham Elalaoui

► **To cite this version:**

Ilham Ratbi, Chafai Siham Elalaoui, Florence Dastot-Le Moal, Michel Goossens, Irina Giurgea, et al.. Mowat-Wilson syndrome in a Moroccan consanguineous family. *Indian Journal of Human Genetics*, 2007, 13 (3), pp.122. 10.4103/0971-6866.38988 . inserm-04136296

HAL Id: inserm-04136296

<https://inserm.hal.science/inserm-04136296v1>

Submitted on 21 Jun 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Mowat-Wilson syndrome in a Moroccan consanguineous family

Ratbi Ilham, Elalaoui Chafai Siham, Dastot-Le Moal Florence¹, Goossens Michel¹, Giurgea Irina¹, Sefiani Abdelaziz

Department of Medical Genetics, National Institute of Health, 27 Avenue Ibn Batouta, Rabat, Morocco, ¹Department of Biochemistry and Genetics, AP-HP and INSERM U841-11 Team, Henri Mondor Hospital, 94010 Créteil, France

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.

Acknowledgments

We thank Dr. Imane Jaouad Cherkaoui for her contribution. Nathalie Collot is thanked for valuable technical assistance. Dr. Wahlen Sandra is acknowledged for re-reading the manuscript.

References

1. Dastot-Le Moal F, Wilson M, Mowat D, Collot N, Niel F, Goossens M. *ZFHX1B* mutations in patients with Mowat-Wilson syndrome. *Hum Mutat* 2007;28:313-21.
2. Adam MP, Schelley S, Gallagher R, Brady AN, Barr K, Blumberg B, *et al.* Clinical features and management issues in Mowat-Wilson syndrome. *Am J Med Genet A* 2006;140:2730-41.
3. Mowat DR, Croaker GD, Cass DT, Kerr BA, Chaitow J, Ades LC, *et al.* Hirschsprung disease, microcephaly, mental retardation and characteristic facial features: Delineation of a new syndrome and identification of a locus at chromosome 2q22-q23. *J Med Genet* 1998;35:617-23.
4. Mowat DR, Wilson MJ, Goossens M. Mowat-Wilson syndrome. *J Med Genet* 2003;40:305-10.
5. Zweier C, Thiel CT, Dufke A, Crow YJ, Meinecke P, Suri M, *et al.* Clinical and mutational spectrum of Mowat-Wilson syndrome. *Eur J Med Genet* 2005;48:97-111.
6. Garavelli L, Cerruti-Mainardi P, Viridis R, Pedori S, Pastore G, Godi M, *et al.* Genitourinary anomalies in Mowat-Wilson syndrome with deletion/mutation in the zinc finger homeo

- box 1B gene (ZFHX1B): Report of three Italian cases with hypospadias and review. *Horm Res* 2005;63:187-92.
7. Amiel J, Rio M, de Portugal L, Redon R, Malan V, Boddaert N, *et al.* Mutations in TCF4, encoding a class I basic helix-loop-helix transcription factor, are responsible for Pitt-Hopkins syndrome, a severe epileptic encephalopathy associated with autonomic dysfunction. *Am J Hum Genet* 2007;80:988-93.
 8. Zweier C, Peippo MM, Hoyer J, Sousa S, Bottani A, Clayton-Smith J, *et al.* Haploinsufficiency of TCF4 causes syndromal mental retardation with intermittent hyperventilation (Pitt-Hopkins syndrome). *Am J Hum Genet* 2007;80:994-1001.
 9. Heinritz W, Zweier C, Froster UG, Strenge S, Kujat A, Syrbe S, *et al.* A missense mutation in the ZFHX1B gene associated with an atypical Mowat-Wilson syndrome phenotype. *Am J Med Genet A* 2006;140:1223-7.
 10. McGaughran J, Sinnott S, Dastot-Le Moal F, Wilson M, Mowat D, Sutton B, *et al.* Recurrence of Mowat-Wilson syndrome in siblings with the same proven mutation. *Am J Med Genet A* 2005;137:302-4.

Source of Support: Nil, **Conflict of Interest:** None declared.