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Myhre Syndrome

Synonyms: Laryngotracheal Stenosis, Arthropathy, Prognathism, and Short Stature (LAPS) Syndrome; Myhre-LAPS Syndrome

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Summary

Clinical characteristics

Myhre syndrome is a multisystem connective tissue disorder involving the skin and the cardiovascular, respiratory, gastrointestinal, and musculoskeletal systems. Affected individuals may experience progressive and proliferative fibrosis. Fibrosis may occur spontaneously or following trauma, invasive medical procedures, or surgery, often resulting in significant complications. Characteristic facial features are found in almost all affected individuals and are more apparent in older children and adults. Cardiovascular issues can include aortic hypoplasia and stenosis, congenital heart defects, pericardial involvement, and restrictive cardiomyopathy. Joint limitations may progress with age and resemble mild joint contractures. Most individuals have developmental delay / cognitive impairment, typically in the mild-to-moderate range. Other findings may include autism spectrum disorder, conductive or mixed hearing loss, short stature, refractive errors, premature puberty, recurrent respiratory infections, mechanical respiratory issues (choanal stenosis, laryngeal narrowing), and stenosis of the upper gastrointestinal tract.

Diagnosis/testing

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

Management

Treatment of manifestations: Feeding therapy with a low threshold for a clinical and/or radiographic swallowing study; referral to nutrition for poor weight gain or obesity; medical therapy for systemic and/or pulmonary hypertension; long-term tracheostomy may be required for those with complete or recurrent tracheal stenosis; aggressive medical management for constipation; physical therapy to keep joints mobile; hearing aids may be

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helpful for those with hearing loss; some keloids can be treated with intralesional steroids with minimal invasiveness for lesion removal; and standard treatment for orofacial clefting / velopharyngeal insufficiency, congenital heart defects / pericardial disease, restrictive lung disease, gastrointestinal stenosis, developmental delay / intellectual disability, refractive errors / strabismus / cataracts, persistent middle ear effusions, immunodeficiency, diabetes mellitus, and pubertal/menstrual irregularities. Note: Growth hormone therapy for short stature is not currently recommended for individuals with Myhre syndrome.

Prevention of secondary complications: Limiting tissue trauma appears to be the single most important preventive measure: the literature suggests increased risk of proliferative fibrosis following otherwise uncomplicated endotracheal intubation and surgical procedures. When possible, alternative noninvasive approaches should be pursued during diagnosis and management.

Surveillance: At each visit: measure growth parameters, blood pressure, and oxygen pulse oximetry; monitor for respiratory insufficiency, signs/symptoms of upper-airway stenosis, constipation, developmental issues, behavioral issues, physical skills and mobility issues, premature puberty (in children), and frequent and/or unusual infections. Annually: perform pulmonary function studies (in children age >6 years who are able to cooperate), ophthalmology evaluation, and audiology evaluation. In asymptomatic individuals with a normal echocardiogram, repeat the echocardiogram every one to three years. Starting in the second decade: low threshold for fasting blood sugar and hemoglobin A1c to assess for diabetes; periodic DXA scan to monitor bone mineral density; monitor females with the c.1486C>T (p.Arg496Cys) pathogenic variant for menstrual irregularities.

Genetic counseling

Myhre syndrome is inherited in an autosomal dominant manner. Most probands with Myhre syndrome have the disorder as a result of a *de novo SMAD4* pathogenic variant; however, vertical transmission from a parent to child has been rarely observed. If the *SMAD4* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is presumed to be slightly greater than that of the general population (though still <1%) because of the theoretic possibility of parental germline mosaicism. Once the *SMAD4* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at theoretic increased risk for Myhre syndrome and preimplantation genetic testing are possible.

Diagnosis

Formal clinical diagnostic criteria for Myhre syndrome have not been published.

Suggestive Findings

Myhre syndrome **should be suspected** in individuals with the following clinical, imaging, and family history findings. Although no single feature is pathognomonic, co-occurrence of some is highly suggestive of Myhre syndrome.

Clinical Findings

Suggestive clinical findings include the following:

- Short stature (height is significantly less than that predicted by parental heights) with compact body habitus in most affected individuals
- Characteristic facial features (See Clinical Description, Craniofacial Features.)
- Conductive and mixed hearing loss
- Respiratory difficulties, usually due to restrictive pulmonary disease; in rare cases due to laryngotracheal narrowing (including subglottic stenosis) or choanal stenosis

- Progressively stiff and thickened skin
- Limited range of motion of the joints
- Effusions involving the serosal surfaces of the heart (pericarditis), lungs, and peritoneum, which may progress to fibrosis
- Mild-to-moderate intellectual disability
- Autism or neurodivergent behaviors
- Severe constipation due to intestinal strictures
- 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 including tetralogy of Fallot and obstructive defects of the left heart (aortic stenosis, mitral stenosis)
- Pericardial involvement ranging from transient effusion to chronic severe constrictive pericarditis
- Restrictive cardiomyopathy
- Pulmonary hypertension

Skeletal radiographs (See Figure 7.)

- Thickened calvarium
- Shortened long bones
- Enlarged vertebrae with shortened pedicles
- Cervical vertebral fusion
- Hypoplastic iliac wings
- Absent or extra ribs

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). Rarely, the family history may be consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations).

Establishing the Diagnosis

The diagnosis of Myhre syndrome **is established** in a proband with characteristic clinical findings and a heterozygous pathogenic (or likely pathogenic) variant in *SMAD4* detected 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 any likely pathogenic variants. (2) Identification of a heterozygous *SMAD4* variant of uncertain significance does not establish or rule out the diagnosis.

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

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be

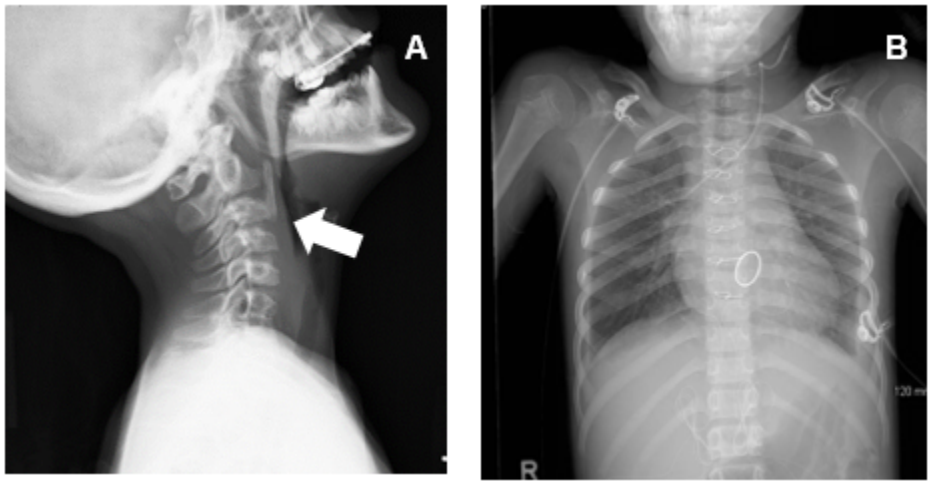

Figure 7. Radiographs of a female with Myhre syndrome at age 14 years

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.

diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of Myhre syndrome has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and radiographic 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* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions.
- **An autism/intellectual disability, hearing loss, or cancer 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 most commonly used; **genome sequencing** is also possible.

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 Probands with a Pathogenic Variant [2] Detectable 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]
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 connective tissue disorder involving the cardiovascular system, respiratory system, gastrointestinal tract, musculoskeletal system, and skin. Affected individuals may experience progressive and proliferative fibrosis that may occur spontaneously or following trauma, invasive medical procedures, or surgery, often resulting in significant complications.

To date, more than 100 affected individuals with a molecularly confirmed diagnosis of Myhre syndrome have been reported [Le Goff et al 2011, Al Ageeli et al 2012, Asakura et al 2012, Caputo et al 2012, Lindor et al 2012, Picco et al 2013, Ishibashi et al 2014, Kenis et al 2014, Michot et al 2014, Hawkes & Kini 2015, Oldenburg et al 2015, Starr et al 2015, Bassett et al 2016, Lin et al 2016, Lin et al 2020, Cappuccio et al 2021, Cappuccio et al 2022, Yang et al 2022]. The following descriptions of the phenotypic features associated with Myhre syndrome are based on these reports.

Table 2. Myhre Syndrome: Frequency of Select Features

Feature [1]	Frequency			Comment
	Nearly all	Common	Infrequent	
Characteristic facial features	●			More apparent in older children & adults
Cardiovascular issues	●			Incl aortic hypoplasia & stenosis, congenital heart defects, pericardial involvement, & restrictive cardiomyopathy
Joint limitations	●			May progress w/age & resemble mild joint contractures
Developmental delays &/or cognitive disability	●			Typically mild to moderate
Short stature	●			Esp in those whose pathogenic variant involves codon 500 (See Genotype-Phenotype Correlations.)
Hearing loss	●			Typically conductive or mixed hearing loss

Table 2. continued from previous page.

Feature [1]	Frequency			Comment
	Nearly all	Common	Infrequent	
Stiff & thickened skin	●			
Autism spectrum disorder		●		May range from mild social disability to severe autism
Proliferative fibrosis &/or abnormal scarring		●		Often after trauma
Recurrent respiratory infections		●		
Abnormal sleep		●		
Refractive error		●		Many affected persons require corrective lenses.
Premature puberty		●		
Small or widely spaced teeth		●		
Choanal stenosis			●	
Laryngeal narrowing			●	
Stenosis of GI tract			●	Esophagus, pylorus, small intestine

GI = gastrointestinal
1. Many features are age-related [Yang et al 2022].

Craniofacial Features

The craniofacial features of Myhre syndrome (Figures 1-6) can vary considerably and 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.

Progression of Findings

The facial characteristics can progress over time. In infancy, the characteristic facial features are usually present but more difficult to recognize than in an older child (see Figures 1, 2, 5, and 6). Although classic coarsening of features is not present, mandibular elongation is notable. In most, short stature and hearing loss develop over time. The other highly distinctive (and often severe) findings of Myhre syndrome (joint stiffness, restrictive lung and cardiovascular disease, progressive and proliferative fibrosis, and thickening of the skin) also develop over time.

Cardiovascular Features

Progressive cardiovascular issues can appear at any age; those with onset in childhood may worsen following instrumentation. Two affected individuals with restrictive cardiomyopathy who were treated with heart and heart/lung transplantation did not survive postoperative complications [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]

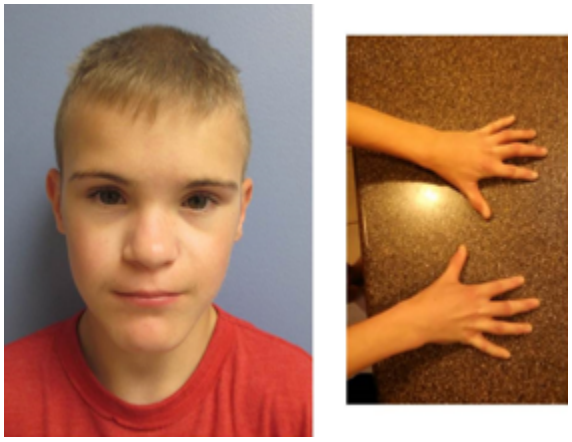

Figure 3. Male with Myhre syndrome at age 12 years with mild facial features (mild maxillary underdevelopment and thin vermilion of the upper lip) and finger contractures.

Reported as Patient 4 in Starr et al [2015]

In 54 individuals with confirmed Myhre syndrome [Lin et al 2016], 70% had a cardiovascular abnormality including structural heart defects (63%), pericardial disease (17%), restrictive cardiomyopathy (9%), and systemic hypertension (15%).

Congenital cardiovascular abnormalities 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, and mitral valve stenosis. These are more common than obstructive defects of the right side, such as valvar and branch pulmonary artery stenosis [Michot et al 2014, Hawkes & Kini 2015, Starr et al 2015].
- Visceral vascular stenoses (in celiac, superior mesenteric, inferior mesenteric, and/or renal arteries)

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]

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.
- 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 [Yang et al 2022].

Skeletal

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). Walking on tiptoes is common. Other features that may be present:

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

- Small hands and feet with brachydactyly, found in more than 80% of affected individuals (See Figures 3 and 4.)
- Clinodactyly in more than half of affected individuals
- Syndactyly of the toes, usually 2-3
- Scoliosis
- Absence of normal lumbar lordosis and straight spine
- Sacral dimple, only rarely associated with a tethered spinal cord

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

Developmental Delay and Intellectual Disability

Mild-to-moderate intellectual disability and developmental delay are common; however, cognition can be within the normal range. Delayed speech can be significant. Of note, acquired and unrecognized hearing loss may also contribute to speech delay and academic and social challenges. Affected adults have been employed and have married and reproduced.

Other Neurodevelopmental Features

Autism spectrum disorder has been noted in most affected individuals [Yang et al 2022].

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

Growth

The majority of affected infants have intrauterine growth restriction (IUGR). Short stature with compact body habitus (with normal head circumference) becomes more apparent over time.

- Most affected individuals have short 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").
- Some infants and children have difficulty with poor feeding and weight gain and may benefit from a feeding tube.
- Overweight (BMI >25, or >99th centile) may begin in adolescence, and is found in most adults.

Hearing Loss

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

- Hearing loss is predominantly conductive or mixed.
- Inner ear anomalies are rare.
- The underlying etiology of the hearing loss is often unclear or unknown; affected individuals most often have a history of bilateral myringotomy tube placement.

Primary Cutaneous 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, hyperkeratosis, 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.

Fibrosis

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.

Respiratory Findings

Respiratory issues can be multifactorial. Laryngotracheal narrowing (including subglottic stenosis) may be congenital rather than post-traumatic. Interestingly, many children have had numerous intubations without developing "traumatic" stenosis. This can be mild in childhood, and rarely progresses to a severe multilevel form. Less common is upper-airway obstruction caused by choanal stenosis, which can rarely progress to complete stenosis (atresia).

Other findings can include the following:

- Restrictive pulmonary disease has been reported, often associated with restrictive thorax.
- "Asthma" may be diagnosed but does not always respond to bronchodilator therapy, as in typical reactive airway disease.
- Interstitial lung disease has been described. Severe pulmonary fibrosis has been noted on autopsy [Starr et al 2015, Starr et al 2022].

- Abnormal sleep is usually associated with autism. In some instances, a sleep study may reveal obstructive sleep apnea.

Immune System

Recurrent infections (especially otitis media and pneumonia) are common.

- Increased frequency of respiratory infections have been reported and may result from mechanical factors. For example, ear canals, sinuses, and mastoid cells may be opacified from proliferative debris.
- Serum immunoglobulin deficiency was detected in three affected individuals.
- Intravenous immunoglobulin was utilized with reported benefit in one affected individual [Starr et al 2015].
- It is unknown if immune deficiency is associated with Myhre syndrome or if it is an incidental finding [Michot et al 2014, Starr et al 2015].

Ophthalmologic Findings

Refractive errors are common and usually include hyperopia with astigmatism. Other findings may include strabismus, cataracts, corectopia, and optic nerve anomalies.

Endocrine Findings

Premature puberty may occur in both sexes. There can be early menarche, meno/metrorrhagia, and macromastia, the latter prompting reduction mammoplasty. Both premature ovarian failure and secondary amenorrhea have been observed.

Insulin-dependent diabetes mellitus has been noted in older adults.

Gastrointestinal Findings

Gastrointestinal involvement may include the following:

- Choking, coughing, and dysphagia
- Severe constipation
- Duodenal atresia
- Late-onset and congenital pyloric stenosis; less commonly stenosis may involve the duodenum and jejunum
- Protein-losing enteropathy associated with right heart failure and restrictive cardiomyopathy (Patient 1 in Lin et al [2016])
- Hirschsprung disease

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 known affected individuals with neoplasia.

Telangiectasias and juvenile polyps, reported in heterozygotes for a *SMAD4* loss-of-function pathogenic variant, have not been reported in Myhre syndrome.

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] (see Genetically Related Disorders).

Genotype-Phenotype Correlations

Genotype-phenotype correlations are still emerging.

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 and postnatal short stature.

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.

Nomenclature

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

Prevalence

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

Genetically Related (Allelic) Disorders

Other phenotypes known to be associated with germline pathogenic variants in *SMAD4*:

- Juvenile polyposis syndrome (JPS)
- Hereditary hemorrhagic telangiectasia (HHT)

Whereas Myhre syndrome is caused by heterozygous gain-of-function *SMAD4* pathogenic variants (see Molecular Genetics), JPS and HHT are caused by heterozygous loss-of-function *SMAD4* pathogenic variants.

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. Table 3 lists these and other syndromes that have more limited overlapping features.

Table 3. Disorders to Consider in the Differential Diagnosis of Myhre Syndrome

Gene(s)	Differential Disorder	MOI	Clinical Features of This Disorder	
			Overlapping w/Myhre syndrome	Distinguishing from Myhre syndrome
ADAMTS10 *ADAMTS17* *FBN1* *LTPBP2*	Weill-Marchesani syndrome [1]	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 • Characteristic facies • Delayed bone age

Table 3. continued from previous page.

Gene(s)	Differential Disorder	MOI	Clinical Features of This Disorder	
			Overlapping w/Myhre syndrome	Distinguishing from Myhre syndrome
FBN1	Acromicric dysplasia (OMIM 102370)	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
FLNB	Spondylo-carpotarsal syndrome (OMIM 272460)	AD	• Short stature • Stiff joints • Conductive hearing loss	• Clubfeet • Dental enamel hypoplasia • Block vertebrae • Carpal/tarsal fusions • No calvarial thickening
TRIM37	MULIBREY nanism (OMIM 253250)	AR	• IUGR • Short stature • Relatively large head • Constrictive pericarditis • Restrictive cardiomyopathy	• 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, 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 and respiratory involvement result in death before age five years in approximately 33% of individuals with geleophysic dysplasia 1.

Management

No clinical practice guidelines for Myhre syndrome have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Myhre syndrome, the evaluations summarized in Table 4 (if not completed previously as part of the diagnostic evaluation) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Myhre Syndrome

System/Concern	Evaluation	Comment
Constitutional	Measurement of growth parameters	To assess for growth restriction & short stature
Craniofacial	• Physical exam for evidence of cleft lip & palate • Assessment for velopharyngeal insufficiency	If present, consider referral to multidisciplinary craniofacial center.

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
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, MRA, or cardiac catheterization of aorta may be indicated to document characteristic hemodynamics of restrictive cardiomyopathy & assess for vasculopathy.
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.	To assess for obstructive &/or restrictive lung disease
	Consider polysomnography.	For sleep disturbance & obstruction
Gastrointestinal	Assessment for recurrent vomiting & chronic constipation	• Low threshold to image for concern of pyloric or other stenosis of GI tract • Intestinal obstruction may contribute to constipation. • Hirschsprung disease has been reported.
Developmental	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education, ABA therapy
Psychiatric/ Behavioral	Neuropsychiatric eval	In persons age >12 mos: screen for concerns incl sleep disturbances, anxiety, &/or findings suggestive of ASD.
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl 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
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.
Integument	Dermatologic eval	Assess for hyperkeratosis pilaris & abnormal scarring.
Immunologic	Quantitate serum immunoglobulins to assess for immunoglobulin deficiency	• If affected person has excessive infections • If abnormal, consider referral to immunologist.
Endocrinologic	Evaluate for pubertal status in children & adolescents, & for signs/symptoms of menstrual irregularities in females.	To assess for premature puberty (in both sexes), premature ovarian failure, & secondary amenorrhea
	Assess for signs & symptoms of insulin-dependent diabetes.	This finding is more common in older adults.
Neoplasia	Currently there are no tumor surveillance guidelines for Myhre syndrome.	It remains unclear whether persons w/Myhre syndrome are at ↑ risk of malignancy over general population risk.

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Genetic counseling	By genetics professionals [1]	To 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; ADL = activities of daily living; ASD = autism spectrum disorder; GI = gastrointestinal; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. 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 5).

Table 5. Treatment of Manifestations in Individuals with Myhre Syndrome

Manifestation/Concern	Treatment	Considerations/Other
Poor weight gain / Failure to thrive	Feeding therapy	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]
Congenital heart defects / Pericardial disease	Standard treatment by cardiologist trained in congenital heart disease, pericardial disease, & restrictive cardiomyopathy	• 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	Long-term tracheostomy [2]	Tracheal resection is contraindicated. [3]
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).

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Restrictive lung disease	Symptomatic & standard treatment per pulmonologist	Oxygen supplementation as necessary
Constipation	Aggressive mgmt incl diet mgmt, stool softeners, prokinetics, osmotic agents, or laxatives as needed	
Gastrointestinal stenosis	Standard treatment per gastroenterologist	• Minimal instrumentation of GI tract is advised because postoperative adhesions can be fatal. [4] • Approach endoscopy w/caution to avoid airway manipulation, which ↑ risk for tracheal/laryngeal scarring/stenosis. [3] • Noninvasive 3D imaging may be preferred.
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Decreased range of motion of joints	PT to keep joints mobile	It is not known if passive range of motion exercises help maintain flexibility.
Strabismus / Refractive error / Cataracts	Standard treatment(s) as recommended by ophthalmologist	
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
Keloids	Some keloids can be treated w/intralesional steroids.	Minimal invasiveness for lesion removal
Immunodeficiency	Standard treatment per immunologist	May incl IVIG therapy [5]
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	
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.

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. McGowan et al [2011], Oldenburg et al [2015], Starr et al [2015]
3. Oldenburg et al [2015]
4. Lindor et al [2012]
5. Starr et al [2015]

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.

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: the literature suggests increased risk of proliferative fibrosis following otherwise uncomplicated endotracheal intubation and surgical procedures. 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/other piercing.
- 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 in Table 6 are recommended.

Table 6. Recommended Surveillance for Individuals with Myhre Syndrome

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 1-3 yrs
	In persons w/abnormal findings at initial diagnosis, more extensive imaging may be indicated given progressive nature of disorder.	As clinically indicated
	Blood pressure measurement	At each visit

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Respiratory	Pulmonary function studies in children age >6 yrs, if able to cooperate w/test maneuvers	Annually
	• Monitor for evidence of respiratory insufficiency & obtain pulse oxygen measurement. • Evaluate for signs/symptoms of upper airway stenosis.	At each visit
Gastrointestinal	Monitor for constipation or signs/symptoms of GI narrowing.	
Developmental	Monitor developmental progress & educational needs.	
Psychiatric/ Behavioral	Behavioral assessment for anxiety, ASD, & aggressive or self-injurious behavior	
Musculoskeletal	Physical medicine, OT/PT, mobility assessment, self-help skills	
Immunologic	Assessment of signs/symptoms of frequent or unusual 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	
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. [2]	At each visit in childhood
	Postpubertal women: monitor for heavy menses [2]	Starting in 2nd decade
Lifestyle	Encourage nonstrenuous exercise, healthy eating, & weight mgmt. [3]	At each visit

ASD = autism spectrum disorder; GI = gastrointestinal
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. These findings are more common in those with the c.1486C>T (p.Arg496Cys) pathogenic variant.
3. 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 individuals' 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, or surgical repair of velopharyngeal insufficiency. Elective tracheal surgery/intubation should be avoided.

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. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

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

Risk to Family Members

Parents of a proband

- Most probands with Myhre syndrome have the disorder as the result of a *de novo SMAD4* pathogenic variant [Lin et al 2016].
- Vertical transmission (from an affected mother to two affected children) has been reported in one family [Meerschaut et al 2019]. Additional families with vertical transmission have been identified [Author, personal observation].
- 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 confirm their genetic status and to allow reliable recurrence risk counseling.
- 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 germline (or somatic and germline) mosaicism, which has not been reported to date in Myhre syndrome. 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 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 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 theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- 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 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 theoretic possibility of reduced penetrance in a heterozygous parent or parental germline 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.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal 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.

- **MedlinePlus**
  Myhre syndrome
- **Myhre Syndrome Foundation**
  www.myhresyndrome.org
- **National Organization for Rare Disorders (NORD)**
  Myhre Syndrome
- **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)
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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 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

Heterozygous **gain-of-function** pathogenic variants in *SMAD4* confer stability of the resulting abnormal protein due to an apparent decrease in monoubiquitination. This affects transforming growth factor beta (TGF-β) signaling, thus altering expression of downstream target genes encoding TGF-β and bone morphogenic proteins (BMP), resulting in abnormal extracellular matrix deposition and altered development of the axial and appendicular skeleton, cardiac muscle, and central nervous system [Caputo et al 2012, Le Goff et al 2014, Piccolo et al 2014].

In contrast, heterozygosity for a **loss-of-function** *SMAD4* pathogenic variant has been well established as the cause of a spectrum of acquired cardiac diseases, including cardiac fibrosis and hypertrophy, aortopathies, atherogenesis, and pulmonary artery hypertension [Andrabi et al 2011, Nasim et al 2011, Heald et al 2015].

Mechanism of disease causation. Gain of function had been suspected; however, new research suggests a dominant-negative mechanism causing an interruption of typical TGF and BMP signaling [Alankarage et al 2022].

Table 7. Notable *SMAD4* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_005359.5 NP_005350.1	c.1486C>T	p.Arg496Cys	• Persons w/this variant are typically not as short in stature based on their familial potential. • 3 affected women w/this variant developed endometrial cancer [Lin et al 2020]. [1]
	c.1498A>G	p.Ile500Val	Highly recurrent pathogenic variant that 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 track (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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