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ACTG2 Visceral Myopathy

Synonyms: Berdon Syndrome, Familial Visceral Myopathy

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Summary

Clinical characteristics

ACTG2 visceral myopathy is a disorder of smooth muscle dysfunction of the bladder and gastrointestinal system with phenotypic spectrum that ranges from mild to severe. Bladder involvement can range from neonatal megacystis and megaureter (with its most extreme form of prune belly syndrome) at the more severe end, to recurrent urinary tract infections and bladder dysfunction at the milder end. Intestinal involvement can range from malrotation, neonatal manifestations of microcolon, megacystis microcolon intestinal hypoperistalsis syndrome, and chronic intestinal pseudoobstruction (CIPO) in neonates at the more severe end to intermittent abdominal distention and functional intestinal obstruction at the milder end.

Affected infants (with or without evidence of intestinal malrotation) often present with feeding intolerance and findings of non-mechanical bowel obstruction that persist after successful surgical correction of malrotation. Individuals who develop manifestations of CIPO in later childhood or adulthood often experience episodic waxing and waning of bowel motility. They may undergo frequent abdominal surgeries (perhaps related to malrotation or adhesions causing mechanical obstruction) resulting in resection of dilated segments of bowel, often becoming dependent on total parenteral nutrition (TPN).

Diagnosis/testing

The diagnosis of *ACTG2* visceral myopathy is established in a proband with suggestive findings and a heterozygous *ACTG2* pathogenic variant identified by molecular genetic testing.

Management

Treatment of manifestations. Treatment is supportive. Specialized centers offer multidisciplinary medical and surgical models of care including comprehensive TPN management and multivisceral transplantation. Chronic bladder dysfunction typically requires management by a urologist and can involve routine urinary catheterization or diversion to reduce the risk of dilation of the upper urinary tract and associated risk for urinary tract infection and renal functional impairment. Bowel dysfunction, microcolon, intestinal dysmotility,

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and associated gastrointestinal comorbidities typically require management by a gastroenterologist and nutritionist familiar with intestinal motility disorders.

Surveillance: Surveillance should be individualized using a multidisciplinary approach.

For bladder and urinary tract comorbidities, monitor voiding, urinary tract anatomy, and renal function.

For intestinal manifestations, monitor nutritional status and possible TPN-associated complications (line infections, liver disease) and consider need for multivisceral or isolated intestinal transplantation.

Agents/circumstances to avoid: Treatment/medications (including opioids) 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 relatives at risk as early diagnosis may help prevent unnecessary surgery for manifestations of intestinal obstruction and may allow early evaluation of bladder and renal function, and of the urinary tract for evidence of dilatation.

Pregnancy management: When a fetus at risk for *ACTG2* visceral myopathy has evidence of bladder distention on prenatal ultrasound examination, consultation with a maternal fetal medicine specialist is recommended.

Genetic counseling

ACTG2 visceral myopathy is typically inherited in an autosomal dominant manner. (Apparent autosomal recessive inheritance, suggested in one family, is not discussed further in the Summary.)

Approximately 73% of individuals with *ACTG2* visceral myopathy have a *de novo* pathogenic variant.

If a parent is known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. Although penetrance of *ACTG2* visceral myopathy appears to be complete, the severity of clinical findings can vary between heterozygous family members.

Each child of an individual with *ACTG2* visceral myopathy has a 50% chance of inheriting the pathogenic variant.

Once the *ACTG2* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for *ACTG2* visceral myopathy have been published.

Suggestive Findings

ACTG2 visceral myopathy **should be suspected** in individuals with the following bladder and/or intestinal findings (which can range in a continuum from severe in neonates to more mild in older children and adults) and family history.

Bladder findings

- Prenatal ultrasound revealing megacystis, defined according to trimester [Fievet et al 2014]:
  - First trimester. Bladder diameter >6 mm
  - Second and third trimesters. Enlarged bladder with failure to empty within 45 minutes
- In neonates, prune-belly sequence (megacystis with lack of abdominal wall musculature, cryptorchidism in males, and distention of the upper urinary tract) in association with impaired gastrointestinal motility
- Postnatal ultrasound examination or cystogram revealing an enlarged bladder

- In individuals of any age, unexplained chronic functional bladder impairment of voiding without mechanical blockage

Intestinal findings

- Neonatal bilious emesis, abdominal distention, and feeding intolerance
- Intestinal malrotation and long-term intestinal motility problems often resulting in chronic abdominal pain and constipation
- Neonatal microcolon
- In individuals of any age, chronic intestinal pseudoobstruction (CIPO) (i.e., unexplained chronic functional intestinal obstruction involving small bowel and/or colon without evidence of mechanical blockage)

Additional suggestive intestinal findings [Gabbard & Lacy 2013]:

- Symptoms lasting more than six months, or more than two months from birth
- Evidence of delayed GI transit and/or decreased GI motility
- Imaging studies that do not show mechanical obstruction
- Radiographic documentation of dilated bowel, air fluid levels without fixed obstruction [Rudolph et al 1997]

Family history is consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *ACTG2* visceral myopathy **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *ACTG2* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *ACTG2* variant of uncertain significance does not establish or rule out the diagnosis.

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

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of *ACTG2* visceral myopathy has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *ACTG2* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

A multigene panel that includes *ACTG2* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and

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

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

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic – and particularly when evidence supports autosomal dominant inheritance – **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis. Note: To date such variants have not been identified as a cause of this disorder.

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 *ACTG2* Visceral Myopathy

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
ACTG2	Sequence analysis [3]	All variants reported to date [4]
	Gene-targeted deletion/duplication analysis [5]	None detected to date

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include 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. Assia Batzir et al [2020] and references therein
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, and multiplex ligation-dependent probe amplification (MLPA), and gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

Individuals with *ACTG2* visceral myopathy can experience functional defects of smooth muscle involving both bladder and bowel. Bladder involvement can range from neonatal megacystis and megaureter (with its most extreme form of prune belly syndrome) at the more severe end to recurrent urinary tract infections and bladder dysfunction at the milder end. Intestinal involvement can range from malrotation, neonatal manifestations of microcolon, and megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS) to chronic intestinal pseudoobstruction (CIPO) in neonates, infants, children, and adults.

The clinical severity can range within a family; mildly affected family members may not be aware of the diagnosis. For example:

- One individual (in a multi-generation Finnish family) with an *ACTG2* pathogenic variant reported episodic mild abdominal pain but no surgery and no signs of visceral myopathy at age 19 years [Lehtonen et al 2012].
- One individual diagnosed with "spastic colon" and irritable bowel syndrome had not required surgery or intervention in middle age [Wangler et al 2014].

Table 2. *ACTG2* Visceral Myopathy: Frequency of Select Features

Feature		Percentage		
		Nearly all	Common	Infrequent
Bladder	Prenatal or postnatal megacystis	89%		
	Chronic functional impairment	92%		
	Prune belly syndrome			4%
Intestinal	Dependence on parenteral nutrition	89%		
	History of abdominal surgery		58%	
	Microcolon		62%	
	Bilious emesis or inability to tolerate feeds as a neonate		54%	
	Later-onset CIPO			4%

Based on Assia Batzir et al [2020]
CIPO = chronic intestinal pseudoobstruction

The following discussion of findings from Table 2 is based on Assia Batzir et al [2020] except where indicated by additional citations.

Urologic. The majority (89%) of individuals with either a *de novo* or inherited *ACTG2* pathogenic variant had prenatal or postnatal megacystis [Assia Batzir et al 2020, Billon et al 2020, Matera et al 2021]. Fetal megacystis is defined as longitudinal bladder diameter ≥7mm in the first trimester [Fong et al 2004].

Approximately 11% of individuals have had a vesicoamniotic shunt placed prenatally [Wangler et al 2014].

Chronic bladder functional impairment seen in the majority of individuals with an *ACTG2 de novo* pathogenic variant can require lifelong bladder catheterization (24/26 [92%]) [Assia Batzir et al 2020].

Prune belly syndrome, characterized by lack of abdominal wall musculature, cryptorchidism in males, and distention of the urinary tract [Pomajzl & Sankararaman 2020], was reported in one male with MMIHS and a *de novo ACTG2* pathogenic variant [Wangler et al 2014].

Gastrointestinal. The majority of neonates with a *de novo ACTG2* pathogenic variant are unable to tolerate feedings. Likewise, intestinal malrotation is common; while many undergo a Ladd surgical procedure (58%), many experience persistent manifestations of bowel obstruction (e.g., vomiting, food intolerance, abdominal pain or tenderness, and distention) after surgical recovery [Wangler et al 2014].

Affected individuals can experience episodic improvement of bowel motility, loss of bowel motility over time, or waxing and waning of reduced bowel motility. Affected individuals may undergo frequent abdominal surgeries (perhaps related to malrotation or presumed adhesions causing mechanical obstruction) resulting in resection of dilated segments of bowel.

Microcolon refers to a small-caliber (but not short) colon in the neonate. The etiology is considered to be lack of use of the colon during fetal development due to proximal functional obstruction. While the caliber of the colon is often noted to be small on contrast enema, no definite radiologic criteria are established.

Affected individuals in many families with a dominantly inherited *ACTG2* pathogenic variant and waxing and waning chronic intestinal pseudoobstruction (CIPO) report lifelong gastrointestinal discomfort and episodic symptoms resulting in surgery and hospitalization. These individuals can survive to an advanced age.

Uterine. Failure to progress during labor and impaired uterine contractions have been reported [Klar et al 2015]. Poor uterine contractility has been severe enough to lead to cesarean delivery.

Biliary tract. Cholelithiasis and cholecystitis have been reported [Klar et al 2015]. Cholelithiasis has been noted as early as age 9 years.

Intellect in individuals with *ACTG2* visceral myopathy is usually normal.

Long-term survival. Poor (severe) outcome, defined as complications leading to death, dependence on total parenteral nutrition (TPN) and/or multivisceral transplantation, was observed in individuals whose mean last age of contact was seven years (range: 2 months-16 years). Their long-term survival usually required total parenteral nutrition and urinary catheterization or diversion (see Management). Most long-term survivors have ileostomies [Assia Batzir et al 2020].

Individuals with a severe outcome are more likely to have a *de novo ACTG2* pathogenic variant compared to families with an inherited *ACTG2* pathogenic variant in which some family members have MMIHS and others (with the same variant) have milder phenotypes [Wangler et al 2014, Assia Batzir et al 2020].

Genotype-Phenotype Correlations

Genotype-phenotype correlations have been identified for the following pathogenic variants (see also Table 4):

p.Arg40. Six of eight probands with missense variants at p.Arg40 had a favorable outcome.

p.Arg178

- All 17/17 probands with missense variants at p.Arg178 had a poor outcome [Assia Batzir et al 2020]. All were TPN dependent and at least one had undergone a multiorgan transplantation.
- Nineteen of 20 (95%) individuals with missense variants at p.Arg178 had microcolon [Assia Batzir et al 2020].

p.Arg257. Sixteen of 26 (61.5%) probands with missense variants at p.Arg257 had a poor outcome. Five of 26 (19%) had microcolon; of these, three had a poor outcome and two a favorable outcome [Assia Batzir et al 2020].

Penetrance

To date penetrance of *ACTG2* visceral myopathy appears to be complete, as no family members heterozygous for a known *ACTG2* pathogenic variant have been completely symptom free.

Nomenclature

Megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS) may also be referred to as familial visceral myopathy or Berdon syndrome.

The broad term "hollow visceral myopathy" includes phenotypically related disorders caused by pathogenic variants in other genes (e.g., *ACTA2*), and therefore should not be used as a synonym for *ACTG2* visceral myopathy [Milewicz et al 2010].

Prune belly sequence may also be referred to as Eagle-Barrett syndrome.

Prevalence

To date 90 individuals with molecularly confirmed *ACTG2* visceral myopathy have been reported [Assia Batzir et al 2020, Matera et al 2021].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with mutation of *ACTG2*.

Differential Diagnosis

Approximately 62% (33/53) of individuals with a clinical diagnosis of visceral myopathy have a heterozygous pathogenic *ACTG2* variant [Assia Batzir et al [2020]. Other genes known to be associated with visceral myopathy are summarized in Table 3.

Note: Because mydriasis has been identified in some individuals with MMIHS (megacystis-microcolon-intestinal hypoperistalsis syndrome) [McClelland et al 2013] but not in those with *ACTG2* visceral myopathy, the presence of mydriasis may suggest a different disorder.

Table 3. Inherited Disorders with Gastrointestinal/Genitourinary Visceral Myopathy in the Differential Diagnosis for *ACTG2* Visceral Myopathy

Gene	Phenotype	MOI	GI/GU Involvement	Other Features
ACTA2	Multisystem smooth-muscle dysfunction syndrome (OMIM 613834) (See also Heritable Thoracic Aortic Disease Overview.)	AD	Hypotonic bladder, cryptorchidism, malrotation & hypoperistalsis of the gut [1]; prune-belly sequence may be associated. [2]	Thoracic aortic aneurysms & aortic dissections, PDA, stenosis & dilatation of cerebral vessels, mydriasis, periventricular white matter hyperintensities on MRI; pulmonary hypertension
CHRM3	Prune belly syndrome (OMIM 100100)	AR	Prune belly syndrome w/distended, areflexic/ hyporeflexic bladder; hydroureter, hydronephrosis; cryptorchidism; constipation [3]	Posterior urethral valves
CHRNA3	CAKUT & autonomic dysfunction (OMIM 191800)	AR	Impaired bladder innervation; thick bladder wall; neurogenic vesicoureteral reflux w/hydroureter, hydronephrosis; secondary small, cystic kidneys & chronic kidney disease	Hypospadias
EDNRB *EDN3* *SOX10*	Waardenburg syndrome type IV (OMIM 131244, 613265, 602229)	AD AR	Hirschsprung disease	Pigmentary abnormalities, hearing loss
FLNA	*FLNA*-related periventricular nodular heterotopia	XL	Intestinal pseudoobstruction	Females present w/seizures at age 14-15 yrs; normal-to-borderline intelligence; ↑ risk for cardiovascular disease, stroke, & other vascular/ coagulation issues. Males most often show early lethality.
LMOD1	MMIHS	AR	Classic features of MMIHS	
MYH11	MMIHS	AR	In 1 person each, overlapping features of: • MMIHS & prune belly sequence • MMIHS & MSMDS	PDA in 1 child [4]

Table 3. continued from previous page.

Gene	Phenotype	MOI	GI/GU Involvement	Other Features
MYL9	MMIHS	AR		Mydriasis
MYLK	MMIHS	AR		
RAD21	Mungan syndrome (OMIM 611376)	AR	Barrett esophagus, megaduodenum	Cardiac abnormalities
SGOL1	Chronic atrial & intestinal dysrhythmia (OMM 616201)	AR	Intestinal pseudoobstruction	Sick sinus syndrome, atrial dysrhythmias [5]
TYMP	MNGIE	AR	Progressive GI dysmotility manifesting as early satiety, nausea, dysphagia, gastroesophageal reflux, postprandial emesis, episodic abdominal pain &/or distention, diarrhea	Cachexia, ptosis, external ophthalmoplegia, sensorimotor neuropathy (usually mixed axonal & demyelinating)

AD = autosomal dominant; AR = autosomal recessive; CAKUT = congenital anomalies of the kidney and urinary tract; GI = gastrointestinal; GU = genitourinary; MMIHS = megacystis-microcolon-intestinal hypoperistalsis syndrome; MNGIE = mitochondrial neurogastrointestinal encephalopathy; MSMDS = multisystemic smooth muscle dysfunction syndrome; MOI = mode of inheritance; PDA = patent ductus arteriosus; XL = X-linked

1. Milewicz et al [2010]
2. Richer et al [2012]
3. Weber et al [2005], Weber et al [2011]
4. Gauthier et al [2015]
5. Chetaille et al [2014]

Management

No clinical practice guidelines for *ACTG2* visceral myopathy have been published.

The following recommendations are adapted from the Megacystis-Microcolon-Intestinal Hypoperistalsis Syndrome Overview.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *ACTG2* visceral myopathy, the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Bladder and urinary tract

- 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 (e.g., BUN, creatinine, GFR) and electrolytes (potassium, phosphorus, calcium)

Gastroenterology

- Bowel imaging:
  - Abdominal x-ray
  - Contrast enema
  - Fluoroscopic upper gastrointestinal series

    - Computed tomography examination of the abdomen as indicated to evaluate for a mechanical obstruction.
- Laboratory assessment 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 of growth parameters

Consultation with a medical geneticist, certified genetic counselor, or certified advanced genetic nurse is recommended to inform affected individuals and their families about the nature, mode of inheritance, and implications of *ACTG2* visceral myopathy in order to facilitate medical and personal decision making.

Treatment of Manifestations

Treatment for *ACTG2* visceral myopathy is supportive. Specialized centers offer multidisciplinary medical and surgical models of care including comprehensive total parenteral nutrition (TPN) management and multivisceral transplantation.

Fetal Management

When a fetus at risk for *ACTG2* visceral myopathy has evidence of bladder distention on prenatal ultrasound examination, consultation with a maternal fetal medicine specialist is recommended. Of note, in some fetuses with prenatal detection of megacystis, vesicoamniotic shunts have been performed.

Management of Children and Adults

Children with *ACTG2* visceral myopathy require multidisciplinary management with specialists in pediatric urology, gastroenterology, and nutrition who are familiar with bladder and intestinal motility disorders, as well as experts in medical genetics.

Adults with *ACTG2* visceral myopathy require similar multidisciplinary care.

Myopathic bladder dysfunction and associated urologic comorbidities. Goals of bladder management include bladder decompression using clean intermittent catheterizations or vesicostomy, and subsequent monitoring to prevent renal scarring and failure.

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

- 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]
- TPN when appropriate for malnutrition due to 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 due to 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].

- For those with chronic intestinal pseudoobstruction (CIPO), high-fat foods (>30% of total calories) and consumption of lactose and fructose may worsen abdominal bloating and discomfort [Gabbard & Lacy 2013].
- Surgical procedures associated with general anesthesia can produce a post-surgical ileus which can persist for an extended period.

Surveillance

Surveillance should be individualized using a multidisciplinary approach.

Bladder and urinary tract comorbidities. Monitor voiding, urinary tract anatomy, and renal function.

Intestinal manifestations. Monitor nutritional status and possible TPN-associated complications (line infections, liver disease) and consider need for multivisceral or isolated intestinal transplantation.

Agents/Circumstances to Avoid

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

Opioids are known to decrease intestinal dysmotility and should be used with caution [Gamboa & Sood 2019].

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of relatives at risk as early diagnosis may help prevent unnecessary surgery for manifestations of intestinal obstruction and may allow early evaluation of bladder and renal function, and of the urinary tract for evidence of dilatation.

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

Pregnancy Management

Among the limited number of mothers with *ACTG2* visceral myopathy reported, some instances of poor labor progression and weak uterine contractions have been noted [Klar et al 2015].

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.

Genetic Counseling

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

Mode of Inheritance

ACTG2 visceral myopathy is typically inherited in an autosomal dominant manner.

Apparent autosomal recessive inheritance of *ACTG2* visceral myopathy has been reported in one family in which two sibs with severe visceral myopathy were found to have biallelic *ACTG2* variants while their heterozygous parents were asymptomatic [Matera et al 2021]. Further study is needed to confirm that the

ACTG2 variants segregating in this family are causative of the phenotype in the affected sibs. (Autosomal recessive inheritance is not discussed further in this section.)

Risk to Family Members (Autosomal Dominant Inheritance)

Parents of a proband

- The majority of individuals with *ACTG2* visceral myopathy have the disorder as the result of a *de novo* pathogenic variant. In a cohort of 26 individuals with *ACTG2* visceral myopathy whose parents underwent molecular genetic testing, 19 probands (~73%) had the disorder as the result of a *de novo* *ACTG2* pathogenic variant [Assia Batzir et al 2020].
- Some individuals diagnosed with *ACTG2* visceral myopathy have the disorder as the result of a pathogenic variant inherited from a heterozygous parent. In a cohort of 26 individuals with *ACTG2* visceral myopathy whose parents underwent molecular genetic testing, seven probands (~27%) had the disorder as the result of a pathogenic variant inherited from a heterozygous, affected parent [Assia Batzir et al 2020]. To date, all parents known to be heterozygous for an *ACTG2* pathogenic variant have had manifestations of visceral myopathy; however, it is possible that a heterozygous parent may have mild symptoms and appear to be unaffected.
- Molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent, the following possibilities should be considered:
    - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
    - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism [Tuzovic et al 2015, Milunsky et al 2017].* Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

      * A parent with somatic and germline mosaicism for an *ACTG2* pathogenic variant may be mildly/minimally affected.
- An individual diagnosed with *ACTG2* visceral myopathy may appear to be the only affected family member. However, because it is possible that heterozygous family members may appear to be clinically asymptomatic because of a milder phenotypic presentation or late onset of the disease, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

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

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- Although penetrance of *ACTG2* visceral myopathy appears to be complete, the severity of clinical findings can vary among heterozygous family members [Lehtonen et al 2012, Klar et al 2015, Assia Batzir et al 2020].
- If the *ACTG2* pathogenic variant found in the proband 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 mosaicism (observed in 2 families reported to date [Tuzovic et al 2015, Milunsky et al 2017]).
- 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 *ACTG2* visceral myopathy because of the possibility of parental mosaicism or reduced penetrance in a heterozygous parent.

Offspring of a proband. Each child of an individual with autosomal dominant *ACTG2* visceral myopathy has a 50% chance of inheriting the pathogenic variant.

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

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 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 or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once the *ACTG2* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for *ACTG2* visceral myopathy are possible. However, clinical severity cannot be accurately predicted by family history or molecular genetic testing.

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

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **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
- **MMIHS Foundation**
  mmihs.org
- **National Digestive Diseases Information Clearinghouse (NDDIC)**
  Intestinal Pseudo-obstruction
- **National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)**
  Phone: 301-496-3583
  niddk.nih.gov
- **Prune Belly Syndrome Network**
  Phone: 855-ASK-PBSN
  prunebelly.org
- **Pull-thru Network**
  Phone: -309-262-0786
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- **The Oley Foundation**
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- **United Ostomy Associations of America, Inc.**
  Phone: 800-826-0826
  ostomy.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. ACTG2 Visceral Myopathy: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
ACTG2	2p13.1	Actin, gamma-enteric smooth muscle	ACTG2	ACTG2

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 ACTG2 Visceral Myopathy (View All in OMIM)

102545	ACTIN, GAMMA-2, SMOOTH MUSCLE, ENTERIC; ACTG2
155310	VISCERAL MYOPATHY 1; VSCM1

Molecular Pathogenesis

ACTG2 encodes γ-2 actin, an enteric actin protein. The abnormal proteins are hypothesized to affect actin filament polymerization and smooth muscle contraction [Thorson et al 2014]. Aggregation of the γ-2 actin molecules may also occur [Lehtonen et al 2012]. Structural data on actin molecules support the role of some of the altered amino acids in actin polymerization [Graceffa & Dominguez 2003].

Mechanism of disease causation. Halim et al [2016] used in vitro assays to support a gain-of-function mechanism for *ACTG2* missense variants. In addition, intestinal smooth muscle cells with *ACTG2* variant p.Arg257Cys showed poor incorporation of the mutated γ-2 actin into actin filament bundles [Hashmi et al 2020].

***ACTG2*-specific laboratory technical considerations.** Thirteen of the 18 ACTG2 arginine residues are encoded by an *ACTG2* "CGX" (CGG, CGC, CGA, and CGU) codon within a CpG dinucleotide. Variants at five of these arginine residues (p.Arg40, p.Arg63, p.Arg178, p.Arg211, and p.Arg257) account for 75% (67/85) of reported *ACTG2* pathogenic variants [Assia Batzir et al 2020]. See Table 4.

Table 4. Notable *ACTG2* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment
NM_001615.4 NP_001606.1	c.119G>A	p.Arg40His	Favorable outcome (See Genotype-Phenotype Correlations.)
	c.118C>T	p.Arg40Cys	
	c.187C>G	p.Arg63Gly	Insufficient data for genotype-phenotype correlations
	c.532C>T	p.Arg178Cys	High rate of a poor outcome [1] or microcolon (See Genotype-Phenotype Correlations.)
	c.533G>A	p.Arg178His	
	c.533G>T	p.Arg178Leu	
	c.632G>A	p.Arg211Gln	Insufficient data for genotype-phenotype correlations
	c.769C>T	p.Arg257Cys	High rate of a poor outcome [1] or microcolon (See Genotype-Phenotype Correlations.)
	c.770G>A	p.Arg257His	

Based on Assia Batzir et al [2020]
Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Poor outcome = mortality and/or multivisceral transplantation

Chapter Notes

Author Notes

The authors are currently using the latest technology including exome sequencing to understand rare mendelian disorders including disorders of intestinal motility.

www.texaschildrens.org/find-a-doctor/michael-f-wangler-md

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Revision History

- 6 May 2021 (bp) Comprehensive update posted live
- 11 June 2015 (me) Review posted live
- 15 July 2014 (mw) Original submission

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