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Funded by the NIH · Developed at GeneTests (www.genetests.org), University of Washington, Seattle

Mowat-Wilson Syndrome

[*Hirschsprung Disease-Mental Retardation Syndrome*]

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Initial Posting: March 28, 2007.
Last Revision: February 11, 2008.

Summary

Disease characteristics. Mowat-Wilson syndrome (MWS) is characterized by distinctive facial features; structural anomalies including Hirschsprung disease, genitourinary anomalies (particularly hypospadias in males), congenital heart defects (abnormalities of the pulmonary arteries and/or valves), agenesis or hypogenesis of the corpus callosum, and eye defects (microphthalmia and Axenfeld anomaly); and functional differences including moderate to severe mental retardation, severe speech impairment with relative preservation of receptive language, seizures, growth retardation with microcephaly, and chronic constipation in those without Hirschsprung disease.

Diagnosis/testing. Mutations and deletions in the gene *ZEB2* (also known as *ZFHX1B* or *SIP-1*) cause MWS. Sequence analysis detects mutations in approximately 81% of individuals; FISH detects large deletions encompassing all or part of *ZEB2* in approximately 15% of persons; chromosomal rearrangements that disrupt the *ZEB2* gene cause MWS in approximately 2% of individuals; and an additional 2% have intermediate-sized deletions that can be detected by techniques such as quantitative PCR, MLPA or gene-specific array CGH.

Management. *Treatment of manifestations:* care by the appropriate specialist for dental anomalies, seizures, ocular abnormalities, congenital heart defects, chronic constipation, Hirschsprung disease, genitourinary abnormalities, and pectus anomalies of the chest and/or foot/ankle anomalies; educational intervention and speech therapy beginning in infancy. *Surveillance:* annual eye examination in childhood to monitor for strabismus and refractive errors; monitoring for otitis media; regular developmental assessments to plan/refine educational interventions; periodic reevaluation by a medical geneticist.

Genetic counseling. Mowat-Wilson syndrome is typically the result of a *de novo* dominant mutation. When MWS results from a *de novo* mutation, the risk to the sibs of a proband is small. No individuals with MWS have been known to reproduce. Although the vast majority of MWS occurs as the result of a *de novo* mutation, molecular genetic testing can be used to

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evaluate a pregnancy at theoretically increased risk because of constitutional and/or germline mosaicism for a *ZEB2* mutation in a clinically unaffected parent.

Parents of an individual with MWS resulting from a structural unbalanced chromosome constitution (e.g., deletion, duplication) are at risk of having a balanced chromosome rearrangement. The risk to sibs of a proband with a structural unbalanced chromosome abnormality depends upon the chromosome findings in the parents. Prenatal diagnosis for pregnancies at increased risk because of parental balanced structural rearrangement is possible by chromosome analysis of fetal cells obtained by amniocentesis or chorionic villus sampling.

Diagnosis

Clinical Diagnosis

Consensus clinical diagnostic criteria for Mowat-Wilson syndrome (MWS) have not been established. Individuals with this condition have characteristic facial features, in addition to a variety of congenital anomalies, which suggest the diagnosis.

The following is a list of typical facial features (see Figure 1). In a study by Zweier et al (2005) all individuals with this combination of characteristics were found to have mutations or deletions in the *ZEB2* gene.

- Ocular hypertelorism
- Medially flared and broad eyebrows
- Prominent columella
- Prominent or pointed chin
- Uplifted earlobes with a central depression. The earlobes have been described as resembling "orechietta pasta" or "red blood corpuscles." The ear configuration does not change significantly with age with the exception of the central depression, which is less obvious in adults.
- Open-mouthed expression

Additional suggestive facial features include the following [Mowat et al 2003, Adam et al 2006]:

- Telecanthus
- Deep-set eyes
- Broad nasal bridge with prominent and rounded nasal tip
- Full or everted lower lip
- Posteriorly rotated ears

Note: The facial phenotype evolves and becomes more pronounced with age (Figure 1), such that the diagnosis is easier to make in older individuals. The nasal tip lengthens and becomes more depressed and the columella becomes more pronounced, leading to the appearance of a short philtrum. The face tends to elongate and the jaw becomes more prominent. The eyebrows may become heavier with an increased medial flare [Wilson et al 2003,Horn et al 2004].

Structural anomalies include the following:

- Hirschsprung disease
- Genitourinary anomalies, particularly hypospadias in males

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- Congenital heart defects, including abnormalities of the pulmonary arteries and/or valves
- Agenesis or hypogenesis of the corpus callosum
- Ophthalmologic anomalies, including microphthalmia and Axenfeld anomaly

Functional differences include the following:

- Mental retardation, typically in the moderate to severe range, with severe speech impairment, but relative preservation of receptive language
- Seizures
- Growth retardation with microcephaly
- Chronic constipation in those without Hirschsprung disease

Testing

Cytogenetic testing. Chromosomal rearrangements that disrupt the *ZEB2* gene cause MWS in approximately 2% of cases [Lurie et al 1994, Dastot-Le Moal et al 2007].

FISH analysis. Large deletions encompassing all or part of the *ZEB2* gene detectable by FISH have been observed in approximately 15% of persons with a clinical diagnosis of MWS [Mowat et al 2003, Dastot-Le Moal et al 2007].

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. Mutations and deletions in the gene *ZEB2* (also known as *ZFHX1B* or *SIP-1*) are known to cause MWS in approximately 81% of cases [Amiel et al 2001, Kaariainen et al 2001, Wakamatsu et al 2001, Dastot-Le Moal et al 2007].

Other loci. The *ZEB2* mutation detection rate (sequencing/FISH/QPCR) for individuals with the "typical MWS" facial phenotype, as defined in Clinical Diagnosis, approaches 100% [Zweier et al 2005; D Mowat, personal communication]. There is no evidence of locus heterogeneity for MWS.

Clinical testing

- **Sequence analysis.** Sequencing of all nine coding exons, splice junctions, and immediate intronic flanking regions of the *ZEB2* gene detects mutations in approximately 81% of individuals with a clinical diagnosis of MWS [Mowat et al 2003, Cerruti Mainardi et al 2004, Dastot-Le Moal et al 2007]. Although a study by Zweier et al (2005) demonstrated that all individuals with "typical MWS" features had a detectable deletion or mutation in the *ZEB2* gene, partial gene deletions may be too small to be detected on FISH analysis and may not be found by sequence analysis.
- **Deletion testing.** Approximately 15% of *ZEB2* mutation are large deletions detectable by FISH. An additional 2% of individuals with MWS have an intermediate-sized deletion that is too small to be detectable by FISH analysis and too large to be detected by sequencing. In this situation quantitative PCR, MLPA or gene-specific array CGH can be used [Dastot-Le Moal et al 2007].

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Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Testing Used in Mowat-Wilson Syndrome

Test Method	Mutations Detected	Mutation Detection Frequency by Test Method	Test Availability
Cytogenetic analysis	Large-scale rearrangements	~2%	Clinical
Sequence analysis	*ZEB2* nonsense / frameshift mutations	~81%	Clinical Testing
FISH	Large deletions of *ZEB2*	~15%	
Deletion/duplication analysis [1]	Intermediate-sized deletions of *ZEB2*	~2%	

1. Quantitative PCR, MLPA, or gene-specific array CGH

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

To confirm the diagnosis in a proband

- When MWS is suspected, *ZEB2* sequence analysis is recommended.
- If a mutation is not found, deletion/duplication analysis and/or FISH testing should be performed, as about 17% of individuals with MWS have deletions or rearrangements detected by these modalities.

Prenatal diagnosis for at-risk pregnancies requires prior identification of the disease-causing mutation in an affected family member.

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with disruptions in the *ZEB2* gene. It is possible that missense mutations in *ZEB2* may lead to a wide range of phenotypes.

Note: Six fetuses found on ultrasound evaluation to have agenesis of the corpus callosum did not have deletion or mutation of *ZEB2*; therefore, disruption of this gene is not likely to be a major cause of isolated agenesis of the corpus callosum [Espinosa-Parrilla et al 2004].

Clinical Description

Natural History

Findings in more than 150 individuals with Mowat-Wilson syndrome (MWS) are summarized below [Lurie et al 1994,Amiel et al 2001,Yamada et al 2001,Zweier et al 2002,Garavelli et al 2003,Mowat et al 2003,Zweier et al 2005,Adam et al 2006,Dastot-Le Moal et al 2007]. Not all features were evaluated in each individual described. The male/female ratio is approximately 1.4 (92/67) [Dastot-Le Moal et al 2007].

Craniofacial. One of the most specific findings in MWS is the distinctive facial appearance (see Clinical Diagnosis).

At least three individuals have been described with a bifid uvula/submucous cleft [Mowat et al 2003]. At least one person with a large deletion has been described with a cleft of the hard palate [Ishihara et al 2004] and one individual with atypical MWS had bilateral cleft lip and palate [Heinritz et al 2006].

Velopharyngeal insufficiency with laryngomalacia, glossoptosis, and micrognathia has been reported in one individual [Adam et al 2006]. A high-arched palate has been reported.

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Congenital tracheal stenosis has been reported in two persons [Ishihara et al 2004, Zweier et al 2005].

Growth parameters. Birth weight and length are typically in the normal range. Short stature (defined as a length or height ≤3rd centile) developed in 17/36 (47%) of persons studied. Growth hormone secretion has not been studied in these individuals.

Microcephaly (head circumference ≤3rd centile) may be present at birth or acquired. Microcephaly was present in 125/151 (83%) of individuals investigated, with at least two having a documented normal head circumference at birth.

Central nervous system. Agenesis or hypogenesis of the corpus callosum identified on neural imaging was present in 60/144 (41%) of individuals examined. Less common findings include cerebral atrophy, poor hippocampal formation, frontotemporal hypoplasia, dilation of the occipital and temporal horns of the lateral ventricles with splaying of the frontal horns of the lateral ventricle and upward protrusion of the third ventricle, moderate ventriculomegaly with external hydrocephalus, and mild ventricular and cortical sulcal prominence without frank hydrocephalus.

Seizures were present in 91/128 (70%) of individuals. Multiple seizure types have been described, including focal, myoclonic, generalized, and absence seizures; no particular seizure type is characteristic of MWS. EEG abnormalities were identified in 28/48 (58%) of individuals studied. Seizure onset, typically in the second year of life, ranges from the neonatal period to over age ten years [Wilson et al 2003]. In some cases, seizures have been more difficult to control in childhood as compared to adolescence or adulthood. In at least one case, anti-seizure medications were discontinued in adulthood with no recurrence of seizures [Adam et al 2006].

One individual developed severe autonomic dysregulation, with central sleep apnea, episodes of marked somnolence, and labile temperature and blood pressure [D Mowat, personal communication].

Psychosocial and cognitive development. All individuals with MWS have moderate to severe mental retardation, although the results of formal IQ testing have not been reported in most studies. All individuals over age one year have severely impaired verbal language skills, with either absent speech or speech restricted to only a few words. One individual with a truncating mutation has over 300 words [D Mowat, personal communication]. Receptive language skills are generally more advanced than expressive language skills. Sign language and communication boards have been used by some affected individuals with success.

Gross motor milestones are generally delayed. Mean age of walking is between ages three and four years (range: 23 months to eight years) [Zweier et al 2005, Adam et al 2006]. Some individuals do not achieve ambulation [Mowat et al 2003]. The gait is typically widely based with the arms held up and flexed at the elbow.

Many individuals have been described as having a happy demeanor with frequent laughter. Hand biting, head banging, and hyperactivity have been described in a few individuals with MWS [Adam et al 2006].

Dental. Widely spaced teeth, malpositioned teeth, delayed tooth eruption, malformed teeth, and/or bruxism have been described [Wilson et al 2003, Adam et al 2006].

Eyes. Structural eye anomalies have been described in six individuals, three with microphthalmia, two with iris/retinal colobomas, and one with Axenfeld anomaly [Zweier et

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al 2005, Dastot-Le Moal et al 2007]. A more common feature is strabismus [Mowat et al 2003, Adam et al 2006]. Several persons have been described with ptosis or cataracts [Mowat et al 2003, Zweier et al 2005, Adam et al 2006]. Nystagmus has been described in some individuals, particularly in infancy, but this often resolves with age. At least two individuals have had myopia. In individuals with blue irides, dark pigmented clumps in the iris may be noted, suggesting heterochromia; however, true iris heterochromia has not been described.

Ears. Recurrent otitis media has been described. Sensorineural hearing loss has not been described.

Cardiac. Structural heart defects were found in 82/156 (53%) of individuals studied. Cardiac defects can vary but appear to frequently involve the pulmonary arteries and/or valves. Pulmonary artery sling has been described in at least five individuals [Ishihara et al 2004, Zweier et al 2005, Adam et al 2006]. Other cardiac anomalies have included patent ductus arteriosus, atrial septal defects, ventricular septal defects, tetralogy of Fallot, coarctation of the aorta, bicuspid aortic valve, and aortic valve stenosis [Mowat et al 2003].

Gastrointestinal. MWS was initially described as a syndromic form of Hirschsprung disease (HSCR); however, only 91/159 (57%) of individuals with MWS have biopsy-proven HSCR. In the largest series of mutation-positive cases the frequency of HSCR was 26/57 (46%) suggesting that with increasing clinical experience the diagnosis can more easily be made in the absence of HSCR [Dastot-Le Moal et al 2007].

Chronic constipation has been described in a subset of persons with MWS without documented HSCR [Zweier et al 2005, Adam et al 2006]. It is unclear whether chronic constipation results from ultrashort HSCR or the presence of some other partial defect in ganglion function [Yamada et al 2001].

Other gastrointestinal problems include pyloric stenosis in eight individuals [Mowat et al 2003, Adam et al 2006, Dastot-Le Moal et al 2007].

Genitourinary. Seventy-three of 145 (50%) persons with MWS had some type of genitourinary anomaly, the most common of which is hypospadias in males. Other findings include cryptorchidism, bifid scrotum, vesicoureteral reflux (VUR), hydronephrosis, short penile chordee or "webbed penis," septum of the vagina, duplex kidney, pelvic kidney, hydrocele, and multicystic renal dysplasia.

Pubertal development. Very little has been written regarding pubertal development in MWS. One 17-year-old female underwent menarche at age 15 years but had inconsistent menstruation. One male underwent normal pubertal development. One male had mildly delayed pubertal development [Adam et al 2006]. One male underwent precocious puberty [D Mowat, personal communication].

Skeletal. A variety of skeletal manifestations have been described in MWS. Among the most common skeletal manifestations are long, slender, tapered fingers. In later childhood and adulthood, the interphalangeal joints may become prominent. Calcaneovalgus deformity of the feet has been described.

The following features have been reported in at least one affected individual: short and broad thumbs, broad halluces, unilateral duplication of the hallux, mild pectus anomalies that did not require surgery, ulnar deviation of the hands, proximally placed thumbs, delayed bone age, significant scoliosis, and camptodactyly [Mowat et al 2003, Adam et al 2006, Dastot-Le Moal et al 2007].

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Skin. At least two individuals have been described with a fair complexion compared to their family background [Adam et al 2006]. One individual with MWS has been described as having gradual onset of widespread "raindrop" depigmentation in the truncal region [Wilson et al 2003].

Genotype-Phenotype Correlations

ZEB2 deletions and truncating mutations result in the typical facial features of MWS. Deletion sizes and breakpoints vary widely, with no obvious correlation between the phenotype and the size of the deletion [Zweier et al 2003], except for several individuals with extremely large deletions (>5 Mb) who were more severely affected [Ishihara et al 2004] than those with other types of mutations.

Because features of those with a deletion and those with truncating mutations are similar, it is hypothesized that haploinsufficiency for *ZEB2* is causative. One particular mutation, p.Arg695X, has been identified in 12 individuals (nine males and three females), of whom six had HSCR, three were reported to have constipation, and two had normal bowel function (no clinical information was available in one) [Dastot-Le Moal et al 2007].

Those individuals with facial features that are "atypical" or "ambiguous" for MWS generally do not have mutations in *ZEB2* [Zweier et al 2005]. Exceptions include the following:

- An adult with mild mental retardation, atypical facial features, and megacolon had a 3-bp in-frame deletion of *ZEB2* [Yoneda et al 2002].
- A person with trisomy 21 in addition to a *ZEB2* point mutation had Hirschsprung disease, mental retardation, ocular colobomas affecting the iris and retina, and atypical facial features [Gregory-Evans et al 2004].
- A person with mild facial features (atypical but reminiscent of the MWS gestalt) had only mild speech delay and a novel splice site mutation in the 5'UTR [Zweier et al 2006].
- A person with a missense mutation had cleft lip/palate, brachytelephalangy, and atypical eyebrows [Heinritz et al 2006].

Positive predictors of a *ZEB2* mutation in those with the typical facial features of MWS include HSCR, agenesis of the corpus callosum, and urogenital anomalies (particularly hypospadias) [Zweier et al 2005].

As yet, no studies have tried to link a particular mutation to an increased risk for the structural anomalies found in MWS. However, at least one individual with a mutation has had the facial phenotype and mental retardation, but no structural anomalies [Wilson et al 2003].

Penetrance

Penetrance appears to be complete.

Anticipation

To date, anticipation has not been observed.

Prevalence

No prevalence estimates for MWS have been published.

MWS has been described in Caucasians, Hispanics, Asians, and African Americans [Ishihara et al 2004, Adam et al 2006].

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Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Many of the congenital anomalies seen in Mowat-Wilson syndrome (MWS) can be seen as isolated anomalies in an otherwise normal individual.

Disorders with overlapping features include the following:

- **Goldberg-Shprintzen syndrome,** characterized by Hirschsprung disease, microcephaly, and mental retardation found to be caused by recessive mutations in the *KIAA1279* gene [Brooks et al 2005]. However, the facial features and spectrum of congenital anomalies differ from those of MWS and include a higher frequency of cleft palate, ptosis, and ocular coloboma than are observed in MWS.
- **Other syndromic forms of HSCR.** For a full review of syndromic and nonsyndromic forms of HSCR, see Hirschsprung Disease Overview.
- **Angelman syndrome (AS),** particularly absent speech, hypopigmentation, seizures, microcephaly, ataxic-like gait, and happy demeaner. AS is caused by absence of maternal expression of the gene *UBE3A* and may be diagnosed in about 80% of affected individuals using methylation analysis of chromosome 15. In infancy, only hypotonia may be evident. However, the multitude of congenital anomalies and characteristic facial features of MWS distinguish these two conditions.
- **Smith-Lemli-Opitz syndrome (SLOS),** particularly hypospadias and mental retardation in males. SLOS is associated with elevated serum concentration of 7-dehydrocholesterol (7-DHC) or an elevated 7-dehydrocholesterol: cholesterol ratio. Molecular genetic testing for mutations of the *DHCR7* gene is clinically available.
- **Rubenstein-Taybi syndrome (RSTS),** particularly the nasal configuration and mental retardation. Several individuals with MWS have had broad thumbs and great toes, and at least one had radial deviation of the thumbs and great toes [Mowat et al 2003, Adam et al 2006]. Mutations or deletions in *CREBBP* or mutations in *EP300* are identified in approximately 70% of persons with RSTS. The facial features and spectrum of congenital anomalies distinguish RSTS from MWS.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with Mowat-Wilson syndrome (MWS):

- Baseline echocardiogram
- Baseline dental evaluation in early childhood
- Baseline ophthalmology evaluation
- Baseline audiology evaluation
- History of chronic constipation
- History of seizures
- Renal ultrasound examination to assess for structural renal anomalies
- Genitourinary evaluation, particularly for hypospadias and cryptorchidism in males
- Physical examination for pectus anomalies and foot/ankle malpositioning

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Treatment of Manifestations

- **Dental.** Referral to an orthodontist if significant dental anomalies are present
- **Neurologic.** Referral to a pediatric neurologist if signs or symptoms suggest seizures. An EEG and/or head MRI may be warranted for diagnostic purposes or refractory seizures. Standard anti-epileptic drugs (AEDs) should be used, as indicated.
- **Developmental.** Educational intervention and speech therapy beginning in infancy because of the high risk for motor, cognitive, speech, and language delay
- **Ophthalmologic.** Treatment and/or following of ocular abnormalities by a pediatric ophthalmologist
- **Cardiovascular.** Referral to a cardiologist or cardiothoracic surgeon for treatment of congenital heart defects
- **Gastrointestinal.** Referral to a gastroenterologist for evaluation and treatment when chronic constipation is present; evaluation for HSCR and ultrashort HSCR. See Hirschsprung Disease Overview.
- **Genitourinary.** Referral to a urologist or nephrologist as indicated
- **Musculoskeletal.** Referral to an orthopedist for significant pectus anomalies of the chest and/or foot/ankle anomalies

Surveillance

- Annual eye examination in childhood to monitor for strabismus and refractive errors
- Monitoring for the development of otitis media (OM); for those individuals with chronic OM, referral to an otolaryngologist
- Regular developmental assessments to plan and refine educational interventions
- Periodic reevaluation by a medical geneticist to apprise the family of new developments and/or recommendations

Testing of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

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Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Mowat-Wilson syndrome (MWS) is typically the result of a *de novo* dominant mutation.

Risk to Family Members — Autosomal Dominant Inheritance

Parents of a proband

- To date, most probands with MWS have the disorder as the result of a *de novo* mutation.
- Parents of a proband are not affected.
- McGaughran et al (2005) suggested germline mosaicism in a parent who had two affected children. A 1-bp deletion in the *ZEB2* gene identified in both children was not found in the DNA extracted from leukocytes of either parent.
- Zweier et al (2005) described a family in which two affected sisters were born to unaffected parents. Mutation analysis from DNA extracted from leukocytes demonstrated a low level of paternal mosaicism for the mutation identified in the affected children.

Sibs of a proband

- Because MWS typically occurs as a *de novo* mutation, the risk to the sibs of a proband is small.
- Germline mosaicism has been suggested in two families with two and three affected sibs, respectively [McGaughran et al 2005; D Mowat, personal communication]. In addition, low-level paternal mosaicism in a family with two affected sibs has been reported [Zweier et al 2005]. Thus, the risk to sibs is low (1%-2%) but greater than that of the general population because of the possibility of constitutional and/or germline mosaicism.

Offspring of a proband. There have been no reports of individuals with MWS reproducing.

Other family members of a proband. Because MWS typically occurs as a *de novo* mutation, other family members of a proband are not at increased risk.

Risk to Family Members — Chromosomal Inheritance

Parents of a proband. Parents of a proband with a structural unbalanced chromosome constitution (e.g., deletion, duplication) are at risk of having balanced chromosome rearrangement and should be offered chromosome analysis.

Sibs of a proband

- The risk to sibs of a proband with a structural unbalanced chromosome constitution depends upon the chromosome findings in the parents.

- If neither parent has a structural chromosome rearrangement, the risk to sibs is negligible.
- If a parent has a balanced structural chromosome rearrangement, the risk to sibs is increased and is dependent upon the specific chromosome rearrangement and the possibility of other variables.

Offspring of a proband. Individuals with MWS and an unbalanced chromosome rearrangement are not likely to reproduce.

Carrier testing. If a parent of the proband is found to have a balanced chromosome rearrangement, at-risk family members can be tested by chromosome analysis.

Other family members. The risk to other family members depends upon the status of the proband's parents. If a parent is found to have a balanced chromosome rearrangement, his or her family members are at risk and can be offered chromosome analysis.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methods and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Although the vast majority of MWS occurs as the result of a *de novo* mutation, prenatal diagnosis can be used to evaluate a pregnancy at theoretically increased risk because of constitutional and/or germline mosaicism in a clinically unaffected parent. In such cases, DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation is analyzed. The disease-causing allele of an affected family member should be identified before prenatal testing can be performed.

Prenatal diagnosis for pregnancies at increased risk because of parental balanced structural rearrangement is possible by chromosome analysis of fetal cells obtained by amniocentesis or chorionic villus sampling.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) may be available for families at increased risk because of parental mosaicism in which the disease-causing mutations have been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

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Table A. Molecular Genetics of Mowat-Wilson Syndrome

Gene Symbol	Chromosomal Locus	Protein Name
ZEB2	2q22	Zinc finger E-box-binding homeobox 2

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Mowat-Wilson Syndrome

235730	MOWAT-WILSON SYNDROME
605802	ZINC FINGER E BOX-BINDING HOMEOBOX 2; ZEB2

Table C. Genomic Databases for Mowat-Wilson Syndrome

Gene Symbol	Entrez Gene	HGMD
ZEB2	9839 (MIM No. 605802)	ZFHX1B

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Normal allelic variants: The *ZEB2* gene has nine coding exons (exons 2-10). Exon 1 is non-coding. A rare G>A single nucleotide polymorphism (SNP) at amino acid Tyr310 has been observed in African-derived populations (dbSNP reference rs6711223). Because this G>A SNP does not result in an amino acid change, the variant is unlikely to be pathogenic.

Pathologic allelic variants: All *ZEB2* mutations described to date in classic MWS are either large deletions or frame shift or nonsense mutations [Lurie et al 1994, Amiel et al 2001, Cacheux et al 2001, Kaariainen et al 2001, Wakamatsu et al 2001, Yamada et al 2001, Nagaya et al 2002, Zweier et al 2002, Garavelli et al 2003, Mowat et al 2003, Cerruti Mainardi et al 2004, Dastot-Le Moal et al 2007]. These results indicate that loss of a single *ZEB2* allele is required to cause classic MWS.

Evidence suggests that less severe mutations result in milder or atypical presentations of MWS.

- Yoneda et al (2002) reported a 3-bp in-frame deletion in a woman with mental retardation and late-onset megacolon but no typical facial features of MWS.
- A splice mutation in the *ZEB2* 5'UTR was described in an individual with mild MWS-like facial features and developmental delays [Zweier et al 2006].
- A p.Gln1119Arg missense mutation was reported in a child with mild features of MWS [Heinritz et al 2006].

Normal gene product: *ZEB2* is a novel member of the two-handed zinc-finger/homeodomain transcription factor family, δEF1/Zfh-1. The protein encoded by *ZEB2* is widely expressed in the developing mouse and plays an important role in the development of the neural crest. Homozygous *ZEB2* knock-out mice fail to develop because of abnormalities of the neural crest [Van de Putte et al 2003, Bassez et al 2004]. The ZEB2 protein, like other δEF1 family members, interacts with SMAD proteins and functions as a transcriptional repressor in response to TGF-β signaling [Verschueren et al 1999]. ZEB2 down-regulates E-cadherin expression, a key step in allowing epithelial cell tumor invasion [Comijn et al 2001]. Recent studies suggest that ZEB2 expression is up-regulated in tumor cells [Maeda et al 2005, Lombaerts et al 2006].

Abnormal gene product: All *ZEB2* mutations associated with classic MWS described to date result in loss of one copy of the *ZEB2* gene either by deletion or premature truncation of the protein. The clinical features of MWS are consistent with haploinsufficiency of *ZEB2* having

a negative impact on neural crest development. Persons with MWS do not have increased *ZEB2* expression and, to date, have not been reported to be at an increased risk for tumor development.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Congenital Heart Information Network
600 North 3rd Street First Floor
Philadelphia PA 19123-2902
Phone: 215-627-4034
Fax: 215-627-4036
Email: mb@tchin.org
http://tchin.org

International Foundation for Functional Gastrointestinal Disorders (IFFGD) - Pediatric
Phone: 888-964-2001
Email: aanastas@iffgd.org
www.aboutkidsgi.org

Medline Plus
Mental retardation

National Center on Birth Defects and Developmental Disabilities
Mental retardation

Pull-thru Network
2312 Savoy Street
Hoover AL 35226
Phone: 205-978-2930
Email: info@pullthrought.org
www.pullthrough.org

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Author Notes

Web site: www.genetics.emory.edu

Revision History

- 11 February 2008 (cd) Revision: del/dup analysis available clinically
- 28 March 2007 (me) Review posted to live Web site
- 1 December 2006 (vrm) Original submission

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Figure 1. An individual with Mowat-Wilson syndrome at (a) one month, (b) two months, (c) five years, (d) 13 years, (e) 20 years, and (f) 21 years. Note how the typical facial features become more pronounced with time.