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## Delineating Phenotypes of Rare Disease

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# DELINEATING PHENOTYPES OF RARE DISEASE

By

**Lois J. Starr, M.D.**

A DISSERTATION

Presented to the Faculty of  
the University of Nebraska Graduate College  
in Partial Fulfillment of the Requirements  
for the Degree of Doctor of Philosophy

Medical Sciences Interdepartmental Area  
Graduate Program  
(Clinical and Translational Research)

University of Nebraska Medical Center  
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Supervisory Committee:

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John Sparks, M.D.

Warren Sanger, Ph.D. (deceased)

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## List of Abbreviations

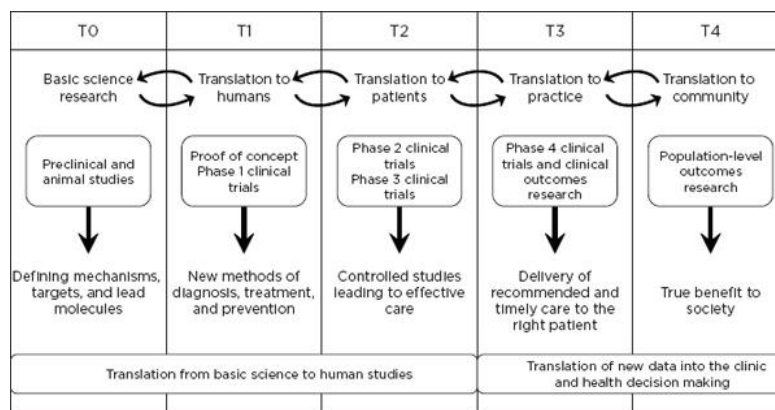
AD	autosomal dominant
AR	autosomal recessive
ASD	atrial septal defect
CT	computerized tomography
EEG	electroencephalogram
ECM	extracellular matrix
ECMO	extracorporeal membrane oxygenator
FEV	forced expiratory volume
FIG	figure
GPI-AP	glycosylphosphatidylinositol-anchored protein
HHT	hereditary hemorrhagic telangiectasia
ICU	intensive care unit
IUGR	intrauterine growth restriction
JPS	juvenile polyposis syndrome
LAPS	Laryngotracheal stenosis, Arthropathy, Prognathism, and Short stature)
LVH	left ventricular hypertrophy
MRI	magnetic resonance imaging
MMP	matrix metalloproteinase
MOI	mode of inheritance
MULIBREY	MUscle, LIver, BRain, and EYes
GlcNAc	N-acetylglucosamine
OMIM	Online Mendelian Inheritance in Man
PIGQ	phosphatidylinositol-glycan biosynthesis class Q
SGA	small for gestational age
SMAD4	SMA- AND MAD-RELATED PROTEIN 4
XL	X-linked

## Introduction: Clinical Translational Research and Rare Disease

There are more than 6,000 unique and identifiable rare diseases that together affect millions of individuals. Underlying genetic etiology, information on surveillance, prognosis and tailored medical treatments are crucial for optimal survival and quality of life for these patients. Particularly when the genetic etiology of a disease is delineated, molecular pathways can be defined and this unlocks potential discovery for additional conditions and mechanisms. Though tremendous progress has been made, we only have specific treatments for approximately 200 rare disorders – and only a handful that could be considered an essential cure.

While having a molecular diagnosis for a patient's rare disease can mean everything to that family, it also holds high value to us in the scientific and medical communities. Understanding multi-faceted biochemical pathways is usually spearheaded by investigating a deficiency or an issue that causes a rare disease. However, all patients, even with the same rare disease, are quite different. They have their own genetic milieu as well as environmental factors that make their clinical story unique.

The work of defining these rare diseases that are being discovered on a regular basis is imperative to support all, but especially levels T1, T2, and T3, of clinical translational research.



Without a solid understanding of what the molecular diagnosis is capable of, we cannot address the medical issues associated.

The work included in this dissertation is limited to my three most important first author published manuscripts since starting the Clinical Translational Research (CTR) Mentored Scholar's Program through the University of Nebraska Medical Center. All are patient-inspired. During these past five years, I have also been involved with 16 additional manuscripts delineating the phenotype and care of rare disease. Two in this dissertation are devoted to Myhre syndrome. I was first introduced to Patient M while a fellow in medical genetics. Now, 8 years later, I am on the Myhre Professional Advisory Board and receive routine requests to provide medical opinions on this progressive condition. The first article outlines 5 new patients with Myhre and was the first article defining the devastating cardiopulmonary issues that they can have. It was recognized that this article could have such medical impact upon submission that the editors recommended publishing it urgently as a rapid communication and it was included in the AJMG Sequence publication as an article of high medical care impact. The second article is the GeneReview for Myhre syndrome. In rare disease it is well-known in the medical community that the go-to review for genetic diseases is the GeneReview. It is an invited article and there is a rigorous editing process. This article is by far the most impactful published work I have contributed to in my career. The third manuscript, PIGQ Glycosylphosphatidylinositol-Anchored Protein (GPI-AP) Deficiency: Characterizing the Phenotype, was published as a new syndrome article in the American Journal of Medical Genetics. This is the first article describing this condition. The editor, Dr. Max Muenke, included this article in his opening editorial of The Journal when referring to advances in identifying new genetic disorders.



## Chapter One:

### Myhre Syndrome: Clinical Features and Restrictive Cardiopulmonary Complications

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## ABSTRACT

Myhre syndrome, a connective tissue disorder characterized by deafness, restricted joint movement, compact body habitus, and distinctive craniofacial and skeletal features, is caused by heterozygous mutations in *SMAD4*. Cardiac manifestations reported to date have included patent ductus arteriosus, septal defects, aortic coarctation and pericarditis. We present five previously unreported patients with Myhre syndrome. Despite varied clinical phenotypes all had significant cardiac and/or pulmonary pathology and abnormal wound healing. Included herein is the first report of cardiac transplantation in patients with Myhre syndrome. A progressive and markedly abnormal fibroproliferative response to surgical intervention is a newly delineated complication that occurred in all patients and contributes to our understanding of the natural history of this disorder. We recommend routine cardiopulmonary surveillance for patients with Myhre syndrome. Surgical intervention should be approached with extreme caution and with as little invasion as possible as the propensity to develop fibrosis/scar tissue is dramatic and can cause significant morbidity and mortality.

**Key Words:** Myhre syndrome; *SMAD4*; connective tissue disorder; restrictive cardiomyopathy; TGF $\beta$

## INTRODUCTION

Over 30 years ago Myhre and colleagues described a syndrome characterized by deafness, dysmorphic facial features, thick or stiff skin, restrictive joint movement, skeletal anomalies, and short stature with muscular/thick-appearing or “compact” body habitus [Myhre et al., 1981]. Subsequent to the original publication, others have further defined the facial, skeletal, respiratory and upper airway features of the syndrome and have expanded the clinical phenotype to include variable neurodevelopmental features [Rulli et al., 2004; Lopez-Cardona et al., 2004; Titomanlio et al., 2001; Burglen et al., 2003; Bachmann-Gagescu et al., 2011, McGowen et al., 2011]. In 2011, the genetic basis for Myhre syndrome was identified with documentation of mutations within a very restricted range of *SMAD4* [Caputo et al., 2012; Le Goff et al., 2012]. To date, *SMAD4* mutations have been reported in 46 patients with Myhre syndrome (OMIM #139210) [Le Goff et al., 2012; Caputo et al., 2012; Lindor et al., 2012; Al Ageeli et al., 2012; Asakura et al., 2012; Picco et al., 2012; Ishibashi et al., 2014; Kenis et al., 2014; Michot et al., 2014; Hawkes et al., 2015; Oldenburg, et al., 2015] with no report of a familial case. While the clinical picture of Myhre syndrome has been further clarified with new reports of molecularly proven cases, there remains a paucity of data on the cardiopulmonary aspects of the disorder, which may be progressive and fatal. We report five new Myhre syndrome patients with *SMAD4* mutations, three of whom died of severe cardiac disease, and provide delineation of the associated fibrotic complications.

## CLINICAL REPORTS

### Patient 1

The patient was born small for gestational age (SGA) at term to healthy, nonconsanguineous 29 year old parents. When seen for initial genetic evaluation as a toddler she was noted to have progressive conductive hearing loss, mild developmental delay, dysmorphic craniofacial features, recurrent choanal stenosis, short stature, hyperopia, advanced bone age, 11 rib pairs, dermal thickening and compact build (Figure 1). Echocardiogram at that time demonstrated a moderate-sized secundum atrial septal defect (ASD) but no valvar abnormalities. Genetic studies at this time included a normal 46,XX karyotype, normal 180K microarray (hg 18), and normal *CREBBP* sequencing. On routine cardiac followup at one year of age the patient was noted to have a small ASD and no other cardiac defects. At seven years of age the patient was evaluated for a new murmur with symptoms of heart failure. Echocardiography at that time demonstrated polyvalvar thickening with moderate mitral valvar stenosis and normal subvalvar apparatus, mild mitral regurgitation, a trileaflet aortic valve with moderate aortic stenosis, mild aortic regurgitation, concentric left ventricular hypertrophy (LVH), mild tricuspid insufficiency and a diffusely small aortic arch without focal narrowing. Further genetic studies included normal sequencing of *ADAMTSL2* and *FBN1* as well as deletion/duplication analysis. Targeted sequencing of *SMAD4* then revealed a c.1499T>C (p.Ile500Thr) mutation.

The patient developed rapid progression of her aortic stenosis and four months later underwent cardiac catheterization. At catheterization, the valve appeared rubbery and dysplastic with easy resolution of narrowing on balloon inflation. However, due to the rubbery nature of the valve, no reduction in gradient could be achieved with a standard-sized balloon. A result was achieved after a second valvuloplasty with a larger balloon with a fall in the peak to peak gradient from 50 to 20 mmHg. The improvement, however, was quite transient. Both right and left ventricular end-diastolic pressures were elevated at 15mmHg, consistent with mild to moderate restrictive physiology. One month following the procedure the patient was again documented to have progressive aortic valvar stenosis as well as mitral stenosis. Eight months following aortic valvuloplasty the patient underwent surgical aortic valve repair, tricuspid valvuloplasty, ASD closure and mitral valve replacement following a failed attempt at mitral valve repair. The mitral valve was characterized by severe fibrosis and dystrophic calcification of the leaflets and subvalvar apparatus. Aortic valvar, subvalvar and supra-valvar fibrosis and calcification were also noted with fibrotic tissue partially covering the right coronary ostia. The tricuspid valve was not fibrotic but had a dysplastic cleft in the anterior leaflet. Surgery was complicated by complete heart block requiring pacemaker placement on postoperative day 10. At the time of pacemaker placement the midline fascia below the sternotomy was noted to be abnormally thickened. In addition, the epicardial surface of the heart was noted to be unusually rubbery and fibrotic. Over the next two months the patient developed progressive heart failure secondary to a restrictive cardiomyopathy culminating in sudden cardiac

arrest and placement on extracorporeal membrane oxygenator (ECMO). Left atrial pressure was markedly elevated at 35mmHg despite a functioning, appropriately-sized mechanical mitral valve. Cardiac catheterization was performed for the purposes of creating an ASD for left heart decompression. Left ventricular function remained severely impaired and the patient underwent cardiac transplantation. Cardiac transplantation was complicated by inability to oxygenate requiring ECMO support for one week, inability to obtain chest closure despite an appropriately-sized donor heart, progressive SVC anastomotic narrowing requiring stenting, respiratory failure with inability to wean from the ventilator, and progressive low cardiac output without evidence of rejection requiring repeat ECMO support two months post transplantation. The patient suffered an intracerebral bleed while on ECMO support and care was withdrawn. She was eight years old.

#### Patient 2:

The patient was the second child of healthy, nonconsanguineous parents (maternal age 29 years; paternal age 37 years). She was born SGA at term. The pregnancy was complicated by polyhydramnios and prenatally diagnosed duodenal atresia. The intestinal defect was repaired on the first day of life. Routine echocardiogram demonstrated mild coarctation of the aorta. The subsequent clinical course was characterized by dysmorphic craniofacial features (Figure 2), persistent short stature, velopharyngeal insufficiency requiring a palatal lengthening procedure, recurrent ear infections requiring placement of multiple sets of bilateral myringotomy tubes, and superimposed bilateral sensorineural hearing loss resulting in severe speech

delay. Overall development was mildly delayed. Skeletal survey showed a narrow sciatic notch, short metacarpals and 11 rib pairs. At seven years of age the aortic coarctation was refractory to balloon angioplasty, for which she underwent stent placement. Despite adequate relief of aortic arch obstruction, the patient developed elevation in pulmonary vascular resistance and was subsequently diagnosed with restrictive cardiomyopathy, interstitial lung disease, and pulmonary hypertension. Pulmonary function testing revealed a severely reduced FEV1 with no response to bronchodilator therapy. Open lung biopsy was performed at 10 years of age which demonstrated diffuse interstitial fibrosis, medial thickening of arteries, arterioles and veins and smooth muscle hyperplasia of the airways with a large amount of collagen present. She had progression of her restrictive cardiomyopathy over a period of three years and underwent bilateral heart and lung transplantation. Transplantation was complicated by diffuse mediastinal fibrosis (pericardium was noted to be normal) and adhesions requiring extensive care in removing. Post-transplant her chest was able to be closed, however, she suffered persistent respiratory failure and blood pressure lability. She suffered an ECMO-related stroke and died 6 days postoperatively at 12 years of age.

The explanted heart demonstrated no abnormality of the pericardium but diffuse fibrosis of the endocardium and subendocardium. Explanted lungs demonstrated diffuse interstitial fibrosis with septal widening and pneumocyte hyperplasia. *SMAD4* sequencing performed post-mortem from previously extracted DNA for other genetic studies (46,XX karyotype, 22q11.2 FISH, chromosome breakage

studies, Feingold studies [*MYCN* sequencing and deletion/duplication analysis]), confirmed a c.1499T>C (p.Ile500Thr) mutation consistent with the diagnosis of Myhre syndrome.

#### Patient 3:

The patient was born SGA to nonconsanguineous parents at term (maternal age 28 years; paternal age 30 years). The clinical course was marked by dysmorphic craniofacial features (Figure 3) significant feeding and swallowing difficulties as an infant. At 24 months she charted at below the 5<sup>th</sup> centile for stature; approximately the 50<sup>th</sup> centile for a 10 month old. Her upper airway was thoroughly evaluated and no obstruction was found, although absent nasal cilia were noted. Over time she had persistence of short stature, progressive conductive hearing loss, progressive skin changes marked by dermal thickening, menorrhagia refractory to medical therapy, and at age 17 presented with unilateral vision loss due to biopsy-confirmed right optic nerve sheath meningioma. The patient had normal intelligence, but required medical treatment of obsessive-compulsive and anxiety disorders. Her initial cardiac evaluation was performed at age two years at which time she was diagnosed with an innocent murmur with normal echocardiogram. A repeat echocardiogram at age four years documented normal cardiac anatomy. At age 16 she was again evaluated by cardiology for dyspnea and hypertension. Spirometry revealed moderate to severe restrictive lung disease which was felt to be secondary to musculoskeletal deformity due to her dwarfism. Echocardiogram documented mild aortic stenosis and normal ventricular function. Hypertension was well controlled on two medical agents.



Over a period of eight years her aortic valve stenosis became progressively more severe with a peak to peak gradient of 80 mmHg. Aortic balloon valvuloplasty was performed. This also required upsizing of the balloon, with the valve appearing dysplastic. A reduction in gradient from 80 to 35 mmHg was achieved. The patient had persistent elevation of both right- and left-sided filling pressures consistent with restrictive physiology. Myhre syndrome was diagnosed at this time with confirmation of a c.1498A>G (p.Ile500Val) mutation in *SMAD4*. Over the ensuing two years the patient developed progressive shortness of breath with LVH and progressive aortic stenosis requiring repeat valvuloplasty attempt at age 26 years. Just prior to her catheterization she was unable to walk across the room or eat a meal without distress. At catheterization, the anesthesia team found her respiratory mechanics to be significantly compromised and counselled the family that she may not tolerate extubation. The catheterization documented progressive aortic stenosis (gradient of 78mmHg), and marked elevation in diastolic pressures in both ventricles. The intervention produced minimal improvement in the aortic valve (reduction to 55mmHg), despite two larger balloon attempts. No aortic insufficiency was created. She was transferred to the ICU, but was unable to wean from mechanical ventilation. After discussion with her family regarding her severely compromised cardiac and lung function, her family elected not to proceed with resuscitation; when she received an optimized trial of extubation, she was unable to maintain adequate ventilation and died.

Patient 4:

The patient was born SGA 3 days prior to due date to 26 year old nonconsanguineous parents. He had poor feeding, gastroesophageal reflux, and subglottic stenosis. His motor development was mildly delayed and at two years of age bilateral hearing loss was found on evaluation for delayed speech. He was found to be growth hormone deficient and placed on growth hormone at age eight. Since starting growth hormone he has progressed from the 5<sup>th</sup> centile to the 30<sup>th</sup> centile for height (at 13 years of age). He had seen genetics at seven years of age for evaluation of dysmorphic craniofacial features (Figure 4a-c), hypotonia, hearing loss, restricted finger joint movement (Figure 4d), and short stature which resulted in a normal microarray and Noonan syndrome testing. At nine years of age he underwent choanal stenosis repair. Spirometry demonstrated persistent restrictive lung disease without response to albuterol. He had a diagnostic right deltoid muscle biopsy which showed small striated muscle fibers of minimal size variation. Histologic analysis showed esterase-positive cellularity within the epimysial connective tissue. The biopsy site required several weeks to heal and resulted in a large fibrotic scar (Figure 4e). He had normal echocardiograms at 6 and 11 years of age. On follow up with genetics, at 11 years of age he was recognized to have findings of Myhre syndrome; *SMAD4* targeted testing confirmed a c.1498A>G (p.Ile500Val) mutation. By 13 years of age he had a total of nine sets of myringotomy tubes and continues to have restrictive pulmonary disease but otherwise well, and is attending school full time.

Patient 5:

The fifth patient was born SGA at 37 weeks gestation to healthy nonconsanguineous parents (maternal age 25 years; paternal age 28 years) with a noncontributory family history. On clinical genetics evaluation at four years of age she was noted to have dysmorphic craniofacial features (Figure 5a-c), bilateral hearing loss (right ear primarily conductive; left ear mixed), strabismus, velopharyngeal insufficiency, asthma, gastroesophageal reflux, prior gastric fundoplication, mild periventricular leukomalacia, limited joint extensibility, and speech and gross motor delays. She had normal social development and intelligence. At that time height was 94 cm, (3<sup>rd</sup> centile), weight was 14.2 kg (10<sup>th</sup> centile) and head circumference was 50.1 cm (45<sup>th</sup> centile). She had a flat nasal bridge, a systolic murmur, and limited movement of the joints. Subsequent clinical course was significant for tonsillectomy and adenoidectomy at age seven years. At age eight years she underwent a superiorly based pharyngeal flap and was noted to have vocal cord paresis and subglottic stenosis with scarring of the vocal cords. She was found to have fusion of the C6 and C7 vertebral bodies with widening of the C5-C6 disc space (Figure 5d). She was diagnosed with systemic hypertension and suffered multiple episodes of otitis media and pneumonias with pleural effusion. She had hypogammaglobulinemia with recurrent variable infections which has responded to IVIG treatment.

At 12 years of age she presented with cough and positional dyspnea. Echocardiogram demonstrated a very large pericardial effusion and severe reduction in left ventricular systolic function with shortening fraction of 10%. Ventricular chambers were normal in size but both atria were dilated. Following drainage of her pericardial

effusion her ventricular function remained poor with evidence of abnormal diastolic function with an E/A ratio > 3:1. During this evaluation intubation required multiple attempts and special measures. She was transferred to a tertiary care center for consideration of advanced heart failure therapies. She was diuresed and started on inotropic support with recovery of ventricular function within 24 hours. One year later the patient developed diffuse edema and dyspnea. Evaluation at that time demonstrated normal sized ventricles with preserved systolic function, dilated atria, abnormal mitral inflow as noted previously, a small pericardial effusion, and elevated BNP consistent with constrictive or restrictive physiology. As part of her vascular workup for chronic hypertension, she was noted to have a diffusely small descending aorta and focal stenosis of the celiac artery. At 13 years of age, the patient developed progressive subglottic stenosis and a tracheostomy was performed. At followup she was noted to have a shelf of scar tissue with complete soft tissue stenosis of the airway. Both her fundoplication (Figure 5e) and tracheostomy incisions resulted in a hypertrophic scar.

Normal genetic studies throughout her course included an amniocentesis 46,XX karyotype, 22q11.2 FISH, subtelomere FISH, and microarray analysis (2013). At 14 years of age *SMAD4* sequencing showed a c.1499T>C (p.Ile500Thr) mutation.

At 15 years of age the patient continues to have significant issues with severe subglottic stenosis that had progressed to grade IV, resulting in inability to vocalize; evaluation for laryngotracheal reconstruction was in process.

## DISCUSSION

Myhre syndrome is caused by apparent gain-of-function mutation in *SMAD4* which, to date, appear to be restricted to heterozygous missense changes in Ile500 within the conserved MAD homology 2 domain of exon 11 [Caputo et al., 2012; LeGoff et al., 2012; LeGoff, et al., 2014] in all but three reported patients. In these three patients with a clinical phenotype of Myhre syndrome, an Arg496 change [Caputo et al., 2014; Michot et al., 2014] was instead documented. These patients were of normal stature and did not have cardiac anomalies. While the Arg496 residue is involved in the transcriptional activation of *SMAD4* it only results in dysregulation via altered expression of matrix metalloproteinases (MMPs) which act as a major contributor to extracellular matrix (ECM) stability [Caputo et al., 2014; Piccolo et al., 2014]. In contrast, the more typical Ile500 aberrations affect the MMPs as well as their related inhibitors [Piccolo et al., 2014].

In Myhre syndrome, because of decreased mono-ubiquitination, stability is inferred upon the *SMAD4* protein which disrupts TGF $\beta$  signaling, resulting in abnormal development of axial and appendicular skeletal structures, skeletal and cardiac muscular development as well as the central nervous system [Caputo, 2012; Le Goff, 2014]. The role of the SMADs has been well established in a spectrum of acquired cardiac diseases, including cardiac fibrosis and hypertrophy, aortopathies, atherogenesis and pulmonary artery hypertension. *SMAD4*, a central cytoplasmic mediator of the TGF- $\beta$  and BMP signaling pathways, has been shown to have increased expression in patients with cardiac atrial fibrosis [Gramley et al., 2010].

Although there has not been a Myhre syndrome-specific mouse model, there have been other mouse models looking at the role of SMAD4 as it relates to cardiac form and function. A mouse model with cardiac myocyte-specific disrupted SMAD4 developed heart failure secondary to significant cardiomyocyte hypertrophy and cardiac fibrosis [Wang et al., 2005]. Cardiac tissue fibrosis has also been induced in cardiac fibroblasts from a mouse model directly targeting SMAD4, increasing the profibrogenic TGF- $\beta$ 1 activity [Huang et al., 2014]. A keratinocyte-specific SMAD4 knockout mouse has been shown to have a significantly accelerated rate of keratinocyte proliferation and wound contraction [Yang et al., 2012].

We present five previously unpublished patients with Myhre syndrome with documented *SMAD4* missense mutations in the isoleucine residue at position 500 (Table I). While all share cardinal features of progressive hearing loss, restricted joint movement, thick skin, and compact habitus, they also demonstrate impressive variability in clinical expression. We are not aware of any prior reports of need for cardiac transplantation in this patient population. While minor cardiac involvement has been reported in many patients with Myhre syndrome the need for and outcome of surgical intervention, has not been thoroughly described. Constrictive pericarditis has been reported in LAPS (Laryngotracheal stenosis, Arthropathy, Prognathism, and Short stature) syndrome, a condition determined to be a phenotypic variant of Myhre syndrome by Lindor et al. in 2012 [Picco et al., 2013; Michot et al., 2014]. In Lindor's series, one patient who underwent pericardectomy for presumed constrictive pericarditis, had persistent restrictive indices on echocardiography suggesting that

restrictive cardiomyopathy may have been the underlying disease process as it was in the four patients we describe with cardiomyopathy.

Specifically, Myhre syndrome patients undergoing transplantation have not been previously reported and we present two patients who were unable to survive post-transplantation complications. These patients had significant fibrotic scarring of the heart itself and surrounding mediastinal structures from presumed previous tissue damage or instrumentation. Of note, the pericardium itself was noted to be normal in these three patients where the pericardium was inspected intraoperatively or on autopsy. This article highlights a potential deleterious effect of surgery in these patients with abnormal tissue response resulting in impaired wound healing, anastamotic strictures, and adverse myocardial remodeling. Prior concern about wound healing in Myhre syndrome was raised by Lindor et al, noting life-threatening adhesions following hysterectomy in a patient who also had chronic restrictive cardiomyopathy which persisted after pericardectomy [Lindor et al., 2012].

In addition, Myhre syndrome patients are prone to complicated airway management. Post-intubation/tracheal-trauma fibrotic scarring resulting in grade IV stenosis is presumed in Patient 5 and has also been reported in multiple other patients with Myhre syndrome [Oldenburg et al., 2015] and we recommend extraordinary caution with intubation.

The decision to take a patient with Myhre syndrome to surgery of any kind should include a discussion of an apparently abnormal wound healing process, abnormal

adhesions and fibrosis that could impact overall success and both short- and long-term morbidity and mortality. The potential for current and future difficult airway management should also be reviewed. For all Myhre syndrome patients, serial echocardiograms should be performed to detect progressive valvar and myocardial disease. We recommend an echocardiogram at the time of diagnosis of Myhre syndrome and at a minimum of every two years thereafter or if symptoms arise. In addition, prompt referral for pulmonary evaluation with functional testing should be performed if symptoms suggest compromise, due to the increased risk for restrictive pulmonary insufficiency. Patients with Myhre syndrome should be closely monitored post-operatively for abnormal fibrotic wound healing and elective surgical procedures should be avoided if at all possible given the attendant risks.

#### **ACKNOWLEDGEMENTS**

We would like to sincerely thank these five patients and their families for their eager participation, support, and advocacy. We would also like to thank Dr. Angela Lin from the Harvard Medical School in Boston, MA for her insight.



TABLE

Patient	Age in years	Cardinal Features*	SMAD 4	Sex	Paternal age	Cardio/pulmonary restrictive disease	Newly reported features
1	8 (deceased)	+	I500T	F	29	+/?	post-transplant (heart) complications
2	12 (deceased)	+	I500T	F	37	+/+	duodenal atresia, post-transplant (heart and lung) complications
3	26 (deceased)	+	I500V	F	30	+/+	optic nerve sheath meningioma
4	13 (at time of report)	+	I500V	M	26	-/+	favorable response to growth hormone
5	15 (at time of report)	+	I500T	F	28	+/+	hypogammaglobulinemia resolved with IVIG treatment

**TABLE I.** Clinical details and newly reported features of the patients reported in this manuscript.

\*hearing loss, typical facial features, compact build, restricted joint movement, thick skin

**FIGURES and LEGENDS**

FIG 1. Patient one at seven years of age. Note midfacial retrusion, relative prognathism, flat nasal bridge, downward pointing nasal tip, microstomia, wide-spaced teeth, thin upper lip, broad ears with a squared shape, limited facial creasing, broad and short neck with an overall compact body habitus. She has brachydactyly and fingers are not Capable of full extension.



FIG 2. Photos of the patient 2 at 1, 2, 3, 5, 10 (standing) and 12 years of age. Note progression of features with midfacial retrusion, prognathism, flat nasal bridge, downward pointing nasal tip, microstomia, thin upper lip, broad ears with a squared

shape, limited facial creasing, broad and short neck with compact body habitus.



FIG 3. Photos of patient 3 at 23 years of age. Note midfacial retrusion, flat nasal bridge, downward pointing nasal tip, microstomia, thin upper lip, prognathism, broad ears with a squared shape, limited facial creasing, broad neck and low posterior hairline. Brachydactyly with limited extension and lordosis is also present.

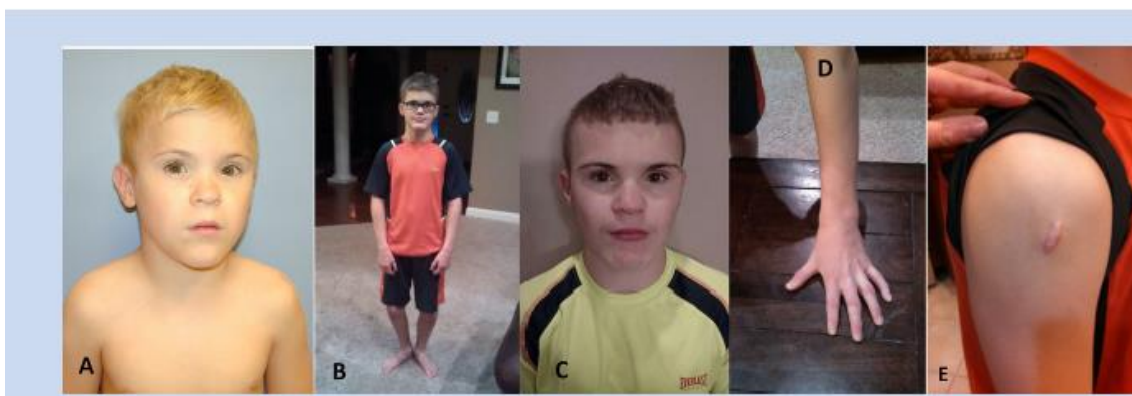


FIG 4a-d. Photos of patient 4 at 7 (a) and 11 (b,c) years of age. Note the mild features of this patient. Broad and flat nasal bridge, mild midfacial retrusion with relative prognathism. Mild brachydactyly is present with limited small and large joint extension (d).

FIG 4e. Hypertrophic scar subsequent to uncomplicated muscle biopsy.

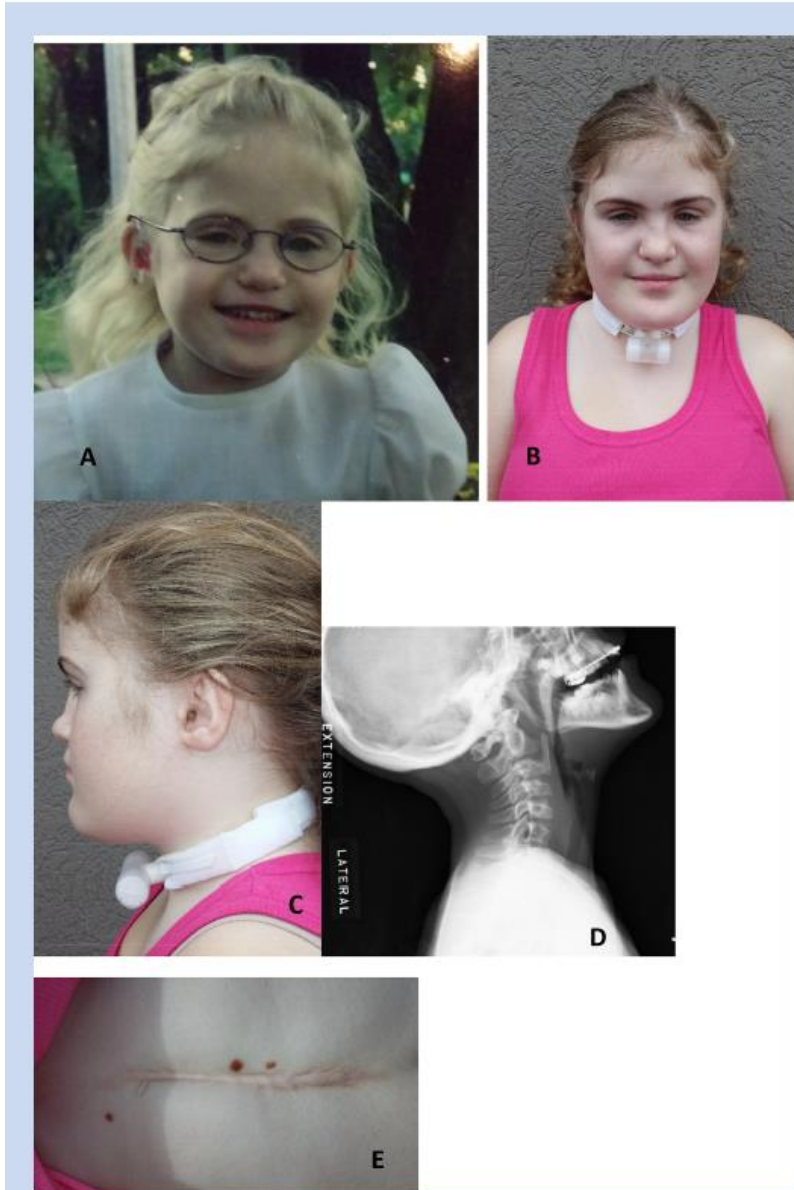


FIG 5a-c. Photos of patient 5 at 3 and 15 years of age. Note progression of midfacial retrusion and prognathism. This patient has a lateral ptosis, low hanging columella, square and broad ears and minimal facial creasing.

FIG 5d. Radiograph of cervical vertebrae at 11 years of age show an anterior bar fusing C2 to C3 and fusion of the C6 and C7 vertebral bodies with widening of the C5-C6 disc space.

FIG 5e. Hypertrophic scars at fundoplication incision site.

## Chapter 2: Myhre Syndrome GeneReview

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

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### Summary

Clinical characteristics.

Myhre syndrome is a connective tissue disorder with multisystem involvement, progressive and proliferative fibrosis that may occur spontaneously or following trauma or surgery, mild-to-moderate intellectual disability, and in some instances, autistic-like behaviors. Organ systems primarily involved include: cardiovascular (congenital heart defects, long- and short-segment stenosis of the aorta and peripheral arteries, pericardial effusion, constrictive pericarditis, restrictive cardiomyopathy, and hypertension); respiratory (choanal stenosis, laryngotracheal narrowing, obstructive airway disease, or restrictive pulmonary disease), gastrointestinal (pyloric stenosis, duodenal strictures, severe constipation); and skin (thickened particularly on the hands and extensor surfaces). Additional findings include distinctive craniofacial features and skeletal involvement (intrauterine growth restriction, short stature, limited joint range of motion). To date, 55 individuals with molecularly confirmed Myhre syndrome have been reported.

Diagnosis/testing.

The diagnosis of Myhre syndrome is established by detecting a de novo SMAD4 heterozygous pathogenic variant in a proband with characteristic clinical findings.

Management.

Treatment of manifestations: Symptomatic treatment (with attention to limiting tissue trauma by minimizing instrumentation during diagnosis and management) by specialty experts of the following involvement: cardiovascular, respiratory (including tracheostomy when tracheal



stenosis is recurrent or complete), and GI; routine management of speech and language delay, intellectual disability, behavioral problems.

Prevention of secondary complications: Limiting of tissue trauma given the apparent increased risk for proliferative fibrosis following otherwise uncomplicated endotracheal intubation and surgical procedures. When possible, alternative noninvasive approaches should be pursued during diagnosis and management

Surveillance: Cardiovascular: echocardiogram every one to three years in asymptomatic individuals with a normal echocardiogram at the time of initial diagnosis; in individuals with abnormal cardiac findings at the time of diagnosis, more extensive imaging (including possible cardiac MRI) may be considered. Respiratory: oxygen saturation in children with monitoring as needed for symptoms suggestive of restrictive/obstructive pulmonary disease; annual pulmonary function studies in children older than age six years if able to cooperate; evaluation of laryngotracheal stenosis based on symptoms. Annual ophthalmology and audiology evaluations.

Agents/circumstances to avoid: Smoking; tissue trauma.

Genetic counseling.

Myhre syndrome is inherited in an autosomal dominant manner. All probands with Myhre syndrome reported to date have the disorder as a result of a de novo SMAD4 pathogenic variant. 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. To date, individuals with Myhre syndrome are not known to reproduce and fertility has not been assessed. 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 diagnosis are possible.

Diagnosis

Formal diagnostic criteria have not been published for Myhre syndrome.

Suggestive Findings

Myhre syndrome should be suspected in individuals with the following clinical and radiographic findings.

Clinical

### **Cardiovascular**

Arterial obstruction: juxtaductal coarctation of the aorta, long- and short-segment descending thoracic and abdominal aortic obstruction, and peripheral arteries in various locations; infrequently, branch pulmonary artery stenosis

Congenital heart defects:

Atrial and ventricular septal defects, patent ductus arteriosus

Valvular stenosis: aortic and mitral valves; infrequently, tricuspid and pulmonic valves

Pericardial involvement: ranges from effusion to constrictive pericarditis; often chronic and severe

Restrictive cardiomyopathy (can be rapidly progressive)

Hypertension: systemic and pulmonary

Respiratory (congenital or acquired)

Laryngotracheal narrowing (including subglottic stenosis)

Choanal stenosis

Obstructive airway disease

Restrictive pulmonary disease (which appears to increase with age)

### **Gastrointestinal**

Congenital or acquired pyloric stenosis

Later onset:

Duodenal strictures

Severe constipation

### **Skin**

Stiff and thickened overall, but particularly on the hands and extensor surfaces

Facial creases fewer than expected for age

Proliferative fibrosis/scarring

May occur spontaneously or following trauma or surgery

May involve the serosal surfaces of the heart, airway and lungs, and gastrointestinal tract as well as the skin

### **Neuropsychiatric**

Mild-to-moderate intellectual disability

Autistic-like behaviors in some

### **Craniofacial**

Characteristic facial features including short palpebral fissures, deeply set eyes, maxillary underdevelopment, short philtrum, narrow mouth, thin vermilion of the upper lip, and prognathism (Figure 1, Figure 2, Figure 3, Figure 4, Figure 5). Facial characteristics can progress over time; although classic coarsening of features is not present, mandibular elongation is notable. Note: Craniofacial features can vary considerably.

Cleft lip and/or palate and velopharyngeal insufficiency reported in 13% [Lin et al 2016]



Figure 1.

Female with Myhre syndrome at ages seven months, four years, and 16 years. Note the short palpebral fissures, thin upper vermilion border and maxillary underdevelopment. She required tracheostomy subsequent to traumatic intubations that resulted in complete tracheal stenosis



Figure 2.

Female with Myhre syndrome at ages newborn, 12 months, 3.5 years, and seven years. Note the short palpebral fissures, thin upper vermilion border, and progression of mild prognathism.



Figure 3. . Female with Myhre syndrome at ages three years, ten years (standing), and 21 years (face, posterior hairline, and hands).

Female with Myhre syndrome at ages three years, ten years (standing), and 21 years (face, posterior hairline, and hands). Note the short palpebral fissures, broad mid-upper nasal bridge, downward pointing nasal tip, thin upper vermilion border, broad and short neck, contracted joints (elbows are fully extended in photos), brachydactyly, and compact habitus.



Figure 4.

Male with Myhre syndrome at age 12 years. Note the mild facial features (mild maxillary underdevelopment and thin upper vermilion border) and finger contractures (hands are on a flat surface).



Figure 5. . Female with Myhre syndrome at age five years.

Female with Myhre syndrome at age five years. Note the short palpebral fissures, thin upper and lower vermilion borders, left-sided facial palsy, and brachydactyly with otherwise mild features. Facial palsy is observed in 4% of individuals with Myhre syndrome [Lin et al 2016].

#### **Skeletal**

Infants typically have intrauterine growth restriction (IUGR)

Short stature (height is significantly less than that predicted by parental heights) with compact body habitus

Range of motion of the joints can be limited

#### **Radiographic**

Findings include the following:

Thickened calvarium

Shortened long bones

Brachydactyly

Broad ribs

Enlarged vertebrae with shortened pedicles; vertebral fusion

Hypoplastic iliac wings

See Figure 6.

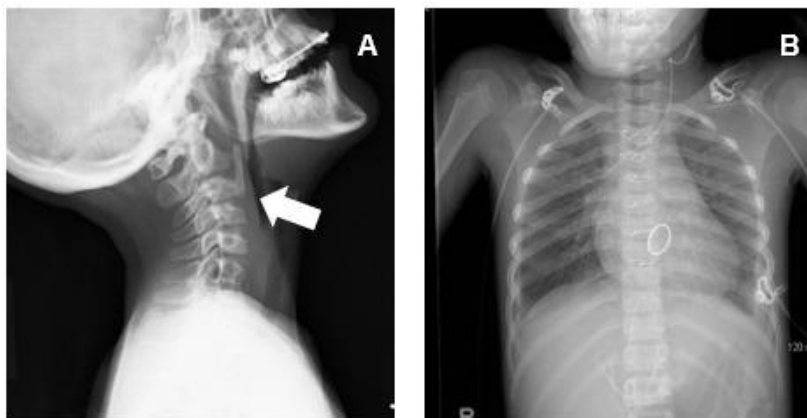


Figure 6.

Radiographs of a female age 14 years A. Thickened calvaria and anterior cervical vertebral fusion (arrow) of C2 and C3

### Establishing the Diagnosis

The diagnosis of Myhre syndrome is established in a proband with characteristic clinical findings and a *de novo* heterozygous pathogenic variant in *SMAD4* detected by molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include a combination of gene-targeted testing (multigene panel or single-gene testing) and genomic testing (comprehensive genome sequencing).

Gene-targeted testing requires the clinician to determine which gene(s) are likely involved, whereas genomic testing may not. Persons with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom a specific diagnosis has been elusive 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. If no pathogenic variant is found, gene-targeted deletion/duplication analysis may be considered; to date, however, no exon or whole-gene deletions have been reported.

A multigene panel that includes *SMAD4* and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and over time. (2) Some multigene panels may include genes not associated with the condition discussed in this GeneReview; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain

significance and pathogenic variants in genes that do not explain the underlying phenotype. (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 (comprehensive genome sequencing), when available, is likely to be the diagnostic modality selected. Comprehensive genome sequencing includes exome sequencing and genome 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 <sup>1</sup>	Test Method	Proportion of Probands with a Pathogenic Variant <sup>2</sup> Detectable by This Method
<i>SMAD4</i>	Sequence analysis <sup>3</sup>	55/55 <sup>4</sup>
	Gene-targeted deletion/duplication analysis <sup>5</sup>	Unknown <sup>6</sup>

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on allelic variants detected in this gene.

3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.

4. 54 patients summarized by Lin et al [2016] and one patient reported by Bassett et al [2016]

5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include: 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 data on detection rate of gene-targeted deletion/duplication analysis are available.

#### Clinical Description

Myhre syndrome is a multisystem connective tissue disorder involving: the cardiovascular system, respiratory system, gastrointestinal tract, and skin; progressive and proliferative fibrosis

that may occur spontaneously or following trauma or surgery, often resulting in significant complications; mild-to-moderate intellectual disability; and behavioral issues in some. Additional findings include distinctive craniofacial features and skeletal involvement.

Myhre syndrome was first described by Myhre et al [1981] in two unrelated males. Since 2011, when heterozygosity for a SMAD4 pathogenic variant was found to be causative, 55 affected individuals with a molecularly confirmed diagnosis of Myhre syndrome have been reported. Lin et al [2016] reported four affected individuals and summarized findings in 50 previously reported individuals [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]. Subsequently Bassett et al [2016] reported one additional affected individual.

Note: Unless otherwise noted, the following findings are reported in Lin et al [2016].

Infancy and progression of findings. In infancy, characteristic facial features are usually present, but more difficult to recognize than in an older child (see Suggestive Findings and Figure 1, Figure 2, Figure 3, Figure 4, Figure 5). Short stature and hearing loss develop over time as well as the 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.

Cardiovascular. Of 54 individuals with a confirmed molecular diagnosis of Myhre syndrome, 70% had a cardiovascular abnormality including structural heart defects (63%); pericardial disease (17%), restrictive cardiomyopathy (9%), and systemic hypertension (15%).

Cardiovascular abnormalities include the following:

Atrial septal defect (4%) and ventricular septal defect (6%)

Patent ductus arteriosus (which can be large) (20%)

Obstructive defects of the left heart, such as juxtaductal aortic coarctation (15%), long-segment aorta narrowing (6%), aortic valve stenosis (15%), and mitral valve stenosis (2%). 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].

Peripheral vascular stenoses (in celiac and/or renal arteries) (7%)

Of note, complex congenital heart defects are not observed.

Pericardial disease (reported in 17%) can present as a short-term or recurrent effusion or as chronic or progressive constrictive pericarditis that may require surgical intervention (see Management).

Restrictive cardiomyopathy, a lethal condition, is the least common form of cardiomyopathy in the general population and can be overlooked unless cardiac catheterization documents the characteristic hemodynamics.



While constrictive pericarditis and restrictive cardiomyopathy can present with similar hemodynamics, they differ in pathogenesis and treatment (see Management).

Pulmonary hypertension has been infrequently reported; however, this may reflect limited evaluation and/or bias toward ascertainment and/or reporting of younger patients (as underlying causes of pulmonary hypertension resulting from involvement of the lungs and cardiovascular circulation may evolve with age).

Progressive cardiovascular issues can appear at any age; those with onset in childhood may worsen following instrumentation: two patients with restrictive cardiomyopathy who were treated with heart and heart/lung transplantation did not survive postoperative complications [Starr et al 2015].

Respiratory. Respiratory issues can be multifactorial. Airway stenosis, typically involving the larynx and trachea, has included subglottic stenosis (17%) that can be recurrent and severe. Less common is upper airway obstruction due to choanal stenosis (11%).

Restrictive and obstructive pulmonary disease are major causes of morbidity at all ages. Interstitial lung disease has been described. Severe pulmonary fibrosis has been noted on autopsy [Starr et al 2015].

Gastrointestinal involvement

Duodenal atresia 3/54 (6%)

Late-onset pyloric stenosis [L Starr, personal observation]

Protein-losing enteropathy (Patient 1 [Lin et al 2016])

Severe constipation [Michot et al 2014, Starr et al 2015]

Cutaneous. Generalized thickening/stiffness of the skin is seen in nearly all individuals with Myhre syndrome. Various terms used to describe the skin include thick, stiff, firm, rough, keratotic, and inelastic. Additional findings are minimal creasing of the facial skin and fibrous and keloid-like scar formation.

Skin changes may not be apparent in infancy; they are often first noted on extensor surfaces, palms, and soles. The changes progress with age.

Neuropsychiatric. Data are limited. Mild-to-moderate intellectual disability and global developmental delay are common; however, cognition can be within the normal range. Of note, acquired and unrecognized hearing loss may also contribute to speech delay and academic and social challenges.

Findings of autism spectrum disorder have been noted in a minority of affected individuals [Michot et al 2014].

Skeletal. The majority of affected infants have intrauterine growth restriction (41/49; 84%). Short stature with compact body habitus (with normal head circumference) becomes more apparent over time. Adult height is expected to be more than two standard deviations below what is predicted by parental heights.

Small hands and feet with brachydactyly is usually notable (see Figure 3, Figure 4, Figure 5).

Posture may be distinct with flexed elbows and bending forward at the hips (see Figure 3 and Ishibashi et al [2014], Figure 1).

Reduced range of motion of large and small joints is characteristic and is exacerbated with age. Walking on tiptoes is common.

Immune system. Recurrent infections (especially otitis media and pneumonia) have been reported in 19 of 34 individuals. Increased susceptibility to infection has been associated with immunoglobulin deficiency in three affected individuals; IVIG was utilized with reported benefit in one affected individual [Starr et al 2015]. At this point, 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. At least one abnormal eye finding was reported in 53% (26/49) of affected individuals:

Strabismus 13/53 (24%)

Refractive errors in 17/53 (31%)

Other. Cataracts, astigmatism, and optic nerve sheath meningioma

Hearing loss is observed in most (83%) individuals with Myhre syndrome.

Hearing loss is predominantly conductive, but can be sensorineural and mixed. The underlying etiology of the hearing loss is often unclear or unknown; most often patients have a history of bilateral myringotomy tube placement.

Of note, most infants pass their newborn hearing screen. In the authors' experience hearing loss usually becomes evident in early childhood and is typically present in adults.

Endocrine. Puberty has been reported to be normal, premature, or delayed. Secondary amenorrhea has been reported.

Neoplasia

Endometrial carcinoma [Lindor et al 2012], optic nerve sheath meningioma [Starr et al 2015], and mesencephalic glioma [Lin et al 2016] have each been reported once.

Telangiectasias and juvenile polyps, reported in heterozygotes for a SMAD4 loss-of-function pathogenic variant, have not been reported in Myhre syndrome; however, information to date is limited.

Genotype-Phenotype Correlations

The gain-of-function SMAD4 pathogenic variants that cause Myhre syndrome involve only two protein residues (codons 496 and 500). To date, no clear genotype-phenotype correlations are evident in affected individuals with either codon abnormality.

Of note, although the three individuals reported with the p.Arg496C variant do not have cardiovascular involvement and are taller in stature – two on the growth curve (2nd-25th centile) and one <1st centile [Michot et al 2014, Caputo et al 2014] – the data are too limited to draw any conclusions about genotype-phenotype correlations.

#### Penetrance

Penetrance appears to be complete; however, no familial cases of Myhre syndrome have been reported.

#### Nomenclature

LAPS (laryngotracheal stenosis, arthropathy, prognathism, and short 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 is unknown.

Since 2011 when a heterozygous pathogenic variant in SMAD4 was discovered to be the cause of Myhre syndrome, 55 affected individuals with a molecularly confirmed diagnosis have been reported worldwide with no apparent ethnic or sex predilection (54 summarized in Lin et al [2016] and one reported by Bassett et al [2016]).

#### 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. MULIBREY nanism should also be considered.

#### Table 2.

Disorders to Consider in the Differential Diagnosis of Myhre Syndrome

Disorder	Gene(s)	MOI	Clinical Features of the Disorder	
			Overlapping with Myhre Syndrome	Distinguishing from Myhre Syndrome
Acromicric dysplasia (OMIM <a href="#">102370</a> )	<i>FBN1</i>	AD	<ul style="list-style-type: none"> <li>• IUGR</li> <li>• Short stature</li> <li>• Brachydactyly</li> <li>• Joint stiffness</li> <li>• Thickened skin</li> </ul>	<ul style="list-style-type: none"> <li>• Characteristic external notch of the fifth metacarpal and internal notch of the femoral head</li> <li>• Absence of hearing loss</li> <li>• Less frequent cardiac anomalies</li> <li>• Absence of calvarial thickening</li> </ul>
<a href="#">Geleophysic dysplasia</a> <sup>1</sup>	<i>ADAMTSL2</i>	AR	<ul style="list-style-type: none"> <li>• IUGR</li> <li>• Short stature</li> <li>• Short hands and feet</li> <li>• Progressive joint limitation and contractures</li> <li>• Progressive cardiac valvar thickening</li> <li>• Thickened skin</li> </ul>	<ul style="list-style-type: none"> <li>• Hepatomegaly</li> <li>• Characteristic facies</li> </ul>
	<i>FBN1</i>	AD		
<a href="#">Weill-Marchesani syndrome</a> <sup>2</sup>	<i>ADAMTS10</i> <i>LTPBP2</i>	AR	<ul style="list-style-type: none"> <li>• IUGR</li> <li>• Short stature</li> <li>• Brachydactyly</li> <li>• Joint stiffness</li> </ul>	<ul style="list-style-type: none"> <li>• Distinctive lens abnormalities <sup>2</sup></li> <li>• Lack of hearing loss</li> </ul>
	<i>FBN1</i>	AD		

Disorder	Gene(s)	MOI	Clinical Features of the Disorder	
			Overlapping with Myhre Syndrome	Distinguishing from Myhre Syndrome
MULIBREY nanism (OMIM <a href="#">253250</a> )	<i>TRIM37</i>	AR	<ul style="list-style-type: none"> <li>• IUGR</li> <li>• Short stature</li> <li>• Relatively large head</li> <li>• Constrictive pericarditis</li> <li>• Restrictive cardiomyopathy</li> </ul>	<ul style="list-style-type: none"> <li>• Shorter stature</li> <li>• Small tongue</li> </ul>

MOI = [mode of inheritance](#)

AD = [autosomal dominant](#)

AR = [autosomal recessive](#)

XL = [X-linked](#)

IUGR = intrauterine growth restriction

1.

**Geleophysic dysplasia.** 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.

2.

**Weill-Marchesani syndrome.** The ocular problems, 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

## Management

### Evaluations Following Initial Diagnosis

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

## Cardiovascular

Upper- and lower-extremity blood pressure measurements

Two-dimensional echocardiography with Doppler

For those with abnormal findings, more extensive imaging if indicated including cardiac catheterization to document the characteristic hemodynamics of restrictive cardiomyopathy

## Respiratory

Assessment for airway stenosis by the least invasive means possible with assessment for signs of upper-airway obstruction including noisy breathing, work of breathing, and oxygen saturation

Assessment of pulmonary function and oxygen saturation for evidence of obstructive or restrictive lung disease

Gastrointestinal. Based on clinical indication (by least invasive means possible), evaluate for evidence of stenosis.

Neuropsychiatric. Neuropsychometric evaluation may be indicated for individuals with autistic behaviors and/or cognitive involvement.

## Other

Ophthalmology evaluation

Speech evaluation

Audiology evaluation

Consultation with a clinical geneticist and/or genetic counselor

## Treatment of Manifestations

Treatment is largely symptomatic and may include the following.

### Cardiovascular

Management by a cardiologist trained in congenital heart disease, including pericardial disease and restrictive cardiomyopathy. At present, no evidence suggests that in Myhre syndrome management of specific lesions would differ from standard care in current clinical practice, except that any unnecessary instrumentation should be avoided as associated tissue trauma may induce stenosis and the scarring-type tissue response unique to Myhre syndrome.

Affected individuals who are in heart failure should be under the care of a cardiovascular specialist with access to a transplant center.

Maximize all medical treatment and minimize instrumentation for all cardiac studies and therapies.

Medical treatment of systemic hypertension and pulmonary hypertension (based on underlying cause).

## Respiratory

Affected individuals have required long-term tracheostomy due to complete and recurrent tracheal stenosis following multiple and/or traumatic intubations [McGowan et al 2011, Oldenburg et al 2015, Starr et al 2015]. To avoid traumatic intubation, consider using a size-smaller uncuffed endotracheal tube. Elective tracheal surgery/intubation should be avoided; tracheal resection is contraindicated [Oldenburg et al 2015].

Symptomatic treatment of restrictive lung disease

Oxygen supplementation as necessary

## Gastrointestinal

Minimal instrumentation of the gastrointestinal tract is advised because post-operative adhesions can be fatal [Lindor et al 2012].

Endoscopy should be approached with caution to avoid airway manipulation which increases the risk for tracheal/laryngeal scarring/stenosis [Oldenburg et al 2015]. Noninvasive 3D imaging may be preferred.

Aggressive management of constipation (through dietary means or medication if necessary) is indicated.

Global developmental delay / intellectual disability educational 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. In the United States, early intervention is a federally funded program available in all states.

Ages 3-5 years. In the United States, 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.

Ages 5-21 years. In the United States, an IEP based on the individual's level of function should be developed by the local public school district. Affected children are permitted to remain in the public school district until age 21.

Discussion about transition plans including financial, vocation/employment, and medical arrangements should begin at age 12 years. Developmental pediatricians can provide assistance with transition to adulthood.

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

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.

In the United States:

Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a 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.

Social/behavioral issues

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

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

Individualized behavioral therapy or pharmacologic treatment for anxiety, depression, or other psychological manifestations as per current clinical practice is appropriate.

Hearing

Hearing loss. Appropriate hearing augmentation (see Deafness and Hereditary Hearing Loss Overview)

Persistent middle ear effusions. Myringotomy tubes as needed

Craniofacial

Individuals with orofacial clefting or velopharyngeal insufficiency should be referred to a craniofacial clinic with pediatric experience. These individuals benefit most from a multidisciplinary approach to care.

A craniofacial clinic associated with a major pediatric medical center usually includes a surgical team (craniofacial surgeon and neurosurgeon), clinical geneticist, ophthalmologist, otolaryngologist, pediatrician, radiologist, psychologist, multiple dental specialists, audiologist, speech therapist, and social worker.

Skeletal

Consider physical therapy to keep joints mobile (no study has been done on efficacy). Note: It is not known if passive range of motion exercises help maintain flexibility.



A systematic study of growth hormone treatment for short stature has not been done. One affected individual has been noted to have anecdotal improvement in growth velocity; however, it is unknown if adult height would be affected [Starr et al 2015].

Ophthalmology. Routine treatment of strabismus and refractive errors. Note: Complications from surgical repair have not been reported.

#### 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 post-surgical fibrosis is highly likely.

#### Surveillance

##### Cardiovascular

After normal baseline evaluations of upper- and lower-extremity blood pressure measurements, two-dimensional echocardiography with Doppler, and cardiology evaluation

In asymptomatic individuals with a normal echocardiogram at the time of initial diagnosis, repeat echocardiogram every 1-3 years. 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].

In individuals with abnormal findings at the time of initial diagnosis, more extensive imaging may be indicated given the progressive nature of the disorder (e.g., MRI to evaluate for pericardial thickening or effusion).

##### Respiratory

Consider oxygen saturation in children, with monitoring as needed for symptoms suggestive of restrictive/obstructive pulmonary disease and annual pulmonary function studies in children older than age six years if able to cooperate with test maneuvers.

Evaluation for upper airway stenosis (e.g., laryngotracheal stenosis) should be considered based on symptoms.

##### Other

Annual ophthalmologic and audiology evaluations

Monitoring of physical skill development and joint mobility

Agents/Circumstances to Avoid

Patients should be aggressively counseled not to smoke.

Limiting tissue trauma appears to be the single most important preventive concept in this disorder to communicate to all health care providers involved in their care (see Prevention of Secondary Findings).

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Search ClinicalTrials.gov in the US and [www.ClinicalTrialsRegister.eu](http://www.ClinicalTrialsRegister.eu) 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, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Myhre syndrome is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

All probands with Myhre syndrome reported to date have the disorder as a result of a de novo SMAD4 pathogenic variant (see Bassett et al [2016]; Lin et al [2016] and references therein).

Recommendations for the evaluation of parents of a proband with an apparent de novo pathogenic variant include molecular genetic testing.

Sibs of a proband. 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.

Offspring of a proband. To date, individuals with Myhre syndrome are not known to reproduce and fertility has not been assessed.

Other family members. The risk to other family members is presumed to be low given that all probands with Myhre syndrome reported to date have the disorder as a result of a de novo SMAD4 pathogenic variant (i.e., no familial cases of Myhre syndrome have been reported).

#### Related Genetic Counseling Issues

##### Family planning

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

It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to parents of affected individuals.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

##### Prenatal Testing and Preimplantation Genetic Diagnosis

Once the SMAD4 pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at theoretic increased risk and preimplantation genetic diagnosis for Myhre syndrome are possible.

##### 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.

##### National Library of Medicine Genetics Home Reference

##### Myhre syndrome

Alexander Graham Bell Association for the Deaf and Hard of Hearing  
3417 Volta Place Northwest  
Washington DC 20007  
Phone: 866-337-5220 (toll-free); 202-337-5220; 202-337-5221 (TTY)  
Fax: 202-337-8314  
Email: [info@agbell.org](mailto:info@agbell.org)

Listening and Spoken Language Knowledge Center  
American Society for Deaf Children (ASDC)  
800 Florida Avenue Northeast  
Suite 2047

Washington DC 20002-3695

Phone: 800-942-2732 (Toll-free Parent Hotline); 866-895-4206 (toll free voice/TTY)

Fax: 410-795-0965

Email: [info@deafchildren.org](mailto:info@deafchildren.org); [asdc@deafchildren.org](mailto:asdc@deafchildren.org)

[www.deafchildren.org](http://www.deafchildren.org)

National Association of the Deaf (NAD)

8630 Fenton Street

Suite 820

Silver Spring MD 20910

Phone: 301-587-1788; 301-587-1789 (TTY)

Fax: 301-587-1791

Email: [nad.info@nad.org](mailto:nad.info@nad.org)

[www.nad.org](http://www.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
<i>SMAD4</i>	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
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600993	MOTHERS AGAINST DECAPENTAPLEGIC, DROSOPHILA, HOMOLOG OF, 4; SMAD4
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### Molecular Genetic Pathogenesis

Myhre syndrome is caused by a heterozygous SMAD4 gain-of-function pathogenic variant that confers stability on the abnormal SMAD4 protein due to an apparent decrease in monoubiquitination. This disrupts TGF $\beta$  signaling, thus altering expression of downstream target genes encoding TGF $\beta$  and bone morphogenic proteins (BMP), resulting in abnormal development of the axial and appendicular skeleton, cardiac muscle, and central nervous system [Caputo et al 2012, Le Goff 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.

Gene structure. The coding exons 2-12 of SMAD4 constitute a 552-residue protein composed of two domains. Exon 1 is noncoding.

Pathogenic variants. The four pathogenic variants reported to date are missense variants that are restricted to residues 496 and 500 (Table 3). No inactivating deletions or duplications have been reported in individuals with Myhre syndrome.

Since 2011, when heterozygosity for a SMAD4 pathogenic variant was found to be causative, 55 affected individuals with a molecularly confirmed diagnosis of Myhre syndrome have been reported. Lin et al [2016] reported four affected individuals and summarized findings in 50 previously reported individuals [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]. Subsequently Bassett et al [2016] reported one additional affected individual.

Table 3.

#### SMAD4 Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.1486C>T	p.Arg496Cys	NM_005359.5 NP_005350.1
c.1498A>G	p.Ile500Val	

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.1499T>C	p.Ile500Thr	
c.1500A>G	p.Ile500Met	

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society ([varnomen.hgvs.org](http://varnomen.hgvs.org)). See Quick Reference for an explanation of nomenclature

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

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Normal gene product. The three functional classes of SMADs are:

SMAD4 that encodes a SMAD protein known as the co-mediator of the SMADs;

SMAD1, SMAD2, SMAD3, SMAD5, and SMAD8 that are the receptor-regulated SMADs (or R-SMADs);

SMAD6 and SMAD7 that are inhibitory SMADs.

SMAD4 (mothers against decapentaplegic homolog 4) forms heterodimers with the receptor-regulated SMADs, which are translocated to the nucleus of the cell, which then (via an unclear mechanism) regulates the expression of TGF $\beta$  and BMP pathway genes.

The 11 coding exons of SMAD4 constitute a 552-residue protein composed of two domains [Shi & Massague 2003, Le Goff et al 2011, Caputo et al 2012]:

Mad homology 1 (MH1), which contributes to DNA binding

Mad homology 2 (MH2), which activates transcription

Abnormal gene product. Codons 496 and 500 are in the Mad homology 2 domain; pathogenic variants in these codons confer a gain of function to the protein. The work of Le Goff et al [2011] indicated that defective transcriptional regulation during development plays a significant role in the disorder.

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. See Chen et al [2014] and references therein.

#### Chapter Notes

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## Chapter 3: PIGQ Glycosylphosphatidylinositol-Anchored Protein (GPI-AP) Deficiency: Characterizing the Phenotype

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### ABSTRACT

*PIGQ* (OMIM \*605754) encodes phosphatidylinositol-glycan biosynthesis class Q (PIGQ) and is required for proper function of the N-acetylglucosamine (GlcNAc) transferase complex in a similar manner to the more established PIGA, PIGC, and PIGH. There are two previous patients reported with homozygous and apparently deleterious *PIGQ* mutations. Here we provide the first detailed clinical report of a patient with heterozygous deleterious mutations associated with a glycosylphosphatidylinositol-anchored protein (GPI-AP) biosynthesis deficiency. Our patient died at 10 months of age. The rare skeletal findings in this disorder expand the differential diagnosis of long bone radiolucent lesions and sphenoid wing dysplasia. This clinical report describes a new and rare disorder — PIGQ GPI-AP biosynthesis deficiency syndrome.

**Keywords:** inherited glycosylphosphatidylinositol-anchored protein (GPI-AP) deficiency, PIGQ, developmental delay, bone lesion, sphenoid wing dysplasia



## INTRODUCTION

The inherited congenital disorders of glycosylation include a subset of disorders that include genes involved in GPI-AP biosynthesis and attachment. When damaged, these phosphatidylinositol-glycan (PIG) genes lead to a variety of clinical features including global developmental delay, multiple congenital anomalies, hypotonia, and epileptic seizures. Collectively, these associated syndromes are inherited GPI-AP biosynthesis deficiencies, with specificity derived from the precise gene involved in each condition. *PIGQ* (OMIM \*605754) encodes phosphatidylinositol-glycan biosynthesis class Q (PIGQ) and is required for proper function of the GlcNAc transferase complex in a similar manner to *PIGA*, *PIGC*, and *PIGH*. *PIGQ* was shown to be critical for the GPI biosynthesis in *in vitro* studies as early as 2001 (Tiede et al., 2001). There are two prior reports of patients with deleterious *PIGQ* mutations. Both reports were complicated by consanguinity with multiple regions of homozygosity, limited clinical information, and no photographs or radiographs. (Alazami et al., 2015; Martin et al., 2014).

Herein, we describe a patient with a multisystem disorder and compound heterozygous deleterious changes in *PIGQ*. His clinical features included coarse, dysmorphic facial features, pectus excavatum, marked abdominal laxity, and deep plantar creases. He had multisystem involvement with epileptic seizure disorder, ophthalmic anomalies, cyclical vomiting, hepatic nodule, bilateral cystic renal dysplasia, prune-belly-like abdomen, and bilateral inguinal hernias. Skeletal anomalies included sphenoid wing

dysplasia, progressive scoliosis and metaphyseal radiolucent lesions in the femora and tibiae.

### **CLINICAL REPORT**

The patient was the third child of nonconsanguineous parents. He was born at 39 weeks gestation at a weight of 3.6 kg via repeat C-section. Pregnancy was complicated by severe polyhydramnios requiring multiple amniocentesis fluid reduction procedures. Prenatal microarray was normal. He was discharged to home at 4 days of age without any recorded medical concerns. Parents noted he had some difficulty feeding and trembling episodes in the newborn period. At 2 months of age there were times where he would gasp and flail his arms. An EEG done at that time was unremarkable, but the episodes in question were not captured during the recording. Neurologic examination, including deep tendon reflexes specifically, was noted by his neurologist to be normal for age.

By 4 months of age (6.3 kg, 15<sup>th</sup> centile, length: 61 cm 5<sup>th</sup> centile, head: 43 cm 85<sup>th</sup> centile), lack of head control, episodes of gasping with lip quivering, central apnea diagnosed via sleep study, and poor feeding prompted further imaging and surveillance. At that time, he could independently raise his head and was suspected to have vision loss due to lack of fixation or tracking. Facial and physical characteristics included coarse facial features, hooded upper eyelids with mild ptosis, telecanthus, fleshy and uplifted ear lobes, thick alae nasi with broad nasal tip, and anteverted nares. He had full, almost pendulous, cheeks, a long and smooth philtrum, thin vermilion of the upper lip, down-

turned corners of the mouth, and mild micrognathia. He also had pectus excavatum, diastasis recti, bilateral inguinal herniae, abdominal wall laxity, soft and sagging skin, and deep plantar creases (Fig. 1). He began to have frequent episodes of vomiting and decreased oral intake. His neurologist noted at 5 months of age that his truncal hypotonia had progressed and his deep tendon reflexes were reduced to 1+.

Ophthalmic involvement included vertical nystagmus, bilateral hyperopia with astigmatism, cortical visual impairment, delayed visual maturation, punctate keratitis of both eyes, and alacrima with decrease of corneal sensation. Cardiovascular system involvement was only significant for a patent foramen ovale identified at 17 weeks of age. Assessment of the gastrointestinal/hepatic systems revealed heterogeneous liver echotexture, right hepatic-lobe lesion (8 x 5 x 6 mm), and normal liver function studies. A cyclic-vomiting disorder developed that required multiple hospital admissions for intravenous fluids. The right kidney (Fig. 2) was small with increased cortical echogenicity and diminished cortical medullary differentiation. Both kidneys had multiple small renal cortical cysts and a triangular focus of hyperechogenicity near the lower pole papilla with twinkle artifact representing calcification or calculi. There was grade three vesicoureteral reflex on the right and grade one on the left. Renal function was otherwise normal until just prior to death.

At age 7-months the patient had persistent clusters of myoclonic jerks with extremity stiffening, lip quivering, back-arching with upper extremities appearing floppy, and decreased responsiveness. Repeat sleep/awake EEG done at this time showed

frequent epileptiform discharges arising from the right temporal, central and bilateral occipital areas. Keppra was initiated with a goal of titration to 20mg/kg/day. Unfortunately, the child was noted to have refractory irritability interfering with sleep and oral intake. He was admitted at this time for epileptic seizure and was given lorazepam. He was loaded with fosphenytoin (20PE/kg) resulting in resolution. The episode lasted a total duration of approximately 33 minutes. He returned to previous baseline after overnight admission. An EEG done the next day showed high amplitude diffuse background slowing but no focal, lateralizing, or epileptiform patterns. Keppra was not resumed and the child was started on phenobarbital at 3mg/kg/day instead. At 9 months of age, a follow-up EEG showed multifocal epileptiform activity in the form of high amplitude spike and slow wave complexes in the right occipital region, as well as spikes and polyspikes with associated slow potentials in bilateral temporal and posterior temporal regions. The infant developed an erratic sleeping pattern with an average of only 4 hours of sleep per day. He also acquired cyclical vomiting with intractable trembling, followed by crying episodes. Phenobarbital was therefore increased to approximately 5mg/kg/day. Clonidine was also trialed for continued episodes of emesis with minor improvement.

At 10 months of age (weight: 7.8 kg 5<sup>th</sup> centile, length: 69 cm < 2%, and head measured 45 cm 50<sup>th</sup> centile) he presented with increased work of breathing and tachycardia. There were sick contacts in the family. He was found to have leukocytosis and severe respiratory acidosis and was therefore transferred to the pediatric intensive care unit for further care. He was febrile during the hospital stay but all cultures remained

negative with negative respiratory viral panel. Over the next 3 days his respiratory status stabilized and he was therefore transferred to the pediatric ward. He was trialed on gabapentin along with increase in clonidine for worsening episodes of vomiting during this admission. The fourth day after admission he was noted to have an epileptic seizure activity in the setting of high fever. Multiple doses of phenobarbital and fosphenytoin eventually led to resolution, but this was followed by respiratory failure, hypotension, and pulseless electrical activity that did not respond to resuscitative efforts resulting in demise. Parents did not want an autopsy to be performed.

MRI of the brain at 5 months of age and CT of the brain at 10 months of age, done for the significant change in mental status, revealed plagiocephaly with ventriculomegaly (left>right) (Fig. 3). The skeletal findings (Fig. 4) included a large anterior fontanelle, sphenoid wing dysplasia and an intrasutural bone of the coronal suture. Thoracolumbar scoliosis and pectus excavatum were apparent by 6 months of age and progressed until death. Transient radiolucent lesions of the long bones were seen on his first osseous survey at 3 months of age. There was resolution of the proximal tibial lesions, enlargement of distal right femoral metaphysis lesion, and a new cortical lucency in the right femoral neck on subsequent radiographs at 10 months of age. Alkaline phosphatase levels were elevated throughout his life at 480-836 U/L (reference: 150 - 440 U/L). Attempts to obtain a sample for flow cytometry were unsuccessful.

Whole exome sequencing performed at age 4-months revealed a maternal frameshift mutation c.968\_969delTG (p.L323Pfs\*119) resulting in premature protein

truncation and a paternal origin in-frame deletion c.1199\_1201delACT (p.Y400del) at position 400, which is completely conserved in vertebrates (0.02% frequency in ExAC database), in *PIGQ*. The mutations of this patient were previously reported as predicted to be highly deleterious by the laboratory that did the exome sequencing in an article demonstrating effectiveness of identifying candidate genes of disease from exome sequencing (Farwell Hagman et al., 2018).

## DISCUSSION

Patients with the variety of PIG GPI-AP disorders share some resemblance to our patient. Global developmental delays, epileptic seizures, and dysmorphic features affect nearly all patients, and ophthalmic, renal, and skeletal anomalies (Bellai-Dussault, Nguyen, Baratang, Jimenez-Cruz, & Campeau, 2018; Nguyen et al., 2018) are common. Individuals with PIGT- and PIGA- associated GPI-AP deficiency share some of the rarer features, including anteverted nares, uplifted fleshy ear lobes, proximally placed great toes, and deep plantar creases (Lam et al., 2015; Tarailo-Graovac et al., 2015; Yang et al., 2018).

The bone lesions reported here are the first such findings reported in patients with GPI-AP deficiency disorders. PIGQ-associated (GPI-AP) deficiency expands the short differential diagnosis for the association of ill-defined radiolucent long bone lesions and sphenoid wing dysplasia. Our patient had normal sequencing with deletion/duplication analysis of *NF1*; completed in response to the sphenoid wing dysplasia. Infantile myofibromatosis and congenital syphilis were also on the differential diagnosis, but

neither fit his clinical findings.

PIGQ is involved in the initial phase of GPI-anchor biosynthesis. Because GPI-anchors are required to attach proteins to the cell surface during embryogenesis, structural development is compromised across most body systems. We postulate that our patient with disrupted PIGQ function could not appropriately utilize bone minerals including phosphorous, calcium, and magnesium because of the lack of proper attachment of alkaline phosphatase to the osteoblast. This may explain the migrating radiolucent bone lesions that our patient exhibited on osseous surveys.

To our knowledge, this is the first clinical report of a patient with compound heterozygous mutations in *PIGQ* and he is the third patient with suspected PIGQ-related disorder (Alazami et al., 2015; Martin et al., 2014). The patient described by Martin et al (2014) had Ohtahara syndrome with homozygous *PIGQ* mutations discovered through whole genome sequencing. The mutation was in a conserved splice acceptor site of exon 3 (homozygous c.690-2A>G), which induced exon-skipping resulting in an in-frame deletion of 44 amino acids. This patient, born to consanguineous parents, had dysmorphic craniofacial features, hypotonia, vision problems, gastrostomy-tube dependency, and profound developmental delay. The Martin group further showed the patient's variant was pathogenic when, *in vitro*, they could not restore expression of GPI-anchored proteins to wild type levels in PIGQ-deficient Chinese hamster ovary cells, suggesting a loss-of-function. This patient died at 2 years of age during a severe respiratory illness. One additional patient, also born to consanguineous parents, was noted in a supplementary

table by Alazami et al., in 2015 with homozygous c.619C>Tp.R207\* mutations proposed to be the etiology of epilepsy, optic atrophy, and developmental delay.

Taken together, the three patients support evidence for a new syndrome — PIGQ-related GPI-AP biosynthesis deficiency syndrome. Phenotypic variability is expected to increase with ongoing reports of these patients. With improved sequencing diagnostic tools now available and more rapid processing, PIG GPI-AP biosynthesis deficiencies will be identified earlier. Treatments based on improving the underlying process may improve the quality of life for these patients.

#### **ACKNOWLEDGMENTS**

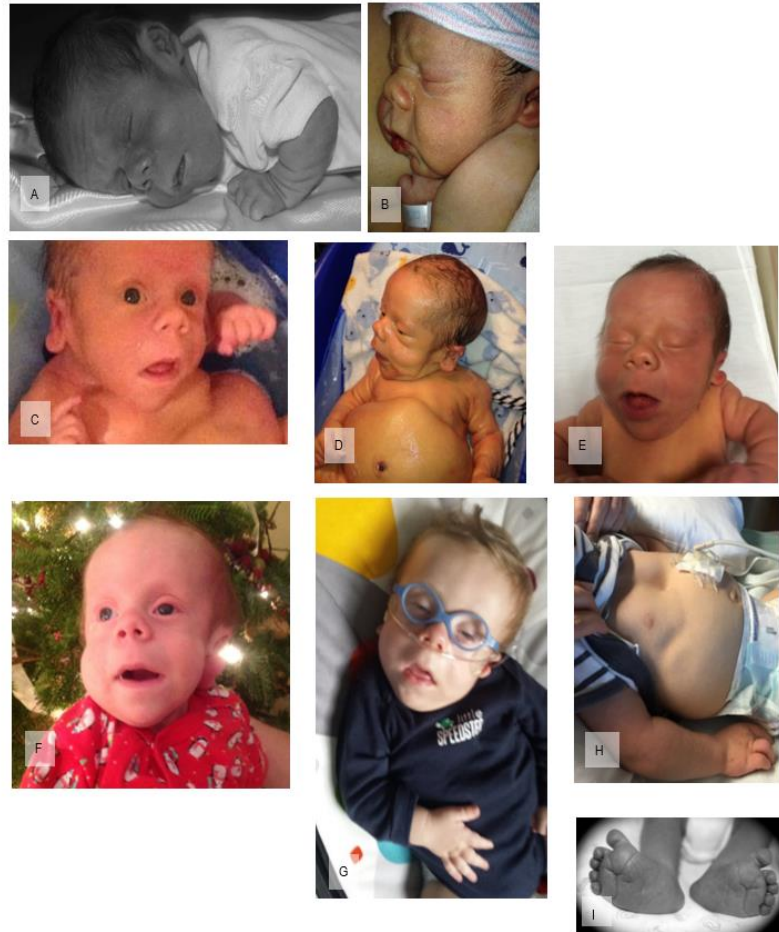
We are immensely grateful to our deceased patient's family and particularly his mother for her assistance with this report and advocacy for her son.

We would also like to thank Harold Schultz, PhD for his editing expertise.

The authors do not have any conflicts of interest in publishing this report.



### FIGURE LEGENDS



**CHAPTER 3., FIGURE 1.** Newborn through 9 months of age. Coarse facial features, hooded upper eyelids, telecanthus, mild ptosis, fleshy and uplifted ear lobes, thick alar nasi with broad nasal tip and anteverted nares, long and smooth philtrum, thin vermillion of the upper lip, down-turned corners of the mouth, mild micrognathia

(A,B,C,D,E,F,G). Abdominal wall laxity (C, D), sagging skin (A,D,E,F), diastasis recti (D), pectus excavatum (H), and deep plantar creases (I).



**CHAPTER 3., FIGURE 2.** Right kidney was small with increased cortical echogenicity and diminished cortical medullary differentiation, multiple small cortical cysts.



MRI of the brain, 5 months



CT of the brain, 10 months

**CHAPTER 3., FIGURE 3.** MRI of the brain at 5 months (A) and CT of the brain at 10 months (B) revealed left greater than right ventriculomegaly and worsening cranial plagiocephaly.



**CHAPTER 3., FIGURE 4.** Skeletal findings. Intrasutural bone (A), sphenoid wing dysplasia at 3 months (B) and 10 months (C). Chest and abdomen radiographs at 3 (D) and 10 (E)

months of age. Note worsening of thoracolumbar scoliosis. (F) 3 months. There are ill-defined radiolucent areas in the metaphyses of the right femur and tibia. (G) 10 months. Compared to the films obtained at age 3 months (F) the femoral lesion has expanded, the tibial lesion has disappeared.

## Bibliography:

### Chapter 1

1. Al Ageeli E, Mignot C, Afenjar A, Whalen S, Dorison N, Mayer M, Esteva B, Dubern B, Momtchilova M, Le Gargasson JF, Bursztyn J, Heron D. 2012. Retinal involvement in two unrelated patients with Myhre syndrome. *Euro J Med Genet* 55:541-547.
2. Asakura Y, Muroya K, Sato T, Kurosawa K, Nishimaura G, Adachi M. 2012. First Case of a Japanese girl with Myhre syndrome due to a heterozygous SMAD4 mutation. *Am J Med Genet Part A* 158:1982-1986.
3. Bachmann-Gagescu R, Hisama FM, Yuen AL. 2011. Myhre syndrome with ataxia and cerebellar atrophy. *Clin Dysmorph* 20:156-159.
4. Burglen L, Héron D, Moerman A, Dieux-Coeslier A, Bourguignon JP, Bachy A, Carel JC, Cormier-Daire V, Manourvier S, Verloes A. 2003. Myhre syndrome: new reports, review, and differential diagnosis. *J Med Genet* 40:546-551.
5. Caputo V, Cianetti L, Niceta M, Carta C, Ciolfi A, Bocchinfuso G, Carrani E, Dentici ML, Biamino E, Belligni E, Garavelli L, Boccone L, Melis D, Andria G, Gelb BD, Stella L, Silengo M, Dallapiccola B, Tartaglia M. 2012. A restricted spectrum of mutations in the SMAD4 tumor-suppressor gene underlies Myhre syndrome. *Am J Hum Genet* 90:161-169.
6. Caputo V, Bocchinfuso G, Castori M, Traversa A, Pizzuti A, Stella L, Grammatico P, Tartaglia M. 2014. Novel SMAD4 mutation causing Myhre syndrome. *Am J Med Genet A* 164:1835-1840.

7. Gramley F, Lorenzen J, Koellensperger E, Kettering K, Weiss C, Munzel T. 2010. Atrial fibrosis and atrial fibrillation: the role of the TGF- $\beta$ 1 signaling pathway. *Int J Cardiol* 143:405-413.
8. Hawkes L, Kini U. 2015. Myhre syndrome with facial paralysis and branch pulmonary stenosis. *Clin Dysmorph* 24:84-85.
9. Huang Y, Qi Y, Du JQ, Zhang DF. 2014. Micro RNA-34a regulates cardiac fibrosis after myocardial infarction by targeting Smad4. *Expert Opin Ther Targets* 12:1355-1365.
10. Ishibashi N, Sasaki Y, Asakura Y. 2014. Myhre syndrome: a rare craniofacial disorder. *Cranio* 32:300-306.
11. Kenis C, Verstreken M, Gieraerts K, De Foer B, Van der Aa N, Offeciers EF, Casselman JW. 2014. *Otol Neurotol* Oct;35(9):e253-5.
12. Le Goff C, Michot C, Cormier-Daire V. 2014. Myhre syndrome. *Clin Genet* 85:503-513.
13. Le Goff C, Cormier-Daire V. 2012. From tall to short: The role of TGF $\beta$  signaling in growth and its disorders. *Am J Med Genet Part C Semin Med Genet* 160C:145-153.
14. Le Goff C, Mahaut C, Abhyankar A, Le Goff W, Serre V, Afenjar A, Destrée A, di Rocco M, Héron D, Jacquemont S, Marlin S, Simon M, Tolmie J, Veroles A, Casanova JL, Munnich A, Cormier-Daire V. 2012. Mutations at a single codon in Mad homology 2 domain of SMAD4 cause Myhre syndrome. *Nat Genet* 44:85-89.
15. Lindor NM. 2009. LAPS syndrome and Myhre syndrome: Two disorders or one. *Am J Med Genet Part A* 149A:798-799.
16. Lindor NM, Gunawardena SR, Thibodeau SN. 2012. Mutations of SMAD4 account for both LAPS and Myhre syndromes. *Am J Med Genet Part A* 158a:1520-1521.

17. Lopez-Cardona MG, Carcia-Cruz D, Garcia-Ortiz JE, Davalos NO, Feria-Velasco A, Rodriguez-Rojas LX, Garcia-Cruz MO, Figuera-Villanueva LE, Stephens A, Larios-Arceo F, Sanchez-Corona J. 2004. Second female case of Myhre syndrome. *Clin Dysmorph* 13:91-93.
18. McGowan R, Gulati R, McHenry P, Cooke A, Butler S, Teik Keng W, Murday V, Whiteford M, Dikkers FG, Sikkema-Raddatz B, van Essen T, Tolmie J. 2011. Clinical features and respiratory complications in Myhre syndrome. *Euro J Med Genet* 54:e553-e559.
19. Michot C, Le Goff C, Mahaut C, Afenjar A, Brooks AS, Campeau PM, Destree A, Di Rocco M, Donnai D, Hennekam R, Heron D, Jacquemont S, Kannu P, Lin AE, Manouvrier-Hanu S, Mansour S, Marlin S, McGowan R, Murphy H, Raas-Rothchild A, Rio M, Simon M, Stolte-Dijkstra I, Stone JR, Szanjer Y, Tolmie J, Touraine R, Ende JVD, Van der Aa N, Essen TV, Verloes A, Munnich A, Comier-Daire V. 2014. Myhre and LAPS syndromes: clinical and molecular review of 32 patients. *Euro J Hum Genet* 1-4.
20. Myhre SA, Ruvalcaba RH, Graham CB. 1981. A new growth deficiency syndrome. *Clin Genet* 20:1-5.
21. Oldenburg MS, Frisch CD, Lindor NM, Edell ES, Kasperbauer JL, O'Brien EK. 2015. Myhre-LAPs syndrome and intubation related airway stenosis: keys to diagnosis and critical therapeutic interventions. *Am J Otolaryngol*. Apr 15. [Epub ahead of print].
22. Picco P, Naselli A, Pala G, Marsciani A, Buoncompagni A, Martini A. 2013. Recurrent pericarditis in Myhre syndrome. *Am J Med Genet Part A* 161A:1164-1166.
23. Piccolo P, Mithbaakar P, Sabatino V, Tolmie J, Melis D, Schiaffino MC, Filocamo M, Andria G, Brunetti-Pierri N. 2014. SMAD4 mutations causing Myhre syndrome result in disorganization of extracellular matrix improved by losartan. *Eur J Hum Genet*. Aug;22(8):988-994.

24. Rulli I, Ferrero GB, Belligni E, Delmonaco AG, Defilippi C, Silengo M. 2005. Myhre's syndrome in a girl with normal intelligence. *Am J Med Genet* 134A:100-102.
  25. Titomanlio L, Marzano MG, Rossi E, D'Armiento M, De Brasi D, Vega GR, Andreucci MV, Orsini AVM, Santoro L, Sebastio G. 2001. Case of Myhre syndrome with autism and peculiar skin histological findings. *Am J Med Genet* 103:163-165.
  26. Wang J, Xu N, Feng X, Hou N, Zhang J, Cheng X, Chen Y, Zhang Y, Yang X. Targeted disruption of Smad4 in cardiomyocytes results in cardiac hypertrophy and heart failure. 2005. *Circ Res.* 2005. 14:821-828.
  27. Yang L, Li W, Wang S, Wang L, Li Y, Yang X, Peng R. 2012. Smad4 disruption accelerates keratinocyte reepithelialization in murine cutaneous wound repair. *Histochem Cell Bio* 138:573-582.
  - e H, Cousens S, Chou D, Oestergaard M, Say L, Moller AB, Lawn J. Born Too Soon: The global epidemiology of 15 million preterm births. *Reprod Health.* 2013;10(Suppl 1):S2.
- Chapter 2
28. Al Ageeli E, Mignot C, Afenjar A, Whalen S, Dorison N, Mayer M, Esteva B, Dubern B, Momtchilova M, Le Gargasson JF, Bursztyn J, Heron D. Retinal involvement in two unrelated patients with Myhre syndrome. *Eur J Med Genet.* 2012;55:541–7. [PubMed: 22683461]
  29. Asakura Y, Muroya K, Sato T, Kurosawa K, Nishimaura G, Adachi M. First case of a Japanese girl with Myhre syndrome due to a heterozygous SMAD4 mutation. *Am J Med Genet Part A.* 2012;158A:1982–6. [PubMed: 22711472]
  30. Bassett JK, Douzgou S, Kerr B. Severe constipation in a patient with Myhre syndrome: a case report. *Clin Dysmorph.* 2016;25:54–7. [PubMed: 26636501]



31. Caputo V, Bocchinfuso G, Castori M, Traversa A, Pizzuti A, Stella L, Grammatico P, Tartaglia M. Novel SMAD4 mutation causing Myhre syndrome. *Am J Med Genet A*. 2014;164A:1835–40. [PubMed: 24715504]
32. Caputo V, Cianetti L, Niceta M, Carta C, Ciolfi A, Bocchinfuso G, Carrani E, Dentici ML, Biamino E, Belligni E, Garavelli L, Boccone L, Melis D, Andria G, Gelb BD, Stella L, Silengo M, Dallapiccola B, Tartaglia M. A restricted spectrum of mutations in the SMAD4 tumor-suppressor gene underlies Myhre syndrome. *Am J Hum Genet*. 2012;90:161–9. [PMC free article: PMC3257749] [PubMed: 22243968]
33. Chen YW, Hsiao PJ, Weng CC, Kuo KK, Kuo TL, Wu DC, Hung WC, Cheng KH. SMAD4 loss triggers the phenotypic changes of pancreatic ductal adenocarcinoma cells. *BMC Cancer*. 2014;14:181. [PMC free article: PMC4007528] [PubMed: 24625091]
34. Garavelli L, Maini I, Baccilieri F, Ivanovski I, Pollazzon M, Rosato S, Iughetti L, Unger S, Superti-Furga A, Tartaglia M. Natural history and life-threatening complications in Myhre syndrome and review of the literature. *Eur J Pediatr*. 2016;175:1307–15. [PubMed: 27562837]
35. Hawkes L, Kini U. Myhre syndrome with facial paralysis and branch pulmonary stenosis. *Clin Dysmorph*. 2015;24:84–5. [PubMed: 25486016]
36. Ishibashi N, Sasaki Y, Asakura Y. Myhre syndrome: a rare craniofacial disorder. *Cranio*. 2014;32:300–6. [PubMed: 25252769]
37. Kenis C, Verstreken M, Gieraerts K, De Foer B, Van der Aa N, Offeciers EF, Casselman JW. Bilateral otospongiosis and a unilateral vestibular schwannoma in a patient with Myhre syndrome. *Otol Neurotol*. 2014;35:e253–5. [PubMed: 24841914]
38. Le Goff C, Michot C, Cormier-Daire V. Myhre syndrome. *Clin Genet*. 2014;85:503–13. [PubMed: 24580733]

39. Le Goff C, Mahaut C, Abhyankar A, Le Goff W, Serre V, Afenjar A, Destrée A, di Rocco M, Héron D, Jacquemont S, Marlin S, Simon M, Tolmie J, Veroles A, Casanova JL, Munnich A, Cormier-Daire V. Mutations at a single codon in Mad homology 2 domain of SMAD4 cause Myhre syndrome. *Nat Genet.* 2011;44:85–8. [PubMed: 22158539]
40. Lin AE, Michot C, Cormier-Daire V, L'Ecuyer TJ, Matherne GP, Barnes BH, Humberson JB, Edmondson AC, Zackai E, O'Connor MJ, Kaplan JD, Ebeid MR, Krier J, Krieg E, Ghoshhajra B, Lindsay ME. Gain-of-function mutations in SMAD4 cause a distinctive repertoire of cardiovascular phenotypes in patients with Myhre syndrome. *Am J Med Genet A.* 2016;170:2617–31. [PubMed: 27302097]
41. Lindor NM, Gunawardena SR, Thibodeau SN. Mutations of SMAD4 account for both LAPS and Myhre syndromes. *Am J Med Genet Part A.* 2012;158A:1520–1. [PubMed: 22585601]
42. McGowan R, Gulati R, McHenry P, Cooke A, Butler S, Teik Keng W, Murday V, Whiteford M, Dikkers FG, Sikkema-Raddatz B, van Essen T, Tolmie J. Clinical features and respiratory complications in Myhre syndrome. *Eur J Med Genet.* 2011;54:e553–e559. [PubMed: 21816239]
43. Michot C, Le Goff C, Mahaut C, Afenjar A, Brooks AS, Campeau PM, Destree A, Di Rocco M, Donnai D, Hennekam R, Heron D, Jacquemont S, Kannu P, Lin AE, Manouvrier-Hanu S, Mansour S, Marlin S, McGowan R, Murphy H, Raas-Rothchild A, Rio M, Simon M, Stolte-Dijkstra I, Stone JR, Szanjer Y, Tolmie J, Touraine R, Ende JVD, Van der Aa N, Essen TV, Verloes A, Munnich A, Cormier-Daire V. Myhre and LAPS syndromes: clinical and molecular review of 32 patients. *Eur J Hum Genet.* 2014;22:1272–7. [PMC free article: PMC4200423] [PubMed: 24424121]

44. Myhre SA, Ruvalcaba RH, Graham CB. A new growth deficiency syndrome. *Clin Genet*. 1981;20:1–5. [PubMed: 7296942]
45. Oldenburg MS, Frisch CD, Lindor NM, Edell ES, Kasperbauer JL, O'Brien EK. Myhre-LAPs syndrome and intubation related airway stenosis: keys to diagnosis and critical therapeutic interventions. *Am J Otolaryngol*. 2015;36:636–41. [PubMed: 25940662]
46. Picco P, Naselli A, Pala G, Marsciani A, Buoncompagni A, Martini A. Recurrent pericarditis in Myhre syndrome. *Am J Med Genet Part A*. 2013;161A:1164–6. [PubMed: 23610053]
47. Shi Y, Massague J. Mechanisms of TGF- $\beta$  signaling from cell membrane to the nucleus. *Cell*. 2003;113:685–700. [PubMed: 12809600]
48. Starr LJ, Grange DK, Delaney JW, Yetman AT, Hammel JM, Sanmann JN, Perry DA, Schaefer GB, Olney AH. Myhre syndrome: Clinical features and restrictive cardiopulmonary complications. *Am J Med Genet A*. 2015;167A:2893–901. [PubMed: 26420300]
- Chapter 3.
49. Alazami, A. M., Patel, N., Shamseldin, H. E., Anazi, S., Al-Dosari, M. S., Alzahrani, F., . . . Alkuraya, F. S. (2015). Accelerating novel candidate gene discovery in neurogenetic disorders via whole-exome sequencing of prescreened multiplex consanguineous families. *Cell Rep*, 10(2), 148-161. doi:10.1016/j.celrep.2014.12.015
50. Bellai-Dussault, K., Nguyen, T. T. M., Baratang, N. V., Jimenez-Cruz, D. A., & Campeau, P. M. (2018). Clinical variability in inherited glycosylphosphatidylinositol deficiency disorders. *Clin Genet*. doi:10.1111/cge.13425
51. Farwell Hagman, K. D., Shinde, D. N., Mroske, C., Smith, E., Radtke, K., Shahmirzadi, L., . . . Tang, S. (2018). Correction: Candidate-gene criteria for clinical reporting: diagnostic

- exome sequencing identifies altered candidate genes among 8% of patients with undiagnosed diseases. *Genet Med*, 20(9), 1099-1102. doi:10.1038/gim.2017.263
52. Lam, C., Golas, G. A., Davids, M., Huizing, M., Kane, M. S., Krasnewich, D. M., . . . Wolfe, L. A. (2015). Expanding the clinical and molecular characteristics of PIGT-CDG, a disorder of glycosylphosphatidylinositol anchors. *Mol Genet Metab*, 115(2-3), 128-140. doi:10.1016/j.ymgme.2015.04.007
53. Martin, H. C., Kim, G. E., Pagnamenta, A. T., Murakami, Y., Carvill, G. L., Meyer, E., . . . Taylor, J. C. (2014). Clinical whole-genome sequencing in severe early-onset epilepsy reveals new genes and improves molecular diagnosis. *Hum Mol Genet*, 23(12), 3200-3211. doi:10.1093/hmg/ddu030
54. Nguyen, T. T. M., Murakami, Y., Wigby, K. M., Baratang, N. V., Rousseau, J., St-Denis, A., . . . Campeau, P. M. (2018). Mutations in PIGS, Encoding a GPI Transamidase, Cause a Neurological Syndrome Ranging from Fetal Akinesia to Epileptic Encephalopathy. *Am J Hum Genet*, 103(4), 602-611. doi:10.1016/j.ajhg.2018.08.014
55. Tarailo-Graovac, M., Sinclair, G., Stockler-Ipsiroglu, S., Van Allen, M., Rozmus, J., Shyr, C., . . . van Karnebeek, C. D. (2015). The genotypic and phenotypic spectrum of PIGA deficiency. *Orphanet J Rare Dis*, 10, 23. doi:10.1186/s13023-015-0243-8
56. Tiede, A., Daniels, R. J., Higgs, D. R., Mehrein, Y., Schmidt, R. E., & Schubert, J. (2001). The human GPI1 gene is required for efficient glycosylphosphatidylinositol biosynthesis. *Gene*, 271(2), 247-254.
57. Yang, J., Wang, Q., Zhuo, Q., Tian, H., Li, W., Luo, F., . . . Xin, H. (2018). A likely pathogenic variant putatively affecting splicing of PIGA identified in a multiple congenital anomalies hypotonia-seizures syndrome 2 (MCAHS2) family pedigree via

whole-exome sequencing. *Mol Genet Genomic Med*, 6(5), 739-748.

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