U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Ambartsumyan L. Megacystis-Microcolon-Intestinal Hypoperistalsis Syndrome Overview. 2019 May 9. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Megacystis-Microcolon-Intestinal Hypoperistalsis Syndrome Overview

Synonyms: Berdon Syndrome, MMHS

Lusine Ambartsumyan, MD[1]

Created: May 9, 2019.

Summary

The purpose of this overview is to increase the awareness of clinicians regarding megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS) and its genetic causes and management. The following are the goals of this overview.

Goal 1

Describe the clinical characteristics of MMIHS.

Goal 2

Review the genetic causes of MMIHS.

Goal 3

Provide an evaluation strategy to identify the genetic cause of MMIHS in a proband (when possible).

Goal 4

Inform genetic counseling of family members of an individual with MMIHS.

Goal 5

Review management of MMIHS.

1. Clinical Characteristics of Megacystis-Microcolon-Intestinal Hypoperistalsis Syndrome

Megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS) is characterized by megacystis (bladder distention in the absence of mechanical obstruction), microcolon, and intestinal hypoperistalsis (dysmotility). This rare disorder is associated with significant morbidity and mortality.

Author Affiliation: 1 Seattle Children's Hospital, Seattle, Washington; Email: lusine.ambartsumyan@seattlechildrens.org.

MMIHS may be suspected prenatally secondary to findings of fetal megacystis on prenatal ultrasound. Affected infants present shortly after birth with symptoms of bowel and bladder obstruction. The most common presenting symptom is abdominal distention that is secondary to a massively dilated bladder in the absence of mechanical obstruction with or without dilated bowel loops. Other symptoms include bilious emesis, failure to pass meconium, and inability to spontaneously void requiring catheterization [Puri & Shinkai 2005, Puri & Gosemann 2012, Soh et al 2015, Wymer et al 2016].

Infants and children with MMIHS have myopathic dysfunction of bladder and associated urologic comorbidities that include febrile urinary tract infections, vesicoureteral reflux (VUR), and hydronephrosis with resultant risk of renal failure [Wymer et al 2016, Hugar et al 2018]. Gastrointestinal complications of MMIHS include microcolon, intestinal dysmotility, and associated gastrointestinal comorbidities including malrotation and complications such as short bowel syndrome and recurrent symptomatic and radiographic evidence of bowel obstruction in the absence of mechanical obstruction, known as chronic intestinal pseudo-obstruction (CIPO).

Intestinal dysfunction ultimately leads to nutritional compromise and intestinal failure resulting in dependence on total parenteral nutrition (TPN). Subsequently individuals may develop complications from the TPN including central line infections, liver dysfunction, and liver failure. Multivisceral or isolated intestinal transplantation should be considered for those who continue to have nutritional failure and are unable to tolerate TPN as a result of liver failure or inability to maintain central venous access [Huang et al 2013, De Sousa et al 2016, Wymer et al 2016].

The prognosis for individuals with MMIHS, in light of its variable genetic causes, has not been well elucidated. Data on individuals prior to molecular diagnosis suggest a poor and often fatal prognosis especially within the first year of life.

Sepsis followed by multiorgan failure and malnutrition have been reported as the most frequent causes of death [Gosemann & Puri 2011].

Specialized centers with multidisciplinary care, multidisciplinary TPN management, and multivisceral transplantation have been credited for improving survival rates from 12.6% (1976-2004) to 55.6% (2004-2011) [Gosemann & Puri 2011, Puri & Gosemann 2012]. A recent Japanese nationwide survey reported five- and ten-year survival to be 63% and 57%, respectively [Soh et al 2015].

Establishing the Clinical Diagnosis of MMIHS

Prenatal Imaging Features of MMIHS

In a recent systematic review, prenatal diagnosis of MMIHS was suspected in 26% of individuals using prenatal ultrasound findings [Tuzovic et al 2014].

Grossly dilated bladder with or without hydroureteronephrosis in the setting of normal or increased amniotic fluid volume may be found on the second trimester prenatal ultrasound [Puri & Gosemann 2012, Tuzovic et al 2014, De Sousa et al 2016, Fontanella et al 2019]. Prenatal bladder manifestations of megacystis with or without hydroureteronephrosis are an initial presenting finding in 88% of individuals [Tuzovic et al 2014].

Gastrointestinal abnormalities on prenatal ultrasound are less common (24%) and include gastric distention (visible in the second trimester) and dilated bowel loops (visible in the third trimester) [Tuzovic et al 2014].

Dilated esophagus and microcolon have been reported using fetal MRI [Munch et al 2009].

Postnatal Clinical and Imaging Features of MMIHS

Clinical features include signs and symptoms of bowel and bladder obstruction [Gosemann & Puri 2011, Puri & Gosemann 2012]. The following are the most common:

- Abdominal distention
- Absent or decreased bowel sounds
- Bilious emesis
- Failure to pass meconium
- Inability to void requiring catheterization

Imaging features

- Abdominal radiograph shows gastric distention and dilatation of small bowel loops with paucity of distal gas [Ballisty et al 2013].
- Fluoroscopic upper-gastrointestinal series reveals dilated stomach and small intestine with associated malrotation [Ballisty et al 2013].
- Contrast enema demonstrates a small-caliber colon (microcolon) and may show an associated malrotation [Ballisty et al 2013, Wymer et al 2016].
- Urologic findings on renal/bladder ultrasound and cystography include a dilated bladder with large capacity, hydroureteronephrosis, and vesicoureteral reflux (VUR) [Ballisty et al 2013].

Table 1. Differential Diagnosis of Megacystis-Microcolon-Intestinal Hypoperistalsis Syndrome (MMIHS)

Presenting Symptom in MMIHS	Differential Diagnosis	Distinguishing Clinical Features
Fetal megacystis	Lower urinary tract obstruction	Imaging or cystoscopy shows posterior urethral valves or urethral atresia/stenosis.
Obstructive symptoms (e.g., abdominal distention, bilious emesis, failure to pass meconium)	Hirschsprung disease	Absence of megacystis; rectal biopsy shows absence of ganglion cells
	Small bowel atresia or colonic atresia	Absence of microcolon; isolated colonic atresia w/out megacystis
	Anorectal malformation	Abnormal anal position/caliber; clinical features of VACTERL association
	Meconium ileus/plug	Family history of cystic fibrosis; failure to thrive; pancreatic insufficiency
	Hypothyroidism	Absence of megacystis & microcolon; laboratory evidence of hypothyroidism
	Sepsis	Absence of megacystis & microcolon; laboratory evidence of sepsis
	Prenatal & intrapartum medication exposure (e.g., magnesium sulfate, opioids)	Absence of megacystis & microcolon
	Diabetic embryopathy	Absence of megacystis
Fetal megacystis & obstructive symptoms	Prune belly sequence [1]	Absence of microcolon
	Multisystemic smooth muscle dysfunction syndrome (MSMDS) [1]	Mydriasis, vascular abnormalities, absence of microcolon

1. Isolated (without additional features of MMIHS)

2. Genetic Causes of Megacystis-Microcolon-Intestinal Hypoperistalsis Syndrome

Table 2. Megacystis-Microcolon-Intestinal Hypoperistalsis Syndrome: Genes and Distinguishing Clinical Features

Gene [1]	% of all MMIHS	MOI	Distinguishing Clinical Features	Other	References
ACTG2	44.1%	AD	Classic features of MMIHS (e.g., megacystis, microcolon, intestinal dysmotility)	• Greater disease severity reported in probands w/a *de novo* (vs inherited) pathogenic variant • Parental somatic & germline mosaicism reported	Wangler et al [2014], Tuzovic et al [2015], Halim et al [2016], Milunsky et al [2017a]
LMOD1	1 person	AR	Classic features of MMIHS	Large del/dups not reported to date.	Halim et al [2017b]
MYH11	2 persons	AR	• Overlapping features of MMIHS & prune belly sequence (1 person) • Overlapping features of MMIHS & MSMDS (1 person)	Large del/dups not assoc w/ MMIHS to date	Gauthier et al [2015], Yetman & Starr [2018]
MYL9	1 person	AR	• Mydriasis • No vascular smooth muscle dysfunction [2]	Homozygous partial-gene deletion reported [3]	Moreno et al [2018]
MYLK	2 families	AR	No vascular smooth muscle dysfunction [2]	Large del/dups not assoc w/ MMIHS to date	Halim et al [2017a]
Unknown	~55%				

AD = autosomal dominant; AR = autosomal recessive; del/dups = deletions/duplications; MMIHS = megacystis-microcolon-intestinal hypoperistalsis syndrome; MOI = mode of inheritance; MSMDS = multisystemic smooth muscle dysfunction syndrome

1. Genes are listed alphabetically.

2. Vascular smooth muscle dysfunction including aortic aneurysms or dissection has not been reported.

3. Moreno et al [2018] identified a homozygous intragenic 6,964-bp deletion of intron 3, exon 4, and 3' UTR in *MYL9* in one of two affected sibs.

3. Evaluation Strategy to Identify the Genetic Cause of Megacystis-Microcolon-Intestinal Hypoperistalsis Syndrome

Establishing a specific genetic cause of megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS):

- Can aid in discussions of prognosis (which are beyond the scope of this *GeneReview*) and genetic counseling;
- Usually involves a medical history, physical examination, laboratory testing, family history, and genomic/genetic testing.

Medical history

The following medical history should raise concern for MMIHS:

- Fetal megacystis on prenatal ultrasound in the setting of normal or increased amniotic fluid specifically in the second or third trimester of pregnancy

- Clinical symptoms of bowel and bladder obstruction shortly after birth characterized by abdominal distention, abnormal bowel sounds, bilious emesis, failure to pass meconium, and inability to void spontaneously requiring catheterization [Puri & Gosemann 2012]

Physical examination. Dilated pupils (mydriasis) suggest *MYL9*-MMIHS. Dilated pupils (mydriasis) and vascular smooth muscle dysfunction (e.g., aortic aneurysm, aortic dissection) should raise concern for *MYH11*-MMIHS (see Table 2).

Family history. A three-generation family history should be taken, with attention to the following:

- Manifestations of MMIHS, bowel/bladder dysfunction, chronic intestinal pseudo-obstruction (CIPO), and multisystemic smooth muscle dysfunction syndrome (MSMDS), as well as familial forms of myopathy, neuropathy, mitochondrial diseases, and other conditions that affect the enteric nervous system or smooth muscle
- Parental consanguinity
- Recurrent fetal loss

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

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

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

Serial single-gene testing can be considered if clinical findings and/or family history indicate that pathogenic variants in a particular gene are most likely (see Table 2).

Comprehensive genomic testing (which does not require the clinician to determine which gene[s] are likely involved) may be considered. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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

4. Genetic Counseling of Family Members of an Individual with Megacystis-Microcolon-Intestinal Hypoperistalsis Syndrome

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

Mode of Inheritance

Megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS) caused by pathogenic variants in *ACTG2* is inherited in an autosomal dominant manner.

MMIHS caused by pathogenic variants in *LMOD1*, *MYH11*, *MYL9*, or *MYLK* is inherited in an autosomal recessive manner.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Some individuals diagnosed with *ACTG2*-MMIHS have the disorder as the result of a *de novo* pathogenic variant [Wangler et al 2014].
- Some individuals diagnosed with MMIHS inherited an *ACTG2* pathogenic variant from a parent. The severity of clinical findings may vary within a family; a parent may be asymptomatic or have a milder phenotype [Wangler et al 2014].
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the proband most likely has a *de novo* pathogenic variant; another possible explanation is germline mosaicism in a parent. Parental somatic and germline mosaicism have been reported in *ACTG2*-MMIHS [Tuzovic et al 2015, Milunsky et al 2017b].
- The family history of some individuals diagnosed with MMIHS may appear to be negative because of failure to recognize the disorder in family members because of a milder phenotypic expression, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless appropriate clinical evaluation and/or molecular genetic testing has been performed on the parents of the proband.
- Note: If the parent is the individual in whom the pathogenic variant first occurred, the parent may have somatic mosaicism for the variant and may be mildly/minimally affected.

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

- If a parent of the proband is affected and/or is known to have the *ACTG2* pathogenic variant identified in the proband, the risk to the sibs is 50%.
- If the proband has a known *ACTG2* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism [Tuzovic et al 2015, Milunsky et al 2017b].
- If the parents have not been tested for the *ACTG2* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for MMIHS because of the possibility of parental germline mosaicism.
- Depending on the specific gene involved, clinical severity and phenotype may differ between individuals with the same variant; thus, age of onset and/or progression may not be predictable.

Offspring of a proband. Each child of an individual with MMIHS has a 50% chance of inheriting the MMIHS-related pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *ACTG2* pathogenic variant, the parent's family members may be at risk.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the causative variant identified in the proband or clinical evidence of

the disorder, the variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., carriers of one MMIHS-related pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with MMIHS are obligate heterozygotes (carriers of a MMIHS-related pathogenic variant).

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a MMIHS-related pathogenic variant.

Carrier detection. Carrier testing for at-risk relatives requires prior identification of the MMIHS-related pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being affected or carriers.

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.

- **MMIHS Foundation**

  mmihs.org

- **Children's Organ Transplant Association**

  Phone: 800-366-2682

  Fax: 812-336-8885

  Email: cota@cota.org

  cota.org

- **International Foundation for Functional Gastrointestinal Disorders (IFFGD)**
  Phone: 414-964-1799
  iffgd.org
- **International Foundation for Functional Gastrointestinal Disorders (IFFGD) - ABOUT KIDS GI**
  aboutkidsgi.org
- **National Digestive Diseases Information Clearinghouse (NDDIC)**
  Intestinal Pseudo-obstruction
- **National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)**
  Phone: 301-496-3583
  www.niddk.nih.gov
- **Prune Belly Syndrome Network**
  Phone: 855-ASK-PBSN
  prunebelly.org
- **Pull-thru Network**
  Phone: -309-262-0786
  Email: info@pullthrunetwork.org
  pullthrunetwork.org
- **The Oley Foundation**
  Phone: 518-262-5079
  Email: info@oley.org
  oley.org
- **United Ostomy Associations of America, Inc.**
  Phone: 800-826-0826
  ostomy.org

5. Management of Megacystis-Microcolon-Intestinal Hypoperistalsis Syndrome

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS), the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Urology

- Urodynamic studies to evaluate the degree of bladder dysfunction (e.g., enlarged bladder capacity for age, detrusor acontractility with failure to empty) [Wymer et al 2016]
- Voiding cystourethrogram to evaluate for outlet obstruction, vesicoureteral reflux (VUR), and bladder capacity [Wymer et al 2016]
- Renal and bladder ultrasound to evaluate for hydronephrosis and renal parenchyma

- Laboratory evaluation of renal function (BUN, creatinine, GFR, etc.) and electrolytes (potassium, phosphorus, calcium)

Gastroenterology

- Bowel imaging: abdominal x-ray, contrast enema, and fluoroscopic upper gastrointestinal series. Computed tomography (CT) examination of the abdomen may be indicated to evaluate for a mechanical obstruction.
- Laboratory monitoring of liver enzymes (AST, ALT, alkaline phosphatase), cholestasis (total and direct bilirubin), and liver function (PT, PTT, INR, albumin)
- Laboratory evaluation of macronutrient (carbohydrates, fat, protein) and micronutrient (vitamins, minerals) deficiencies in the setting of intestinal dysfunction and progressive malabsorption
- Nutrition evaluation and close monitoring of growth parameters

Cardiology. Cardiology evaluation with echocardiogram in individuals with *MYH11* pathogenic variants that raise suspicion of multisystemic smooth muscle dysfunction syndrome (MSMDS) [Yetman & Starr 2018]

Genetic. Referral to a clinical geneticist and/or genetic counselor

Other. Ophthalmologic evaluation for mydriasis

Treatment of Manifestations

Myopathic bladder dysfunction and associated urologic comorbidities. Clean intermittent catheterizations or vesicostomy to ensure bladder decompression and prevent renal scarring and failure

Bowel dysfunction, microcolon, intestinal dysmotility, and associated gastrointestinal comorbidities (malrotation, short bowel syndrome, recurrent non-mechanical bowel obstruction):

- Surgical interventions such as enterostomies (e.g., gastrostomy, jejunostomy) for nutrition administration and proximal bowel decompression [Puri & Gosemann 2012, Soh et al 2015, De Sousa et al 2016, Wymer et al 2016].
- Bowel diversion (e.g., ileostomy, colostomy) for distal bowel decompression [Puri & Gosemann 2012, Soh et al 2015, De Sousa et al 2016, Wymer et al 2016]
- Total parenteral nutrition (TPN) when appropriate for malnutrition as a result of intestinal failure from intestinal dysmotility
- Multivisceral or isolated intestinal transplantation should be considered for those who continue to have nutritional failure and are unable to tolerate TPN because of complications (e.g., liver dysfunction and cholestasis, lack of adequate central venous access, recurrent central line-associated bloodstream infections) [Huang et al 2013, De Sousa et al 2016, Wymer et al 2016].

Vascular smooth muscle dysfunction in individuals with *MYH11* and *ACTA2* pathogenic variants that cause concern for multisystemic smooth muscle dysfunction syndrome (MSMDS) [Yetman & Starr 2018]:

- Referral to cardiologist and monitoring for pulmonary hypertension, aortic dilatation, patent ductus arteriosus
- Referral to neurologist for evaluation for abnormal cerebral vasculature [Yetman & Starr 2018]

Surveillance

The prognosis for individuals with MMIHS in light of its variable genetic causes has not been well elucidated. Data on individuals prior to molecular diagnosis suggests a poor and often fatal prognosis within the first year of life with reported lifetime survival rates of 55.6% (2004-2011) [Puri & Gosemann 2012]. A Japanese nationwide survey reported five- and ten-year survival rates of 63% and 57%, respectively [Soh et al 2015].

The evaluation and management are primarily supportive. Specialized centers offer multidisciplinary medical and surgical models of care including comprehensive TPN management and multivisceral transplantation.

Goals of bladder management include bladder decompression and subsequent monitoring and prevention of renal failure.

Goals of bowel management include providing means of nutrition in the setting of intestinal dysmotility via enteral or parenteral means while monitoring for nutritional failure and TPN-associated complications (line infections, liver disease).

Agents/Circumstances to Avoid

Treatment/medications to be avoided or limited include those that diminish bowel and bladder motility.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic younger at-risk relatives of an affected individual as early diagnosis may help prevent unnecessary surgery for symptoms of intestinal obstruction and may allow early evaluation of bladder function, the urinary tract (for evidence of dilatation), and renal function.

Evaluations can include:

- Molecular genetic testing if the pathogenic variant(s) in the family are known;
- Abdominal or bladder ultrasound and contrast enema if the pathogenic variant(s) in the family are not known. Evidence of megacystis (on the abdominal or bladder ultrasound) and microcolon (on the contrast enema) are highly suggestive of MMIHS.

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

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Chapter Notes

Author Notes

Author's web page

The author specializes in the diagnosis and management of individuals with gastroparesis, chronic intestinal pseudo-obstruction, achalasia, defecation disorders, and scleroderma. Her primary research involves the study of mechanisms of functional and organic fecal incontinence, spinal cord modulation of anorectal function, and the physiological relationship between the anorectum and the bladder.

Revision History

- 9 May 2019 (sw) Review posted live
- 5 December 2018 (la) Original submission

References

Literature Cited

Ballisty MM, Braithwaite KA, Shehata BM, Dickson PN. Imaging findings in megacystis-microcolon-intestinal hypoperistalsis syndrome. Pediatr Radiol. 2013;43:454–9. PubMed PMID: 22926452.

De Sousa J, Upadhyay V, Stone P. Megacystis microcolon intestinal hypoperistalsis syndrome: case reports and discussion of the literature. Fetal Diagn Ther. 2016;39:152–7. PubMed PMID: 26645214.

Fontanella F, Maggio L, Verheij JBGM, Duin LK, Adama van Scheltema PN, Cohen-Overbeek TE, Pajkrt E, Bekker M, Willekes C, Bax CJ, Gracchi V, Oepkes D, Bilardo CM. Fetal megacystis: a lot more than LUTO. Ultrasound Obstet Gynecol. 2019;53:779–87. PubMed PMID: 30043466.

Gauthier J, Ouled Amar Bencheikh B, Hamdan FF, Harrison SM, Baker LA, Couture F, Thiffault I, Ouazzani R, Samuels ME, Mitchell GA, Rouleau GA, Michaud JL, Soucy JF. A homozygous loss-of-function variant in MYH11 in a case with megacystis-microcolon-intestinal hypoperistalsis syndrome. Eur J Hum Genet. 2015;23:1266–8. PubMed PMID: 25407000.

Gosemann JH, Puri P. Megacystis microcolon intestinal hypoperistalsis syndrome: systematic review of outcome. Pediatr Surg Int. 2011;27:1041–6. PubMed PMID: 21792650.

Halim D, Brosens E, Muller F, Wangler MF, Beaudet AL, Lupski JR, Akdemir ZHC, Doukas M, Stoop HJ, de Graaf BM, Brouwer RWW, van Ijcken WFJ, Oury JF, Rosenblatt J, Burns AJ, Tibboel D, Hofstra RMW, Alves MM. Loss-of-function variants in MYLK cause recessive megacystis microcolon intestinal hypoperistalsis syndrome. Am J Hum Genet. 2017a;101:123–9. PubMed PMID: 28602422.

Halim D, Hofstra RM, Signorile L, Verdijk RM, van der Werf CS, Sribudiani Y, Brouwer RW, van IJcken WF, Dahl N, Verheij JB, Baumann C, Kerner J, van Bever Y, Galjart N, Wijnen RM, Tibboel D, Burns AJ, Muller F, Brooks AS, Alves MM. ACTG2 variants impair actin polymerization in sporadic megacystis microcolon intestinal hypoperistalsis syndrome. Hum Mol Genet. 2016;25:571–83. PubMed PMID: 26647307.

Halim D, Wilson MP, Oliver D, Brosens E, Verheij JB, Han Y, Nanda V, Lyu Q, Doukas M, Stoop H, Brouwer RW, van IJcken WF, Slivano OJ, Burns AJ, Christie CK, de Mesy Bentley KL, Brooks AS, Tibboel D, Xu S, Jin ZG, Djuwantono T, Yan W, Alves MM, Hofstra RM, Miano JM. Loss of LMOD1 impairs smooth muscle cytocontractility and causes megacystis microcolon intestinal hypoperistalsis syndrome in humans and mice. Proc Natl Acad Sci U S A. 2017b;114:E2739–47. PubMed PMID: 28292896.

Huang CM, Tseng SH, Weng CC, Chen Y. Isolated intestinal transplantation for megacystis microcolon intestinal hypoperistalsis syndrome: case report. Pediatr Transplant. 2013;17:E4–8. PubMed PMID: 23167913.

Hugar LA, Chaudhry R, Fuller TW, Cannon GM, Schneck FX, Ost MC, Stephany HA. Urologic phenotype and patterns of care in patients with megacystis microcolon intestinal hypoperistalsis syndrome presenting to a major pediatric transplantation center. Urology. 2018;119:127–32. PubMed PMID: 29752972.

Milunsky A, Baldwin C, Zhang X, Primack D, Curnow A, Milunsky J. Diagnosis of chronic intestinal pseudo-obstruction and megacystis by sequencing the ACTG2 gene. J Pediatr Gastroenterol Nutr. 2017a;65:384–7. PubMed PMID: 28422808.

Milunsky A, Lazier J, Baldwin C, Young C, Primack D, Milunsky JM. Prenatal diagnosis of chronic intestinal pseudo-obstruction and paternal somatic mosaicism for the ACTG2 pathogenic variant. Prenat Diagn. 2017b;37:1254–6. PubMed PMID: 29072330.

Moreno CA, Sobreira N, Pugh E, Zhang P, Steel G, Torres FR, Cavalcanti DP. Homozygous deletion in MYL9 expands the molecular basis of megacystis-microcolon-intestinal hypoperistalsis syndrome. Eur J Hum Genet. 2018;26:669–75. PubMed PMID: 29453416.

Munch EM, Cisek LJ Jr, Roth DR. Magnetic resonance imaging for prenatal diagnosis of multisystem disease: megacystis microcolon intestinal hypoperistalsis syndrome. Urology. 2009;74:592–4. PubMed PMID: 19501881.

Puri P, Gosemann JH. Variants of Hirschsprung disease. Semin Pediatr Surg. 2012;21:310–8. PubMed PMID: 22985836.

Puri P, Shinkai M. Megacystis microcolon intestinal hypoperistalsis syndrome. Semin Pediatr Surg. 2005;14:58–63. PubMed PMID: 15770589.

Soh H, Fukuzawa M, Kubota A, Kawahara H, Ueno T, Taguchi T. Megacystis microcolon intestinal hypoperistalsis syndrome: a report of a nationwide survey in Japan. J Pediatr Surg. 2015;50:2048–50. PubMed PMID: 26413901.

Tuzovic L, Anyane-Yeboa K, Mills A, Glassberg K, Miller R. Megacystis-microcolon-intestinal hypoperistalsis syndrome: case report and review of prenatal ultrasonographic findings. Fetal Diagn Ther. 2014;36:74–80. PubMed PMID: 24577413.

Tuzovic L, Tang S, Miller RS, Rohena L, Shahmirzadi L, Gonzalez K, Li X, LeDuc CA, Guo J, Wilson A, Mills A, Glassberg K, Rotterdam H, Sepulveda AR, Zeng W, Chung WK, Anyane-Yeboa K. New insights into the genetics of fetal megacystis: ACTG2 mutations, encoding gamma-2 smooth muscle actin in megacystis microcolon intestinal hypoperistalsis syndrome (Berdon syndrome). Fetal Diagn Ther. 2015;38:296–306. PubMed PMID: 25998219.

Wangler MF, Gonzaga-Jauregui C, Gambin T, Penney S, Moss T, Chopra A, Probst FJ, Xia F, Yang Y, Werlin S, Eglite I, Kornejeva L, Bacino CA, Baldridge D, Neul J, Lehman EL, Larson A, Beuten J, Muzny DM, Jhangiani S, Gibbs RA, Lupski JR, Beaudet A, et al. Heterozygous de novo and inherited mutations in the smooth muscle actin (ACTG2) gene underlie megacystis-microcolon-intestinal hypoperistalsis syndrome. PLoS Genet. 2014;10:e1004258. PubMed PMID: 24676022.

Wymer KM, Anderson BB, Wilkens AA, Gundeti MS. Megacystis microcolon intestinal hypoperistalsis syndrome: case series and updated review of the literature with an emphasis on urologic management. J Pediatr Surg. 2016;51:1565–73. PubMed PMID: 27421821.

Yetman AT, Starr LJ. Newly described recessive MYH11 disorder with clinical overlap of multisystemic smooth muscle dysfunction and megacystis microcolon hypoperistalsis syndromes. Am J Med Genet A. 2018;176:1011–14. PubMed PMID: 29575632.

License