Mini-Review

DOI: 10.5582/irdr.2022.01060

Smooth muscle motility disorder phenotypes: A systematic review of cases associated with seven pathogenic genes (*ACTG2*, *MYH11*, *FLNA*, *MYLK*, *RAD21*, *MYL9* and *LMOD1*)

Ninon Fournier[1], Alexandre Fabre[1,2,*]

[1] APHM, Timone Enfant, Pediatric Multidisciplinary Department, Marseille, France;
[2] Aix-Marseille Université, INSERM, GMGF, Marseille, France.

SUMMARY Smooth muscle disorders affecting both the intestine and the bladder have been known for a decade. However, the recent discovery of genes associated with these dysfunctions has led to the description of several clinical phenotypes. We performed a systematic review of all published cases involving seven genes with pathogenic variants, *ACTG2*, *MYH11*, *FLNA*, *MYLK*, *RAD21*, *MYL9* and *LMOD1*, and included 28 articles describing 112 patients and 5 pregnancies terminated before birth. The most commonly described mutations involved *ACTG2* (75/112, 67% of patients), *MYH11* (14%) and *FLNA* (13%). Twenty-seven patients (28%) died at a median age of 14.5 months. Among the 76 patients for whom this information was available, 10 (13%) had isolated chronic intestinal pseudo-obstruction (CIPO), 17 (22%) had isolated megacystis, and 48 (63%) had combined CIPO and megacystis. The respective proportions of these phenotypes were 9%, 20% and 71% among the 56 patients with *ACTG2* mutations, 20%, 20% and 60% among the 10 patients with *MYH11* mutations and 50%, 50% and 0% among the 7 patients with *FLNA* mutations.

Keywords smooth muscle motility disorders, chronic intestinal pseudo-obstruction, megacystis, ACTG2, MYH11, FLNA, MYLK, RAD21, MYL9, LMOD1, mutations

1. Introduction

Smooth muscle motility disorders are a set of congenital diseases often associated with chronic intestinal pseudo obstruction (CIPO), hypoperistalsis, megacystis and/or microcolon (*1-3*). There are no pathognomonic signs and until recently, these disorders could only be diagnosed clinically, often at birth but sometimes prenatally (*4,5*). The characteristic symptom is abdominal distension, suggestive of mechanical obstruction but without radiologically or surgically detectable mechanical obstruction or any organic, systemic or metabolic disease (*6,7*). The rarity of these conditions means that epidemiological data are scarce and only small case series have been reported (*8*). In the last few years however, several genes with pathogenic variants that encode proteins involved in smooth muscle contraction have been associated with these phenotypes: *ACTG2* (*9-24*), *MYH11* (*24-28*), LMOD1 (*29*), *MYLK* (*30*), MYL9 (*31*), *FLNA* (*32-34*) and *RAD21* (*35*). Little is known about the different phenotypes or their evolution. We therefore performed a systematic review of all published cases of smooth muscle motility disorders associated with mutations in these seven genes to summarize current genetic knowledge and provide an overview of the clinical phenotypes, treatment methods and outcomes of these congenital diseases in terms of the associated mutations.

2. Literature search strategies and analysis methods

2.1. Search strategies

The literature review was conducted according to PRISMA guidelines. A MEDLINE (PubMed) search was performed on 2 October 2020 using the following terms: "ACTG2 CIPO", "ACTG2 hypoperistalsis", "ACTG2 smooth muscle motility disorders", "MYH11 CIPO", "MYH11 hypoperistalsis", "MYH11 smooth muscle motility disorders", "FLNA hypoperistalsis", "FLNA CIPO", "FLNA smooth muscle motility disorders", "MYLK CIPO", "MYLK hypoperistalsis", "MYLK smooth muscle motility disorders", "RAD21 CIPO", "RAD21 hypoperistalsis", "RAD21 smooth muscle motility disorders", "MYL9 hypoperistalsis",

"MYL9 CIPO", "MYL9 smooth muscle motility disorders", "LMOD1 CIPO", "LMOD1 hypoperistalsis", and "LMOD1 smooth muscle motility disorders".

Another search was performed on March 2020 in Google Scholar for articles cited by Halim *et al.* 2017 (*29*), Moreno *et al.* 2018 (*31*), Gauthier *et al.* 2015, Bonora *et al.* 2015 (*33*), Oda *et al.* 2016 (*34*), and Wangler *et al.* 2014 (*10*).The resulting articles were included if they contained a clinical description of patients with mutations in one of the seven considered genes. No ethics approval was required under French law as the study only involved data analysis. Database data were used in accordance with the corresponding data use agreements.

2.2. Selection and description of cases

Cases were included if they were associated with mutations in either *ACTG2*, *MYH11*, *FLNA*, *MYLK*, *RAD21*, *MYL9* or *LMOD1* and if gastrointestinal or urologic symptoms were described. The data collected were the patients' sex, anthropometric data at birth and at last follow-up, prenatal manifestations (megacystis, hydronephrosis, dilated bowel), and digestive and urinary manifestations (signs of CIPO, presence of megacystis, description of colon). The mode of inheritance of the mutation, use and duration of parenteral nutrition, need for ostomy, bladder catheterization or vesicostomy, and mortality and cause of death were also recorded.

2.3. Statistical analysis

Statistical analyses were performed using biostatgv (*https://biostatgv.sentiweb.fr/*). Variables were expressed as number, percentage and median. Birth weight percentiles were calculated using Audipog (*https://www.audipog.net/Courbes-morpho*). Weight Z-scores were calculated using Peditool (*https://www.peditools.org/*). P-values < 0.05 were considered statistically significant. Protein–protein interaction networks were built using the STRING (Search Tool for the Retrieval of Interacting Genes/Proteins; *https://string-db.org/*) database, using defaults settings with the highest confidence score (0.9) and without text mining.

3. Results

3.1. Population

Sixty-one articles were retrieved using the search terms, of which 28 satisfied the inclusion criteria (Supplemental Figure S1, *http://www.irdrjournal.com/action/getSupplementalData.php?ID=119*). Among the 117 cases described (61 male, 53 female, 3 of unknown sex), 5 (2 male, 2 female and 1 of unknown sex) were only included in the analysis of prenatal signs because the corresponding pregnancies were terminated before birth. The patients' clinical characteristics are listed by gene mutation in Table 1. Follow-up information was available for 83 patients. The median age at last follow-up was 16.5 years (198 months; range, 0.2–882 months). The mortality rate was 28% (the information of the outcome was known for 95 patients, among them 27 patients have died), with a median age at death of 14.5 months (range, 0.2–414 months).

3.2. Mortality

The outcome of 17 patients (15%) was unknown. The mortality rate was 8.8 per 1,000 patients-years. Information on the cause of death was available in 16/27 cases: four patients each died of sepsis, multisystem organ failure, and single organ failure (liver failure, pancreatitis, cardiac arrest, and respiratory failure), two patients died after treatment was discontinued, one died of surgical complications and for one there was no obvious cause of the death. The Kaplan–Meier survival curve is shown in Supplemental Figure S2 (*http://www.irdrjournal.com/action/getSupplementalData.php?ID=119*).

3.3. Prenatal signs

Prenatal signs were described for 58/117 patients (50%), including 44/77 (57%) of those with an *ACTG2* mutation, 5/18 (28%) of those with an *MYH11* mutation, 4/14 (29%) of those with a *FLNA* mutation and all 5 patients with a *MYLK*, *MYL9* or *LMOD1* mutation (Supplemental Table S2, *http://www.irdrjournal.com/action/getSupplementalData.php?ID=119*). The prenatal signs were mainly in the urinary tract: megacystis (55 patients), hydronephrosis (14 patients), polyhydramnios (13 patients) and oligohydramnios (11 patients). Prenatal gastrointestinal signs such as a dilated or echogenic bowel were reported in six patients. For the 14 patients with available data the median birth term was 38 weeks and the median birthweight Z-score was 0.175 (Supplemental Table S3, *http://www.irdrjournal.com/action/getSupplementalData.php?ID=119*).

3.4. Pattern of inheritance

The inheritance pattern of the *ACTG2* mutations was in most cases (54/77) autosomal dominant but five cases involved a family history of the mutation. The inheritance of the *MYH11*, *MYLK*, *MYL9* and *RAD21* mutations was autosomal recessive in 20/36 cases. X-linked recessive inheritance was described for one *FLNA* mutation.

3.5. Phenotypes

Information on the patients' clinical symptoms, including bladder and/or intestinal involvement, was available for 76 patients (Supplementary

Table 1. Patient clinical characteristics according to gene mutation

Gene	*n*	Male/Female	Alive/Dead	Age at last follow-up (months)	Age at death (months)	Death rate per 1,000 patients-year[a]	Prenatal signs[b], yes/no	CIPO yes/no	MEGACYSTIS yes/no	Colon micro/normal/mega
ACTG2	75 (67%)	33/40 (44%)	45/20	138 (0.2-882, *n* = 54)	21.5 (0.2-414, *n* = 12)	13.51	44/6	56/11	59/5	21/24/2
MYH11	16 (14.3%)	10/6 (63%)	14/2	378 (0.5-846, *n* = 16)	9.25 (0.5-18, *n* = 2)	3.52	5/0	14/2	8/2	3/-/-
FLNA	14 (12.5%)	13/1 (93%)	7/0	240 (72-618, *n* = 7)	-	0	4/0	7/7	3/2	-
MYLK	2 (1.8%)	1/1 (50%)	0/2	0.5 (*n* = 1)	0.5 (*n* = 1)	-	3/0	2/0	1/0	1/-/-
RAD21	3 (2.7%)	2/1 (67%)	2/1	354 (318-366, *n* = 3)	354 (*n* = 1)	11.6	-	3/0	-	-
MYL9	1 (0.9%)	0/1	0/1	20 (*n* = 1)	20 (*n* = 1)	-	1/0	1/0	1/0	1/0/0
LMOD1	1 (0.9%)	0/1	0/1	0.2 (*n* = 1)	0.2 (*n* = 1)	-	1/0	0/1	1/0	1/0/0
TOTAL	112	59/51 (54%)	68/27 (72%)	198 (0.2-882, *n* = 83)	14.5 (0.2-414, *n* = 18)	8.8/1000 patients per year	58/6 (91%)	83/21 (80%)	73/9 (89%)	27/24/2 (51%)

Data are expressed as number (percentage) or median (range, number of observations). *calculated only if more than 2 patients.CIPO, chronic intestinal pseudo-obstruction.

Table 1. Patient clinical characteristics according to gene mutation (continued)

Gene	Parenteral nutrition yes/no	Age at start of parenteral nutrition (months)	Parenteral nutrition weaning yes/no	Age at parenteral nutrition weaning (months)	Stomy yes/no	Ileostomy yes/no	Bladder catheterization or vesicostomy yes/no
ACTG2	39/9	0 (0-42, *n* = 19)	2/25	90 (*n* = 1)	16/42	29/28	36/3
MYH11	3/6	0 (0-0, *n* = 2)	0/2	-	1/7	1/7	1/0
FLNA	4/0	0 (0-0, *n* = 2)	1/1	9 (*n* = 1)	2/5	0/2	3/2
MYLK	-	-	-	-	0/1	1/0	1/0
RAD21	1/0	-	0/1	-	0/2	0/2	-/-
MYL9	1/0	0 (*n* = 1)	0/1	-	1/0	1/0	1/0
LMOD1	1/0	0 (*n* = 1)	0/1	-	0/1	0/1	1/0
TOTAL	49/15 (77%)	0 (0-42, *n* = 25)	3/31 (9 %)	49.5 (9-90, *n* = 2)	20/58 (26%)	32/40 (44%)	43/5 (90%)

Data are expressed as number (percentage) or median (range, number of observations). *calculated only if more than 2 patients.CIPO, chronic intestinal pseudo-obstruction.

Table S1, *http://www.irdrjournal.com/action/getSupplementalData.php?ID=119*). Figure 1 shows a Venn diagram of the most common clinical phenotypes, along with separate diagrams for the three most commonly associated genes, *ACTG2*, *MYH11* and *FLNA*. The most common phenotype was CIPO associated with megacystis (in 68% of patients whose symptoms were described). A few patients with *FLNA* and *LMOD1* mutations had isolated CIPO and 4/10 patients with a *MHY11* mutation had either isolated CIPO (n = 2) or isolated megacystis (n = 2). Descriptions of the bladder (normal or enlarged) were lacking for all three patients with *RAD21* mutations; none of these patients had CIPO (Supplemental Table S1, *http://www.irdrjournal.com/action/getSupplementalData.php?ID=119*).

The colon was described in 47/75 patients with an *ACTG2* mutation, among which 21 had microcolon, but only in 3/16 patients with a *MYH11* mutation, all three of whom had microcolon. Descriptions of the colon were given for all two patients with either a *MYL9* or *LMOD1*, and it was a microcolon for each. Only one description of the colon (microcolon) over the two patients for *MYLK* mutation. The colon was not described for any of the 17 patients with *FLNA* (n = 14) or *RAD21* (n = 3) mutations.

3.6. Managements

Total parenteral nutrition (TPN) was known for 64/112 patients and required in 49/64 patients (77%), 39 of whom had an *ACTG2* mutation. TPN was typically started soon after birth (median age at start, 0 months; range, 0.2–42 months, n = 25) and weaning, when mentioned (n = 34), was only achieved in 3 patients (9%). The age at weaning was only described for two patients, who were respectively weaned at 9 and 90 months. Intermittent catheterization or vesicostomy to ensure bladder decompression and prevent renal scarring or failure was mentioned for 48 patients, and performed for 43 of these (90%). Surgery was mentioned in 84 cases and performed for 71 of these patients (85%).

3.7. Protein interactions

Predicted protein-protein interactions using the STRING database indicate that five of the seven analyzed genes (*ACTG2*, *MYH11*, *MYLK*, *MYL9* and *LMOD1*) are functionally associated as part of a larger unit (Supplementary Figure 3, *http://www.irdrjournal.com/action/getSupplementalData.php?ID=119*). The networks built separately for each protein in turn show that LMOD1 interacts with all four other proteins, while the remaining four (ACTG2, MYH11, MYL9 and MYLK) only interact with three of the other four. This analysis also confirms that RAD21 and FLNA do not interact with the other proteins. Note that three proteins appear in several networks: ACTA2 and TPM2 interact with ACTG2, MYH11, MYL9 and LMOD1, and TPM1 interacts with ACTG2, MYL9 and LMOD1.

4. Discussion

In this study, we reviewed all 117 published cases of smooth muscle motility disorder linked to seven genes with pathogenic mutations: *ACTG2*, *MYH11*, *FLNA*, *MYLK*, *RAD21*, *MYL9* and *LMOD1*. The main finding is that the most commonly described phenotype is combined CIPO and megacystis, similar to what has been described for megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS) (*1,2,4*) — although microcolon was not systematically reported in the cases reviewed here — and to pediatric intestinal pseudo-obstruction (PIPO) (*36*).

We identified five major genes implicated in these cases, *ACTG2*, *MYH11*, *MYLK*, *MYL9* and *LMOD1*, as noticed previously by Ambartsumyan *et al.* (*6*). We started our analysis with the seven genes associated in the literature with smooth muscle motility disorder, and then classified the phenotypes of the corresponding patients, rather than starting with known phenotypes (such as MMIHS, CIPO, multisystemic smooth muscle dysfunction syndrome, hollow visceral myopathy, prune belly syndrome) to identify genes as done in previous studies. This is a major strength of this study, one of the largest reviews of published cases of smooth muscle motility disorder. Our results confirm that there is high phenotype variability for all the considered gene mutations, which clearly limits the possibility of associating distinct forms of smooth muscle motility disorder with particular genes. Note that other phenotypes, such as isolated megacystis and isolated CIPO, are also possible.

In a systematic review of patient outcomes in MMIHS (*37*), Gosemann and Puri found that 80% of children with MMIHS died before adulthood (the oldest MMIHS patents alive were reported to be 19 and 24 years old). The mortality rate in the cases reviewed here was 28%, with 84% survival at five years and 80% at ten years. The major causes of death were sepsis and multisystemic organ failure, probably as a result of improved management of these diseases. Soh *et al.* (*38*) found likewise in their 2015 review of cases in Japan, with 42% of children diagnosed with MMIHS dying of enteritis or sepsis and five and ten-year survival rates of 63% and 57%. Further studies to explore the outcomes and clinical effectiveness of total parenteral nutrition and with multiorgan transplantation with multidisciplinary care are required to evaluate current survival rates, even if no specialized treatment is yet available. Our review confirms that smooth muscle motility disorders are severe diseases, with total parenteral nutrition required in many cases and weaning

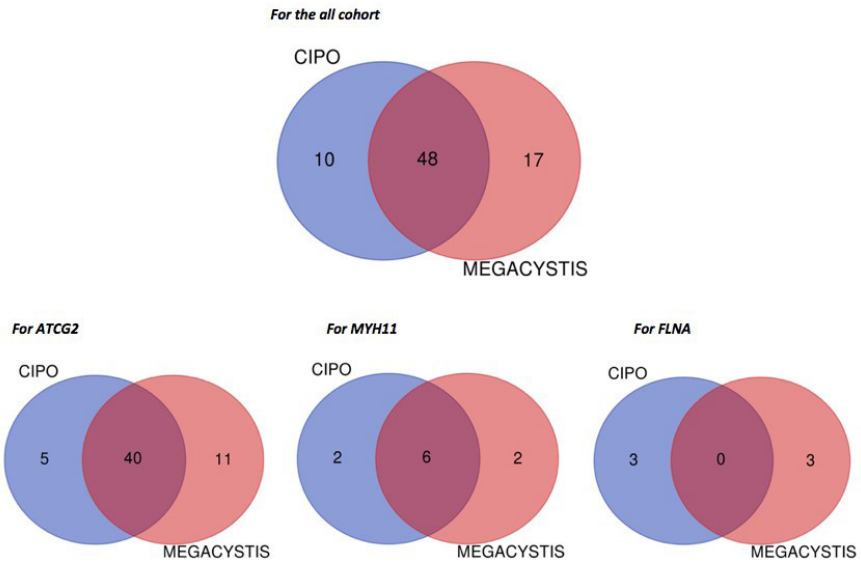

Figure 1. Venn diagrams of the most common clinical phenotypes among 112 patients with a pathogenic variant of *ACTG2*, *MYH11*, *FLNA*, *MYLK*, *RAD21*, *MYL9* or *LMOD1*, and separate diagrams for the three most commonly associated genes.

very rare (in only 9% of cases this series). It is unclear whether the better outcomes identified in this study are due to gene analyses or to improved care in the past few years.

The limitations of this study include different levels of missing patient data in the included articles, and the fact that cases were selected based on gastrointestinal and/or urological symptoms only, meaning, for example, that patients with an *FLNA* mutation but only neurological symptoms were not included. Our results may also be biased by the initial distribution of the genes with 67% of cases associated with an *ACTG2* mutation, the main gene encoding the smooth muscle actin found in enteric tissues, 14% associated with *MYH11* mutations, and 13% with *FLNA*, while only 6% of cases involved *MYLK*, *MYL9*, *RAD21* or *LMOD1* mutations.

Our analysis based on the STRING database suggests the five main genes (*ACTG2*, *MYH11*, *MYLK*, *MYL9* and *LMOD1*) are related as part of a protein interaction network, the same five genes identified by Ambartsumyan *et al.* (*6*) in cases of MMIHS. These proteins also share interaction partners, namely ACTA2, TPM1, TPM2. An *ACTA2* mutation has been described in a case of multisystemic smooth muscle dysfunction (*24*), a severe phenotype with visceral myopathy. Heterozygous variants of *ACTA2* were first described in individuals with familial thoracic aortic aneurysm (*39*), a phenotype also described for pathogenic *MYH11* variants. It would be interesting to see if the two other shared interaction partners, TPM1 and TPM2, are also implicated in other forms of motility disorders or might be predicted to be if no case has yet been described in the literature.

In conclusion, smooth muscle motility disorders are rare, often unrecognized, severe diseases, due to impaired smooth muscle function, whose complications are disabling and can be life-threatening in short to medium term. Our review highlights the variability of clinical phenotypes for each gene mutation, preventing any simple gene–phenotype association. Multigene panel testing of *ACTG2*, *MYH11*, *MYLK*, *MYL9* and *LMOD1* should be considered in patients with hypoperistalsis, signs of CIPO and/or enlarged bladder, or with prenatal signs such as megacystis. The variability of symptoms makes this group of smooth muscle motility disorders a diagnostic challenge but information on associated genetic variants should facilitate diagnosis and classification.

Acknowledgements

We thank Paul Guerry (Green Grow Scientific) for editing the article.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Berdon WE, Baker DH, Blanc WA, Gay B, Santulli TV, Donovan C. Megacystis-microcolon-intestinal hypoperistalsis syndrome: A new cause of intestinal obstruction in the newborn. Report of radiologic findings in five newborn girls. AJR Am J Roentgenol. 1976; 126:957-964
2. Puri P, Shinkai M. Megacystis microcolon intestinal hypoperistalsis syndrome. Semin Pediatr Surg. 2005;

14:58-63.
3. Thapar N, Saliakellis E, Benninga MA, Borrelli O, Curry J, Faure C, De Giorgio R, Gupte G, Knowles CH, Staiano A, Vandenplas Y, Di Lorenzo C. Paediatric intestinal pseudo-obstruction: Evidence and consensus-based recommendations from an ESPGHAN-led expert group. J Pediatr Gastroenterol Nutr. 2018; 66:991-1019.
4. Lashley DB, Masliah E, Kaplan GW, McAleer IM. Megacystis microcolon intestinal hypoperistalsis syndrome: bladder distension and pyelectasis in the fetus without anatomic ooutflow obstruction. Urology. 2000; 55:774.
5. 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.
6. Ambartsumyan L. Megacystis-Microcolon-Intestinal Hypoperistalsis Syndrome Overview. 2019. In: Adam MP, Ardinger HH, Pagon RA, *et al.*, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021.
7. El-Chammas K, Sood MR. Chronic intestinal pseudo-obstruction. Clin Colon Rectal Surg. 2018; 31:99-107.
8. 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; 51:1565-1573.
9. Thorson W, Diaz-Horta O, Foster J 2nd, Spiliopoulos M, Quintero R, Farooq A, Blanton S, Tekin M. De novo ACTG2 mutations cause congenital distended bladder, microcolon, and intestinal hypoperistalsis. Hum Genet. 2014; 133:737-742.
10. Wangler MF, Gonzaga-Jauregui C, Gambin T, *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.
11. Klar J, Raykova D, Gustafson E, Tóthová I, Ameur A, Wanders A, Dahl N. Phenotypic expansion of visceral myopathy associated with ACTG2 tandem base substitution. Eur J Hum Genet. 2015; 23:1679-1683.
12. Tuzovic L, Tang S, Miller RS, *et al.* New insights into the genetics of fetal megacystis: ACTG2 mutations, encoding γ-2 smooth muscle actin in megacystis microcolon intestinal hypoperistalsis syndrome (Berdon Syndrome). Fetal Diagn Ther. 2015; 38:296-306.
13. Wangler MF, Beaudet AL. ACTG2-Related Disorders. 2015. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2020.
14. Halim D, Hofstra RM, Signorile L, *et al.* ACTG2 variants impair actin polymerization in sporadic megacystis microcolon intestinal hypoperistalsis syndrome. Hum Mol Genet. 2016; 25:571-583.
15. Lu W, Xiao Y, Huang J, Tao Y, Yan W, Lu L, Cao Y, Cai W. Mutation in actin γ-2 Responsible for Megacystis Microcolon Intestinal Hypoperistalsis Syndrome in 4 Chinese Patients. J Pediatr Gastroenterol Nutr. 2016; 63:624-626.
16. Matera I, Rusmini M, Guo Y, *et al.* Variants of the ACTG2 gene correlate with degree of severity and presence of megacystis in chronic intestinal pseudo-obstruction. Eur J Hum Genet. 2016; 24:1211-5.
17. Ravenscroft G, Pannell S, O'Grady G, *et al.* Variants in ACTG2 underlie a substantial number of Australasian patients with primary chronic intestinal pseudo-obstruction. Neurogastroenterol Motil. 2018; 30:e13371.
18. Whittington JR, Poole AT, Dutta EH, Munn MB. A Novel mutation in ACTG2 gene in mother with chronic intestinal pseudoobstruction and fetus with megacystis microcolon intestinal hypoperistalsis syndrome. Case Rep Genet. 2017; 2017:9146507.
19. Collins RRJ, Barth B, Megison S, Pfeifer CM, Rice LM, Harris S, Timmons CF, Rakheja D. ACTG2-associated visceral myopathy with chronic intestinal pseudoobstruction, intestinal malrotation, hypertrophic pyloric stenosis, choledochal cyst, and a novel missense mutation. Int J Surg Pathol. 2019; 27:77-83.
20. 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. 2017; 65:384-387.
21. 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. 2017; 37:1254-1256.
22. Korğalı EÜ, Yavuz A, Şimşek CEÇ, Güney C, Kurtulgan HK, Başer B, Atalar MH, Özer H, Eğilmez HR. Megacystis microcolon intestinal hypoperistalsis syndrome in which a different de novo Actg2 gene mutation was detected: A case report. Fetal Pediatr Pathol. 2018; 37:109-116.
23. Assia Batzir N, Kishor Bhagwat P, Larson A, *et al.* Recurrent arginine substitutions in the *ACTG2* gene are the primary driver of disease burden and severity in visceral myopathy. Hum Mutat. 2020; 41:641-654.
24. Moreno CA, Metze K, Lomazi EA, Bertola DR, Barbosa RH, Cosentino V, Sobreira N, Cavalcanti DP. Visceral myopathy: Clinical and molecular survey of a cohort of seven new patients and state of the art of overlapping phenotypes. Am J Med Genet A. 2016; 170:2965-2974.
25. Dong W, Baldwin C, Choi J, Milunsky JM, Zhang J, Bilguvar K, Lifton RP, Milunsky A. Identification of a dominant MYH11 causal variant in chronic intestinal pseudo-obstruction: Results of whole-exome sequencing. Clin Genet. 2019; 96:473-477.
26. Kloth K, Renner S, Burmester G, Steinemann D, Pabst B, Lorenz B, Simon R, Kolbe V, Hempel M, Rosenberger G. 16p13.11 microdeletion uncovers loss-of-function of a MYH11 missense variant in a patient with megacystis-microcolon- intestinal-hypoperistalsis syndrome. Clin Genet. 2019; 96:85-90.
27. Wang Q, Zhang J, Wang H, Feng Q, Luo F, Xie J. Compound heterozygous variants in MYH11 underlie autosomal recessive megacystis-microcolon-intestinal hypoperistalsis syndrome in a Chinese family. J Hum Genet. 2019; 64:1067-1073.
28. Gilbert MA, Schultz-Rogers L, Rajagopalan R, Grochowski CM, Wilkins BJ, Biswas S, Conlin LK, Fiorino KN, Dhamija R, Pack MA, Klee EW, Piccoli DA, Spinner NB. Protein-elongating mutations in MYH11 are implicated in a dominantly inherited smooth muscle dysmotility syndrome with severe esophageal, gastric, and intestinal disease. Hum Mutat. 2020; 41:973-982.
29. Halim D, Wilson MP, Oliver D, *et al.* 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. 2017; 114: E2739-E2747.
30. Halim D, Brosens E, Muller F, *et al.* Loss-of-Function Variants in MYLK Cause Recessive Megacystis Microcolon Intestinal Hypoperistalsis Syndrome. Am J Hum Genet. 2017; 101:123-129.
31. 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; 26:669-675.
32. Jenkins ZA, Macharg A, Chang CY, *et al.* Differential regulation of two FLNA transcripts explains some of the phenotypic heterogeneity in the loss-of-function filaminopathies. Hum Mutat. 2018; 39:103-113.
33. Iqbal NS, Jascur TA, Harrison SM, Edwards AB, Smith LT, Choi ES, Arevalo MK, Chen C, Zhang S, Kern AJ, Scheuerle AE, Sanchez EJ, Xing C, Baker LA. Prune belly syndrome in surviving males can be caused by Hemizygous missense mutations in the X-linked Filamin A gene. BMC Med Genet. 2020; 21:38.
34. Oda H, Sato T, Kunishima S, *et al.* Exon skipping causes atypical phenotypes associated with a loss-of-function mutation in FLNA by restoring its protein function. Eur J Hum Genet. 2016; 24:408-414.
35. Bonora E, Bianco F, Cordeddu L, *et al.* Mutations in RAD21 disrupt regulation of APOB in patients with chronic intestinal pseudo-obstruction. Gastroenterology. 2015; 148:771-782.e11.
36. Gamboa HE, Sood M. Pediatric intestinal pseudo-obstruction in the era of genetic sequencing. Curr Gastroenterol Rep. 2019; 21:70.
37. Gosemann JH, Puri P. Megacystis microcolon intestinal hypoperistalsis syndrome: systematic review of outcome. Pediatr Surg Int. 2011; 27:1041-1046.
38. 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; 50:2048-2050.
39. Guo DC, Pannu H, Tran-Fadulu V, *et al.* Mutations in smooth muscle α-actin (ACTA2) lead to thoracic aortic aneurysms and dissections. Nat Genet. 2007; 39:1488-1493.

Received May 25, 2022; Revised August 15, 2022; Accepted August 25, 2022.

Address correspondence to:
Alexandre Fabre, Pediatric Multidisciplinary Department, Timone Enfant Hospital, APHM, Aix-Marseille University, 264 Rue Saint Pierre 13005 Marseille, France.
E-mail: alexandre.fabre@ap-hm.fr

Released online in J-STAGE as advance publication August 29, 2022.