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Myhre Syndrome

Synonym: Myhre-LAPS Syndrome

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Summary

Clinical characteristics

Myhre syndrome is a multisystem progressive connective tissue disorder that often results in significant complications. The highly distinctive (and often severe) findings of joint stiffness, restrictive lung and cardiovascular disease, progressive and proliferative fibrosis, and thickening of the skin usually occur spontaneously. Some proliferation such as abnormal scarring or adhesions may follow trauma, invasive medical procedures, or surgery. Effusions of the heart, airways, lungs, uterus, and peritoneum may occur and can progress to fibrosis. Most affected individuals have characteristic facial features (short palpebral fissures, deeply set eyes, maxillary underdevelopment, short philtrum, thin vermilion of the upper lip, narrow mouth, and prognathism) and developmental delay / cognitive disability, typically in the mild-to-moderate range. Neurobehavioral issues may include autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), and/or anxiety. Although immunoglobulin (Ig) G and IgA deficiency are rare, affected individuals can experience recurrent infections (including otitis media, sinusitis, mastoiditis, or croup). Hearing loss can progress over time. Growth may be impaired in early life. Most adolescents develop obesity. Eye findings can include refractive errors, astigmatism, corectopia, and optic nerve anomalies. Gastrointestinal (GI) issues may include gastroesophageal reflux disease, constipation, and encopresis. Less commonly, stenosis of the GI tract, Hirschsprung disease, and/or metabolic dysfunction-associated liver disease may be observed.

Diagnosis/testing

The diagnosis of Myhre syndrome is established in a proband with characteristic clinical findings and a heterozygous (typically recurrent) pathogenic variant in *SMAD4* identified by molecular genetic testing.

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Management

Treatment of manifestations: Feeding therapy for those with poor weight gain or feeding issues; gastrostomy tube placement may be required for persistent feeding issues; referral to nutrition for those who develop obesity; consideration of balloon dilation or long-term tracheostomy for those with complete or recurrent tracheal stenosis; use of smaller-size, uncuffed endotracheal tubes for anesthesia; intralesional steroids for some keloids; physical therapy for decreased range of motion of joints; orthotics for tiptoe walking; dietary management, stool softeners, prokinetics, osmotic agents, or laxatives for constipation; guarded treatment with minimal instrumentation of the GI tract for gastrointestinal stenosis. Standard treatment for orofacial clefting, velopharyngeal insufficiency, developmental delay / intellectual disability, cardiovascular disease including systemic/pulmonary hypertension, restrictive lung disease, sleep apnea, immunodeficiency, tethered spinal cord, frequent fractures, eye/vision issues, hearing loss, protein-losing enteropathy, liver dysfunction, diabetes mellitus, cryptorchidism, hypospadias, and epilepsy.

Prevention of secondary complications: Limiting tissue trauma appears to be the single most important preventive measure. When possible, alternative noninvasive approaches should be pursued during diagnosis and management.

Surveillance: At each visit, measure growth parameters; right upper arm blood pressure (if tolerated); monitor for evidence of respiratory insufficiency and obtain pulse oxygen measurement; evaluate for signs/symptoms of upper airway stenosis and sleep apnea; monitor for constipation and signs/symptoms of GI stenosis; monitor developmental progress and educational needs, including mobility and self-help skills; assess for signs/symptoms of anxiety, ASD, and ADHD; assess for signs/symptoms of frequent infections; monitor for premature puberty in childhood; encourage nonstrenuous exercise, healthy eating, and weight management. Annually (or as clinically indicated), pulmonary function studies or impulse oscillometry in children age six years and older, if able to cooperate with test maneuvers; ophthalmology evaluation; hearing evaluation; assessment for abnormal scarring. Every two years, echocardiogram (in an asymptomatic person with a normal echocardiogram at initial diagnosis). Every five to ten years starting in childhood (age 5-10 years), CT or MR angiogram of the aorta, the exact frequency of which is based on the presence and degree of aortic disease. The decision to use CT or MR depends on the age and behavior of individual, the imaging center, and the availability of supportive services ("Child Life") to accomplish without anesthesia. Starting in the second decade, low threshold for fasting blood sugar and hemoglobin A1c to assess for diabetes mellitus; periodic DXA scan to assess bone mineral density; monitor for heavy menses. As clinically indicated, more extensive cardiovascular imaging in persons with abnormal findings at initial diagnosis; renal bladder ultrasound, if there is intractable incontinence. As needed, in the third decade of life, coronary CT angiography; evaluation for sleep apnea and need for intervention.

Agents/circumstances to avoid: Smoking; tissue trauma; elective tracheal surgery/intubation (if possible); tracheal resection; growth hormone therapy.

Genetic counseling

Myhre syndrome is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant. *De novo SMAD4* pathogenic variants that have been evaluated for parent of origin to date have all been paternal and have been associated with advanced paternal age. A few individuals diagnosed with Myhre syndrome have the disorder as the result of a *SMAD4* pathogenic variant inherited from an affected parent. Each child of an individual with Myhre syndrome has a 50% chance of inheriting the *SMAD4* pathogenic variant. Once the *SMAD4* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for Myhre syndrome have been published.

Suggestive Findings

Myhre syndrome **should be suspected** in individuals with the following clinical and imaging findings and family history. Although no single feature is pathognomonic, co-occurrence of some findings is highly suggestive of Myhre syndrome (see Table 2 for frequency of select features).

Clinical findings

- Short stature (height is significantly less than predicted mid-parental height) with compact body habitus
- Characteristic facial features (See Clinical Description, **Craniofacial** and Figures 1, 2, 3, 4, 5, and 6.)
- Conductive and mixed hearing loss
- Respiratory difficulties, usually due to restrictive thorax or, infrequently, multilevel airway stenosis (including choanal, subglottic, laryngotracheal, and/or bronchial)
- Progressively stiff, thickened skin and subcutaneous tissue
- Limited range of motion of the joints with occasional contractures
- Effusions involving the heart, airways, lungs, uterus, and peritoneum, which may progress to fibrosis
- Mild-to-moderate intellectual disability
- Autism spectrum disorder or neurodivergent behaviors
- Severe constipation and/or encopresis
- Premature puberty

Imaging findings

- **Echocardiographic findings**
  - Aortic narrowing, such as typical juxtaductal aortic coarctation, diffuse long-segment aortic hypoplasia, or segmental stenosis (branch arteries)
  - Congenital heart defects (See Clinical Description, **Cardiovascular**.)
  - Pericardial involvement ranging from transient effusion to chronic severe constrictive pericarditis
  - Restrictive cardiomyopathy and diastolic dysfunction
  - Pulmonary hypertension
- **Skeletal radiographs** (See Figure 7.)
  - Thickened calvarium
  - Shortened long bones
  - Enlarged (tall) or flattened (platyspondyly) vertebrae with shortened pedicles
  - Cervical vertebral fusion
  - Hypoplastic iliac wings
  - Absent or extra ribs
  - Small exostoses and/or enostoses (bone islands)

Family history. Because Myhre syndrome is typically caused by a *de novo* pathogenic variant, most probands represent a simplex case (i.e., a single occurrence in a family). Infrequently, the family history may be consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations) [Meerschaut et al 2019, Demir et al 2023, Vanbelleghem et al 2024].

Figure 1. The same female with Myhre syndrome at ages seven months, four years, and 16 years (lateral and frontal views). Note the short palpebral fissures, thin vermilion of the upper lip, and maxillary underdevelopment. She required tracheostomy at age 13 years for complete tracheal stenosis, attributed in part to traumatic intubations.

Reported as Patient 5 in Starr et al [2015]

Figure 2. The same female with Myhre syndrome as a newborn and at ages 12 months, 3.5 years, and seven years. Note the mild left-sided facial asymmetry (7th cranial nerve palsy), short palpebral fissures, thin vermilion of the upper lip, and progression of mild prognathism.

Reported as Patient 1 in Starr et al [2015]

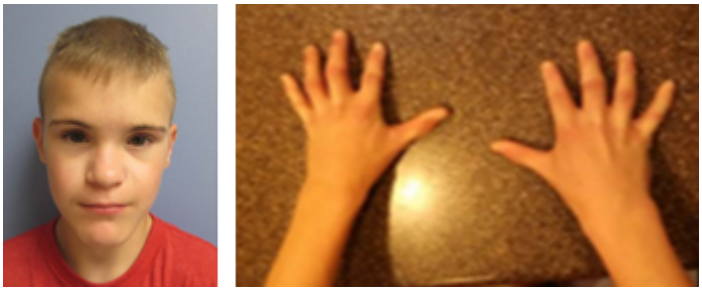

Figure 3. Male with Myhre syndrome at age 12 years with mild facial features (mild maxillary underdevelopment and thin vermilion of the upper lip) and finger contractures.

Reported as Patient 4 in Starr et al [2015]

Figure 4. Female with Myhre syndrome at age five years. Note the short palpebral fissures, thin vermilion of the upper and lower lips, left-sided facial palsy, and brachydactyly, with otherwise mild features.

Reported by Hawkes & Kini [2015]

Figure 5. The same male with Myhre syndrome at various ages from toddlerhood (lower right corner) to age 19 years (upper left corner).

Figure 6. Two different women with Myhre syndrome at ages 40 years (A) and 50 years (B). The women are shown together in C.

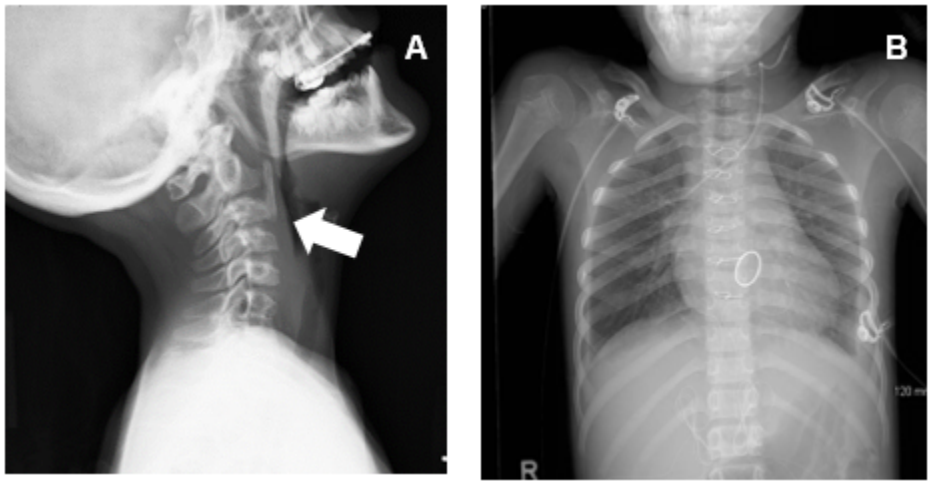

Figure 7. Radiographs of a female with Myhre syndrome at age 14 years

A. Lateral cervical spine shows thickened calvaria and anterior cervical vertebral fusion (arrow) of C2 and C3.

B. Chest radiograph shows broad ribs and vertebrae, and 11 rib pairs.

Establishing the Diagnosis

The diagnosis of Myhre syndrome **is established** in a proband with characteristic clinical findings and a heterozygous (typically recurrent) pathogenic (or likely pathogenic) variant in *SMAD4* identified by molecular genetic testing (see Table 1).

Note: (1) 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 likely pathogenic variants. (2) Identification of a heterozygous *SMAD4* variant of uncertain significance does not establish or rule out the diagnosis. (3) Individuals described as having "Myhre-like syndrome" require genetic testing for confirmation.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

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

- **Single-gene testing.** Sequence analysis of *SMAD4* may be performed first to detect the recurrent pathogenic missense variants associated with Myhre syndrome.
- **A multigene panel** that includes *SMAD4* 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 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 Myhre syndrome has not been considered, genomic testing may be used. **Comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is often used; **genome sequencing** is also possible. ACMG recommends exome and genome sequencing as first- or second-tier diagnostic testing for children with intellectual disability and/or multiple congenital anomalies [Manickam et al 2021]. To date, all of the *SMAD4* pathogenic variants reported (missense pathogenic variants impacting amino acid positions 496 and 500 causing Myhre syndrome) are within the coding region and are likely to be identified on exome sequencing.

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

Table 1. Molecular Genetic Testing Used in Myhre Syndrome

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
SMAD4	Sequence analysis [3]	100% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [6]

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. 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.
4. Lin et al [2016], Cappuccio et al [2021], Yang et al [2022], Lin et al [2024]
5. 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.
6. No exon or whole-gene deletions/duplications have been reported. However, these are not expected to occur since all variants detected so far result in disease by a gain-of-function mechanism (see Molecular Genetics).

Clinical Characteristics

Clinical Description

Myhre syndrome is a multisystem progressive connective tissue disorder that often results in significant complications. The highly distinctive (and often severe) findings of joint stiffness, restrictive lung and cardiovascular disease, progressive and proliferative fibrosis, and thickening of the skin may occur spontaneously or following trauma, invasive medical procedures, or surgery. In most, short stature and hearing loss also develop over time.

To date, more than 200 affected individuals with a molecularly confirmed diagnosis of Myhre syndrome have been reported [Bassett et al 2016, Lin et al 2016, Lin et al 2020, Cappuccio et al 2021, Cappuccio et al 2022, Yang et al 2022, Lin et al 2024, Vanbelleghem et al 2024]. The following descriptions of the phenotypic features

associated with Myhre syndrome are based on these reports, which will not be cited again unless there is specific or unique data pertaining to a particular citation.

Table 2. Myhre Syndrome: Frequency of Select Features

Feature	Frequency			Comments
	Most (>75%)	Common (25%-75%)	Infrequent (<25%)	
Characteristic facial features	●			More apparent in older children & adults
Developmental delays &/or cognitive disability	●			Typically mild to moderate
Growth issues	●			Small for gestational age, intrauterine growth restriction, & short stature have been observed; [1, 2] many adults are overweight.
Cardiovascular issues	●			Incl aortic hypoplasia & stenosis, congenital heart defects, pericardial involvement, restrictive cardiomyopathy
Respiratory issues	●			Incl reactive airway disease, [3] restrictive lung disease, [4] & rarely choanal stenosis, multisite airway stenosis, &/or sleep apnea
Recurrent infections	●			May incl otitis media, sinusitis, mastoiditis, or croup, w/resulting stridor; IgG & IgA deficiency is rare.
Skin issues	●			Stiff & thickened skin is most common, although proliferative fibrosis &/or abnormal scarring (often after trauma) may be seen.
Musculoskeletal findings	●			Incl joint limitations, contractures, & stiff gait that often progresses w/age
Neurobehavioral/psychiatric findings		●		Incl ASD, ADHD, &/or anxiety; rarely, psychosis
Abnormal sleep		●		May incl obstructive sleep apnea
Abnormal tone		●		Hypertonia, hypotonia
Eye findings		●		Refractive error & astigmatism are more common, w/optic nerve abnormalities being less common, & corectopia rarer still.
Hearing loss		●		Typically conductive or mixed hearing loss; recurrent otitis media is common.
Oropharyngeal findings		●		May incl small or widely spaced teeth, restricted mouth opening, VPI, & rarely cleft palate
Gastrointestinal issues		●		May incl GERD, constipation, encopresis, or rarely stenosis of GI tract, HSCR, or metabolic dysfunction-assoc liver disease
Endocrinologic issues		●		Premature puberty &/or adult-onset diabetes mellitus
Genitourinary findings			●	

Table 2. continued from previous page.

Feature	Frequency			Comments
	Most (>75%)	Common (25%-75%)	Infrequent (<25%)	
Impairment in balance			●	

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; GERD = gastroesophageal reflux disease; GI = gastrointestinal; HSCR = Hirschsprung disease; Ig = immunoglobulin; VPI = velopharyngeal insufficiency
1. Length or height that is more than two standard deviations below the mean for age and sex.
2. Short stature is more common in those whose pathogenic variant involves codon 500 (see Genotype-Phenotype Correlations).
3. Usually unresponsive to bronchodilator therapy
4. Typically due to a restrictive thorax

Craniofacial. The craniofacial features of Myhre syndrome (see Figures 1, 2, 3, 4, 5, and 6) can vary considerably and progress over time (see also Figure 5 in Lin et al [2024]), which make the features more apparent in older individuals. Although classic coarsening of features is not present, mandibular prominence is notable and attributed to disharmonic maxillary/mandibular growth. Facial features typically also include:

- Short palpebral fissures (See Figure 4.)
- Deeply set eyes
- Maxillary underdevelopment
- Short philtrum
- Narrow mouth
- Thin vermilion of the upper lip (See Figure 3.)
- Small and/or widely spaced teeth
- Prognathism

While cleft lip and palate is rare, velopharyngeal insufficiency is common.

Developmental delay and intellectual disability. Mild-to-moderate developmental delay and intellectual disability are common. Cognition can be within the normal range, although this is not the most common outcome. Delayed speech can be significant. Most affected individuals are ultimately verbal, using verbal communication as their primary means of communication, although some remain essentially nonverbal. Most affected individuals are supported by parents and under guardianship of their parents. Activities of daily living are achieved by many adults, although delayed toilet training and hygiene (e.g., bathing, dental care, menstrual assistance) can be a challenge to independence. Less commonly, affected individuals have attended college (generally smaller schools or two-year programs that provide accommodations for individuals with learning challenges). Several adults have been employed, have a partner, reproduced, and engaged in recreational activities such as musical theater, singing, and writing.

Other neurodevelopmental features

- **Abnormalities of tone** can include low truncal tone (hypotonia) transitioning to high tone (hypertonia).
- **Tiptoe walking** is observed often, but not well understood. In many children, it is viewed as an autism spectrum disorder behavior. In a few affected individuals, MRI imaging shows a form of tethered cord (rarely, classic) for which surgery is performed (see Management).
- **Balance issues** are attributed to lack of general fitness and stiff joints.
- **Epilepsy** is not common. Some affected individuals have had abnormal movements and staring spells, during which EEG was either not completed or was normal.

Neurobehavioral/psychiatric. Autism spectrum disorder (ASD) has been noted in 40%-70% of affected individuals and may range from mild social disability to severe autism. Attention-deficit/hyperactivity disorder (ADHD) and anxiety have also been observed in affected individuals. Psychosis has been rarely observed.

Neuroimaging. When performed, brain MRI has commonly found white matter hyperintensities, which are better characterized as white matter injury related to intrinsic cerebral microvasculopathy and not true external injury or birth trauma.

Growth. Intrauterine growth restriction (IUGR) has been found during the pregnancies of the majority of affected infants. Short stature with compact body habitus (with normal head circumference) becomes more apparent over time.

- Most affected individuals have shortened long bones.
- Adult height is expected to be more than two standard deviations below what is predicted by parental heights in more than 80% of affected individuals, particularly in those who have a pathogenic variant at codon position 500 (see Genotype-Phenotype Correlations).
- Although head circumference is rarely greater than or equal to two standard deviations above the mean for age and sex, it is commonly proportionally greater than height ("relative macrocephaly").
- Although Myhre syndrome-specific growth charts have not been developed, growth is expected to be at the lower end or below the typical growth charts for weight and length/height for infants and children.
- Overweight (BMI >25, or >99th centile) may begin in adolescence and is found in most adults.

Gastrointestinal/feeding. Many infants and children have difficulty with poor feeding and weight gain and some may benefit from a feeding tube (see **Growth** in this section and Management). Other gastrointestinal findings may include:

- Choking, coughing, and/or dysphagia
- Mild-to-severe constipation
- Duodenal atresia
- Late-onset and congenital pyloric stenosis; less commonly stenosis may involve the duodenum, jejunum, and anus.
- Protein-losing enteropathy associated with right heart failure and restrictive cardiomyopathy (Patient 1 in Lin et al [2016])
- Hirschsprung disease
- Abnormal liver function tests can suggest a pattern of metabolic dysfunction-associated steatotic liver disease (MASLD); however, this is an emerging observation.

Cardiovascular. Progressive cardiovascular issues can appear at any age; those with onset in childhood may worsen following instrumentation. Two affected individuals with restrictive cardiomyopathy (which is rare) who were treated with heart and heart/lung transplantation did not survive due to postoperative complications [Starr et al 2015], and thus, transplantation has not been used in other reported affected individuals.

In 47 individuals with confirmed Myhre syndrome evaluated at Massachusetts General Hospital [Lin et al 2024], 77% had a cardiovascular abnormality including structural heart defects (47%), mild long-segment aorta hypoplasia (60%), systemic hypertension (38%), moderate-to-severe narrowing including coarctation (21%), additional arterial stenoses (13%), pericardial disease (13%), and restrictive cardiomyopathy (4%).

- **Congenital cardiovascular abnormalities** can include the following:
  - Atrial septal defect or ventricular septal defect
  - Patent ductus arteriosus
  - Tetralogy of Fallot

    - Obstructive defects of the left heart, such as juxtaductal aortic coarctation, long-segment aortic narrowing, aortic valve stenosis, mitral valve stenosis, and multiple levels of obstruction. These are more common than obstructive defects of the right side, such as valvar and branch pulmonary artery stenosis.
    - Visceral vascular stenoses (in celiac, superior mesenteric, inferior mesenteric, and/or renal arteries)
- **Pericardial disease** can present as short-term or recurrent effusions, or as chronic or progressive constrictive pericarditis that may require surgical intervention (see Management).
    - Restrictive cardiomyopathy, a lethal condition, can be difficult to diagnose without cardiac catheterization to assess hemodynamics.
    - While constrictive pericarditis and restrictive cardiomyopathy can present with similar hemodynamic impairment, they differ in their pathogenesis and treatment (see Management).
- **Pulmonary hypertension,** either primary or as a result of left ventricular dysfunction, has been infrequently reported; however, this may reflect limited evaluation and/or bias toward ascertainment and/or reporting of younger affected individuals (as underlying causes of pulmonary hypertension resulting from involvement of the lungs and cardiovascular circulation may evolve with age). It is unknown how often this is secondary to right-sided cardiac dysfunction or severe left-sided obstruction, although both have been observed.

Respiratory. Respiratory findings are usually multifactorial. The cause of multilevel airway stenosis ranging from the choanae distally to include laryngotracheal narrowing, subglottic stenosis (ranging from mild to complete), and the bronchi is unknown. There may be a congenital predisposition, which is exacerbated by trauma or infection. However, many children have had numerous intubations without developing "traumatic" stenosis. There can be mild stridor and croup in childhood, which rarely progresses to a severe multilevel form. Upper airway obstruction caused by choanal stenosis progressing to atresia is rare and a dramatic manifestation of airway occlusion from the proliferative process.

Other findings can include the following:

- Restrictive pulmonary disease, often associated with restrictive thorax
- "Asthma" that does not always respond to bronchodilator therapy, as in typical reactive airway disease
- Interstitial lung disease and severe pulmonary fibrosis on autopsy [Starr et al 2022].
- Abnormal sleep, most often associated with autism. In some instances, a sleep study may reveal obstructive sleep apnea.
- Sleep apnea

Immune system. The precise immunologic profile in people with Myhre syndrome has not been fully studied. Increased frequency of infections involving the respiratory tract (including otitis media, sinusitis, mastoiditis, or croup) has been reported and may result from mechanical factors. For example, ear canals, sinuses, and mastoid cells may be opacified from proliferative debris. Compromised innate immunity originating from epithelial cells may contribute to increased susceptibility to upper respiratory tract infections [Lindsay et al 2024]. Serum immunoglobulin (Ig) G and IgA deficiency have been noted in a small number of affected individuals [Lin et al 2024]. Intravenous Ig was utilized with reported benefit in at least two affected individuals [Lin et al 2024] (see Management).

Cutaneous and serosal findings. Thick, firm skin is seen in nearly all individuals with Myhre syndrome, and stiffness may progress in many adults. Various terms used to describe the skin include thick, stiff, firm, rough, hyperkeratotic, and inelastic. Skin changes may not be apparent in infancy; they are often first noted on the extensor surfaces, palms, and soles. The changes progress with age. Additional skin findings include minimal creasing of the facial skin and unusual white linear scars.

Proliferative fibrosis / abnormal scarring can occur following trauma or surgery. Some individuals develop hypertrophic, keloid-like scars. In addition to the skin, proliferation can also involve the large airways (trachea and bronchi) and the serosal surfaces of the heart, lungs, and peritoneum.

Musculoskeletal. Reduced range of motion of large and small joints is characteristic of Myhre syndrome and is exacerbated with age. Posture may be distinct, with flexed elbows and bending forward at the hips (see Ishibashi et al [2014], Figure 1). Other features that may be present include:

- Small hands and feet with brachydactyly, found in most individuals (See Figures 3 and 4.)
- Clinodactyly
- Syndactyly of the toes, usually 2-3
- Scoliosis
- Absence of normal lumbar lordosis and straight spine
- Sacral dimple, sometimes associated with a tethered spinal cord
- Bony fractures, which may be associated with childhood activities and/or trauma
- Leg pain involving the calf, which can be severe. Pain is not relieved with standard analgesics and is poorly understood. It can be associated with lower spinal cord compression.

Characteristic radiographic findings in affected individuals are listed in Suggestive Findings.

Ophthalmologic. Refractive errors are common and usually include hyperopia with astigmatism. Other findings may include strabismus, cataracts, corectopia, and optic nerve anomalies. Nasolacrimal duct stenosis or atresia is common and may be difficult to manage due to recurrent stenosis related to progressive fibrosis.

Hearing. Hearing loss is observed in most individuals with Myhre syndrome. Most newborns pass their neonatal hearing screen; hearing loss usually becomes evident in early childhood to late teens.

- Hearing loss is predominantly conductive or mixed; affected individuals most often have a history of bilateral myringotomy tube placement.
- The underlying etiology of the hearing loss is often unclear or unknown and may require inner ear imaging to diagnose structural anomalies, although this is thought to be rare.

Endocrine. Endocrine findings may include premature puberty (reported in both sexes), early menarche, meno- or metrorrhagia, and macromastia, the latter prompting reduction mammoplasty in some. Both premature ovarian failure and secondary amenorrhea have been observed.

Glucose intolerance in adults may be more common than the few reports of diabetes. One teenage girl had hyperinsulinism and an impaired glucose tolerance test, which may indicate insulin resistance [Kilci et al 2022].

Genitourinary. Genitourinary findings are infrequent but have included mild hypospadias and undescended testes in males.

Neoplasia. Since a report of neoplasia in six individuals with Myhre syndrome (3 of whom were women with endometrial cancer) [Lin et al 2020], there have been no additional reports of affected individuals with neoplasia. Anecdotally, there are additional cases, including one further person with endometrial cancer and two with hypothalamic hamartoma.

Genotype-Phenotype Correlations

Genotype-phenotype correlations are still emerging [Yang et al 2022, Lin et al 2024] with a detailed analysis in adults [Vanbelleghem et al 2024].

c.1498A>G (p.Ile500Val). Based on limited data, individuals with the highly recurrent c.1498A>G (p.Ile500Val) pathogenic variant are more likely to have prenatal growth deficiency with postnatal short stature and severe aortic obstruction.

c.1486C>T (p.Arg496Cys). Individuals with the c.1486C>T (p.Arg496Cys) pathogenic variant are more likely to have a height within the normal range for age and sex. Females with this pathogenic variant are more likely to have premature puberty and heavy menses (see Management). Of the six individuals reported with neoplasia, three were women with endometrial cancer, two of whom were heterozygous for the c.1486C>T (p.Arg496Cys) pathogenic variant. To date, all known affected individuals who have developed seizures have had this specific pathogenic variant.

Nomenclature

In the 2023 revision of the Nosology of Genetic Skeletal Disorders [Unger et al 2023], Myhre syndrome is referred to as *SMAD4*-related Myhre dysplasia and included in the acromelic dysplasias group [Table 1 in Costantini et al 2023].

LAPS (*l*aryngotracheal stenosis, *a*rthropathy, *p*rognathism, and *s*hort stature) syndrome was determined to be allelic to Myhre syndrome with pathogenic variants in the same codons [Lindor et al 2012, Picco et al 2013, Michot et al 2014] (see Genetically Related Disorders); the term is no longer in use.

Prevalence

The prevalence of Myhre syndrome is unknown. A rough estimate of the prevalence is 1:900,000 individuals.

Genetically Related (Allelic) Disorders

Other phenotypes known to be associated with germline pathogenic variants in *SMAD4* are listed in Table 3.

Table 3. *SMAD4* Allelic Disorders

Disorder	MOI	Class of Variants
Juvenile polyposis syndrome (JPS)	AD	Loss of function
Hereditary hemorrhagic telangiectasia (HHT) [1]	AD	Loss of function

AD = autosomal dominant; MOI = mode of inheritance

1. Hereditary hemorrhagic telangiectasia (HHT) and Myhre syndrome have opposing phenotypes consistent with *SMAD4* loss of function and gain of function, respectively [Gheewalla et al 2022]. Telangiectasias and juvenile polyps, reported in heterozygotes for a *SMAD4* loss-of-function pathogenic variant, have not been reported in people with Myhre syndrome.

Sporadic tumors (including colorectal cancer and pancreatic tumors) occurring as single tumors in the absence of any other findings of Myhre syndrome frequently contain a somatic variant in *SMAD4* that is not present in the germline [Chen et al 2014]. In these circumstances predisposition to these tumors is not heritable. See Molecular Pathogenesis, **Cancer and benign tumors**.

Differential Diagnosis

The disorders that most closely resemble Myhre syndrome are the other acromelic dysplasias – geleophysic dysplasia, acromicric dysplasia, and Weill-Marchesani syndrome – which share the findings of thickened skin, short stature, short hands, and stiff joints [Costantini et al 2023]. Table 4 lists these and other syndromes that have more limited overlapping features.

Table 4. Disorders of Interest in the Differential Diagnosis of Myhre Syndrome

Gene(s)	Disorder	MOI	Clinical Features of Disorder	
			Overlapping w/Myhre syndrome	Distinguishing from Myhre syndrome
ADAMTS10 *ADAMTS17* *FBN1* *LTPBP2*	Weill-Marchesani syndrome	AR AD	• IUGR • Short stature • Brachydactyly • Joint stiffness	• Distinctive lens abnormalities [1] • No hearing loss
ADAMTSL2 *FBN1* *LTBP3*	Geleophysic dysplasia [2]	AR AD	• IUGR • Short stature • Short hands & feet • Progressive joint limitation & contractures • Progressive cardiac valvar thickening • Thickened skin	• Hepatomegaly • Distinctive facial features • Delayed bone age
FBN1 *LTBP3*	*FBN1*-related acromicric dysplasia (OMIM 102370) & *LTBP3*-related acromicric dysplasia [3]	AD	• IUGR • Short stature • Brachydactyly • Joint stiffness • Thickened skin	• Characteristic external notch of 5th metacarpal & internal notch of femoral head • No hearing loss • Less frequent congenital cardiac anomalies • No calvarial thickening
FBN1	Stiff skin syndrome (OMM 184900)	AD	• Stiff skin • Stiff joints	• Skin has rock-hard involvement. • Not dysmorphic • Few cardiovascular features • No calvarial thickening
TRIM37	MULIBREY nanism (OMIM 253250)	AR	• IUGR • Short stature • Relatively large head • Constrictive pericarditis • Restrictive cardiomyopathy • Hearing loss	• Shorter stature • Small tongue • No calvarial thickening

AD = autosomal dominant; AR = autosomal recessive; IUGR = intrauterine growth restriction; MOI = mode of inheritance
1. The ocular manifestations of Weill-Marchesani syndrome, typically recognized in childhood, include microspherophakia (small spherical lens), myopia secondary to the abnormal shape of the lens, ectopia lentis (abnormal position of the lens), and glaucoma, which can lead to blindness.
2. Major findings are likely to be present in the first year of life. Cardiac, airway, and pulmonary involvement result in death before age five years in approximately 33% of individuals with geleophysic dysplasia.
3. McInerney-Leo et al [2016]

Management

Although formal evidence-based clinical management guidelines for Myhre syndrome have not yet been published, expert consensus recommendations provide pragmatic clinical guidance (Table 5 in Lin et al [2024] and Table 2 in Vanbelleghem et al [2024]).

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Myhre syndrome, the evaluations summarized in Table 5 (if not completed previously as part of the diagnostic evaluation) are recommended.

Table 5. Myhre Syndrome: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Constitutional	Measurement of growth parameters	To assess for short stature & either growth restriction in younger persons or obesity in older persons
Craniofacial	• Physical exam for evidence of cleft lip & palate • Assessment for velopharyngeal insufficiency	If present, consider referral to multidisciplinary craniofacial center, which may also evaluate progressive mandibular overgrowth ("prognathism").
Developmental	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language evals • Eval for early intervention / special education, ABA therapy
Neurobehavioral/ Psychiatric	Consider neuropsychologic & psychiatric assessments based on age.	In persons age >12 months: screen for concerns incl sleep disturbances, anxiety, &/or findings suggestive of ASD; assessment for features of ADHD & psychiatric issues in older persons
Cardiovascular	Measurement of upper & lower extremity blood pressure	• To assess for aortic obstruction & systemic hypertension • Consider referral to nephrologist for those w/systemic hypertension.
	2D echocardiography w/Doppler	To assess for structural heart disease, vasculopathy, & cardiac function; if abnormal, refer to cardiologist.
	CT angiogram or MRA of aorta	• In children who are able to complete procedure w/o anesthesia (age 5-10 yrs) or if there is hypertension • Cardiac catheterization may be indicated to document characteristic hemodynamics of restrictive cardiomyopathy & pulmonary hypertension.
Respiratory	Assess for airway stenosis by least invasive means possible.	Auscultation & observation w/ & w/o activity for signs of upper airway obstruction incl noisy breathing, work of breathing, & oxygen saturation.
	Consider assessment of pulmonary function, oxygen saturation levels, 3- and 6-minute walk test, [1] & impulse oscillometry (when available).	To assess for obstructive &/or restrictive lung disease
	Consider polysomnography.	For sleep disturbance & obstruction
Immunologic	Quantitative serum Ig to assess for Ig deficiency in those w/excessive infections or who are of school age or older	If abnormal, consider referral to immunologist.
Integument	Dermatologic eval	Assess for hyperkeratosis pilaris & abnormal scarring.
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To include assessment of: • Gross motor & fine motor skills • ↓ range of motion of joints (OT modifications may be indicated.) • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
	Consider skeletal survey.	To assess for bony anomalies
	Assess for history of frequent bony fractures.	Consider referral to orthopedist &/or endocrinologist.

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
Eyes	Ophthalmologic eval	• To assess for strabismus, refractive error, & cataracts • Give special attention to optic nerve.
Hearing	Audiologic eval	• Assess for degree & type of hearing loss. • Newborn hearing screen may be normal; low threshold for repeat testing. • Consider inner ear imaging for those w/hearing loss.
Gastrointestinal	Assessment for recurrent vomiting & chronic constipation	Low threshold to image for concern of pyloric or other stenosis of GI tract. [2, 3]
	Assessment for signs/symptoms of protein-losing enteropathy & metabolic dysfunction-assoc liver disease	• Obtain baseline serum laboratory tests. [4] • Consider standard coagulation tests. • Evaluate cardiovascular hemodynamics under care of cardiologist & liver specialist. • Consider referral to GI specialist.
Endocrinologic	Evaluate for pubertal status in children & adolescents, & for signs/symptoms of menstrual irregularities & macromastia in females.	To assess for premature puberty (in both sexes), premature ovarian failure, menorrhagia, & secondary amenorrhea
	Assess for signs/symptoms of insulin-dependent diabetes. [5]	More common in older adults
	Monitor onset of menses & assess for dysfunctional uterine bleeding. [6]	Consultation w/endocrinologist & gynecologist
Genitourinary	Physical exam for cryptorchidism & hypospadias in males	Consider referral to urologist.
	Renal ultrasound w/Doppler [7]	To assess for renal anomalies & renal artery stenosis
Neurologic	Neurologic eval	Consider brain MRI & EEG if seizures are a concern.
Genetic counseling	By genetics professionals [8]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of Myhre syndrome to facilitate medical & personal decision making
Family support & resources	Myhre Syndrome Foundation (MSF)	• Assess need for social work involvement for parental support. • Consider palliative care counseling to support family & affected person when there are serious complications (e.g., cardiopulmonary, airway, or neoplastic involvement).

ABA = applied behavior analysis; ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; ASD = autism spectrum disorder; GI = gastrointestinal; MOI = mode of inheritance; MRA = magnetic resonance angiography; OT = occupational therapy; PT = physical therapy

1. When a person is old enough to cooperate with this evaluation.

2. Intestinal obstruction may contribute to constipation.

3. Hirschsprung disease has been reported.

4. Basic chemistry and liver function tests (AST, ALT, etc.), with consideration of adding albumin and total protein in those who have protein-losing enteropathy

5. Consider obtaining a hemoglobin A1c in those with suggestive signs/symptoms or as a baseline in adolescents and adults.

6. Which could suggest endometrial cancer

7. Consider obtaining kidney function tests, such as electrolytes, blood urea nitrogen, creatinine, and cystatin C in those with hypertension or renal artery stenosis.

8. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for Myhre syndrome. Supportive care to improve quality of life, maximize function, and reduce complications is recommended, ideally involving multidisciplinary care by specialists in relevant fields (see Table 6).

Table 6. Myhre Syndrome: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Poor weight gain / Feeding difficulties	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study if clinical signs/ symptoms of dysphagia
Obesity	Consider referral to nutritionist for interventions.	May be difficult to manage
Orofacial clefting / Velopharyngeal insufficiency	Standard treatment, ideally by craniofacial team	Multidisciplinary teams may incl surgical team (craniofacial surgeon), clinical geneticist, otolaryngologist, pediatrician, radiologist, psychologist, multiple dental specialists, audiologist, speech therapist, & social worker.
Short stature	Growth hormone therapy is **not** currently recommended.	There is no systematic study of growth hormone treatment in Myhre syndrome. [1]
Developmental delay / Intellectual disability / Neurobehavioral issues	See Developmental Delay / Intellectual Disability Management Issues.	
Congenital heart defects / Pericardial disease / Myocardial disease	Standard treatment by cardiologist trained in congenital heart disease, pericardial disease, & restrictive cardiomyopathy [2]	• Avoid any unnecessary instrumentation, as assoc tissue trauma may induce stenosis & scarring-type tissue response. • Affected persons who are in heart failure should be under care of cardiovascular specialist w/access to transplant center. Cardiac & lung transplantation are assoc w/ high risk of mortality.
Systemic/pulmonary hypertension	Medical therapy based on underlying cause	
Complete or recurrent tracheal stenosis	Consider balloon dilation; long-term tracheostomy can also be considered. [3]	Tracheal resection is contraindicated. [4]
Anesthesia	To avoid traumatic intubation, consider using smaller-size, uncuffed endotracheal tube.	Elective tracheal surgery/intubation should be avoided but can be managed w/preoperative multidisciplinary discussion when necessary (see Agents/Circumstances to Avoid).
Restrictive lung disease	Symptomatic & standard treatment per pulmonologist	Oxygen supplementation as necessary
Sleep apnea	Treatment per sleep specialist	May incl use of CPAP, BiPAP, or oxygen supplementation
Immunodeficiency	Standard treatment per immunologist	May incl IVIG therapy [5]
Keloids	Some keloids can be treated w/intralesional steroids.	Minimal invasiveness for lesion removal
Decreased range of motion of joints	Physical therapy	It is not known if passive range of motion exercises help maintain flexibility; however, physical activity to maintain conditioning is encouraged.

Table 6. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Tiptoe walking	Orthotics may be recommended by orthopedic consultants, but adherence is not always achieved.	For those w/o tethered cord
Tethered spinal cord	Standard treatment per neurosurgeon	
Frequent fractures	Standard treatment per orthopedist	No special treatment or preventive therapy is currently known to be effective.
Strabismus / Refractive error / Cataracts	Standard treatment(s) as recommended by ophthalmologist	
Optic nerve abnormalities	Ophthalmic subspecialist may be appropriate.	
	Low vision services	• Children: through early intervention programs &/or school district • Adults: low vision clinic &/or community vision services / OT / mobility services
Hearing loss	Hearing aids may be helpful, per audiologist/otolaryngologist.	Community hearing services through early intervention or school district
Persistent middle ear effusions	Standard treatment per otolaryngologist	May incl myringotomy tubes & cerumen removal
Constipation	Aggressive mgmt incl diet mgmt, stool softeners, prokinetics, osmotic agents, or laxatives as needed	
GI stenosis	Guarded treatment per gastroenterologist	• Minimal instrumentation of GI tract is advised because postoperative adhesions can be fatal. [6] • Approach endoscopy w/caution to avoid airway manipulation, which ↑ risk for tracheal/laryngeal scarring/stenosis. [4] • Noninvasive 3D imaging may be preferred.
Protein-losing enteropathy & liver dysfunction	Standard treatment per gastroenterologist &/or hepatologist	
Diabetes mellitus	Treatment & monitoring by endocrinologist	May be difficult to manage & require insulin pumps
Premature ovarian failure / Secondary amenorrhea / Menstrual irregularities	Standard treatment per gynecologist &/or endocrinologist	
Cryptorchidism &/or hypospadias	Standard treatment per urologist	
Epilepsy	Standardized treatment w/ASM by experienced neurologist	

Table 6. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Family/Community	• Ensure appropriate social work involvement to connect families w/ local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

CPAP = continuous positive airway pressure; BiPAP = bilevel positive airway pressure; GI = gastrointestinal; IVIG = intravenous immunoglobulin; PT = physical therapy

1. Growth hormone therapy is not endorsed because its anabolic action may interact with the activating *SMAD4* action.
2. All individuals with Myhre syndrome should be under the care of a cardiologist.
3. McGowan et al [2011], Oldenburg et al [2015], Starr et al [2015]
4. Oldenburg et al [2015]
5. Starr et al [2015]
6. Lindor et al [2012]

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 (US) 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 whether 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 the 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, and modified assignments.
- 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).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

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 child 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.

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. Also consider using American Sign Language (ASL) for those with hearing loss and minimal expressive language.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Prevention of Secondary Complications

Limiting tissue trauma appears to be the single most important preventive measure. When possible, alternative noninvasive approaches should be pursued during diagnosis and management [Oldenburg et al 2015, Starr et al 2015].

- Extreme care with intubation and use of an endotracheal tube without a cuff (or careful monitoring of pressures with a cuff) may help prevent airway stenosis [Oldenburg et al 2015].
- Minimize abdominal and pelvic procedures as extensive adhesions may develop postoperatively [Lindor et al 2012].

- Hysterectomy should be an option of last resort for treatment of menorrhagia as postsurgical fibrosis can occur.
- Recognize risk of thickened scars or keloids with ear or other piercings.
- Use of orthodontic braces may stimulate gum hypertrophy.

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 7 are recommended.

Table 7. Myhre Syndrome: Recommended Surveillance

System/Concern	Evaluation	Frequency
Growth	Measurement of growth parameters	At each visit
Cardiovascular [1]	In asymptomatic persons w/normal echocardiogram at initial diagnosis, repeat echocardiogram.	Every 2 yrs
	In persons w/abnormal findings at initial diagnosis, more extensive imaging may be indicated given progressive nature of disorder.	As clinically indicated
	Right upper arm blood pressure measurement (if tolerated)	At each visit
	CT angiogram or MRA of aorta [2]	Every 5-10 yrs starting in childhood (age 5-10 yrs) [3]
	Coronary CT angiogram	As needed in 3rd decade of life
Respiratory	Pulmonary function studies or impulse oscillometry in children age >6 yrs, if able to cooperate w/test maneuvers	Annually
	Eval for sleep apnea & need for intervention	As needed in 3rd decade of life
	• Monitor for evidence of respiratory insufficiency & obtain pulse oxygen measurement. • Evaluate for signs/symptoms of upper airway stenosis & sleep apnea.	At each visit
Gastrointestinal	Monitor for constipation & signs/symptoms of GI stenosis.	
Developmental	Monitor developmental progress & educational needs.	
Neurobehavioral/ Psychiatric	Assessment for anxiety, ASD, & ADHD	
Musculoskeletal	Physical medicine, OT/PT, mobility assessment, self-help skills	
Immunologic	Assessment of signs/symptoms of frequent infections	
Family/ Community	Assess family need for social work support (e.g., palliative/ respite care, home nursing, other local resources) & care coordination.	
Eyes	Ophthalmologist eval	Annually or as clinically indicated
Hearing	Audiologist eval	
Integument	Assessment for abnormal scarring	

Table 7. continued from previous page.

System/Concern	Evaluation	Frequency
Endocrinologic	• Low threshold for fasting blood sugar & hemoglobin A1c to assess for diabetes mellitus • Periodic DXA scan to assess bone mineral density	Starting in 2nd decade
	Monitor for premature puberty. [4]	At each visit in childhood
	Postpubertal women: monitor for heavy menses. [4]	Starting in 2nd decade
Genitourinary	Renal/bladder ultrasound	If there is intractable incontinence
Lifestyle	Encourage nonstrenuous exercise, healthy eating, & weight mgmt.. [5]	At each visit

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; DXA = dual-energy x-ray absorptiometry; GI = gastrointestinal; MRA = magnetic resonance angiography; OT = occupational therapy; PT = physical therapy

1. Note that pericardial effusion and restrictive cardiomyopathy may occur at any age and may be clinically asymptomatic [Starr et al 2015, Garavelli et al 2016, Lin et al 2016].

2. The decision to use CT angiogram or MRA depends on the age and behavior of individual, the imaging center, and the availability of supportive services ("Child Life") to accomplish without anesthesia.

3. The exact frequency is based on the presence and degree of aortic disease.

4. These findings are more common in those with the c.1486C>T (p.Arg496Cys) pathogenic variant.

5. Vaccines are endorsed.

Agents/Circumstances to Avoid

Affected individuals should be aggressively counseled not to smoke.

Limiting tissue trauma (injury) appears to be the single most important preventive concept in this disorder to communicate to all health care providers involved in an individual's care (see Prevention of Secondary Complications). Decision making with affected individuals and their families should include nonintervention as an option in, for example, ear piercing, orthodontic braces, exploratory procedures, or surgical repair of velopharyngeal insufficiency.

Elective tracheal surgery/intubation should be avoided when possible. Tracheal resection is contraindicated.

Growth hormone therapy is **not** currently recommended for affected individuals with short stature.

Evaluation of Relatives at Risk

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

Therapies Under Investigation

The antihypertensive drug losartan is an angiotensin II type 1 receptor blocker. Through this mechanism, it also indirectly antagonizes transforming growth factor beta (TGF-β) signaling. In Myhre syndrome fibroblasts, losartan corrected an extracellular matrix deposition defect [Piccolo et al 2014]. Thus, in a small uncontrolled open-label pilot study, three individuals with Myhre syndrome were treated with losartan. Improvements in skin thickness, joint range of motion, and myocardial strain were observed [Cappuccio et al 2021]. However, long-term controlled clinical trials with a larger number of affected individuals are needed to establish the efficacy of losartan on skin, joint, and heart abnormalities in Myhre syndrome.

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.

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

Myhre syndrome is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with Myhre syndrome have the disorder as the result of a *de novo SMAD4* pathogenic variant [Lin et al 2016]. *De novo SMAD4* pathogenic variants that have been evaluated for parent of origin to date have all been paternal and have been associated with advanced paternal age [Wood et al 2024].
- A few individuals diagnosed with Myhre syndrome have the disorder as the result of a *SMAD4* pathogenic variant inherited from an affected parent. Transmission from an affected mother to two affected children has been reported in three families segregating the p.Arg496Cys *SMAD4* pathogenic variant [Meerschaut et al 2019, Demir et al 2023, Vanbelleghem et al 2024].
- If the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to evaluate their genetic status and inform recurrence risk assessment.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with gonadal (or somatic and gonadal) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ (gonadal) cells only.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- If the *SMAD4* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the possibility of parental gonadal mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *SMAD4* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for Myhre syndrome because of the possibility of parental gonadal mosaicism.

Offspring of a proband. Each child of an individual with Myhre syndrome has a 50% chance of inheriting the *SMAD4* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *SMAD4* pathogenic variant, the parent's family members may be at risk.

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 parents of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *SMAD4* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for Myhre syndrome are possible.

Note: Severe features (e.g., tetralogy of Fallot with pulmonary atresia, severe growth restriction) have been reported in prenatally diagnosed fetuses not known to be at increased risk of Myhre syndrome [Hui et al 2023, Jury et al 2024].

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic testing to be a personal decision, discussion of these issues may be helpful.

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.

- **Myhre Syndrome Foundation**
  myhresyndrome.org
- **Alexander Graham Bell Association for the Deaf and Hard of Hearing**
  Phone: 866-337-5220 (toll-free); 202-337-5221 (TTY)
  Fax: 202-337-8314
  Email: info@agbell.org
  Listening and Spoken Language Knowledge Center
- **American Society for Deaf Children**
  Phone: 800-942-2732 (ASDC)
  Email: info@deafchildren.org
  deafchildren.org
- **National Association of the Deaf**
  Phone: 301-587-1788 (Purple/ZVRS); 301-328-1443 (Sorenson); 301-338-6380 (Convo)
  Fax: 301-587-1791
  Email: nad.info@nad.org
  nad.org

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. Myhre Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SMAD4	18q21.2	Mothers against decapentaplegic homolog 4	SMAD4 database	SMAD4	SMAD4

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 Myhre Syndrome (View All in OMIM)

139210	MYHRE SYNDROME; MYHRS
600993	SMAD FAMILY MEMBER 4; SMAD4

Molecular Pathogenesis

SMAD4 encodes mothers against decapentaplegic homolog 4 (SMAD4), signal transduction protein that has roles in many diverse signaling pathways including canonical transforming growth factor beta (TGF-β), bone morphogenetic protein (BMP), and activin signaling. Heterozygous **gain-of-function** pathogenic variants in *SMAD4* that cause Myhre syndrome have been thought to confer stability of the resulting abnormal protein due to an apparent decrease in monoubiquitination. The *SMAD4* pathogenic variant p.Ile500Val increases stability of the SMAD3/SMAD4 transcriptional complex [Lindsay et al 2024]. Both of these biochemical activities may be at play, as they would both affect the TGF-β signaling pathway, altering expression of downstream target genes. Signaling perturbations result in altered development of the axial and appendicular skeleton, cardiac muscle, and central nervous system during development and abnormal extracellular matrix deposition during early development and adulthood [Caputo et al 2012, Le Goff et al 2014, Piccolo et al 2014].

In contrast, heterozygous **loss-of-function** *SMAD4* pathogenic variants have been well established as the cause of a spectrum of acquired cardiac and neoplastic diseases, including arteriovenous malformations, aortopathies, pulmonary artery hypertension, and colon cancer susceptibility in the context of juvenile polyposis and hereditary hemorrhagic telangiectasia syndromes [Andrabi et al 2011, Nasim et al 2011, Heald et al 2015].

Mechanism of disease causation. Gain of function (increased TGF-β signaling potency) has been demonstrated in some studies [Lindsay et al 2024]; however, other research suggests a dominant-negative mechanism causing an interruption of typical TGF-β and BMP signaling [Alankarage et al 2022]. Resolution of the observed differences is still outstanding.

Table 8. *SMAD4* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_005359.6 NP_005350.1	c.1486C>T	p.Arg496Cys	• Persons w/this variant are typically not as short in stature. • 3 affected women w/this variant developed endometrial cancer [Lin et al 2020]. [1]
	c.1498A>G	p.Ile500Val	• Highly recurrent pathogenic variant • This variant may be assoc w/↑ risk for pre- & postnatal growth deficiency.

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.
1. It remains unclear if this specific pathogenic variant is associated with an increased risk of developing neoplasia (see Genotype-Phenotype Correlations).

Cancer and benign tumors. Although germline *SMAD4* loss-of-function (inactivating) pathogenic variants predispose to hamartomatous polyps in the gastrointestinal tract (see Juvenile Polyposis Syndrome), the gain-of-function pathogenic variants associated with Myhre syndrome show no such associations (see Clinical Description, **Neoplasia**).

Note that somatic inactivation of *SMAD4*, a gastrointestinal malignancy-specific tumor suppressor gene, is found in one third of colorectal cancer specimens and half of pancreatic tumors [Chen et al 2014].

Chapter Notes

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