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Exploring Gastrointestinal Health in MECP2 Duplication Syndrome

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Abstract

Introduction: MECP2 Duplication Syndrome (MDS) is a rare neuro-genetic syndrome caused by duplications of *MECP2* at the Xq28 region. Although constipation and gastrointestinal reflux are reported in MDS, a comprehensive characterization of gastrointestinal health has not been fully explored.

Methods: We conducted a parent survey to explore the characteristics of gastrointestinal health in individuals with MDS using a secure online registry and compared differences in gastrointestinal symptoms between individuals with MDS and those with Rett syndrome (RTT).

Results: One hundred six surveys were analyzed. Symptoms commonly associated with constipation occurred in 72% to 89% of MDS individuals. Eleven percent of MDS individuals underwent surgery for complications associated with constipation. We observed a bimodal distribution for gastroesophageal reflux disease (GERD) and gastrostomy feeding, with higher prevalence in 0-3 and >12 year old MDS individuals. Constipation and GERD were significantly more common and gas bloating was significantly less common in MDS than in RTT. Biliary tract disease requiring surgery was an unrecognized problem in 5% of MDS individuals. We determined that gastrointestinal problems in MDS individuals contribute to caretaker burden.

Conclusion: Our study is the first in depth investigation that characterizes gastrointestinal health in MDS and enumerates differences in gastrointestinal symptoms between MDS and RTT.

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AUTHOR CONTRIBUTIONS

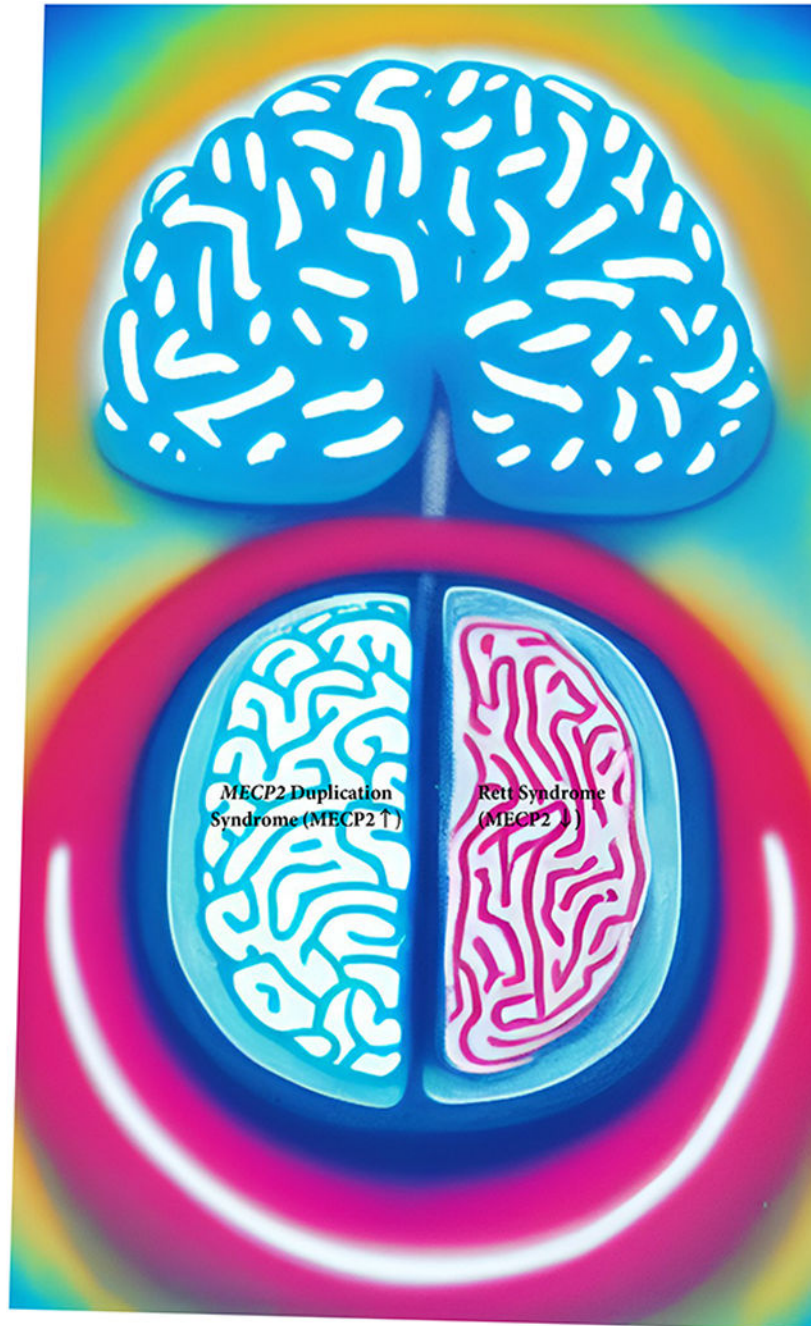
DP was responsible for study design; data acquisition, analysis, and interpretation; drafting, reviewing and approving the final version of the manuscript; and agreeing to be accountable for all aspects of the study. MA was responsible for data acquisition and interpretation. DGG and BS were responsible for study design, data interpretation, and reviewing and approving the final version of the manuscript. KJM was responsible for study design, data interpretation, reviewing and approving the final version of the manuscript, and agreeing to be accountable for all aspects of the study.

CONFLICT OF INTEREST

Authors declare no conflict of interest related to this work.

Strategies to reduce gastrointestinal symptoms will alleviate caregiver burden in MDS. Further studies are needed to examine the mechanisms that cause gastrointestinal problems in MDS.

Graphical Abstract



Keywords

biliary tract disease; chewing and swallowing difficulty; constipation; gastroesophageal reflux; parental burden

1 | INTRODUCTION

The *MECP2* gene (MIM #300005), a dose-sensitive gene located at the Xq28 locus, encodes methyl CpG-binding protein 2. The MECP2 protein binds to methylated DNA and up- or down-regulates transcription of thousands of genes. The MECP2 protein is required for maturation of neurons; deleterious variants in *MECP2* cause a neurodevelopmental disorder (NDD). How MECP2 alters gastrointestinal function is largely unknown. However, it is well known that MECP2 is highly expressed in the gastrointestinal tract, including the enteric nervous system.¹ Increased copies of *MECP2*, including duplications or triplications, are known to cause MECP2 Duplication Syndrome (MDS, MIM #300260). Although not well studied, the prevalence of MDS is reported to be 1 in 100,000 live male births in Australia.²

MDS is characterized by severe to profound developmental and intellectual delay, absent to poor speech, infantile hypotonia, autistic features, drug-resistant epilepsy, and recurrent infections.³⁻⁵ Although gastrointestinal problems such as feeding difficulty, gastroesophageal reflux disease (GERD), and constipation have been reported,⁶⁻¹⁰ the full scope of gastrointestinal health has not been investigated thoroughly in MDS individuals. We recently conducted a meaningfulness survey to investigate the symptoms most bothersome to MDS individuals for which caregivers sought treatment. In this survey, constipation ranked among the major concerns.⁵

MECP2 deletion and loss of function mutations, in contrast to *MECP2* duplication mutations, are known to cause Rett syndrome (RTT) (MIM 312750).¹¹ RTT is another neurodevelopmental disorder with multiple comorbidities, including chewing and swallowing difficulty, GERD, biliary tract disease, gas bloating, and constipation.¹²⁻¹⁵ RTT is approximately 10-fold more common than MDS.¹⁶ Consequently, gastrointestinal health has been better studied in RTT.^{12-15,17,18} Since RTT and MDS are neurodevelopmental disorders originating from alterations of the same gene, we hypothesized that gastrointestinal problems will be equally as common in MDS as in RTT. Although they share several diagnostic features, we anticipated that the age of presentation and severity differ between MDS and RTT.

In this study, we explored in depth gastrointestinal symptoms in MDS individuals and investigated the role of age on their presentation. We examined the extent of caregiver burden caused by gastrointestinal problems in MDS individuals. We compared differences in gastrointestinal health between MDS and RTT.

2 | MATERIAL and METHODS

2.1 | Survey and Study Population

The survey questionnaire was developed by the senior author (K.J.M.) based on her 20-plus year experience in MECP2-related disorders and validated in individuals with RTT.¹⁹ The questionnaire consisted of 55 items divided into four categories. These categories included: 1) gastrointestinal problems related to general health and pain (5 questions), eating, chewing, and swallowing (9 questions), gastroesophageal reflux (3 questions), gas and bloating (5 questions), and diarrhea and constipation (6 questions); 2) personality and mood

(5 questions), 3) medications (9 questions) and surgical interventions (5 questions); and 4) parental concerns (8 questions). Symptoms were queried for two weeks prior to survey participation. The duration of time to complete the survey was ~20 minutes. Caregivers were required to answer all questions. Only one caregiver per MDS individual was allowed to complete the survey.

The survey population consisted of parents or caregivers of all individuals with MDS. Participants were from all around the world but the majority were from North America, Europe and Australia. The survey language was English. The parents or caregivers of individuals with RTT participated in the initial survey validation studies and were recruited during their local clinic visit or at the time of local and national family support events. The characteristics of the RTT population are detailed in our published study.¹⁹

2.2 | MDS Registry and Survey Distribution

We developed an online Health Insurance Portability and Accountability Act (HIPAA)-compliant registry portal (<https://mds.nrihub.org>) to conduct cross-sectional studies in a secure fashion. We hosted the survey at the registry portal between Dec 9, 2021, and January 20, 2022. We invited caregivers of all MDS individuals to participate in the survey via their email address in the registry. We required caregivers to upload the genetic report confirming the molecular diagnosis of MDS to participate in this study. We advertised the survey through the social media accounts of the family-based organizations.

The Institutional Review Board at Baylor College of Medicine (BCM) approved the study under protocol number H-46176. Caregivers provided written consent for portal registration, participation in survey studies, and publication of results.

2.3 | Statistical Approach

Parents or caregivers responded to each survey question using a 5-point Likert scale with values ranging from 0-4 for ratings of ascending severity and categorized as never, almost never, sometimes, often, or almost always. The data obtained from the registry were stored in BCM and Texas Children's Hospital password-protected, secure computers. The IBM SPSS Statistics for Macintosh program, Version 28.0 (Armonk, NY: IBM Corp), was used for statistical analyses. Percentage frequency means, standard deviations, medians, and upper and lower limit values were calculated for individual questions with a confidence interval of 95%. Kruskal-Wallis tests were used to detect differences in the mean scores of each survey item and age group between MDS and RTT groups. Chi-Square tests were used to find differences between the categorical variables. The Bonferroni method was used to detect the difference between the age groups. P -value <0.05 was considered to be statistically significant.

3 | RESULTS

3.1 | Study population

One hundred twenty-two caregivers completed the survey. One hundred six surveys were eligible for analysis. Sixteen surveys were excluded because the MDS individuals were

females (females do not show the classic clinical features of MDS) or parents did not provide the genetic report for their child (Figure 1). The majority of MDS individuals (n=102) were male. Four female MDS individuals were included because their genetic mutation resulted from translocation to an autosomal chromosome, thereby presenting as classic MDS. The median age of the MDS individuals was 6.6 years with a range of 0.9 to 36.6 years. Eighty-eight (83.0%) caregivers who completed the survey were mothers and 18 were fathers.

3.2 | Descriptive Findings in MDS

All gastrointestinal descriptive findings from the survey are documented in Table 1.

Constipation/Diarrhea—Difficulty pushing out stool was present sometimes in 30 (28.3%), often in 30 (28.3%), and almost always in 34 (32.0%) individuals, or 88.6% of all MDS individuals. Big stool was present sometimes in 41 (38.6%), often in 32 (30.1%), and almost always in 17 (16.0%) individuals, or 84.7% of all MDS individuals. Hard stool was observed sometimes in 41 (38.6%), often in 20 (18.9%), and almost always in 16 (15.1%) individuals, or 72.6% of all MDS individuals. Eighty-five (80.2%) individuals sometimes, often, or almost always received laxatives to increase the frequency of stooling. Three (2.8%) individuals underwent a cecostomy or ileostomy due to severe constipation and nine (8.5%) individuals required surgery for volvulus of the bowels or stomach.

Eating, Chewing, and Swallowing Function—Chewing difficulty was present almost always in 38 (35.9%), often in 14 (13.2%), and sometimes in 23 (21.7%) individuals, or 70.8% of all MDS individuals. Drooling was observed almost always in 42 (39.6%), often in 17 (16.0%), and sometimes in 22 (20.8%) individuals, or 76.4% of all MDS individuals. The duration of eating extending longer than 30 minutes to finish a meal occurred almost always in 32 (30.2%), often in 12 (11.3%), and sometimes in 19 (17.9%) individuals, or 59.4% of all MDS individuals. Gastrostomy feeding was required almost always or often in 30 (28.3%) MDS individuals.

Gastroesophageal Reflux, Biliary Tract Disease, Gas and Bloating—Regurgitation of fluid or food was observed never or almost never in 52 (49.1%), sometimes in 27 (25.5%), often in 17 (16.0%), and almost always in 10 (9.4%) MDS individuals. While 74 (69.8%) MDS individuals never or almost never received medications to reduce gastric acid production, 30 (28.3%) MDS individuals often or almost always received these medications. Eighteen (17.0%) individuals underwent a fundoplication. Five (4.7%) individuals had a cholecystectomy for biliary tract disease.

Ninety (84.9%) MDS individuals sometimes, almost never, or never had burping or belching. Ninety-six (90.5%) MDS individuals never or almost never received medications to reduce gas.

General Health and Pain—The majority of parents never or almost never reported problems of breath holding (84.9%), air swallowing (72.7%), or difficulty gaining weight (67.0%) in their MDS children. Parents reported that 82.1% of their MDS children were never, almost never, or sometimes irritable.

Parental Burden—Parents reported that they almost always (31.1%), often (31.1%), or sometimes (22.6%) worried about their child’s stomach or intestinal problems worsening. Parents reported that they almost always (38.7%), often (19.8%), or sometimes (24.5%) were constantly vigilant due to their child’s stomach or intestinal problems.

3.3 | The effect of age on gastrointestinal problems

Constipation, characterized as having difficulty pushing out stool, having hard and large stool, and requiring laxatives for bowel movements, was common across all ages and did not differ among age groups (Figure 2A). MDS individuals tended to choke or gag while eating food or drinking liquids more frequently throughout childhood and adolescence, but these symptoms occurred less frequently after age 18 years (Figure 2B). Drooling was common across all ages and did not differ significantly among the age groups (Figure 2B). Formula feeding by mouth or via gastrostomy as the main source of nutrition was more frequent in the 0-3 and >12 year age groups (Figure 2C). Gastroesophageal reflux tended to be more common in early childhood (0-3 years old), improved between 6-12 years of age, and increased as individuals became older (>12 years). (Figure 2C). The frequency of surgical gastrostomy placement and fundoplication increased with age ($p=0.028$) (Figure 2D). The difference was found significant between all age groups compared to 12-15 and >18 years age groups.

The frequency of the fundoplication procedure was greater above the age of 18 years compared with younger ages ($p=0.003$). Nine (8.5%) individuals required surgery for volvulus of the bowels or stomach. Older MDS individuals (18 years and above) were more likely to develop a volvulus ($p=0.019$).

3.4 | Comparison between MDS and RTT

Dysautonomia features, including breath holding, air swallowing, and abdominal fullness, were significantly more common in RTT than in MDS (Table 2). Two features of constipation, difficulty pushing out stools and the use of laxatives to have a bowel movement, were significantly more common in MDS than in RTT individuals. RTT individuals refused to eat by mouth significantly more often than MDS individuals did. In contrast, RTT individuals were significantly less likely to have difficulty chewing than MDS individuals (Table 2). While 48.5% of RTT individuals often or almost always drank formula or received formula through a gastrostomy, this eating pattern was observed in significantly fewer (28.3%) MDS individuals. Regurgitation of fluid or food was significantly more common in MDS than in RTT individuals (Table 2).

Parents of MDS individuals reported frustration, vigilance, inability to relax, worry, and having life revolve around their child’s gastrointestinal problems significantly more frequently than parents of RTT individuals (Table 2).

4 | DISCUSSION

Gastrointestinal problems are reported frequently in MDS,^{7,8,20} but the full scope of gastrointestinal health in these individuals has not been investigated thoroughly. In the present study, we identified a high prevalence of constipation, gastroesophageal reflux,

and chewing and swallowing difficulty in MDS and found that these symptoms caused pronounced caregiver burden. While the prevalence of constipation was similar across all age groups, gastroesophageal reflux and gastrostomy feedings showed a bimodal occurrence in early life and adolescence. Biliary tract disease was rare and unrecognized in MDS. Lastly, the pattern of gastrointestinal symptoms differed between MDS and RTT individuals.

4.1 | Constipation is highly prevalent and severe in MDS

Constipation is common in autism^{21,22} and other neurodevelopmental disorders²³⁻²⁵ including RTT.¹⁵ The frequency of constipation previously reported for MDS ranged from 32% to 81%.^{2,7,8,10,26} In the present study, at least three-fourths of MDS individuals had difficulty pushing out stool and passed large, hard stool and 80% of MDS individuals required laxatives to have a bowel movement. The severity of constipation was illustrated further by nearly 3% of individuals who required a cecostomy or ileostomy for severe constipation and nearly 10% of individuals who underwent surgery for bowel obstruction. All three aspects of constipation were highly common and did not differ across age groups. MDS individuals were two-fold more likely to have constipation than RTT individuals based on symptoms and laxative use.

The mechanism of constipation in MDS is unknown. Several studies in RTT,^{7,72} as well as other neurodevelopmental disorders,²⁷ showed dysbiosis of the gut microbiota which may lead to an altered gut metabolome and possible neurotransmitter dysfunction. Intrinsic changes in the enteric or autonomic nervous system also may explain gastrointestinal dysfunction.^{28,29} In addition, decreased mobility in neurodevelopmental disorders may aggravate slower gastrointestinal motility.^{29,30}

4.2 | Eating/chewing/swallowing dysfunction are common in MDS

Eating, chewing, and swallowing dysfunction is common in acquired neurological disorders (e.g. cerebral palsy, stroke, traumatic brain injury) and neurogenetic syndromes (e.g. RTT, Down syndrome).^{31,32} In the present study, chewing difficulty was reported frequently in nearly one-half of the cohort, resulting in the duration of mealtime extending longer than 30 minutes in 41% of MDS individuals. Swallowing dysfunction was present in almost two-thirds of MDS individuals when drinking liquids or eating solids. Consequently, 30% of MDS individuals required gastrostomy placement and more than one-third drank or received formula through a gastrostomy as their main source of nutrition.

Chewing difficulty was less likely to be a problem in RTT compared with MDS due to the increased frequency of feeding refusal in RTT individuals and more severe hypotonia in early life in MDS individuals. Choking or gagging when drinking and eating was common and relatively stable in the first 12 years of life, but worsened until 18 years of age in MDS individuals. One plausible explanation is the neuromotor regression due to worsening of epilepsy after the first decade of life.^{33,34} Gastrostomy feedings in MDS showed an age-related bimodal distribution. The increased frequency of gastrostomy feeding is likely due to congenital hypotonia in early life, one of the defining features of MDS, and known to cause chewing-swallowing dysfunction, and to neuromotor regression associated with poorly controlled epilepsy after age 12 years. The relative stability in gagging and choking

after age 18 years may be related to increased gastrostomy feeding and decreased oral food consumption.

4.3 | GERD is relatively uncommon and showed a bimodal distribution in MDS

The prevalence of gastroesophageal reflux in MDS is reported to be 44% to 66% in cohort studies.^{7,8,20} In the present study, nearly one-half of the participants reported frequent regurgitation. Only 16% required a fundoplication. Gastroesophageal reflux was two-fold more common in MDS than in RTT and peaked in the first 3 years of life and between ages 12-18 years. Gastroesophageal reflux showed a bimodal decline in early childhood, likely secondary to improvement in the tone, and adolescence, which is possibly secondary to the fundoplication procedure.

4.4 | Dysautonomia is an occasional and less severe problem in MDS

Individuals with RTT are known to have severe dysautonomia, resulting in cold hands and feet, drooling, prolonged cardiac QTc intervals, gastroparesis, and breath holding and hyperventilation spells.^{35,36} Gastroparesis and breath-holding spells may be associated with severe gas bloating in RTT.^{35,37} In contrast, about one-third of MDS individuals reported having too much gas or a lot of noise in the tummy and strong burping or belching. One-half of RTT individuals reported frequent breath holding due to gastrointestinal problems compared with 6% of MDS individuals. On the other hand, drooling is a common and life-long problem in individuals with MDS. Although drooling may be related to dysautonomia, low oral muscle tone also causes drooling in MDS.

4.5 | Biliary tract disease is an unexpected feature of MDS

Frelinger³⁸ reported the prevalence of cholelithiasis and cholecystectomy as 2.3% and 1.8%, respectively, whereas Motil et al.¹³ reported the prevalence of biliary tract disease as 4% in RTT. In the present study, cholecystectomy was performed for biliary tract disease in nearly 5% of MDS individuals, a value higher than expected based on our clinical experience.

4.6 | Parental burden secondary to gastrointestinal health is increased in MDS

We previously studied the most meaningful symptoms in MDS for which caregivers routinely sought treatment.⁴ Constipation ranked among the top six symptoms.⁵ Similar to our meaningfulness study, gastrointestinal problems caused significant parental burden in the present study. Approximately two-thirds of parents reported that they are constantly vigilant and worry that their child's gastrointestinal problems will get worse. More than one-half of them make extensive preparations for their child before leaving the house because of gastrointestinal problems. MDS parents report a higher burden related to gastrointestinal problems compared with RTT parents.

Potential limitations of this study include those of social bias whereby parents report what they think physicians want to know and acquiescence bias whereby parents tend to agree with positive responses regardless of their options. The cross-sectional basis of this study, rather than being a longitudinal assessment, also may not be representative of the full scope of symptom prevalence and severity. In addition, the majority of our participants were from USA and Europe. Consequently, food culture and socioeconomic status of these countries

may affect the results and interpretation of some survey items related to feeding. Lastly, the present study was conducted during the COVID pandemic, which may have affected parental burden responses.

4.7 | Conclusion

This study represents the first comprehensive parental survey to investigate in depth gastrointestinal health in MDS. Constipation was more common and severe in MDS than in other neurodevelopmental disorders and potentially one of the main contributors to parental burden. Gastroesophageal reflux and gastrostomy feeding showed a bimodal distribution, presumably due to neonatal hypotonia and neuromotor regression associated with poorly controlled epilepsy in adolescence. Biliary tract disease was an unexpected feature of MDS. Treatment strategies that address these clinical problems will improve the health and quality of life in MDS individuals and decrease caregiver burden.

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KEY POINTS

- A comprehensive characterization of gastrointestinal health in the MECP2 Duplication Syndrome (MDS), a rare neuro-genetic syndrome caused by duplications of the *MECP2* gene, has not been fully explored.
- Using a computer-based registry, parents reported that constipation was a common and severe feature of MDS and potentially one of the main contributors to parental burden, whereas biliary tract disease was an unexpected finding in MDS.
- Treatment strategies that address gastrointestinal dysfunction in the MECP2 Duplication syndrome will decrease caregiver burden and improve the health and quality of life of individuals affected with this disorder.

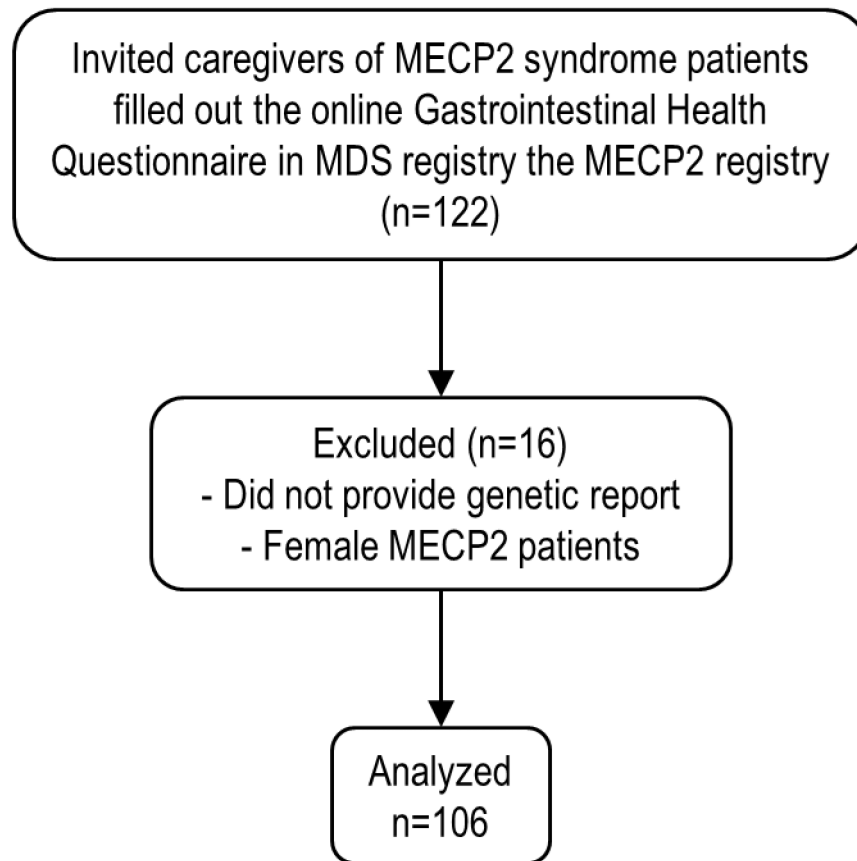


Figure 1.
Eligibility of participants for study

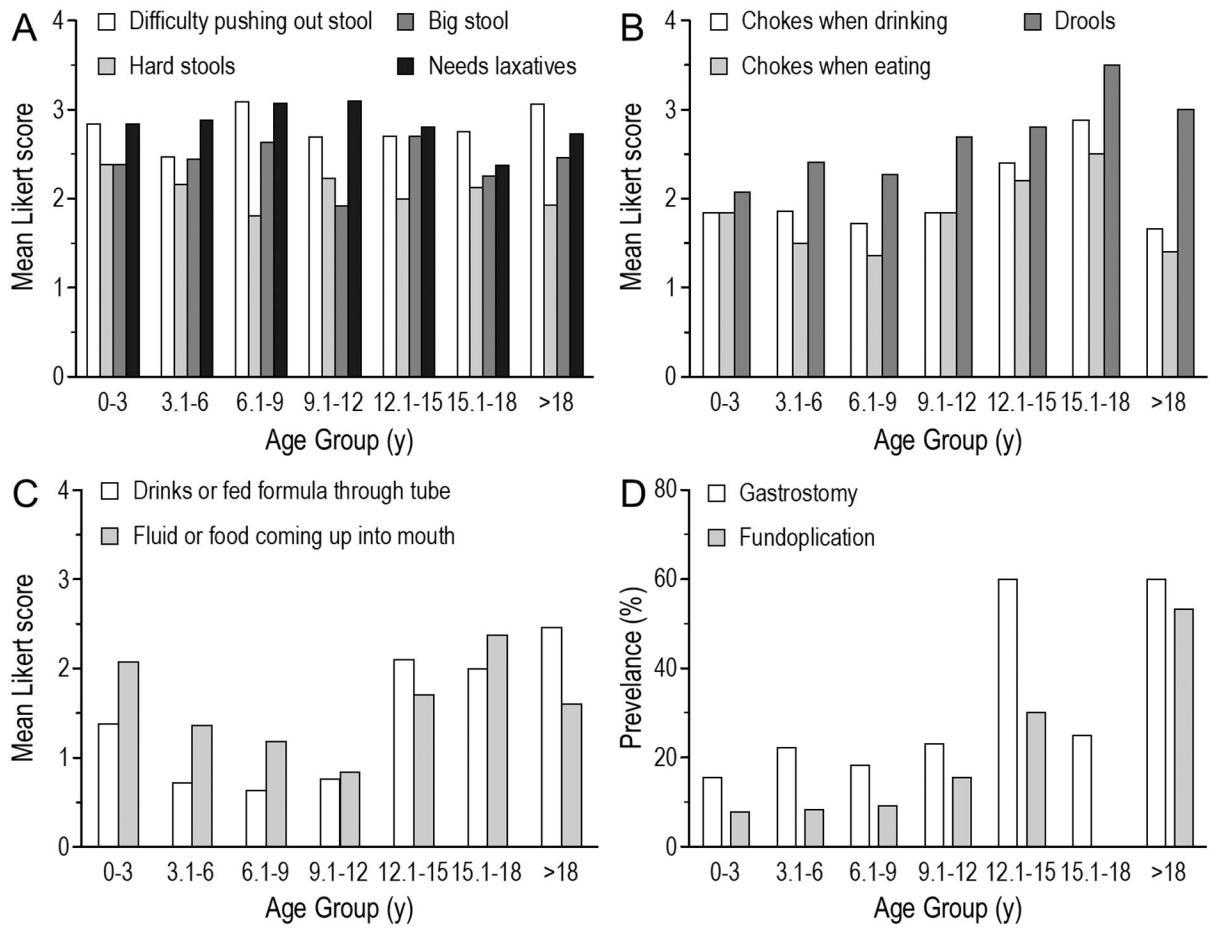


Figure 2. Prevalence of gastrointestinal symptoms and surgical interventions, reported as Likert scores in ascending frequency, in individuals with MECP2 duplication syndrome

Table 1.

Frequency of Gastrointestinal Symptoms, Medications, Surgical Procedures and Parental Concerns in Individuals with MECP₂ Duplication Syndrome

Items	Never (n, %)	Almost Never (n, %)	Sometimes (n, %)	Often (n, %)	Almost Always (n, %)
Diarrhea and Constipation					
Has bowel movements more than 3 times daily	42 (39.6)	30 (28.3)	23 (21.7)	6 (5.7)	5 (4.7)
Has watery or loose stools	29 (27.4)	33 (31.3)	23 (21.7)	14 (13.2)	7 (6.6)
Has difficulty pushing out stools	8 (7.6)	4 (3.8)	30 (28.3)	30 (28.3)	34 (32.1)
Has hard stools	11 (10.4)	18 (17.0)	41 (38.7)	20 (18.9)	16 (15.1)
Has big stools	7 (6.6)	9 (8.5)	41 (38.7)	32 (30.2)	17 (16.0)
Needs laxatives to have a bowel movement	12 (11.3)	9 (8.5)	19 (17.9)	9 (8.5)	57 (53.8)
Medication					
Has trouble taking medications prescribed for stomach or intestinal problems	70 (66.0)	17 (16.0)	9 (8.5)	4 (3.8)	6 (5.7)
Receives medication to block stomach acid (ranitidine (Zantac), lansoprazole (Prevacid), omeprazole (Prilosec), esomeprazole (Nexium))	70 (66.0)	4 (3.8)	2 (1.9)	2 (1.9)	28 (26.4)
Receives medication to help the stomach and intestinal tract move (bethanechol (Urecholine), erythromycin (Eryped), metoclopramide (Reglan))	79 (74.5)	7 (6.6)	3 (2.8)	1 (0.9)	16 (15.1)
Receives medication to reduce stomach or intestinal pain (dicyclomine (Bentyl), hyoscyamine (Levsin))	98 (92.4)	5 (4.7)	1 (0.9)	N/A	2 (1.9)
Receives medication to reduce gas (simethicone (Gas-X))	87 (82.1)	9 (8.5)	2 (1.9)	2 (1.9)	6 (5.7)
Receives medication to reduce bad bacteria in the intestines (metronidazole (Flagyl))	94 (88.7)	5 (4.7)	3 (2.8)	1 (0.9)	3 (2.8)
Receives medication to increase good bacteria in the intestines (probiotics)	57 (53.8)	6 (5.7)	9 (8.5)	11 (10.4)	23 (21.7)
Receives medication to increase the frequency of stooling (polyethylene glycol, lactulose, mineral oil, milk of magnesia, sennosides)	30 (28.3)	9 (8.5)	13 (12.3)	7 (6.6)	47 (44.3)
Receives medication to reduce the frequency of stooling (such as loperamide (Imodium))	95 (89.6)	4 (3.8)	2 (1.9)	2 (1.9)	3 (2.8)
Surgery					
Does your child have a gastrostomy button?	No n (%)	Yes n (%)			
Does your child have a fundoplication?	74 (69.8)	32 (30.2)			
Has your child had her/his gall bladder removed (cholecystectomy)?	88 (83.0)	18 (17.0)			
Has your child had surgery for twisting (volvulus) or blockage (obstruction) of the bowels or stomach?	101 (95.3)	5 (4.7)			
Does your child have an ileostomy or cecal button for constipation?	97 (91.5)	9 (8.5)			
	103 (97.2)	3 (2.8)			

Eating, Chewing & Swallowing							
Has refused to eat or does not eat by mouth	48 (45.3)	19 (17.9)	17 (16.0)	4 (3.8)	18 (17.0)		
Has trouble chewing food	12 (11.3)	19 (17.9)	23 (21.7)	14 (13.2)	38 (35.9)		
Takes longer than 30 minutes to eat a meal or get tube feedings	29 (27.4)	14 (13.2)	19 (17.9)	12 (11.3)	32 (30.2)		
Drools a lot	13 (12.3)	12 (11.3)	22 (20.8)	17 (16.0)	42 (39.6)		
Chokes or gags when drinking liquids	21 (19.8)	24 (22.6)	26 (24.5)	10 (9.4)	25 (23.6)		
Chokes or gags when eating food	25 (23.6)	23 (21.7)	31 (29.3)	13 (12.3)	14 (13.2)		
Drinks formula or is fed through a tube as the main source of nutrition	66 (62.3)	3 (2.8)	7 (6.6)	2 (1.9)	28 (26.4)		
Eats foods that are finely chopped or blenderized	32 (30.2)	9 (8.5)	17 (16.0)	14 (13.2)	34 (32.1)		
Eats foods primarily for oral stimulation or pleasure	48 (45.3)	8 (7.6)	28 (26.4)	7 (6.6)	15 (14.2)		
Gastroesophageal Reflux							
Has fluid or food coming up into her/his mouth	37 (34.9)	15 (14.2)	27 (25.5)	17 (16.0)	10 (9.4)		
Has vomiting during or after eating	49 (46.2)	33 (31.1)	15 (14.2)	3 (2.8)	6 (5.7)		
Wakes up at night with irritability	36 (34.0)	27 (25.5)	29 (27.4)	5 (4.7)	9 (8.5)		
Gas and Bloating							
Has strong burping or belching	29 (27.4)	30 (28.3)	31 (29.25)	9 (8.49)	7 (6.6)		
Has fullness (too much gas) in the tummy	19 (17.9)	18 (16.9)	36 (34.0)	25 (23.6)	8 (7.6)		
Stomach gets big and hard	23 (21.7)	24 (22.6)	34 (32.1)	13 (12.3)	12 (11.3)		
Has lots of noise in her/his tummy	24 (22.6)	32 (30.2)	29 (27.4)	14 (13.2)	7 (6.6)		
Passes a lot of gas from her/his bottom	15 (14.2)	19 (17.9)	40 (37.7)	19 (17.9)	13 (12.3)		
General Health/Pain							
Has been unwell because of stomach or intestinal problems	24 (22.6)	30 (28.3)	34 (32.1)	11 (10.4)	7 (6.6)		
Is irritable because of stomach or intestinal problems	33 (31.1)	18 (17.0)	36 (34.0)	15 (14.2)	4 (3.8)		
Has difficulty gaining weight because of stomach or intestinal problems	41 (38.7)	30 (28.3)	18 (17.0)	11 (10.4)	6 (5.7)		
Has more frequent breath holding because of stomach or intestinal problems	57 (53.8)	33 (31.1)	9 (8.5)	6 (5.7)	1 (0.9)		
Has more frequent air swallowing because of stomach or intestinal problems	39 (36.8)	38 (35.9)	17 (16.0)	8 (7.6)	4 (3.8)		
Parenting							
You are frustrated because of your child's stomach or intestinal problems	11 (10.4)	17 (16.0)	50 (47.2)	13 (12.3)	15 (14.2)		
You worry that your child's stomach or intestinal problems will get worse	7 (6.6)	10 (9.4)	24 (22.6)	33 (31.1)	32 (31.1)		
You feel that your life revolves around your child's stomach or intestinal problems	19 (17.9)	25 (23.6)	30 (28.3)	17 (16.0)	15 (14.2)		

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You are constantly vigilant about your child's stomach or intestinal problems	8 (7.6)	10 (9.4)	26 (24.5)	21 (19.8)	41 (38.7)
You have concerns about arranging suitable care (e.g. babysitting, respite) because of your child's stomach or intestinal problems	30 (28.3)	21 (19.8)	14 (13.2)	16 (15.1)	25 (23.6)
You are not able to relax at home because you need to attend to your child's stomach or intestinal problems	30 (28.3)	25 (23.6)	29 (27.4)	4 (3.8)	18 (17.0)
You have to make extensive preparations for your child before leaving the house because of stomach or intestinal problems	27 (25.5)	22 (20.8)	23 (21.7)	12 (11.3)	22 (20.8)
You worry about your child's future because of your child's stomach or intestinal problems	15 (14.2)	9 (8.5)	29 (27.4)	17 (16.0)	36 (34.0)

Table 2. Comparison of Gastrointestinal Symptoms between MECP2 Duplication Syndrome (MDS) and Rett Syndrome (RTT)

Items	Never (n, %)	Almost Never (n, %)	Sometimes (n, %)	Often (n, %)	Almost Always (n, %)	P-Value*	
Has more frequent breath holding because of stomach or intestinal problems	MDS	57 (53.8)	33 (31.1)	9 (8.5)	6 (5.7)	1 (0.9)	<0.001
	RTT	40 (33.6)	25 (21.0)	27 (22.7)	19 (16.0)	9 (33.6)	
Has more frequent air swallowing because of stomach or intestinal problems	MDS	39 (36.8)	38 (35.8)	17 (16.0)	8 (7.5)	4 (3.5)	<0.001
	RTT	42 (35.3)	25 (21.0)	21 (17.6)	14 (11.8)	17 (14.3)	
Has refused to eat or does not eat by mouth	MDS	48 (45.3)	19 (17.9)	17 (16.0)	4 (3.8)	18 (17.0)	<0.001
	RTT	36 (30.0)	16 (13.3)	39 (32.5)	10 (8.3)	19 (15.8)	
Has trouble chewing food	MDS	12 (11.3)	19 (17.9)	23 (21.7)	14 (13.2)	38 (35.8)	=0.014
	RTT	36 (30.0)	13 (10.8)	21 (17.5)	15 (12.5)	35 (29.2)	
Drinks formula or is fed through a tube as the main source of nutrition	MDS	66 (62.3)	3 (2.8)	7 (6.6)	2 (1.9)	28 (26.4)	=0.021
	RTT	55 (45.8)	3 (2.5)	4 (3.3)	10 (8.5)	48 (40.0)	
Has fluid or food coming up into her/his mouth	MDS	37 (34.9)	15 (14.2)	27 (25.5)	17 (16.0)	10 (9.4)	=0.004
	RTT	62 (51.7)	27 (22.5)	18 (15.0)	8 (6.7)	5 (4.2)	
Has fullness (too much gas) in the tummy	MDS	19 (17.9)	18 (17.0)	36 (34.0)	25 (23.6)	8 (7.5)	=0.023
	RTT	26 (21.7)	27 (22.5)	24 (20.0)	21 (17.5)	22 (18.3)	
Has difficulty pushing out stools	MDS	8 (7.5)	4 (3.8)	30 (28.3)	30 (28.3)	34 (32.1)	<0.001
	RTT	11 (9.2)	17 (14.2)	50 (41.7)	24 (20.0)	18 (15.0)	
Needs laxatives to have a bowel movement	MDS	12 (11.3)	9 (8.5)	19 (17.9)	9 (8.5)	57 (53.8)	<0.001
	RTT	44 (37.0)	22 (18.5)	21 (17.6)	10 (8.4)	22 (18.5)	
You are frustrated because of your child's stomach or intestinal problems	MDS	11 (10.4)	17 (16.0)	50 (47.2)	13 (12.3)	15 (14.2)	<0.001
	RTT	40 (33.3)	13 (10.8)	32 (26.7)	18 (15.0)	17 (14.2)	
You feel that your life revolves around your child's stomach or intestinal problems	MDS	19 (17.9)	25 (23.6)	30 (28.3)	17 (16.0)	15 (14.2)	<0.002
	RTT	47 (39.2)	28 (23.3)	15 (12.5)	18 (15.0)	12 (10.0)	
You are constantly vigilant about your child's stomach or intestinal problems	MDS	8 (7.5)	10 (9.4)	26 (24.5)	21 (19.8)	41 (38.7)	<0.001
	RTT	34 (28.3)	25 (20.8)	14 (11.7)	18 (15.0)	29 (24.2)	
You are not able to relax at home because you need to attend to your child's stomach or intestinal problems	MDS	30 (28.3)	25 (23.6)	29 (27.4)	4 (3.8)	18 (17.0)	<0.003

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Items	Never (n, %)	Almost Never (n, %)	Sometimes (n, %)	Often (n, %)	Almost Always (n, %)	P-Value*
You worry about your child's future because of your child's stomach or intestinal problems	RTT	50 (41.7)	14 (11.7)	31 (25.8)	15 (12.5)	10 (8.3)
	MDS	15 (14.2)	9 (8.5)	29 (27.4)	17 (16.0)	36 (34.0)
	RTT	52 (43.0)	13 (10.8)	28 (23.3)	9 (7.5)	18 (15.0)
						< 0.001

* P-value determined by Chi-squared tests