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REVIEW

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Mowat-Wilson syndrome: unraveling the complexities of diagnosis, treatment, and symptom management

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Abstract

Mowat-Wilson syndrome can be mentioned as one of the most severe and, at the same time, rare genetic abnormalities. The inheritance pattern of this disorder is an autosomal dominant pattern. In this disease, the *ZEB2* gene becomes abnormal. The severity of the disease and associated signs and symptoms can vary widely but may include distinct facial features, developmental delay, intellectual disability, and Hirschsprung. MWS treatment may vary based on the specific symptoms that appear in each individual. This review will examine the gene involved in this disease, phenotype, clinical manifestations, ways of diagnosis, and treatment of this disease.

Keywords Hirschsprung, Mowat-Wilson syndrome, MWS, Rare disease, ZEB2

Introduction

Mowat-Wilson syndrome (MWS: OMIM 235730) is a rare genetic disorder inherited in an autosomal dominant pattern attributed to a chromosomal imbalance in 2q22 or a heterozygote mutation in the *ZEB2* gene. *ZEB2* interacts with the histone deacetylase complex through TGF-β and SMADs pathways, playing a crucial role in brain and nervous system formation [1, 2].

Drs. David R. Mowat and Meredith J. Wilson identified this disease in 1998 known by other names such as Hirschsprung disease-mental retardation syndrome, Hirschsprung disease-intellectual disability syndrome, and MWS. The prevalence of this disorder is not correctly identified as people may sometimes not develop specific phenotype symptoms. However, one of the most important ways to identify these patients is their facial characteristics. However, since this disease includes a variety of symptoms from mild to severe, some mild cases may not be diagnosed, and therefore, the number of patients is higher than expected [3, 4]. Still, they may include distinctive facial features, skeletal abnormalities, congenital heart defects, genital and urinary abnormalities, Hirschsprung, slow growth before and after birth, and intellectual disability [5]. This disease overlaps with some diseases, such as Pitt–Hopkins syndrome, genitopatellar syndrome, and several other diseases [6]. Therefore, the accurate diagnosis of this disease is both a challenging and vital task because the subsequent treatments and measures to improve the physical condition and the spirit of the patient and his family depend on the correct diagnosis [7, 8]. Since this disease can endanger the affected person's life in severe cases, it is imperative to start treatment early. Also, genetic counseling for family members is one of the most fundamental approaches to prevent more cases. Considering the importance of genetic disorders and their spread in some societies, we reviewed MWS syndrome, its disease mechanism, diagnosis, and other related issues.

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ZEB2

Another name of the *ZEB2* (zinc-finger E-box-binding protein 2) gene is *ZFHX1B*, *KIAA0569*, and *SIP1*, located in the long arm of chromosome 22 at 2q22. It can be said that this gene consists of six main domains, which are shown in Fig. 1. These domains, from the right, are CZF (C-terminal zinc-finger cluster), CID (C-terminal binding protein interacting domain), HD (homeodomain-like domain), SBD (SMAD-binding domain), NZF (N-terminal zinc-finger), and NIM (NuRD interacting motif) [9–12].

Mutations in the *ZEB2* gene lead to the production of a nonfunctional or insufficient ZEB2 protein and MWS disease. The altered protein fails to perform its normal regulatory functions in the intricate processes of embryonic development. This disruption has cascading effects on the expression of other genes involved in the development of the nervous system, face, and several internal organs. Individuals with Mowat-Wilson syndrome typically exhibit a distinct set of features, including characteristic facial abnormalities (such as a broad nasal bridge and prominent chin), intellectual disabilities, delayed development, seizures, and congenital heart defects. The severity of symptoms can vary among affected individuals. *ZEB2* mutations are mainly of the frameshift type, creating a premature termination codon. The frequency of nonsense mutations is next. Nevertheless, sometimes the whole gene is completely deleted, which causes a very severe phenotype of the disease. On the other hand, the missense mutation causes minor disease severity. Most mutations in this gene affect the nervous system [13–17].

ZEB2 protein plays a central role in cell function by participating in important pathways, especially the TGF-β/SMAD pathway. Through this interaction, the protein contributes to the regulation of cellular responses and developmental processes. Additionally, an important aspect of ZEB2 protein function is that it may play an important role in the restoration of histone deacetylase in the context of cancer. These features suggest that this protein is involved in epigenetic regulation, influencing gene expression patterns and cell behavior in the biological environment of tumors. Importantly, the relationship between the ZEB2 protein and CtBP further emphasizes its importance. This interaction implies a sophisticated level of coordination in cellular regulatory mechanisms, suggesting that the ZEB2 protein is not merely a passive participant but a key orchestrator in the complex interplay of molecular events governing cellular homeostasis and pathological processes [18, 19].

TGF-β/SMAD signaling

TGF-β or transforming growth factor-β is a cytokine with essential controls such as reproduction, distinction, and cell death. It is also involved in the immune and cancer system. Each TGF-β is a dimmer of the same or different subgroups that, after secretion of the cell, are inactivated and in connection with inhibitory proteins in the outer cell [20, 21]. One of the ways to activate TGF-β is the proteolytic degradation of the inhibitory proteins by the substrate enzymes. The target cells of active TGF-β may be the same cells that secrete it or cells close to them. Active TGF-β signaling is mainly carried out through the SMADs pathway. This path can be explained in 7 steps.

The dimer of TGF-β binds indirectly in the first step or directly in the second step to a receptor known as RII. In the indirect method, TGF-β first binds to RIII. RIII, a cell surface proteoglycan, acts as a co-receptor and facilitates the binding of TGF-β to RII. Also, RII is an active serine/threonine kinase that exists as a dimer in the membrane of target cells [22].

In the third step, binding the ligand to this receptor causes a dimer of another serine/threonine kinase named RI to form a complex with the RII dimer. In this complex, RII phosphorylates its target sites in RI and activates RI. In the fourth step, activated RI activates its downstream cytosolic proteins called SMADs by phosphorylation. Phosphorylation of two SMADs causes the formation of a SMAD complex that includes these two phosphorylated SMADs plus another SMAD called co-SMAD [23, 24].

In the fifth step, co-SMAD, common to all types of complexes, is not activated by the receptor. NLS sequences are expressed in phosphorylated R-SMADs in the complex formed and can bind to importin. As a result, in the sixth stage, the complex enters the nucleus. In the seventh step, importin is separated, and the complex binds to other transcription regulatory factors to recognize target sequences and regulate the expression of target genes [20]. These steps are schematically shown in Fig. 2. TGF-β, a stromal factor, can regulate and activate

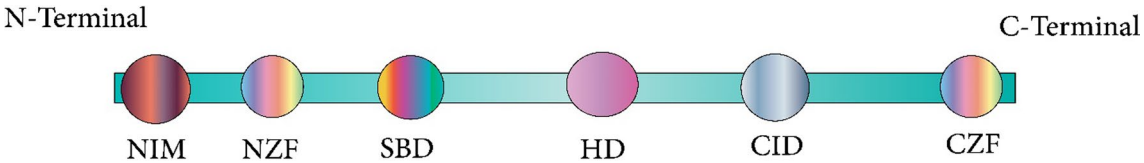

Fig. 1 Structure of the *ZEB2* gene

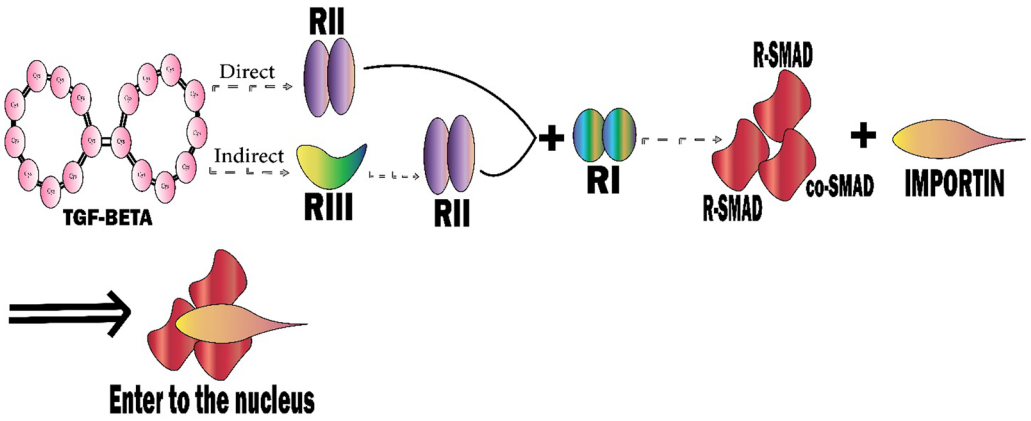

Fig. 2 TGF-β/SMAD signaling pathway for regulating the expression of target genes

the transcription factor ZEB2. As a result, defects in any of the components of this pathway can lead to different diseases.

Clinical signs

The clinical symptoms of MWS can be classified as follows:

Hirschsprung and Mowat-Wilson

Hirschsprung's disease (HSCR) is a polygenic disorder that can be considered as a disease independently or as one of the symptoms of another disease. The genes involved in this disease can include *SOX10*, *NRTN*, *GEMIN2*, *ZEB2*, *GDNF*, and many other genes that cause diseases such as metastatic melanoma, Megacolon, MWS, etc. [25–27]. The most crucial symptom of HSCR is intestinal disorders, which can range from mild to severe and must be confirmed by intestinal biopsy. The treatment of HSCR can be the isolation of the part of the intestine with an abnormality or an intestinal transplant. HSCR is seen in more than 40% of people with MWS as a secondary disease in association with the primary disease, or better words, as one of the main symptoms of MWS [3, 28–31].

Growth parameters

Usually, the three parameters that are measured to check the growth status of people with MWS include height, weight, and head circumference. At birth, growth parameters are usually in the normal range. However, from age 7, developmental problems gradually appear, and with increasing age, the difference between affected and non-affected people in the population increases. The average birth weight for these people is between 3200 and 3800 g, the average height is between 45 and 55, and the average head circumference is between 30 and 36 cm. It should be noted in the diagnosis that the head circumference of babies may be smaller than expected, but there is no microcephaly [32]. However, microcephaly is common in these patients and is seen in about 80% of cases. Most adult patients are under 150 cm tall and 50 kg in weight. One of the distinctive features of people with MWS is having a thin body, but the fit of the body is there to some extent. This narrowness can also be due to a lack of weight and BMI in affected people. Charts related to the height and weight growth of children with MWS should be provided to the pediatrician from the very beginning so that necessary measures can be taken to minimize the height and weight problems. Also, the growth charts help the doctor examine the clinical investigations related to the disease and deviation from the typical growth pattern [33].

Neurological symptoms, developmental delay, and behavioral characteristics

The mutations in the genes responsible for MWS disease can have extensive effects on the nervous system. For example, it disrupts the development of the axons and the neural tube of the fetus in the early stages, so the abnormalities related to the nervous system and brain are one of the most important These are the symptoms that the doctor should consider in the examination of patients with MWS. For example, if the expression of the Fibroblast Growth Factor 9 gene is inhibited in the six-layered cortex, it leads to a decrease in the growth of nerve progenitor cells [34]. In addition, when the transcription of secreted frizzled related protein 1, located in the anterior part of the brain, is suppressed by MWS disease mutation, it increases the apoptosis of corpus callosum cells. It is also possible that astrocytes such as Bergmann glia become abnormal, and as a result, a person with MWS

shows symptoms such as moderate-to-severe mental retardation [35–39].

Among other neurological symptoms, it is possible to refer to multiple episodes of epilepsy and sleep disorders, which are seen in about 80% of affected people and are probably due to defects in nerve cells that need GABA transmitters for their activity. Agenesis of the corpus callosum and poor hippocampal formation are observed in about 45% and 15% of patients, respectively. In these patients, the brain's lateral ventricles may expand, resulting in changes such as ventriculomegaly. Cortical atrophy with less prevalence may be present [40–42].

Developmental delay in patients is usually diagnosed with hypotonia, which is present in more than 90% of patients. Also, the time of sitting, walking, and talking in affected people has been estimated after two years, after three years, and after five years, respectively, although they may never be able to walk or talk well [43].

In many cases, psychotic symptoms have been observed, probably related to the disorder of neurons related to GABA transmitters, for example, unexplained laughter, symptoms similar to bipolar and schizophrenia, and social personality [44–46].

Heart problems

Heart problems are seen in more than half of affected cases, and it can be said that it is one of the common symptoms in MWS patients, although congenital heart symptoms are not the same in all of these people differ from person to person. Among these, the pulmonary artery is one of the cases that can be more involved. For example, in affected people, the pulmonary arteries or the valves that control the blood flow between the heart and the lungs may not be formed, or they may be narrowed due to disorders related to MWS. These abnormalities can cause complications such as pulmonary atresia and peripheral pulmonary stenosis [47, 48].

Another thing that can be mentioned is aortic valve stenosis, which can reduce blood flow or block it, so it must be evaluated in the initial examinations. Also, the aorta may not develop properly or be narrower than usual. Abnormality of the shape of the aorta has also been seen in some patients, where the aortic valve has two cusps instead of three [49–51].

In patients with MWS, ventricular septal and atrial septal defects may also be present. Also, mitral valve defect and tetralogy of fallot are other congenital heart complications in sufferers [52, 53].

Musculoskeletal abnormalities

People with MWS, mostly, and more than 90%, have a narrow body, and spinal deviation in the form of scoliosis is standard in them. One problem that falls under the musculoskeletal abnormalities category is delayed bone age. This means that when the age of patients with MWS disease increases, their age and bone growth do not increase in the same direction, but it is a much slower process than healthy people in society [33, 36, 53, 54]. Checking the bone age is considered one of the measured criteria for checking the growth and maturity of people, and it can be easily measured with an X-ray or MRI. Of course, when diagnosing, it should be noted that the delay in the bone age of a person can have many reasons and is not only specific to MWS. For example, endocrine abnormalities or disorders related to the thyroid gland can also lead to this disorder. Intra-sutural bones are another bone abnormality that may be seen in MWS people. However, it is not specific to this syndrome as in the previous case because it is also seen in many other diseases such as Osteogenesis imperfecta, Down syndrome, and rickets. In this case, if an additional bone fragment is seen in one of the joints in the skull, the patient may suffer from this condition [8, 55].

The subsequent disorder in this category is chest problems, among which pectus excavatum can be mentioned. This disorder causes depression in the chest and thorax, which overlaps with Marfan's syndrome and is one of the main symptoms of Marfan's syndrome if it is not a specific symptom of MWS disease. In this case, due to the depression in the chest, the normal function of the heart and lungs may be affected, so it is imperative to quickly diagnose this symptom because it may affect vital organs and endanger the health and life of the affected person [6, 47, 53]. Unlike pectus excavatum, which causes depression, another symptom can be pigeon chest protrusion of the sternum and chest. The side effects of this condition are not as severe as the previous one, but the heart and lungs are still affected, and it may cause complications such as shortness of breath.

Skeletal problems related to the foot in MWS sufferers are more common than other skeletal problems but have fewer side risks. For example, the bunion is a complication related to the big toe, which causes it to bend toward the other toes. Eventually, it can be a little painful or make walking difficult for these people. MWS patients may also have double toes [56]. Sometimes the toes are unusually long, about twice the length of the toes of a healthy person, which is similar to Marfan's syndrome and homocystinuria. Flat soles may also be observed, which a small percentage of patients suffer from.

Meanwhile, one of the foot problems that can cause more pain is calcaneovalgus, which causes the affected person's ankle to be deformed and the ankle to bend inward so that the toes touch the leg. Although this problem is not common, it can cause severe problems in walking if left untreated. It should be noted that the

correct diagnosis should be made in this case because this symptom can also be seen in other diseases, such as myelomeningocele and polio, and is not specific to MWS. Flat soles and clubfoot have also been reported in several cases [57].

The affected person may be unable to bend his fingers well due to complications in the proximal interphalangeal joint. The thumb of these people is short, comprehensive, and crooked, while the other fingers are long and elongated; they may also have an extra thumb. It is also possible that the finger joints of their hands are protruding [53].

Dislocation of the patella from its natural position is one of the complications seen in MWS patients. In addition, knock-knee may occur, in which the knees come into contact with each other, but at the same time, the soles of the feet are much further apart than usual, and they become crossed. About 75 to 90 percent of patients have abnormal knee abnormalities [55].

Abnormalities in the neck up

Affected people have a square face, protruding forehead, and circular skull. These people usually have a triangular chin and a small jaw. A small jaw is a problem that may not seem acute, but it is likely to disturb breathing, so treatment measures should be taken for this problem quickly. Eyebrows have a continuous state, where they are joined together, broad, and thick, and as they are separated, the eyebrow hairs become thinner and more scattered [58, 59].

As it was said, these people have developmental delays, affecting things like teething and causing teeth to grow later. Also, if the teeth grow, they are crowded and disorganized and are placed at a long distance from each other. Ear abnormalities can occur in otitis media and hearing loss, which can occur in about 35 to 40 percent of affected people [56, 60].

Eye problems are observed in less than ten percent of cases. However, various eye complications observed in patients can occur from mild to severe. For example, coloboma of the iris or retina also overlaps with Charge's syndrome. Another thing is that these people sometimes have smaller eyes than usual, and it is possible for them to have problems like myopia or astigmatism. In some cases, it has been seen that the color of the affected person's iris is different. For example, one is dark, and the other is blue. Nevertheless, more severe cases can be a wide drooping of the eyelid, which sometimes disturbs the vision. It is also possible that the pupils of the two eyes are not aligned and deviate [61, 62].

The lips of these people have a one-sided or two-sided gap with a broad lower lip and an upper lip shaped like the letter M. In addition to these, sometimes the affected person's tongue is not in the right place since the newborn period, which is a problematic case and can block the airway or make it difficult for him to swallow. The tip of the nose is prominent, bent downward, and has an eagle shape, and the distance between the nostrils is considerable. In addition, the distance between the upper lip and the nose has also increased. The baby may produce a strange and abnormal sound when breathing while awake or sleeping, probably due to an abnormality in the vocal cords, which may be due to a problem in the tissue of the larynx, which, of course, needs to be examined by a doctor [6, 53, 60, 63–65]. Visible symptoms are shown in Fig. 3.

Skin abnormalities

The presence of many wrinkles in the palms and feet of the affected person can be one of the skin symptoms that appear in them. However, it should be noted that this symptom overlaps with Costello's syndrome, and a dermatologist should make the diagnosis accurately. Sometimes, it is also possible that some areas of the skin lack pigment [16].

Genital and urinary abnormalities

In male patients, one of the testicles may be missing, and the urinary-genital duct may be defective and not formed properly. Also, sometimes it has been observed that the scrotum is divided into two parts or that the skin of the testicles sticks to the trunk of the genital organ [66].

The presence of two kidneys or kidneys with an abnormal shape and the return of urine between the kidney and the bladder are other cases seen in a small percentage of affected people. All these cases can be detected by ultrasound [67].

Other abnormalities

Secondary cases of the disease include the absence of a spleen, frequent vomiting attacks, and the presence of an extra nipple in the middle of the chest [68].

Diagnosis

MWS sufferers have specific facial features, including the shape of the eyebrows and mouth, along with epilepsy and neurological problems. Also, affected people have symptoms similar to some abnormalities, for example, in terms of Hirschsprung and microcephaly, they overlap with Shprintzen-Goldberg. In addition, the sign of hypospadias is shared between MWS and Smith-Lemli-Opitz. Moreover, Charge syndrome, which is a rare genetic syndrome, can be similar to MWS in terms of heart abnormalities, eye problems, learning problems, and cryptorchidism. It can also be said that seizures and microcephaly are common between MWS and one of the

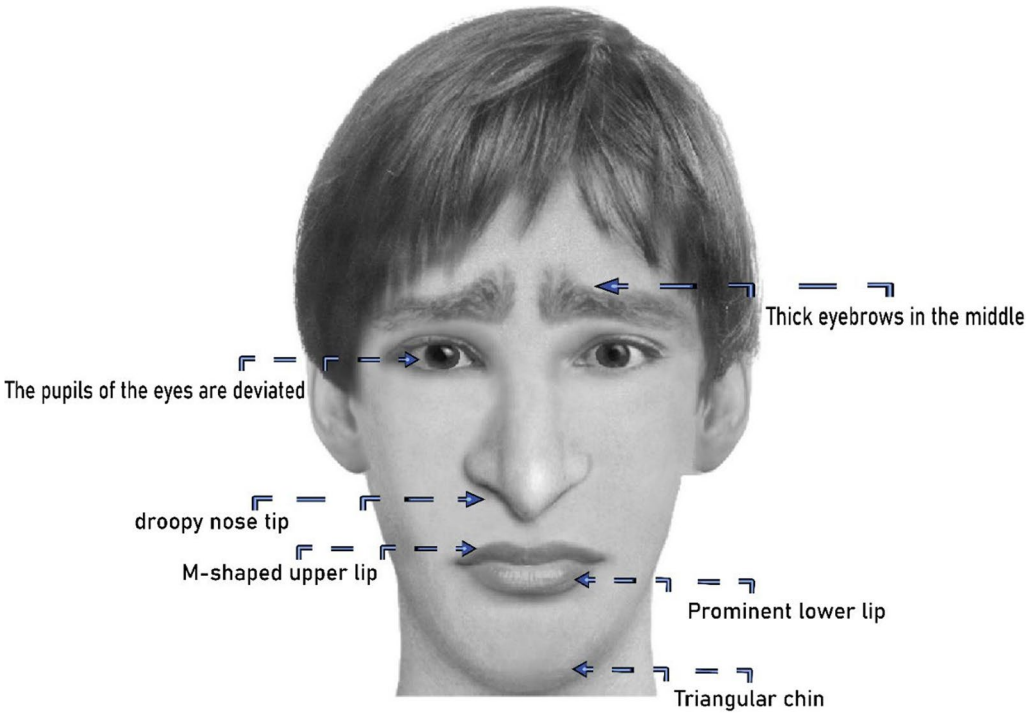

Fig. 3 Image related to MWS facial features. (*Note*: out of respect for patients' rights, this image is not related to a real person and is designed by the software)

other important genetic abnormalities called Pitt–Hopkins syndrome. Therefore, as mentioned, the diagnosis of this disease is complex and requires detailed molecular and genetic tests.

Mutations in MWS can take various forms including missense, frameshift, deletion, and chromosomal imbalance. Microdeletions can be identified using the FISH technique, while the CGH array technique detects translocations and chromosomal imbalances in 2q22. Nevertheless, in some cases, more detailed methods like next-generation sequencing may be required for a comprehensive investigation. The genetic analysis must be performed on the *ZEB2* gene [69–72]. Sequencing may reveal abnormalities, and if none are observed, targeted gene testing can be conducted, often to identify large deletions and exon duplications, but this method lacks precision in determining the exact mutation size, necessitating additional microarray tests. In addition, the valuable karyotype technique can identify genetic abnormalities even before birth. It can be said that according to the condition of the patient in each stage of the disease, one of these techniques can be used for diagnosis or confirmation of the diagnosis [73].

Therapeutic approaches

MWS is characterized by highly variable phenotypes, resulting in diverse complications contingent on the extent of gene mutation and overall health conditions. Due to the variability in symptoms among affected individuals, there is no universal treatment. Instead, treatment proposals are tailored to the specific phenotype and affected organ. So far, no standard treatment has been found for this disease, and all solutions have supported increasing patients' quality of life. Genetic counseling is one of the crucial things suggested to people with MWS and the patient's family because it can help manage the disease better and more efficiently [74].

Since this patient shows symptoms almost from the beginning of birth, medical follow-up is necessary to prevent severe complications of the disease because sometimes some of the complications can be life-threatening. Pediatricians typically serve as the primary caregivers for children with MWS. In Table 1, some suitable treatments and also the corresponding specialist doctors are mentioned.

Cognitive issues may be a symptom of MWS, although not all affected individuals experience this, so it is better to educate affected people who do not have this problem to protect their health against the emergency of the disease.

A critical aspect of the treatment process is the psychological impact of the disease [44]. Individuals around the affected person or responsible for their care may undergo emotional stress. Psychological counseling

Table 1 Some of the symptoms of MWS, with the suggested treatment and its specialist doctor

Disorder	Treatment	Specialist
Short stature	Growth hormone injection	Pediatrician
Epileptic seizures	Levetiracetam/ Zonisamide/ Sodium valproate/ Vagus Nerve Stimulator (VNS) Implantation	Neurologist
Dental problems	Orthodontic procedures	Dentist
Movement problems	Physiotherapy	Physiotherapist
Speech problems	Occupational therapy	Occupational therapist
Weight gain	Diet therapy	Nutritionist
Cryptorchidism	Corrective surgery	Surgeon
Scoliosis	Use of brace	Orthopedic Specialist
Hearing problems	Use of hearing aids or cochlear implants	ENT specialist
Sleep problems	Niaprazine/ Benzodiazepines/ Melatonin	Neurologist
Bunion	NSAIDs/ Use of orthosis	Orthopedic doctor
Severe aortic stenosis	Surgery in infancy	Cardiac surgeon
Calcaneovalgus	Splint placement	Orthopedic doctor

proves beneficial in helping these individuals maintain a peaceful daily life alongside their loved ones with the condition.

A solution for the future

One way to advance research and treatment for MWS in the future is to use laboratory models such as mice or hamsters. A critical consideration involves controlling the expression of the *ZEB2* gene, as this gene can exhibit varying expressions across different organisms, which are different from humans.

Activation or deactivation of each allele should be achievable under specific laboratory conditions based on the desired goals. Subsequently, complications in the laboratory models should be thoroughly investigated. It is also possible to find a solution to reduce the complications or even cure the disease with the CRISPR method through gene therapy. For example, the researchers stated that by using this technique and removing the enhancer number two of the *ZEB2* gene, the expression of this gene decreased and reduced the symptoms. Since this gene has the greatest effect on the neurodevelopmental symptoms of this disease, the CRISPR method may be used more in the future to reduce the neurological symptoms of patients [75].

One of the possible treatments in the future can be the use of stem cells because these cells can differentiate into the desired cells and be effective in the treatment of genetic disorders. Regarding Mowat-Wilson syndrome, a wide range of physical abnormalities may occur and the use of pluripotent stem cells can reduce the symptoms of the disease least possibly and help repair the damaged tissues caused by this disease. However, it should be noted that this treatment solution may face challenges such as identifying the appropriate type of stem cells, their differentiation path toward the desired tissue, the safety of the method, and ethical issues [76, 77].

Conclusion

Mowat-Wilson syndrome (MWS) is a complex genetic disorder primarily associated with heterozygous mutations in the *ZEB2* gene in the majority of observed cases. However, some genes effective in causing the disease remain unknown, so it seems that more tests should be considered to find other causes of this disease, and genome sequencing can be beneficial. Presently, definitive treatments for MWS are lacking, and supportive care is the mainstay of management. Perhaps conducting experiments based on CRISPR/Cas9 and gene therapy can eventually lead to treating this genetic disease.

Abbreviations

MWS	Mowat-Wilson syndrome
ZEB2	Zinc-finger E-box binding homeobox 2
TGF-β	Transforming Growth Factor-β
SMAD	Suppressor of Mothers against Decapentaplegic
CZF	C-terminal zinc-finger cluster
CID	C-terminal binding protein interacting domain
HD	Homeodomain-like domain
SBD	SMAD-binding domain
NZF	N-terminal zinc-finger
NIM	NuRD interacting motif
CtBP	C-terminal binding protein
NLS	Nuclear localization signal
HSCR	Hirschsprung's disease
SOX10	SRY-box transcription factor 10
NRTN	Neurturin
GEMIN2	Gem Nuclear Organelle Associated Protein 2
GDNF	Glial cell line-derived neurotrophic factor
GABA	Gamma-aminobutyric acid
MRI	Magnetic resonance imaging
FISH	Fluorescence in situ hybridization
array-CGH	Array comparative genomic hybridization
VNS	Vagus nerve stimulator

NSAIDs	Non-steroidal anti-inflammatory drugs
CRISPR	Clustered regularly interspaced short palindromic repeats
cas9	CRISPR-associated protein 9

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Consent for publication
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Competing interests
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