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Mowat-Wilson Syndrome

Synonym: Hirschsprung Disease – Intellectual Disability Syndrome

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Summary

Clinical characteristics

Mowat-Wilson syndrome (MWS) is characterized by distinctive facial features (widely spaced eyes, broad eyebrows with a medial flare, low-hanging columella, prominent or pointed chin, open-mouth expression, and uplifted earlobes with a central depression), congenital heart defects with predilection for abnormalities of the pulmonary arteries and/or valves, Hirschsprung disease or chronic constipation, genitourinary anomalies (particularly hypospadias in males), and hypogenesis or agenesis of the corpus callosum. Most affected individuals have moderate-to-severe intellectual disability. Speech is typically limited to a few words or is absent, with relative preservation of receptive language skills. Growth restriction with microcephaly and seizure disorder are also common. Most affected people have a happy demeanor and a wide-based gait that can sometimes be confused with Angelman syndrome.

Diagnosis/testing

The diagnosis of MWS is established in a proband with classic dysmorphic facial features and developmental delay / intellectual disability and/or a heterozygous pathogenic variant in *ZEB2* identified by molecular genetic testing.

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.

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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 clinical geneticist.

Genetic counseling

MWS is an autosomal dominant disorder caused by a pathogenic variant in *ZEB2*, a heterozygous deletion of 2q22.3 involving *ZEB2*, or (rarely) a chromosome rearrangement that disrupts *ZEB2*. Almost all individuals reported to date have been simplex cases (i.e., a single occurrence in a family) resulting from a *de novo* genetic alteration; rarely, recurrence in a family has been reported when a parent has a low level of somatic or presumed germline mosaicism for a MWS-causing pathogenic variant. Individuals with MWS are not known to reproduce. Once the causative genetic alteration has been identified in the proband, prenatal testing may be offered to parents of a child with MWS because of the recurrence risk associated with the possibility of parental mosaicism or a balanced chromosome rearrangement.

Diagnosis

Formal clinical diagnostic criteria for Mowat-Wilson syndrome (MWS) have not been published. However, the facial features are recognizable and, when accompanied by other features of the condition (e.g., Hirschsprung disease and/or chronic constipation, developmental delay / intellectual disability), can establish the clinical diagnosis.

Suggestive Findings

Mowat-Wilson syndrome **should be suspected** in individuals with the following clinical features and head imaging findings:

Clinical findings

- Typical facial features (see Figure 1) include the following (see also Clinical Characteristics):
  - Widely spaced eyes
  - Broad eyebrows with a medial flare
  - Low hanging columella
  - Open-mouth expression
  - Prominent or pointed chin
  - Uplifted earlobes often with a central depression, described as resembling "orechietta pasta" or "red blood corpuscles"
- Growth restriction with microcephaly
- Intellectual disability, typically in the moderate to severe range, with severe speech impairment but relative preservation of receptive language skills
- Congenital heart defects, particularly abnormalities of the pulmonary arteries and/or valves
- Hirschsprung disease and/or chronic constipation
- Genitourinary anomalies, particularly hypospadias in males
- Seizures
- Wide-based gait
- Happy personality

Head imaging findings. Abnormalities of the corpus callosum (hypogenesis or agenesis)

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.

Establishing the Diagnosis

The diagnosis of Mowat-Wilson syndrome **is established** in a proband with classic dysmorphic facial features and developmental delay / intellectual disability and/or by the identification of **one of the following** on molecular genetic testing (see Table 1):

- A heterozygous pathogenic (or likely pathogenic) variant involving *ZEB2* (in ~84% of affected individuals) [Garavelli et al 2009, Saunders et al 2009]
- A heterozygous deletion of 2q22.3 involving *ZEB2* (~15% of affected individuals) [Dastot-Le Moal et al 2007, Ivanovski et al 2018]

Note: (1) Chromosome rearrangements that disrupt *ZEB2* cause MWS in approximately 1% of cases [Dastot-Le Moal et al 2007]. (2) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include any likely pathogenic variants. (3) Identification of a heterozygous *ZEB2* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (chromosomal microarray analysis, exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of MWS is broad, individuals with the distinctive features described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of MWS has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic findings suggest the diagnosis of MWS, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *ZEB2* detects missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected.

  Perform sequence analysis first. If no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

  Note: Larger deletions or duplications of chromosome 2q22.3 that include *ZEB2* and adjacent genes will be detected through gene-targeted deletion/duplication analysis, but such testing cannot determine how large the deletion or duplication is or whether adjacent genes are involved. Chromosomal microarray in this scenario could be used to determine this information.

- **An intellectual disability or seizure disorder multigene panel** that includes *ZEB2* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of MWS is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Chromosomal microarray analysis (CMA)** is often performed first. If CMA is normal, **exome sequencing** is the most commonly used next genomic testing method; **genome sequencing** is also possible.

Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *ZEB2*) that cannot be detected by sequence analysis.

If **exome sequencing** is not diagnostic, exome array (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis or may be too small to be detected by CMA.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Karotype. If the phenotype is consistent with MWS but the above-mentioned studies do not detect a pathogenic variant involving *ZEB2*, conventional cytogenetic analysis can be considered to exclude other large cytogenetic abnormalities or rare chromosome rearrangements that involve *ZEB2* [Kluk et al 2011].

Table 1. Molecular Genetic Testing Used in Mowat-Wilson Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2, 3] Detectable by Method
ZEB2	Sequence analysis [4]	~82% [5, 6]
	Gene-targeted deletion/duplication analysis [7]	~17% [8, 9]
	Chromosomal microarray analysis (CMA) [10]	~15% [9]
	Karyotype	~1% [11]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. The ability of the test method used to detect a variant that is present in the indicated gene
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Approximately 50% of *ZEB2* pathogenic variants localize to exon 8 [Saunders et al 2009].
6. Garavelli et al [2009], Ivanovski et al [2018]
7. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
8. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes may not be detected by these methods.
9. Dastot-Le Moal et al [2007], Ivanovski et al [2018]
10. CMA uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *ZEB2*) that cannot be detected by sequence analysis. The ability to determine the size of the deletion/duplication depends on the type of microarray used and the density of probes in the 2q22.3 region. CMA designs in current clinical use target the 2q22.3 region.
11. Mowat et al [1998]

Clinical Characteristics

Clinical Description

More than 300 individuals with Mowat-Wilson syndrome (MWS) have been reported in the medical literature [Ivanovski et al 2018]. The male-to-female ratio is roughly equivalent (183:161), although earlier reports suggested a male predominance [Ivanovski et al 2018].

Table 2. Selected Clinical Features in Mowat-Wilson Syndrome by Frequency

Clinical Feature	Approximate Frequency
Seizures	79%
Microcephaly [1]	78%
Hypospadias in males	60%
Congenital heart defects	58%
Short stature [2]	46%
Hirschsprung disease (HSCR)	44%
Cryptorchidism in males	41%

Table 2. continued from previous page.

Clinical Feature	Approximate Frequency
Constipation (w/o known HSCR)	29%
Renal anomalies	25%
Structural eye anomalies	10%
Pyloric stenosis	7%
Pulmonary artery sling	3%
Cleft palate	2%

Adapted from Ivanovski et al [2018]
1. Head circumference ≥2 SD below the mean for age and sex
2. Length or height ≥2 SD below the mean for age and sex

Craniofacial Features

Distinctive craniofacial features are one of the most specific findings (see Suggestive Findings), present in more than 90% of affected individuals.

The facial phenotype evolves and becomes more pronounced with age (Figure 1), such that the diagnosis is easier to make in older individuals [Garavelli et al 2009]:

- The eyebrows may become heavier, broad, and horizontal.
- The nasal tip lengthens and becomes more depressed and the nasal profile becomes more convex.
- The columella becomes more pronounced, leading to the appearance of a short philtrum.
- The face tends to elongate and the jaw becomes more prominent.

However, the ear configuration does not change significantly with age, with the exception of the central depression, which is less obvious in adults.

Additional suggestive facial features include the following:

- Telecanthus
- Deeply set eyes
- Wide nasal bridge with prominent and rounded nasal tip
- Thick or everted vermilion of the lower lip
- Increased posterior angulation of the ears

Other rare craniofacial findings include the following:

- Palatal anomalies (bifid uvula, submucous cleft palate, and cleft of the hard palate)
- Right unicoronal craniosynostosis [Wenger et al 2014]

Growth

Birth weight and length are typically in the normal range.

Microcephaly (head circumference ≥2 SD below the mean) is most often acquired but can be present at birth.

Short stature (defined as length or height 2 SD below the mean) typically develops over time, with a mean adult height of 165.1 cm in males and 150.5 cm in females [Ivanovski et al 2018].

Body habitus is frequently lean and slender, with about 30% of affected individuals having a weight below the third centile for age and sex.

Eyes

Strabismus is the most common finding, present in more than half of affected individuals. Astigmatism and myopia are also common findings. Nystagmus has been described in some individuals, particularly in infancy; it often resolves with age.

About 10% of affected individuals have structural eye anomalies, including the following [Ivanovski et al 2018]:

- Microphthalmia
- Iris/retinal colobomas, which sometimes can lead to a suspicion of CHARGE syndrome [Wenger et al 2014] (See Differential Diagnosis.)
- Axenfeld anomaly
- Ptosis
- Cataract
- Retinal aplasia

Ears

Recurrent otitis media, which can cause conductive hearing loss, has been described in about one third of affected individuals. Due to a high pain threshold seen in many affected individuals (see Psychosocial and Cognitive Development), unexplained fever should prompt the clinician to consider otitis media as a potential cause.

Sensorineural hearing loss has only rarely been described [Abdalla & Zayed 2014, Ivanovski et al 2018].

Dental Findings

Widely spaced teeth, malpositioned teeth, delayed tooth eruption, malformed teeth, dental crowding, gingival hypertrophy, and/or bruxism have been described [Kiraz et al 2013, Ivanovski et al 2018].

Cardiovascular Defects

Structural heart defects are present in almost 60% of individuals with MWS. The most common findings are septal defects and patent ductus arteriosus. More complex congenital heart defects, however, have been reported and include the following [Ivanovski et al 2018]:

- Pulmonary stenosis (in ≤20%)
- Coarctation of the aorta (in ≤10%)
- Bicuspid aortic valve
- Aortic valve stenosis
- Tetralogy of Fallot
- Pulmonary artery sling, with or without congenital tracheal stenosis (<4%). However, this finding is even less common in the general population, and thus pulmonary artery sling alone should prompt the clinician to consider a diagnosis of MWS.

Gastrointestinal Issues

MWS was initially described as a syndromic form of Hirschsprung disease (HSCR); however, only 44% of individuals with MWS have biopsy-proven HSCR.

Chronic constipation has been described in about 30% of persons with MWS without documented HSCR [Garavelli et al 2009, Ivanovski et al 2018]. It is unclear whether chronic constipation results from ultrashort HSCR or the presence of some other partial defect in ganglion function.

Chronic constipation typically becomes more common with age, likely due to a combination of factors, including insufficient liquid intake, low-fiber diet, and less vigilance in tracking stool output and consistency by caregivers [Niemczyk et al 2017].

Surgical outcomes for Hirschsprung disease in individuals with MWS are generally worse than surgical outcomes for those with nonsyndromic HSCR; complications may include prolonged need for total parenteral nutrition and/or recurrent enterocolitis [Bonnard et al 2009, Smigiel et al 2010]. The increased complication rate may be due in part to a generalized gut motility disorder.

Other gastrointestinal findings include the following:

- Repeated vomiting attacks in about 20% [Ivanovski et al 2018]
- Pyloric stenosis in 5% of affected individuals
- Dysphagia (rare) [Garavelli et al 2009, Prijoles & Adam 2010]

Renal Anomalies

Renal anomalies are present in about one quarter of affected individuals and most commonly consist of vesicoureteral reflux and hydronephrosis. Other, less common findings may include duplex kidney, pelvic kidney, and multicystic renal dysplasia.

Genital Anomalies

About 60% of males have hypospadias, while about 40% have cryptorchidism. Less common findings in males may include bifid scrotum, penile chordee or "webbed penis," micropenis, or hydrocele.

Septum of the vagina has been described rarely in females.

Pubertal Development

Very little has been written regarding pubertal development in MWS. One female age 17 years 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]. In the experience of the authors, most affected adults undergo typical pubertal development.

Skeletal Findings

A variety of skeletal manifestations have been described in individuals with 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 is also common.

Findings seen in up to 50% of affected individuals include the following:

- Pectus anomalies (excavatum or carinatum)
- Scoliosis
- Adducted thumbs
- Ulnar deviation of the hands
- Mild contractures of the joints and/or camptodactyly
- Genu valgus
- Pes planus
- Long toes with or without long and/or broad halluces
- Hallux valgus
- Delayed bone age
- Syndactyly

Rarely, individuals with MWS have sustained frequent fractures that responded to bisphosphonate therapy [Author, personal observation]. This is most likely a secondary finding resulting from decreased weight-bearing activity.

Neurologic Findings

Neurologic findings are very common in individuals with MWS.

Tone. A majority of individuals younger than age one year have hypotonia. Hypotonia occasionally transitions to spasticity in adolescence or adulthood. Spasticity can lead to joint contractures and mobility issues, which in turn can cause decreased weight-bearing activity and an increased risk of low bone mineral density with propensity to fractures.

Seizures are one of the most common neurologic issues in individuals with MWS, present in almost 80% [Cordelli et al 2013, Ivanovski et al 2018].

Mean age of onset is around three years, although first presentation of seizure as early as age one month and as late as 11 years has been reported [Ivanovski et al 2018].

Multiple seizure types have been described; types most frequently seen are focal and atypical absence seizures. For many individuals, the first seizure is a focal seizure associated with fever.

Up to 25% of affected individuals have seizures that are difficult to control (more so in childhood than in adolescence or adulthood) or refractory to conventional anti-seizure medications:

- Vagal nerve stimulator implantation resulted in reduction of seizure frequency in at least two affected individuals.
- In at least one other case, anti-seizure medications were discontinued in adulthood with no recurrence of seizures.

EEG abnormalities may be age dependent. EEGs performed at seizure presentation frequently demonstrate only mild slowing of background activity or are interpreted as normal. Repeat studies may show irregular diffuse frontally dominant and occasionally asymmetric spike and wave discharges. During slow-wave sleep the abnormalities are accentuated, resulting in continuous or near-continuous spike and wave activity [Cordelli et al 2013].

- Electrical status epilepticus during sleep (ESES) has been described in several individuals who have undergone overnight EEG studies [Bonanni et al 2017].
- The presence of ESES can negatively affect behavior as well as motor and cognitive function.
- Evaluation for ESES should be considered in any affected individual who has experienced regression in cognitive function or motor skills, such as the development of ataxia or dyspraxia.
- Seizure activity does not appear to correlate with structural brain anomalies.

Central Nervous System

Central nervous system anomalies are present in approximately half of individuals who have been imaged. The most common findings are abnormalities of the corpus callosum (i.e., hypoplasia, partial or complete agenesis). A variety of other anomalies, including the following [Garavelli et al 2017], have been described.

- Ventricular enlargement (lateral ventricle or ventricular temporal horn)
- Abnormalities of the hippocampus
- Cortical malformations (polymicrogyria, periventricular heterotopia, focal cortical dysplasia)
- Reduction of white matter thickness
- Localized signal alterations of the white matter

- Posterior fossa malformations (absent or small cerebellar vermis, macrocerebellum)
- Large basal ganglia

Psychosocial and Cognitive Development

All individuals with classic MWS have moderate to severe intellectual disability, although the results of formal IQ testing have not been reported in most studies. Individuals with pathogenic missense variants may have milder features, including milder cognitive disabilities (see Genotype-Phenotype Correlations).

Speech. The vast majority of affected individuals older than age one year have severely impaired verbal language skills, with either absent or severely restricted speech. Rare individuals with classic MWS have some speech capabilities, including the ability to use short sentences [Author, personal observation].

- Receptive language skills are generally more advanced than expressive language skills.
- Sign language and communication boards have been used by some affected individuals with limited success.

Gross motor milestones are generally delayed.

- Mean age of walking is between ages three and four years (range: 23 months to 8 years); some individuals do not achieve ambulation.
- The gait is typically wide based with the arms held up and flexed at the elbow.

Fine motor skills are also delayed. Most affected individuals require lifelong help with dressing and other activities of daily living.

Toileting. Most individuals with MWS remain incontinent of both feces and urine throughout life [Niemczyk et al 2017].

- Adaptive toileting skills (waking at night to urinate, using the toilet) improve with age, although most affected individuals are unable to be completely toilet trained.
- Treatment of chronic constipation may help with urinary incontinence (see Gastrointestinal Issues).

Behavior. Many individuals have been described as having a happy demeanor with frequent laughter. In comparison to individuals who have moderate-to-severe cognitive impairment due to other causes, individuals with MWS display similarly high levels of behavioral or emotional findings, including disruptive/antisocial behavior, self-absorbed behavior, and anxiety [Evans et al 2012]. Other associated behaviors seen in more than half of affected individuals include:

- Repetitive behaviors
- Oral behaviors, including mouthing and/or chewing objects or body parts
- Underreaction to pain

Sleep. About half of individuals with MWS have some degree of sleep disturbance, which may include frequent nighttime waking and early morning wakening [Evans et al 2016]. Clinicians should consider screening individuals with MWS for features of sleep disturbance, with referral to a sleep disorders clinic if there are clinical concerns.

Immunologic Findings

Asplenia has been reported in several individuals with MWS; one individual had a severe course that included purpura fulminans [Nevarez Flores et al 2019]. Immunodeficiency in individuals with MWS has not been systematically studied, although several affected individuals have required treatment with intravenous immunoglobulin (IVIG) for antibody deficiency leading to recurrent infections [Author, personal observation].

Anesthesia Risk

The most common management issue is the rare finding of a difficult airway at the time of intubation [Deshmukh et al 2016, Packiasabapathy et al 2016]. Other reported anesthetic challenges have included longer time to wean respiratory support, presence of anemia, and concomitant lower respiratory-tract infection [Spunton et al 2018]. However, there does not appear to be a true increased risk of adverse outcome from anesthesia due to this condition itself.

Additional Findings

The following findings have each been described in one affected individual. It is unclear whether these are rare features of MWS or if they represent unrelated co-occurrences.

- Cholestasis with histopathologic features of biliary atresia [Cui et al 2011]
- Medulloblastoma and glioblastoma [Valera et al 2013]
- Rhabomyosarcoma [Rogac et al 2017]
- Supernumerary intestinal muscle coat [Leong et al 2010]

Prognosis

It is unknown if life span in individuals with Mowat-Wilson syndrome is abnormal. One reported individual is alive at age 60 years [Author, personal observation], demonstrating that survival into adulthood is possible. Since many adults with disabilities have not undergone advanced genetic testing, it is likely that adults with this condition are underrecognized and underreported.

Genotype-Phenotype Correlations

ZEB2 deletions and truncating variants 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, except for individuals with extremely large deletions (>5 Mb) that include multiple adjacent genes.

In general, those with a whole-gene deletion are more likely to have earlier onset of seizures and are at greater risk for epilepsy that is refractory to multiple medications, compared to those in whom a defective protein is likely to be produced [Garavelli et al 2017].

Missense, splice site, or in-frame variants in *ZEB2* represent fewer than 5% of all reported cases and fewer than 2% of those with typical MWS [Garavelli et al 2017]. These types of variants are frequently associated either with a milder form of MWS or with atypical features. Individuals reported in the literature with atypical features of MWS include the following:

- Three missense variants in the highly conserved C-zinc-finger domain of *ZEB2* appear to lead to the facial gestalt of MWS with moderate intellectual impairment but without other features of MWS [Ghoumid et al 2013].
- An adult with mild intellectual disability, atypical facial features, and megacolon had a 3-bp in-frame deletion of *ZEB2* [Yoneda et al 2002].
- A person with mild facial features (atypical but reminiscent of the MWS gestalt) had only mild speech delay and a novel splice site variant in the 5'UTR [Zweier et al 2006].
- A person with a missense variant had cleft lip/palate, brachytelephalangy, and atypical eyebrows [Heinritz et al 2006].

Prevalence

The prevalence of MWS has been estimated at between 1:50,000 and 1:70,000 live births [Mowat & Wilson 2010].

Genetically Related (Allelic) Disorders

No phenotype other than those discussed in this *GeneReview* is currently known to be associated with pathogenic variants in *ZEB2*.

Differential Diagnosis

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 are summarized in Table 3.

Table 3. Disorders and Genes of Interest in the Differential Diagnosis of Mowat-Wilson Syndrome (WMS)

Gene(s)	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/MWS	Distinguishing from MWS
CHD7	CHARGE syndrome	AD	• Iris/retinal colobomas • Congenital heart defects • Cryptorchidism in males • ID	• Facial features, incl different ear configurations • Choanal atresia/stenosis • Higher frequency of iris/retinal colobomas than in MWS • No Hirschsprung disease
CREBBP *EP300*	Rubenstein-Taybi syndrome	AD	• Nasal configuration & ID • Several persons w/MWS have had broad thumbs & great toes; at least 1 had radial deviation of thumbs & great toes similar to hand & foot findings in RSTS. [1]	Facial features & spectrum of congenital anomalies
DHCR7	Smith-Lemli-Opitz syndrome [2]	AR	Hypospadias in males, microcephaly, & ID	• Facial features • Higher frequency of cleft palate than in MWS • Postaxial polydactyly • 2-3 toe syndactyly
KIFBP (formerly *KIF1BP*)	Goldberg-Shprintzen syndrome (OMIM 609460)	AR	HSCR, microcephaly, & ID	• Facial features & spectrum of congenital anomalies • Higher frequency of cleft palate, ptosis, & ocular coloboma than in MWS
TCF4	Pitt-Hopkins syndrome	AD	Significant ID w/mean age of walking at 4-6 yrs; absent or severely impaired verbal language, behavioral issues, hand stereotypic movements, seizures, microcephaly, & constipation	• Characteristic facial features • PTHS may be assoc w/episodic hyperventilation &/or breath holding while awake.

Table 3. continued from previous page.

Gene(s)	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/MWS	Distinguishing from MWS
UBE3A	Angelman syndrome	See footnote 3.	• Absent speech, hypopigmentation, seizures, microcephaly, ataxic-like gait, & happy demeanor • In infancy, only hypotonia may be evident.	Absence of multitude of congenital anomalies & characteristic facial features of MWS

AD = autosomal dominant; AR = autosomal recessive; DiffDx = differential diagnosis; HSCR = Hirschsprung disease; ID = intellectual disability; MOI = mode of inheritance; RSTS = Rubenstein-Taybi syndrome

1. Mowat et al [2003], Adam et al [2006]

2. Smith-Lemli-Opitz syndrome is associated with elevated serum concentration of 7-dehydrocholesterol (7-DHC) or an elevated 7-dehydrocholesterol:cholesterol ratio.

3. Angelman syndrome is caused by disruption of maternally imprinted *UBE3A* located within the 15q11.2-q13 Angelman syndrome / Prader-Willi syndrome (AS/PWS) region. The risk to sibs of a proband depends on the genetic mechanism leading to the loss of *UBE3A* function: typically less than 1% risk for probands with a deletion or UPD, and as high as 50% for probands with an imprinting defect or a *UBE3A* pathogenic variant.

Other syndromic forms of Hirschsprung disease (HSCR) may also be considered.

Management

Clinical management guidelines for Mowat-Wilson syndrome have been published [Ivanovski et al 2018] (full text).

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with Mowat-Wilson syndrome, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Mowat-Wilson Syndrome

System/Concern	Evaluation	Comment
Eyes	Ophthalmologic eval	To assess for eye anomalies, strabismus, & refractive error
Ears	Audiologic eval	To assess for hearing loss
Mouth	Dental eval	Early in childhood, typically starting at age ~3 yrs
Cardiovascular	EKG & echocardiogram, ideally w/ cardiologist consultation	To assess for structural heart defects
Gastrointestinal	Assess for signs & symptoms of dysphagia.	Consider VFSS for those w/suggestive features.
	Assess for history of chronic constipation.	Referral to GI specialist for eval of possible HSCR &/or primary gut motility issues
		Treatment of chronic constipation may improve rates of urinary incontinence.

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Genitourinary	Abdominal ultrasound	To assess for structural renal anomalies AND presence of a spleen
	Assessment for hypospadias &/or cryptorchidism in males	Consider referral to urologist.
	Assessment for degree of incontinence in older children, adolescents, & adults	Consider referral to functional incontinence clinic, typically directed by urologist.
Musculoskeletal	Assessment for pectus anomalies & foot/ankle malposition	Consider referral to orthopedist.
Neurologic	Head MRI & EEG [1] if seizures are suspected	Consider referral to neurologist.
Development	Developmental assessment	• Incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Psychiatric/ Behavioral	Consider neuropsychiatric eval.	Incl screening for presence of behavioral findings, incl sleep disturbances, ADHD, anxiety
		Consider polysomnogram if concerns about sleep disturbance.
Immunologic	Abdominal ultrasound	To assess for presence of spleen AND for renal anomalies
	Consider immunologic eval [2] & referral to immunologist.	For those w/recurrent or unexplained infection
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	Incl genetic counseling
	Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.

ADHD = attention-deficit/hyperactivity disorder; HSCR = Hirschsprung disease; VFSS = videofluoroscopic swallowing study
1. EEG in awake and asleep state is recommended; consider overnight EEG to evaluate for electric status epilepticus during sleep (ESES), particularly for those with regression of developmental skills or focal neurologic dysfunction, dyspraxia, or ataxia [Bonanni et al 2017].
2. Which may include immunoglobulin levels (IgG, IgM, Ig A) and T and B cell subsets

Treatment of Manifestations

Table 5. Treatment of Manifestations Following in Individuals with Mowat-Wilson Syndrome

Manifestation/Concern	Treatment	Comment
Strabismus, refractive error, eye anomalies	Standard treatment per ophthalmologist	
Hearing loss / chronic otitis media	Standard treatment per otolaryngologist	
Dental anomalies	Standard treatment per dentist/orthodontist	
Congenital heart defects	Standard treatment per cardiologist	

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Comment
Dysphagia/GERD	Standard treatment, which may incl thickened feeds & appropriate positioning after meals in infants & toddlers	Pharmacologic treatment for GERD may be considered.
	Consider gastrostomy tube.	In those w/severe feeding difficulties &/or poorly coordinated suck & swallow
Hirschsprung disease	Standard treatment, incl resection of aganglionic section	
Chronic constipation	Standard treatment, incl osmotic laxatives & suppositories	Consider referral to gut motility specialist for those w/refractory issues.
Hydronephrosis	Standard treatment per urologist &/or nephrologist	
Hypospadias &/or undescended testes	Standard treatment per urologist	
Urinary incontinence	Multifaceted approach typically directed by urologist based on degree of cognitive abilities & constellation of medical issues [1]	Treatment of chronic constipation may help.
Foot/ankle malposition	Standard treatment per orthopedist	
Frequent fractures	Consider bisphosphonate therapy w/referral to endocrinologist	Continue to encourage weight-bearing activities, incl standing &/or walking
Spasticity	Orthopedics / physical medicine & rehab / PT/OT incl stretching to help avoid contractures & falls	Consider need for positioning & mobility devices, disability parking placard
Seizure disorder	Standard treatment per neurologist	Standard ASMs are effective for most affected persons.
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Asplenia	Standard treatment [2]	
Immunoglobin deficiency	IVIG therapy	For those w/recurrent infections
Family/Community	Ensure appropriate social work involvement to connect families w/local resources, respite, & support.	Ongoing assessment for need of home nursing
	Care coordination to manage multiple sub-specialty appointments, equipment, medications, & supplies	

ASM = anti-seizure medication; GERD = gastroesophageal reflux disease; IVIG = intravenous immunoglobulin therapy
1. See von Gontard [2013]
2. Including administration of pneumococcal vaccine (and other vaccines as indicated); consideration of prophylactic antibiotics in children

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or

cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine if any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation, fractures).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, or orthopedic procedures.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses or feeding refusal that is not otherwise explained. Assuming that the individual is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Social/Behavioral Concerns

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavioral management strategies or providing prescription medications, when necessary.

Surveillance

The specific features present in any given individual typically guide surveillance. Follow up with a cardiologist, gastroenterologist, neurologist, urologist, and developmental pediatrician as clinically indicated. In addition, the evaluations summarized in Table 6 should be considered.

Table 6. Recommended Surveillance for Individuals with Mowat-Wilson Syndrome

System/Concern	Evaluation	Frequency
Constitutional	Assess growth parameters.	Every 6 mos for 1st 3 yrs of life, then annually
Eyes	Ophthalmologic eval	Annually until age 6 yrs or based on clinical concerns
Ears	Audiologic eval	Annually until age 3 yrs, then based on clinical concerns
Mouth	Dental eval	At least annually
Gastrointestinal	Assess for chronic constipation.	At each visit
Neurologic	Monitor those w/seizures as clinically indicated.	
Development	Monitor developmental progress & educational needs.	At each visit during childhood & adolescence
Miscellaneous/ Other	Assess family need for social work support (e.g., respite care, home nursing; other local resources) & care coordination.	At each visit

Agents/Circumstances to Avoid

At least one individual with tantrums and difficulties focusing had worsening aggression after a trial of stimulant medication [Besterman & Hendren 2015]. Stimulant medication should be used with caution in individuals with MWS.

Evaluation 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 in the US and EU Clinical Trials Register in Europe 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.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Mowat-Wilson syndrome (MWS), an autosomal dominant disorder, is caused by a pathogenic variant in *ZEB2*, a heterozygous deletion of 2q22.3 involving *ZEB2*, or a chromosome rearrangement that disrupts *ZEB2*.

Almost all individuals reported to date have represented simplex cases (i.e., a single occurrence in a family) resulting from a *de novo* genetic alteration.

Risk to Family Members – Pathogenic Variant in *ZEB2* or 2q22.3 Deletion

Parents of a proband

- Most probands reported to date with MWS whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo ZEB2* pathogenic variant or 2q22.3 deletion.
- Parents of a proband are not affected.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the genetic alteration found in the proband cannot be detected in the leukocyte DNA of either parent, the pathogenic variant most likely occurred *de novo* in the proband. Another possible explanation is that the proband inherited a pathogenic variant from a parent with germline mosaicism (or somatic and germline mosaicism). Somatic and presumed parental germline mosaicism has been reported [McGaughran et al 2005, Zweier et al 2005, Cecconi et al 2008, Ohtsuka et al 2008].

Sibs of a proband

- Because MWS typically occurs as a *de novo* pathogenic variant, the risk to sibs is low (~2%) but greater than that of the general population because of the possibility of parental germline mosaicism.
- Presumed parental germline mosaicism has been reported in rare families with recurrence of MWS in sibs [McGaughran et al 2005, Zweier et al 2005, Cecconi et al 2008, Ohtsuka et al 2008].

Offspring of a proband. Individuals with MWS are not known to reproduce.

Other family members. Given that most probands with MWS reported to date have the disorder as a result of a *de novo* genetic alteration, the risk to other family members is presumed to be low.

Risk to Family Members – Chromosome Rearrangement

Parents of a proband

- Parents of a proband are not affected with MWS but are at risk of having a balanced chromosome rearrangement.
- Recommendations for the evaluation of asymptomatic parents of a proband with a chromosome rearrangement include routine karyotyping with additional FISH analysis to determine if a balanced chromosome rearrangement involving the 2q22.3 region is present.

Sibs of a proband. The risk to sibs of a proband with a chromosome rearrangement that disrupts *ZEB2* depends on the chromosome findings in the parents:

- If neither parent has a chromosome rearrangement, the risk to sibs is negligible.
- If a parent has a balanced chromosome rearrangement, the risk to sibs is increased and depends on the specific chromosome rearrangement.

Offspring of a proband. Individuals with MWS are not known to reproduce.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has a balanced chromosome rearrangement, the parent's family members may be 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/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who may be at risk of having a child with MWS.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Prenatal testing for at-risk pregnancies and preimplantation genetic testing require prior identification of the MWS-causing genetic alteration in the proband and/or of balanced carrier status in a parent. However, risk to future pregnancies is presumed to be low as the MWS-causing genetic alteration in the proband most likely occurred *de novo*.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **CDC - Developmental Disabilities**
  Phone: 800-CDC-INFO
  Email: cdcinfo@cdc.gov
  Intellectual Disability

- **MedlinePlus**
  Intellectual Disability

- **Pull-thru Network**
  Phone: -309-262-0786
  Email: info@pullthrunetwork.org
  pullthrunetwork.org

- **Mowat-Wilson Syndrome Patient Registry**

Mowat-Wilson Syndrome Foundation
4009 Tyler William Lane
Las Vegas NV 89130-2628
Phone: 702-658-5391
www.mowat-wilson.org/matrix

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Mowat-Wilson Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ZEB2	2q22.3	Zinc finger E-box-binding homeobox 2	ZEB2 database	ZEB2	ZEB2

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Mowat-Wilson Syndrome (View All in OMIM)

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

Molecular Pathogenesis

ZEB2, a novel member of the two-handed zinc-finger/homeodomain transcription factor family ΔEF1/Zfh-1, comprises nine coding exons (exons 2-10). Exon 1 is noncoding.

ZEB2 is widely expressed in the developing mouse and plays an important role in the development of the neural crest, consistent with the clinical features of MWS. 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]. Homozygous *Zeb2* knockout mice fail to develop because of abnormalities of the neural crest [Van de Putte et al 2003, Bassez et al 2004].

Studies in animal models may help explain the clinical features of MWS:

- **Seizures.** Mouse models have shown that murine Zeb2 is required for differentiation and guidance of cortical neurons, a process critical for proper neurodevelopment [McKinsey et al 2013, van den Berghe et al 2013].
- **Hirschsprung disease.** Murine Zeb2 interacts with Sox10, a protein critical for the development of the enteric nervous system [Stanchina et al 2010].

Mechanism of disease causation. All *ZEB2* pathogenic variants described to date in individuals with classic features of MWS are either large deletions or frameshift or nonsense variants [Dastot-Le Moal et al 2007, Ivanovski et al 2018]. These results indicate that loss of a single *ZEB2* allele is required to cause classic MWS.

Evidence suggests that less severe pathogenic variants result in milder or atypical presentations of MWS (Table 7).

Table 7. Notable *ZEB2* Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_014795.3	c.-69-1G>A	--	Described in an individual w/mild MWS-like facial features & DD [Zweier et al 2006]
NM_014795.3 NP_055610.1	c.3134A>G	p.His1045Arg	Assoc w/facial gestalt of MWS w/moderate ID but w/o other features of MWS [Ghoumid et al 2013]
	c.3164A>G	p.Tyr1055Cys	
	c.3211T>C	p.Ser1071Pro	
	c.298_300delAAC	p.Asn100del	Reported in a woman w/ID & late-onset megacolon but w/o typical facial features of MWS [Yoneda et al 2002]
	c.3356A>G	p.Gln1119Arg	Reported in a child w/mild features of MWS [Heinritz et al 2006]

DD = developmental delay; ID = intellectual disability
Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

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