New Insights into the Genetics of Fetal Megacystis: ACTG2 Mutations, Encoding γ-2 Smooth Muscle Actin in Megacystis Microcolon Intestinal Hypoperistalsis Syndrome (Berdon Syndrome)

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Key Words
Megacystis microcolon intestinal hypoperistalsis syndrome · Berdon syndrome · ACTG2 · γ-2 smooth muscle actin · Fetal megacystis · Gonadal mosaicism · Prenatal diagnosis

Abstract
Objective: To identify the molecular basis for prenatally suspected cases of megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS) (MIM 249210) in 3 independent families with clinical and radiographic evidence of MMIHS.

Methods: Whole-exome sequencing (WES) and Sanger sequencing of the ACTG2 gene.

Results: We identified a novel heterozygous de novo missense variant in ACTG2 c.770G>A (p.Arg257His) encoding γ-2 smooth muscle actin (ACTG2) in 2 siblings with MMIHS, suggesting gonadal mosaicism of one of the parents. Two additional de novo missense variants (p.Arg257Cys and p.Arg178His) in ACTG2 were identified in 2 additional MMIHS patients. All of our patients had evidence of fetal megacystis and a normal or slightly increased amniotic fluid volume. Additional findings included bilateral renal hydronephrosis, an enlarged fetal stomach, and transient dilated bowel loops. ACTG2 immunostaining of the intestinal tissue showed an altered muscularis propria, a markedly thinned longitudinal muscle layer, and a reduced amount and abnormal distribution of ACTG2.

Conclusion: Our study demonstrates that de novo mutations in ACTG2 are a cause of fetal megacystis in MMIHS and that gonadal mosaicism may be present in a subset of cases. These findings have implications for the counseling of families with a diagnosis of fetal megacystis with a preserved amniotic fluid volume and associated gastrointestinal findings.

Introduction
Megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS) (MIM 249210), also known as Berdon syndrome, is a rare genetic syndrome initially described in 5 female newborns who presented with neonatal massive abdominal distention [1]. MMIHS is characterized by a massively enlarged bladder and intestinal hypoperistalsis causing intestinal pseudoobstruction. More than 200 cases have been documented. Most cases are sporadic, with a small number of familial cases with reported...
consanguinity, suggesting possible autosomal recessive inheritance [1–5].

MMIHS primarily affects the genitourinary and gastrointestinal systems and is characterized by a massively enlarged, atonic bladder and dilatation of the ureters and renal calyces. Renal function is usually preserved, although patients require lifelong intermittent catheterizations due to bladder atony. There is widespread intestinal hypoperistalsis causing intestinal pseudoobstruction, often in the neonatal period [1, 6]. Microcolonic and intestinal malrotation have also been described [1]. Previous histopathological studies have observed increased numbers of ganglion cells in the submucosal and myenteric plexuses [7, 8]. Thinning of the intestinal longitudinal muscle layer and increased connective tissue proliferation between the intestinal smooth muscle layers have also been observed [7]. On electron microscopy, ‘central core’ vacuolar degeneration in the center of smooth muscle cells has been described in smooth muscle cells in the bowel and bladder [7, 9, 10]. Immunohistochemical staining with antibodies against α-smooth muscle actin and caldesmon has shown markedly reduced staining in the longitudinal and circular layers of the small and large bowel and bladder [8–10]. Recently familial [11–13] and de novo [13, 14] ACTG2 mutations have been implicated in the etiology of familial visceral myopathy (FVM) as well as MMIHS.

Here we describe the use of whole-exome sequencing (WES) to identify apparent de novo ACTG2 mutations in 2 siblings of the opposite sex suspected prenatally to have MMIHS based on the constellation of typical prenatal sonographic findings. We further used Sanger sequencing to search for additional ACTG2 mutations in 2 unrelated families with MMIHS in which the probands also presented with massive fetal megacystis during prenatal life. We expand the prenatal phenotype associated with de novo ACTG2 mutations in humans.

Methods

All studies were approved by the Institutional Review Board of Columbia University Medical Center, and all subjects provided written informed consent. Parental consent was obtained for children.

We studied 3 unrelated families with a total of 4 affected individuals with clinical and radiographic evidence of MMIHS and their unaffected parents. In order to determine a molecular basis for the MMIHS phenotype, we performed WES from blood on 2 of the affected siblings and unaffected parents from family 1. We confirmed the presence or absence of the ACTG2 variant with diodeoxy (Sanger) sequencing in all family members.

WES Analysis

Genomic DNA from the patients and available first-degree relatives was isolated from whole blood. Samples were prepared using the SureSelect Target Enrichment System (Agilent Technologies, Santa Clara, Calif., USA). Exome libraries were sequenced using paired-end, 100-cycle chemistry on the Illumina HiSeq 2000 (Illumina, San Diego, Calif., USA). Sequence quality filtering was performed with Illumina CASAVA software (version 1.8.2; Illumina, Hayward, Calif., USA). The sequence data were aligned to the reference human genome (GRCh37), and variant calls were generated using CASAVA. Exons plus at least 2 bases into the 5’ and 3’ ends of all of the introns were analyzed. The data analysis focused on nonsense variants, small insertions and deletions, canonical splice site alterations, or nonsynonymous missense changes. Alterations were annotated with the Ambry Variant Analyzer (AVA) tool, including sequence changes in the cDNA and protein, nucleotide and amino acid conservation, population frequency (ESP and 1000 Genomes), and the predicted functional impact (including PolyPhen and SIFT in silico prediction tools). The Human Gene Mutation Database (HGMD), Online Mendelian Inheritance in Man (OMIM), and online search engines (e.g. PubMed) were used to search for previously described disease-causing genes and mutations. Stepwise filtering removed common single-nucleotide polymorphisms (SNPs), non-splice-related noncoding variants, and synonymous variants. Variants were further filtered based on autosomal and X-linked dominant and recessive inheritance models. Sanger confirmation of the identified candidate alterations was performed using ABI3730 (Life Technologies, Carlsbad, Calif., USA).

In silico Prediction Analysis

Various online prediction tools were used to assess the pathogenicity of the newly identified variants: PolyPhen-2 (Polyorphism Phenotyping v2; http://genetics.bwh.harvard.edu/pph2/index.shtml), SIFT (Sorting Intolerant from Tolerant; http://sift.jcvi.org), the GERP (Genomic Evolutionary Rate Profiling) score, LRT (likelihood ratio test), MutationTaster, and PhylotoP.

Sanger Sequencing of the ACTG2 Gene

Individuals from families 2 and 3 were analyzed by Sanger sequencing of all of the coding exons of ACTG2 (primer sequences are available upon request). PCR reactions were run in 25-μl reaction volumes applying a touchdown protocol and annealing at temperatures of 65 and 57°C. PCR products were then run onto a 2% agarose gel cleaned over Sephadex columns and applied to BigDye reactions following the manufacturer’s recommendations. Sequencher 4.7 software was used to visualize the electrophorograms.

Immunohistochemistry

A full-thickness small-bowel specimen (jejunum) was available from the proband in family 2. Sections obtained from formalin-fixed paraffin-embedded tissues were immunohistochemically stained with antibody against human γ-2 smooth muscle actin (ACTG2) (NB100-91649; Novus Biologicals, Littleton, Colo., USA) in a Leica Autostainer (Leica Biosystems) at a 1:400 dilution. Immunohistochemistry for calponin, caldesmon, α-smooth muscle actin, c-Kit, and Ki-67 was performed with a Leica Autostainer (Leica Biosystems) following the manufacturer’s instructions.
Clinical Description of the Patients
The clinical details and radiologic findings are summarized in Table 1 and Figure 1.

Description of the Prenatal and Postnatal Findings
All 4 affected individuals showed evidence of disease prenatally. The prenatal ultrasonographic findings of the affected individuals in family 1 were described in detail elsewhere [15] and are summarized in Table 1. The proband in family 1, a female child from a nonconsanguineous Chinese family, presented with fetal megacystis during the second trimester as well as evidence of an echogenic bowel. Her brother was followed serially in our prenatal diagnostic unit throughout the pregnancy. The initial prenatal finding was isolated bilateral renal hydronephrosis at 18 weeks of gestation followed by detection of fetal megacystis at 22 weeks of gestation.

Table 1. Phenotypic characteristics of patients with identified ACTG2 mutations

<table>
<thead>
<tr>
<th>ACTG2 variant (heterozygous)</th>
<th>Family 1</th>
<th>Family 2</th>
<th>Family 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>II.1 R257H (c.770G&gt;A)</td>
<td>II.2 R257H (c.770G&gt;A)</td>
<td>patient 1 R178H (c.533G&gt;A)</td>
<td>patient 1 R257C (c.769C&gt;T)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th>Ethnic background</th>
<th>Age of onset</th>
<th>Age at the time of reporting</th>
<th>Prenatal findings</th>
<th>Growth parameters at birth</th>
<th>Presentation at birth</th>
<th>Growth parameters at age at the time of reporting</th>
<th>Genitourinary findings after birth</th>
<th>Gastrointestinal findings after birth</th>
<th>Motility studies (intestinal manometry)</th>
<th>TPN dependent</th>
<th>Rectal biopsy (ganglion cells present)</th>
<th>Malrotation</th>
<th>Microcolon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>Asian</td>
<td>Fetal life</td>
<td>3 years</td>
<td>Megacystis</td>
<td>Weight: 4,090 g (90–95%)</td>
<td>Abdominal distention, intolerance of oral intake, large bladder</td>
<td>Weight: 75–90%</td>
<td>Megacystis, no obstruction, no VUR</td>
<td>Intestinal hypomotility</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Male</td>
<td>Asian</td>
<td>Fetal life</td>
<td>15 months</td>
<td>Megacystis, bilateral hydronephrosis first detected at 20 weeks, normal to increased amniotic fluid index, transient dilated bowel loop</td>
<td>Weight: 4,325 g (90%)</td>
<td>Abdominal distention, inability to pass meconium, intolerance of oral intake, large bladder</td>
<td>Weight: 10–25%, height: 25–50%</td>
<td>Megacystis, no obstruction, no VUR</td>
<td>Intestinal hypomotility</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>Hispanic/Asian</td>
<td>Fetal life</td>
<td>7 months</td>
<td>Megacystis, normal to increased amniotic fluid index, bilateral hydronephrosis, dilated stomach</td>
<td>Weight: 2,780 g (10–25%)</td>
<td>Abdominal distention, intolerance of oral intake, large bladder</td>
<td>Weight: 25%, height: 25–50%</td>
<td>Megacystis, no obstruction, no VUR</td>
<td>Intestinal hypomotility</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>Asian</td>
<td>Fetal life</td>
<td>18 months</td>
<td>Large intra-abdominal cystic mass of unclear origin, normal amniotic fluid index</td>
<td>Weight: 3,060 g (25%)</td>
<td>Abdominal distention, poor feeding, large bladder</td>
<td>Weight: 50%, height: 25–50%</td>
<td>Megacystis, no obstruction, no VUR</td>
<td>No colonic motility and poor antroduodenal motility</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
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VUR = Vesicourethral reflux.

ACTG2 Mutations and Fetal Megacystis in Berdon Syndrome

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The proband in family 2, a female from a nonconsanguineous couple of mixed Hispanic/Philippine ethnicity, was born at 39 weeks of gestation via primary cesarean section due to breech presentation. Her birth weight was 2,780 g. Fetal megacystis was first detected at 21 weeks of gestation at the time of anatomical ultrasound scan. An enlarged stomach and bilateral renal hydronephrosis were also observed. The amniotic fluid volume appeared normal and remained normal or slightly increased throughout gestation. The bladder became progressively enlarged throughout gestation and was markedly enlarged before birth, measuring 99...
An abdominal ultrasound performed at birth confirmed the presence of a massively enlarged bladder and the existence of bilateral renal hydronephrosis. A vesicoureterogram demonstrated no vesicoureteral reflux and the renal function remained preserved. At 10 h of life, abdominal distention and bilious vomiting first became apparent. The newborn did not pass meconium in the first 24 h of life. A plain abdominal X-ray was consistent with an enlarged stomach. Upper gastrointestinal series demonstrated a delayed passage of contrast into the small bowel, and a barium enema was consistent with microcolon. She underwent an exploratory laparotomy on day 1 of life that confirmed an enlarged stomach without evidence of mechanical obstruction or intestinal malrotation. A rectal biopsy showed grossly normal bowel mucosa and the presence of ganglion cells in the rectum.

At the age of 6 months, she was unable to feed orally and was completely TPN dependent. She also could not void independently and required intermittent bladder catheterizations every 6 h. At the time of reporting, she was a candidate for intestinal transplantation.

The proband in family 3 is a female from a nonconsanguineous family of Asian/Chinese ethnicity. She was born at 39 weeks of gestation via a normal spontaneous vaginal delivery. Her prenatal history was complicated by detection of a large fetal intra-abdominal cystic mass of unclear origin. The amniotic fluid volume appeared normal. No additional prenatal findings were reported. At birth, marked abdominal distention was noted. The abdominal ultrasound at birth confirmed the presence of a 7-cm thin-walled cystic structure of unclear origin. No significant hydronephrosis was noted. On day 1 of life she underwent an exploratory laparotomy that revealed that the large cystic mass corresponded to the enlarged atomic bladder. A vesicoureterogram demonstrated no evidence of vesicoureteral reflux. Her immediate neonatal period was characterized by a prolonged NICU stay of 7 months with poor feeding, failure to thrive, frequent episodes of abdominal distention, and vomiting. She was TPN-dependent for several months due to inability to sustain enteral feeds.

Overall, all 4 patients from this series presented with fetal megacystis. Fetal megacystis became apparent in the second trimester of pregnancy and became progressively enlarged, reaching massive dimensions before birth. In 1 patient, bilateral renal hydronephrosis preceded the development of fetal megacystis and was the first prenatal ultrasonographic finding detected. Overall, renal hydronephrosis was noted in 2 out of 4 patients without evidence of fetal hydroureter. Prenatal intestinal findings were noted in 3 out of 4 patients and included detection of an enlarged stomach at 21 weeks of gestation, transient dilated bowel loops, and a transient echogenic bowel. The amniotic fluid volume remained normal or slightly increased in all of our cases. All of our patients had otherwise uncomplicated gestations and were delivered full term.

All patients presented at birth with abdominal distention, inability to pass meconium, and intestinal hypoperistalsis (table 1). In all 4 patients, the existence of large megacystis was confirmed at birth. Two out of 4 individuals underwent gastrointestinal manometry that demonstrated global intestinal hypomotility. At the time of reporting, 3 of the 4 patients were dependent on total parenteral nutrition (TPN) due to intestinal hypomotility.

Results

WES of Family 1

WES of the proband II.2, the unaffected mother, and the unaffected father and filtering based on autosomal and X-linked dominant and recessive and Y-linked inheritance models identified 46 genes with a total of 76 alterations (online suppl. table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000381638). Manual review to remove sequencing artifacts and polymorphisms along with a medical evaluation to rule out genes lacking clinical overlap with the patient’s phenotypes resulted in 28 genes of possible interest with 35 unique variants (online suppl. table 1). Such phenotype-driven analysis prioritized a single heterozygous de novo missense alteration (c.770G>A, p.Arg257His) located in exon 7 in ACTG2. Cosegregation analysis demonstrated that the affected sister was also heterozygous for the same alteration in ACTG2. The c.770G>A ACTG2 variant was confirmed by dideoxy (Sanger) sequencing (fig. 2).

Dideoxy sequencing of all coding exons of ACTG2 in 2 other unrelated probands from families 2 and 3 identified 2 additional novel, de novo heterozygous missense variants: c.533G>A (p.Arg178His) in family 2 and c.769C>T (p.Arg257Cys) in family 3 affecting the same amino acid as in family 1 (fig. 2).

Conservation of the ACTG2 variants among orthologues and paralogues and in silico predictions showed that the arginine at positions 178 and 257 is highly conserved residue across different species and in all 6 human actin genes in the actin gene family (ACTA1, ACTC1, ACTA2, ACTG2, ACTG1, and ACTB) (fig. 3). All 3 variants, i.e. p.Arg178His, p.Arg257Cys, and p.Arg257His, were found to be conserved by PhyloP and had a high GERP score (online suppl. table 2).

Both p.Arg257His and p.Arg257Cys in ACTG2 were predicted to be probably damaging and deleterious by PolyPhen-2 and SIFT in silico analyses, respectively. The p.Arg178His variant was predicted to be benign by PolyPhen-2 and tolerated by SIFT. All 3 variants were found to be deleterious by LRT prediction (with a score of 1) and disease causing by MutationTaster prediction. The 3 variants were not observed among the 6,503 exomes available from the National Heart, Lung, and Blood Institute (NHLBI) Exome Sequencing Project Exome Variant Server (ESP6500), 1000 Genomes, and the dbSNP database (online suppl. table 2).
Sections of small intestine from the proband in family 2 revealed a muscularis mucosa that appeared normal, whereas the muscularis propria showed a markedly reduced thickness of the longitudinal layer with a relatively preserved thickness of the inner/circular layer. This finding was noted in hematoxylin and eosin (H&E)-stained sections as well as by immunohistochemical staining with the muscle markers calponin, caldesmon, α and γ-2 smooth muscle actin (fig. 4a–d). ACTG2 immunohistochemistry further highlighted an altered cellular staining pattern in smooth muscle cells of the muscularis propria. In the proband, in addition to the markedly thinned outer muscular layer, the smooth muscle cells of the inner layer showed abnormal aggregates or clumps of stain in the cytoplasm resulting in a rarefied and granular appearance compared to a normal control, which had uniform and evenly distributed cytoplasmic immunoreactivity of ACTG2 in the muscularis propria smooth muscle cells (fig. 4e, f). In addition, the muscularis propria of the proband also revealed a high proliferation rate, highlighted by Ki-67 immunohistochemistry, with <5% Ki-67-posit
tive nuclei in normal muscle and >20% in diseased muscle (fig. 5).

c-Kit staining showed normal staining between inner and outer layers of muscularis propria. H&E staining of the full-thickness bowel specimen showed prominent submucosal nerve plexuses with an unusually high number of ganglion cells (fig. 6). Nerve plexuses were also unusually prominent in the myenteric plexus.

Fig. 3. a Alignment of human actin amino acid sequences demonstrating conservation of arginine residues at positions 178 and 257. b Cross-species alignment of the ACTG2 amino acid sequence demonstrating conservation of arginine residues at positions 178 and 257.
Discussion

Our study demonstrates the use of exome sequencing to identify de novo mutations in ACTG2 as the cause of MMIHS in a prenatally suspected case with massive fetal megacystis in 2 siblings of the opposite sex indicating a presumed parental gonadal mosaicism and independently confirms mutations in ACTG2 in 2 other independent patients with massive fetal megacystis. Actin proteins are present in all eukaryotic cells [16] and are further subdivided into α, β, and γ isoforms based on their specific isoelectric properties [17]. ACTG2 is the predominant actin isoform in smooth muscle cells of the intestine, bladder, and uterus [18, 19]. There are 6 human actin genes with >90% sequence homology [20].

We identified 2 different de novo missense mutations at the Arg257 position. The arginine residue at that position is highly conserved in all 6 human actins and across different species (fig. 3). Missense changes in the corresponding amino acids in ACTA1 (p.Arg258His and p.Arg258Lys), ACTA2 (p.Arg258His and p.Arg258Cys), and ACTG1 (p.Arg256Trp) have been reported as disease causing for nemalin myopathy, thoracic aortic aneurysms and dissections, and Baraitser-Winter syndrome [21–24].

Fig. 4. Immunohistochemistry for ACTG2. Sections of small intestine from the proband in family 2 (a, c, e) and a normal control (b, d, f). The muscularis mucosa is well preserved (a, d) while the muscularis propria shows a markedly reduced thickness of the longitudinal layer (diamond in a and line with diamonds at each end in b) with a relatively preserved thickness of the inner/circular layer (line in a and b). ACTG2 immunohistochemistry showed an altered cellular staining pattern in smooth muscle cells of the muscularis propria (c, e) compared to the normal control (d, f). The smooth muscle cells of the inner layer showed abnormal aggregates or clumps of stain in the cytoplasm, resulting in a rarified and granular appearance (e) compared to a normal control (f), with uniform and evenly distributed cytoplasmic immunoreactivity of ACTG2 in the muscularis propria smooth muscle cells.
The highly homologous ACTA2 gene encodes for αsmooth muscle actin, the predominant isoform in the smooth muscle of the vascular wall. p.Arg258His and p.Arg258Cys in ACTA2 have been implicated as disease-causing mutations in families with thoracic aortic aneurysm and dissections [22]. The biochemical effect of the p.Arg258His ACTA2 mutation has been studied in vitro and results in significant defects in actin polymerization and shorter actin filaments, suggesting filament destabilization [20–25].

Our third mutation, i.e. p.Arg178His, is highly conserved among different Actin genes and species (fig. 2). The orthologous p.Arg179His mutation in ACTA2 causes severe multisystem smooth muscle cell dysfunction with early-onset vascular disease similar to moyamoya disease [26]. The p.Arg179His mutation in ACTA2 has also been reported in a patient with prune belly sequence and first-trimester-onset fetal megacystis [27]. The mutation at amino acid 179 in ACTA2 causes a more severe vascular phenotype than the mutation at amino acid 258 [22]. We did not observe a significant genotype-phenotype correlation among our patients, although our sample size was limited.

Immunohistochemistry of intestinal specimens with antibody against γ-2 muscle actin in our patient with the p.Arg178His mutation showed a marked reduction of γ-2 muscle actin with cytoplasmic aggregates compared to the even staining in the control, possibly due to an accumulation of unpolymerized, nonfunctional ACTG2 fibers. These histologic findings are supportive of pathoge-
nicity of the mutation and comparable to ACTG2 immuno
nostaining in a previously described case of FVM [11].

Mutations in ACTG2 were recently implicated in rare forms of FVM [11–13] resembling chronic idiopathic intestinal pseudoobstruction as well as cases suggestive of MMIHS [13, 14].

Phenotypically, several important distinguishing features exist in our patients with MMIHS compared to the FVM cases also caused by ACTG2 mutations [11]. The age of presentation of the FVM cases described in the study of Lehtonen et al. [11] ranged from 11 to 20 years. The disease severity ranged from mild episodic abdominal pain and constipation to severe intestinal pseudoobstruction leading to death [11, 28, 29]. None of the patients had megacystis. All of our patients had prenatally evident fetal megacystis as early as the second trimester of pregnancy that became progressively enlarged reaching a massive diameter at birth. Gastrointestinal involvement was evident prenatally in 2 cases (dilated fetal stomach and transient dilated bowel loops). There were no apparent genotype-phenotype correlations between the prenatal phenotype and the identified de novo ACTG2 mutations.

Prenatal diagnosis of fetal megacystis represents a diagnostic challenge [30, 31]. In the first trimester, the longitudinal bladder diameter (>7 mm) appears to be a useful sonographic marker for fetal aneuploidy [32]. If the fetal bladder diameter is between 7 and 15 mm, the risk of major chromosomal abnormalities, mainly trisomy 13 or 18, is approximately 25%. If the bladder diameter is >15 mm, the risk of a major chromosomal abnormality is approximately 10% [32] or less [33]. Furthermore, in patients with an initial bladder diameter >15 mm in the first trimester, the risk of persistence into the second trimester is high [32].

In this series, all of the patients presented with fetal megacystis with bladder diameters >15 mm in the second trimester and a normal karyotype and SNP-chromosome microarray. We have previously reported on prenatal sonographic findings associated with MMIHS and delineated features that might be useful in distinguishing fetal megacystis associated with MMIHS [15]. Overall, fetal megacystis associated with MMIHS presents in the second trimester, although reports on its presence in the first trimester have also been published [34]. Of note, differentiated smooth muscle cells are evident in the bladder wall from a 52-mm crown-rump length which corresponds to a gestational age of 10 weeks, approximately [35]. In cases of MMIHS, fetal megacystis with or without hydroureteronephrosis is the initial sonographic finding in almost 88% of cases. In the remaining cases, fetal renal hydronephrosis or a fetal dilated stomach usually precedes the development of fetal megacystis. The amniotic fluid volume remains normal or is increased in the majority of cases, indicating preserved overall renal function [15].

In addition to this report, 13 additional patients have been reported with apparent de novo ACTG2 mutations. Of these, 8 involved prenatal existence of megacystis, although data on specific prenatal findings were limited. Three of these cases had also prenatal vesico-amniotic shunt placement with a subsequent preterm delivery [13, 14].

This is the first extensive report on ACTG2 mutations in association with prenatal sonographic findings suggestive of MMIHS. MMIHS appears to represent the most severe end of the spectrum of ACTG2 phenotypes extending from MMIHS to milder forms of chronic intestinal pseudoobstruction. We expanded the clinical phenotype to include detailed prenatal sonographic findings associated with ACTG2 mutations. Furthermore the detection of ACTG2 mutations in 2 siblings of the opposite sex is a first reported case of presumed gonadal mosaicism associated with ACTG2 mutations. This provides an explanation for previously the presumed and suggested autosomal-recessive inheritance of MMIHS. These data have important implications for the clinical diagnosis and counseling of families when there is a prenatal finding of unexplained fetal megacystis with a preserved amniotic fluid volume, and especially in the setting of associated gastrointestinal abnormalities. We recommend considering genetic testing for ACTG2 mutations, especially residue Arg257 and Arg178, in all cases of fetal megacystis with sonographic findings not indicative of an obstructive etiology in which the fetal karyotype is normal. Establishing the correct diagnosis of MMIHS is important to avoid unnecessary fetal therapeutic procedures as well as unnecessary postnatal surgical explorations.

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References


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