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Gastrointestinal Dysfunction in Genetically Defined Neurodevelopmental Disorders

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Abstract

Gastrointestinal symptoms are common in most forms of neurodevelopment disorders (NDDs) such as in autism spectrum disorders (ASD). The current patient-reported outcome measures with validated questionnaires used in the general population of children without NDDS cannot be used in the autistic individuals. We explore here the multifactorial pathophysiology of ASD and the role of genetics and the environment in this disease spectrum and focus instead on possible diagnostics that could provide future objective insight into the connection of the gut-brain-microbiome in this disease entity. We provide our own data from both humans and a zebrafish model of ASD called Phelan-McDermid Syndrome. We hope that this review highlights the gaps in our current knowledge on many of these profound NDDs and that it provides a future framework upon which clinicians and researchers can build and network with other interested multidisciplinary specialties.

Keywords

gastrointestinal; autism spectrum disorders; neurodevelopmental disorders; abdominal pain; constipation; transit testing

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Introduction to Autism and Gastrointestinal Symptoms

Autism spectrum disorder (ASD) is a condition defined by impairments or difficulties with social communication and interaction in association with restricted and repetitive behaviors or interests, beginning in infancy or early childhood, and resulting from alterations in developmental processes.[1] The diagnostic criteria for ASD have evolved over time, increasingly reflecting the phenotypic heterogeneity of the condition.[2] The prevalence of ASD diagnoses has been increasing globally, with recent estimates suggesting a median prevalence of around 100/10,000 with a male-to-female ratio of 4.2.[3,4] The potential reasons for this increase in diagnosis are unclear and may not necessarily be due to an increase in incidence; however, it has been difficult to quantify how much various factors contribute to this increase.[5] Changes in diagnostic practices, coding tendencies, and community awareness[6] have all contributed to the increase in diagnosis of ASD, but a true increase (i.e., one due to changes in etiologic factors) cannot be ruled out.[5] Although the exact etiology of ASD is unclear, research points to a multifactorial model of interacting genetic and environmental factors, leading to developmental aberrations that impact neurological function and behavior throughout the lifespan.[7,8] An ever-growing body of research into the genetics of ASD has described, to date, more than 100 associated genes that play critical roles in gene expression and neuronal communication in the developing brain from embryologic life to early childhood.[9]

Co-occurring mental, behavioral, and physical conditions, sometimes referred to as comorbidities, are extremely common among autistic individuals. These include anxiety disorders, sleep disorders, seizures or epilepsy, and gastrointestinal (GI) conditions.[2] According to a meta-analysis of autism studies between 1980 and 2016, the prevalence range for GI symptoms was 4.2 to 96.8% (median: 46.8%).[10] The notably wide range of this data is a concern, and the challenges that result in this variability will be expanded upon below. More recently, a 2022 meta-analysis similarly estimated that about half of autistic individuals report GI symptoms, again with high heterogeneity (I^2 = 99.5%).[11]

The most common GI issues in autistic individuals are thought to be chronic constipation, abdominal pain, and encopresis, which is a consequence of the constipation.[12] GI symptoms are often associated with feeding issues (e.g., strong dietary aversions, food sensitivities, and food allergies), toileting problems, and internalizing and externalizing behaviors (e.g., aggression, irritability, self-injurious behaviors, anxiety, and mood problems).[13-23]

The various GI symptoms (►Table 1; genetic neurodevelopmental disorders [NDDs]) can be incredibly disabling, leading to reduced well-being and quality of life for autistic individuals, as well as their family.[24,25] As this burden is present across the lifespan, GI comorbidities also may contribute to an increased risk of mortality in individuals with ASD.[26,27]

Challenges with Existing GI Questionnaires

The absence of cohesive data on GI symptomology in ASD is partially due to the difficulty in obtaining informative data directly from the autistic individual. Autistic individuals—in

particular those who have intellectual disability (ID), interoception difficulties, or significant language impairments—may have difficulty self-reporting or describing GI symptoms, such as abdominal pain, to their caregivers. Even autistic individuals with fluent speech may have trouble communicating GI distress to their parent.[12,25] Therefore, parents of autistic children and dependent adults often rely on nonverbal behaviors (e.g., sleep difficulties, irritability, aggression) and bodily signs (e.g., abdominal swelling, gas, diarrhea) to recognize when their child is experiencing GI symptoms.[12,25,28]

Advances in the creation of appropriate questionnaires for capturing the varied GI symptoms in ASD have been made, including a 2019 psychometric investigation of the Autism Speaks Autism Treatment Network GI Signs and Symptoms Inventory-17.[28] Typically, questionnaires used in developing children do not usually contain a sufficient range of nonverbal expressions (such as facial grimacing, unusual posturing, and self-injurious behavior) that can be used to capture GI symptoms in many autistic children.[10,12,28] However, this specific GI symptom-focused questionnaire included GI-motoric items, which is particularly helpful in identifying GI distress in a non- or minimally verbal child on the autism spectrum. In addition, Holingue et al developed and assessed the psychometric properties of the ASD Gastrointestinal and Related Behaviors Inventory (ASD-GIRBI), a 36-item measure, which draws items from two existing tools, the Autism Treatment Network Gastrointestinal Inventory and the Brief Autism Mealtime Behavior Inventory (ASD-GIRBI) and also includes de novo items.[24,29] The reason for combining these tools was to leverage the use of GI-motoric and other nonverbal behaviors from the existing ATN GI Inventory and also to complement them with items related to eating times and behaviors, which were missing from the GI Inventory but were central to the Brief Autism Mealtime Behavior Inventory. Additionally to improve the content validity, new items, such as questions about flatulence, alternating constipation and diarrhea, and unexplained irritability, were added to the ASD-GIRBI based on a review of literature, qualitative interviews with parents of autistic children, and the expertise of the research team (for details, see Holingue et al[24]). Most recently, the ASD-GIRBI has been piloted among autistic children 3 to 17 years old[24] and the next steps of this work include developing self-report and caregiver-report versions of both pediatric and adult tools, to accommodate individuals across the autism spectrum with a focus on clinical validation to ensure the measure is appropriately capturing GI conditions.

However, an ongoing limitation to questionnaires is the absence of more objective markers of GI dysfunction. This is particularly relevant because disorders of gut–brain interaction (DGBI), formerly referred to as functional gastrointestinal disorders, are primarily diagnosed from reporting of symptoms. If a patient or their caregiver cannot reliably and accurately report these symptoms, confidently diagnosing a DGBI is impossible. In this setting, while advances in questionnaires have provided some insight, they still do not provide an objective measure for identifying GI symptoms. Furthermore, established treatments that rely on consistent, timely patient feedback (such as proton-pump inhibitor [PPI] therapy for gastroesophageal reflux disease [GERD]), which requires patients notifying their clinicians when symptoms of heartburn and regurgitation have resolved or if they linger, cannot be effectively executed. Moreover, established diagnostic methods, such as motility testing, cannot be completed in all autistic individuals or those with other

neurodevelopmental conditions due to limitations that will be described later in section "Need for Noninvasive, Objective Measures of GI Motility in ASD."

There is a paucity of evidence-based recommendations for the evaluation and management of GI problems in autistic individuals, although the consensus expert opinion is that this population deserves the same thoroughness and standard of care as that received by others in the diagnostic workup and treatment of GI conditions.[12] However, this can be difficult to accomplish in practical terms due to difficulties with self-report and caregiver-report information and the absence and inadequacy of available, noninvasive diagnostics.[12] Recognizing the limitations of the current paradigm, an effort toward improving the assessment of GI symptoms, has recently been made by patients, foundations, caregivers, and their physicians.[30] Expert panels have been meeting with the NIH to not only highlight the gaps in knowledge but also to showcase the need for questionnaires that incorporate the motor, behavioral, food-related, and GI symptoms reported and can be completed jointly by patients/parents and physicians. As the etiology of ASD and its associated GI symptoms are so heterogenous, this article focuses on a specific genetic form of the spectrum, Phelan-McDermid syndrome (PMDS), in the hopes of elucidating potential treatment options through elimination of noise from the wider population.

Phelan-McDermid Syndrome and Its GI Comorbidities

PMDS is caused by deletions of the terminal end of chromosome 22 (22q13.3) or mutations in the *SHANK3* gene specifically.[31,32] The array of symptoms experienced by people with PMDS is mirrored by what is known about the molecular genetics of *SHANK3* gene. The SHANK3 protein is best known for its function in the central nervous system (CNS), where it serves as a scaffolding protein in the postsynaptic densities of excitatory glutamatergic synapses[33]; consistent with this, loss of Shank3 in mouse models leads to impaired synaptic transmission and smaller postsynaptic densities.[34-37] In addition to its role in the mature CNS, animal and human stem cell models have shown a role for Shank3 in embryonic brain development,[38,39] WNT signaling,[40,41] in peripheral somatosensory neurons,[42] in intestinal cell type homeostasis and barrier function,[43,44] and in uptake of dietary zinc.[45] By some estimates, PMDS accounts for over 2% of ASD with moderate to profound ID.[46]

Patients with PMDS experience profound autism characterized by global developmental delay accompanied by impaired speech, hypotonia, epilepsy, and stereotyped behavior, as well as a significant complement of GI symptoms.[31,45,47,48] The most prevalent GI symptoms in PMDS are constipation and/or diarrhea (38–41%), GERD (42%), cyclic vomiting, and rumination disorder which is a functional GI disease associated with NDDs characterized by repetitive regurgitation of undigested food oftentimes incorrectly reported as vomiting by caregivers. In the latter disorder, the subject eventually ingests the meal and the food regurgitated does not get expelled through the mouth as it does with true vomiting. These symptoms frequently result in malnutrition and failure to thrive.[32,48,49] Additionally, hypotonia often appears after the age of 1 year and also contributes to poor feeding.[50] In one study utilizing the ROME IV questionnaires, abdominal pain was reported in 41% of individuals with PMDS, further limiting oral intake in ASD.[51] However, the vast majority

of PMDS GI symptom data has been collected retrospectively, with few prospective clinical studies specifically focused on GI symptoms.[45,51]

A more personal sense of symptoms and their respective impacts in PMDS emerges from summaries of Phelan McDermid Family Conferences, at which families, clinicians, and basic scientists discuss the most pressing challenges facing families. For example, in a 2018 conference survey, constipation and the "need for toilet training" ranked second only to behavioral disturbances as areas of concern. Moreover, caregivers of teens and adults with PMDS verbalized concerns about GI dysfunction more frequently than caregivers of infants and toddlers.[52] Several caregivers report rumination in their children.[53] Chronic constipation in children with PMDS is often accompanied by regression in developmental milestones and behavior, which may explain their delay in toilet training (typically to ages 4–5).[51,54] Additionally, high rates of non-retentive fecal incontinence (13/17 patients) have been reported separately from any constipation.[51] A large German study of 41 adults and children with PMDS (48% male, age range: 4–55, and mean age: 13.4 years) found nocturnal enuresis, daytime urinary incontinence, and daily fecal incontinence requiring a diaper during the day to be common (> 70%) in all age groups; conversely, constipation was present only in 19% overall and a hard stool consistency was infrequently reported.[55] PMDS Foundation registry data also have shown that almost a quarter of patients with PMDS have feeding tubes, such as gastrostomy tubes or gastrojejunostomy tubes, necessitated by diagnosed pyloric stenosis, gastroparesis, or failure to thrive.

Using the framework of PMDS symptomology, we discuss the potential mechanisms of GI dysfunction in ASD patients, current attempts at treatments, and insights produced through studies in animal models.

Food Selectivity, Nutrition, and GERD

Food sensitivity/selectivity is highly reported in ASD.[28,56] This food selectivity tends toward a preference for processed foods that are high in simple carbohydrates and fats. From a gut motility perspective, carbohydrates and fats, while lacking in vitamins and fiber, are easier to digest than more nutritious foods like fruits, vegetables, and complex carbohydrates. In fact, neurotypical patients with gastroparesis are advised to follow low residue diets, avoiding insoluble fibers, as low residue diets are more easily digested.[57,58] This is also in striking contrast to the dietary modifications often formulated as comanagement in patients with drug-resistant epilepsy (such as the ketogenic diet or modified Atkins diet).[59] A downside of selective eating is that diets may lack essential nutrients, like zinc. In some studies, the zinc/copper ratio is low in autistic patients, and a twofold higher incidence of zinc deficiency is reported in PMDS versus the general population.[45,60,61] In PMDS, zinc deficiencies extend beyond nutrition, since SHANK3 has been shown to co-localize at enterocyte plasma membranes with the zinc transporters ZIP2 and ZIP4 in the human intestinal enterocytes. Moreover, ZIP2 and ZIP4 mRNAs are downregulated in PMDS enterocytes compared with controls, with negative consequences such as weight loss and loss of alertness from zinc deficiency.[45]

GERD is frequent in PMDS (59%), may include manifestations such as choking (41%), and often is treated with PPIs (47%) or histamine receptor blockers (H2Ras) (18%).[51]

PPIs, however, may alter the gut microbiome negatively.[62] Since therapeutic trials of these acid suppressive medications often are used to distinguish GERD from other causes of regurgitation (e.g., vomiting due to cyclic vomiting or pyloric stenosis) and since for this patient feedback on symptom improvement is essential, other diagnostics must be incorporated to accommodate a nonverbal population and avoid misdiagnosis. For example, either a catheter-less capsule called the Bravo capsule (Medtronic) or less invasive pH probes can be used to diagnose GERD without need for endoscopy.[63,64] Pyloric stenosis can be ruled out by performing upper endoscopy or obtaining an upper GI series.[51]

Constipation and GI Motility

Constipation is a frequent manifestation in PMDS (37–65%).[31] Potential etiologies include GI dysmotility referring to impaired physiologic contractions in the colon which can result from neurological or muscular diseases, oftentimes systemic, and which often leads to delayed transit, changes in the gut's microbiome leading to dysbiosis, and lack of dietary fiber.[65] Constipation is of concern to both patient and caregiver, since it is associated with worsening of behavioral issues, such as aggression and sleep disturbances, in several monogenic forms of ASD.[66,67] The exacerbation of neurological and psychiatric issues, such as seizures and aggression, by GI dysfunction has been noted even outside of the profound autism cohort.[19,26,68,69]

Some studies from the Autism Treatment Network and affiliated clinics have suggested that constipation symptoms reported in ASD are more common in patients with rigid-compulsive behavioral patterns who are treated with medications, such as risperidone and other anticholinergic and atypical antipsychotic medications ($p = 0.01$), that may produce constipation as an adverse effect. However, an association was found to exist between functional constipation symptoms and rigid-compulsive behaviors unrelated to serotonin levels mediated by those drugs.[70]

In the general population, diagnosing constipation is based solely on patient report without the need for diagnostics other than physical examination by health care providers. But in a nonverbal patient group, physicians must utilize physiological diagnostic markers to examine gut transit and motility. Many reported GI symptoms in profound forms of ASD like PMDS may be caused by impairments in GI motility that prolong whole gut transit. This is similar to what is seen in other neurologic diseases, such as Parkinson's disease.[71-73] GI motility is accomplished by contraction of the smooth muscles of the intestinal wall propelling food, nutrients, nondigestible products, and metabolites through the digestive tract. These peristaltic contractions are mediated in part by serotonin.[74,75] Various animal models of monogenic forms of ASD have displayed disruptions to these muscular contractions.[43,76-79] In a clinical ASD population, any of these disruptions could alter GI transit, impairing food bolus and thus nutrient absorption, potentially resulting in increased hospitalization, malnutrition, and emergency department visits.[43,76-80]

An NIH study by Witmer et al was one of few studies using both patient-reported outcome measures (PROMs), such as ROME IV criteria, and diagnostic testing in patients specifically with PMDS.[51] Transit time in the colon was measured by colonic manometry (invasive and performed via colonoscopic placement) and a radiopaque marker study. Colonic transit

was abnormal in 2 of 13 (15%) of subjects who completed the testing. This is higher than the average of slow transit constipation reported in the general population of children with constipation (<1%).[51] The laxatives used by parents in this study included osmotic laxatives, which comprised 41% of laxative use (e.g., polyethylene glycol was the most common in this group), followed by enemas or suppositories for fecal retention (24%), and stimulants (18%).

For defecation disorders, noninvasive physiotherapy, which uses pelvic floor exercises to improve gut motility and transit, is another treatment often used in children with toileting issues and constipation. This type of therapy has been evaluated in a randomized-controlled trial in 35 children with various NDDs and shows promise when structured noninvasive physiotherapy is used as compared to conventional physiotherapy.[80]

Serotonin's Role in Constipation

Serotonin (5-hydroxytryptamine or 5-HT) is a monoamine neurotransmitter commonly associated with neurological reward pathways and mood modulation, but is also significant in discussions of ASD for its role in physiological processes like GI motility.[74] Studies across autistic populations have found that 25 to 30% of patients have increased blood levels of serotonin.[81] However, researchers have yet to find significant correlation between higher blood serotonin levels and either constipation or behavioral symptoms.[70]

The vast majority (about 90%) of the body's 5-HT is produced by cells in the GI tract, including serotonergic neurons and enterochromaffin cells. In a study of SHANK3 model zebra fish, researchers found a reduction in 5-HT-positive enterochromaffin cells when compared to wild-type subjects, which was accompanied by reduced GI transit and motility.[43] This reduced GI motility mirrors the clinical symptoms of constipation that affect more than half of PMDS patients.[31] Similarly, reduced GI motility, accompanied by a 50% reduction in 5-HT levels in intestinal tissues, has been observed in BTBR model mice, another ASD model.[82]

Changes in serotonin production can also be the result of shifts in microbiome composition. The GI microbiome plays a large role in nutrition processing and metabolism, and can impact neurological and behavioral function.[83-86] For example, serotonin levels are positively correlated with increased relative abundance of spore-forming bacteria. These spore-forming bacteria produce metabolites that induce elevated TPH1, the rate-limiting component of EC-produced serotonin.[82,86] In contrast, there is a marked decrease of plasma serotonin in germ-free mice.[86,87] These findings correspond with those from clinical studies, which have identified changes in *Clostridiales* species concentrations in the gut microbiomes of ASD patients. These shifts have been associated with changes in tryptophan and serotonin production, similar to those seen in mice studies.[86,88] Surveys of autistic children have documented altered microbiomes and increased bacterial metabolites, such as short chain fatty acids (SCFAs).[89,90] This is mirrored in animal models, such as the previously mentioned BTBR mouse model.[82]

In the United States, prucalopride is the only available and Food and Drug Administration (FDA)-approved drug that targets serotonin. It has been approved for the treatment of

constipation. As an agonist of the serotonin 5-HT4 receptor, prucalopride promotes motility through its action on serotonin and the enteric nervous system, and is often used as a prokinetic in children.[91] This drug also improves symptoms of delayed gastric emptying, such as nausea and vomiting, when administered to diabetics with vagal neuropathy.[92,93] Therefore, prucalopride may also be helpful for treating constipation in PMDS and ASD more broadly. However, there is a critical need for studies examining the impact of prucalopride on GI function throughout the gut which includes gastric, small bowel, and colonic motility changes in children and adults with ASD.

Need for Noninvasive, Objective Measures of GI Motility in ASD

To diagnose GI motility disorders, the following validated measures exist: liquid and solid gastric and whole gut emptying scintigraphy,[94,95] wireless motility capsules[96,97] and gastric emptying breath tests with either C-Octanoic acid or C-Spirulina,[98,99] radiopaque marker studies,[91] fluoroscopy, and various high-resolution manometric evaluations of the gut. Most of these tests have significant limitations (listed in ►Table 2), including the following: use of gluten for the meals ingested (gastric and whole gut scintigraphy); radioactive dyes (scintigraphy); exposure to radiation (marker studies); long duration of scanning (4 hours for gastric scintigraphy and days for whole gut) requiring a compliant patient; lack of FDA-approval in children; contraindications for swallowing a capsule (radiopaque marker and wireless motility capsule); and dislike of/refusal to consume Spirulina-containing meal due to food selectivity issues. The current recommended diagnostic studies for the evaluation of motility disturbances in NDDs, along with their limitations in applying them to ASD patients, are summarized in ►Table 1. Determining if there is a potential pelvic floor impairment or slow transit constipation in ASD has been hampered by our inability to perform noninvasive diagnostic measures other than imaging of abdomen. This is often not helpful other than to show a large amount of stool retention, which is not necessarily evidence of slow transit constipation or a pelvic floor disorder. Answering those questions with current diagnostic methods would require performance of anorectal manometry or colonic manometry—tests that are considered routine in children without developmental delay to determine causes of constipation but are not well-tolerated by children with ASD.[100]

The Blue Muffin Pilot Study

To address the shortcomings of current diagnostic options, we developed a new noninvasive, nonradioactive method of assaying food transit in the clinical population. Drs. Dallman and Moshiree (Provisional U.S. patent 63/283,665) collaborated with families of ASD patients to create and refine a muffin recipe that is composed of the meal administered during gastric and whole gut scintigraphy testing used as standard for motility evaluation in the general population of all ages, along with an organic blue dye (►Table 3). Participants are asked to ingest two of these gluten-free, blue-dye muffins. The muffins are equal to 256 calories and composed of egg whites, cream of tartar, sugar, jam, gluten-free flour, and either soy or whey protein (depending on subjects' allergies) mixed with 1 tsp of blue food coloring. Once ingested and transited through the GI tract, the blue dye can then be detected in the stool upon exit. This technique avoids gluten, radiation, scanning, and the need to swallow

a capsule. The muffins were also accepted by patients, including those with food selectivity issues and those who are profoundly nonverbal, based on our pilot feasibility testing (IRB# IRB00083216). However, our approach is limited in that in cannot be applied to those on feeding tubes and not orally feeding. Precedence for such a measure had been set by a study looking at the feasibility of blue dye to study small intestinal transit in patients with ostomies and short gut syndrome.[101] Additionally, a nutrition-focused gut microbiome study from England called the “blue poo” study showed that in nearly a thousand healthy patients, the blue dye meal measure of gut transit time was a better predictor of microbiome function than either stool consistency or frequency.[102]

Although our results presented here in six patients with genetic forms of PMDS are preliminary, they establish the feasibility of such analysis for the measurement of whole gut transit in children with profound ASD who are fed orally. Moreover, these pilot data indicate that this approach can detect delayed transit of up to 10 days from ingestion and is a sensitive way to measure lag phase (►Fig. 1). Combined with prospective symptom tracking using a caregiver-assisted ePROM, this test can also determine the relationship among diverse symptoms in PMDS (►Fig. 2).

Discussion

As a group of clinician-scientists, we have identified the gaps in knowledge surrounding the most profound forms of ASD, exemplified here through focusing on PMDS, and discussed the challenges in obtaining a history and accurately identifying GI pathologies with the currently available diagnostic measures. These challenges have contributed to the systematic exclusion of individuals with profound autism who experience limited communication and/or ID. This negatively impacts both research and, most importantly, clinical care for ASD patients with eating difficulties and/or altered sensory processing, since constipation due to motility issues in autistic children carries a high risk of morbidity, ER visits, and hospitalizations (►Fig. 3).

Therefore, there is a critical need for noninvasive, objective measures of GI symptoms, GI transit, absorption, and motility. Additionally, similar to the cystic fibrosis population that now requires longitudinal treatment as a result of longer lifespan due to improved therapies, the care of an autistic patient needs both adult and pediatric neurologists and gastroenterologists who understand the multidimensional care required, especially by those with profound autism. To better clarify the actual temporality and causality between neurologic symptoms, behavioral manifestations, and GI dysfunction seen in ASD, a longitudinal assessment will be necessary (►Table 3). We hope that with the partnership of the NIH, the RARE Diseases Clinical research network, Developmental Synaptopathies, and foundations who have already jointly formed a consortium of experts dedicated to deciphering these questions, we will be empowered to develop an infrastructure by which we can do larger scale studies in the future.

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References

1. Myers SM, Challman TD. Autism Spectrum Disorder. 2nd ed. American Academy of Pediatrics; 2018
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, DC 2013
3. Baxter AJ, Brugha TS, Erskine HE, Scheurer RW, Vos T, Scott JG. The epidemiology and global burden of autism spectrum disorders. Psychol Med 2015;45(03):601–613 [PubMed: 25108395]
4. Zeidan J, Fombonne E, Scorah J, et al. Global prevalence of autism: a systematic review update. Autism Res 2022;15(05):778–790 [PubMed: 35238171]
5. Rice CE, Rosanoff M, Dawson G, et al. Evaluating changes in the prevalence of the autism spectrum disorders (ASDs). Public Health Rev 2012;34(02):1–22 [PubMed: 26236074]
6. Lyall K, Croen L, Daniels J, et al. The changing epidemiology of autism spectrum disorders. Annu Rev Public Health 2017;38:81–102 [PubMed: 28068486]
7. Moreno-De-Luca A, Myers SM, Challman TD, Moreno-De-Luca D, Evans DW, Ledbetter DH. Developmental brain dysfunction: revival and expansion of old concepts based on new genetic evidence. Lancet Neurol 2013;12(04):406–414 [PubMed: 23518333]
8. Yasuda Y, Matsumoto J, Miura K, Hasegawa N, Hashimoto R. Genetics of autism spectrum disorders and future direction. J Hum Genet 2023;68(03):193–197 [PubMed: 36038624]
9. Satterstrom FK, Kosmicki JA, Wang J, et al. ; Autism Sequencing Consortium iPSYCH-Broad Consortium. Large-scale exome sequencing study implicates both developmental and functional changes in the neurobiology of autism. Cell 2020;180(03):568–584.e23 [PubMed: 31981491]
10. Holingue C, Newill C, Lee LC, Pasricha PJ, Daniele Fallin M. Gastrointestinal symptoms in autism spectrum disorder: a review of the literature on ascertainment and prevalence. Autism Res 2018;11(01):24–36 [PubMed: 28856868]
11. Wang J, Ma B, Wang J, Zhang Z, Chen O. Global prevalence of autism spectrum disorder and its gastrointestinal symptoms: a systematic review and meta-analysis. Front Psychiatry 2022;13:963102 [PubMed: 36081466]
12. Buie T, Campbell DB, Fuchs GJ III, et al. Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with ASDs: a consensus report. Pediatrics 2010;125(Suppl 1):S1–S18 [PubMed: 20048083]
13. Tory JC, Joel ER, Joni JB, Terry SF, Jeffrey RL, Marc SA. Constipation associated with self-injurious and aggressive behavior exhibited by a child diagnosed with autism. Educ Treat Child 2008;32(01):89–103
14. Coury DL, Ashwood P, Fasano A, et al. Gastrointestinal conditions in children with autism spectrum disorder: developing a research agenda. Pediatrics 2012;130(Suppl 2):S160–S168 [PubMed: 23118247]
15. Fulceri F, Morelli M, Santocchi E, et al. Gastrointestinal symptoms and behavioral problems in preschoolers with autism spectrum disorder. Dig Liver Dis 2016;48(03):248–254 [PubMed: 26748423]

16. Kral TV, Eriksen WT, Souders MC, Pinto-Martin JA. Eating behaviors, diet quality, and gastrointestinal symptoms in children with autism spectrum disorders: a brief review. J Pediatr Nurs 2013;28(06):548–556 [PubMed: 23531467]
17. Maenner MJ, Arneson CL, Levy SE, Kirby RS, Nicholas JS, Durkin MS. Brief report: association between behavioral features and gastrointestinal problems among children with autism spectrum disorder. J Autism Dev Disord 2012;42(07):1520–1525 [PubMed: 22012246]
18. Mannion A, Leader G. Gastrointestinal symptoms in autism spectrum disorder: a literature review. Rev J Autism Dev Disord 2013;1(01):11–17
19. Mazefsky CA, Schreiber DR, Olino TM, Minshew NJ. The association between emotional and behavioral problems and gastrointestinal symptoms among children with high-functioning autism. Autism 2014;18(05):493–501 [PubMed: 24104507]
20. Mazurek MO, Vasa RA, Kalb LG, et al. Anxiety, sensory over-responsivity, and gastrointestinal problems in children with autism spectrum disorders. J Abnorm Child Psychol 2013;41(01):165–176 [PubMed: 22850932]
21. Peters B, Williams KC, Gorrindo P, et al. Rigid-compulsive behaviors are associated with mixed bowel symptoms in autism spectrum disorder. J Autism Dev Disord 2014;44(06):1425–1432 [PubMed: 24293040]
22. Radford J, Anderson M. Encopresis in children on the autistic spectrum. Early Child Dev Care 2003;173(04):375–382
23. Vissoker RE, Latzer Y, Gal E. Eating and feeding problems and gastrointestinal dysfunction in autism spectrum disorders. Res Autism Spectr Disord 2015;12:10–21
24. Holingue C, Kalb LG, Musci R, et al. Characteristics of the autism spectrum disorder gastrointestinal and related behaviors inventory in children. Autism Res 2022;15(06):1142–1155 [PubMed: 35302292]
25. Holingue C, Poku O, Pfeiffer D, Murray S, Fallin MD. Gastrointestinal concerns in children with autism spectrum disorder: a qualitative study of family experiences. Autism 2022;26(07):1698–1711 [PubMed: 34903078]
26. Penzol MJ, Salazar de Pablo G, Llorente C, et al. Functional gastrointestinal disease in autism spectrum disorder: a retrospective descriptive study in a clinical sample. Front Psychiatry 2019;10:179 [PubMed: 31024351]
27. Guan J, Li G. Injury mortality in individuals with autism. Am J Public Health 2017;107(05):791–793 [PubMed: 28323463]
28. Margolis KG, Buie TM, Turner JB, et al. Development of a brief parent-report screen for common gastrointestinal disorders in autism spectrum disorder. J Autism Dev Disord 2019;49(01):349–362 [PubMed: 30350113]
29. Lukens CT, Linscheid TR. Development and validation of an inventory to assess mealtime behavior problems in children with autism. J Autism Dev Disord 2008;38(02):342–352 [PubMed: 17578658]
30. Consortium for autism, neurodevelopmental disorders & digestive diseases. https://www.candidgi.com/
31. De Rubeis S, Siper PM, Durkin A, et al. Delineation of the genetic and clinical spectrum of Phelan-McDermid syndrome caused by *SHANK3* point mutations. Mol Autism 2018;9:31 [PubMed: 29719671]
32. Phelan K, McDermid HE. The 22q13.3 deletion syndrome (Phelan-McDermid syndrome). Mol Syndromol 2012;2(3-5):186–201 [PubMed: 22670140]
33. Naisbitt S, Kim E, Tu JC, et al. Shank, a novel family of postsynaptic density proteins that binds to the NMDA receptor/PSD-95/GKAP complex and cortactin. Neuron 1999;23(03):569–582 [PubMed: 10433268]
34. Arons MH, Thynne CJ, Grabrucker AM, et al. Autism-associated mutations in ProSAP2/Shank3 impair synaptic transmission and neurexin-neuroligin-mediated transsynaptic signaling. J Neurosci 2012;32(43):14966–14978 [PubMed: 23100419]
35. Bozdagi O, Tavassoli T, Buxbaum JD. Insulin-like growth factor-1 rescues synaptic and motor deficits in a mouse model of autism and developmental delay. Mol Autism 2013;4(01):9 [PubMed: 23621888]

36. Peça J, Feliciano C, Ting JT, et al. Shank3 mutant mice display autistic-like behaviours and striatal dysfunction. Nature 2011;472(7344):437–442 [PubMed: 21423165]
37. Yang M, Bozdagi O, Scattoni ML, et al. Reduced excitatory neurotransmission and mild autism-relevant phenotypes in adolescent Shank3 null mutant mice. J Neurosci 2012;32(19):6525–6541 [PubMed: 22573675]
38. Kozol RA, Cukier HN, Zou B, et al. Two knockdown models of the autism genes SYNGAP1 and SHANK3 in zebrafish produce similar behavioral phenotypes associated with embryonic disruptions of brain morphogenesis. Hum Mol Genet 2015;24(14):4006–4023 [PubMed: 25882707]
39. Kozol RA, James DM, Varela I, Sumathipala SH, Züchner S, Dallman JE. Restoring Shank3 in the rostral brainstem of shank3ab−/− zebrafish autism models rescues sensory deficits. Commun Biol 2021;4(01):1411 [PubMed: 34921227]
40. Breen MS, Browne A, Hoffman GE, et al. Transcriptional signatures of participant-derived neural progenitor cells and neurons implicate altered Wnt signaling in Phelan-McDermid syndrome and autism. Mol Autism 2020;11(01):53 [PubMed: 32560742]
41. Harris KP, Akbergenova Y, Cho RW, Baas-Thomas MS, Littleton JT. Shank modulates postsynaptic wnt signaling to regulate synaptic development. J Neurosci 2016;36(21):5820–5832 [PubMed: 27225771]
42. Orefice LL, Mosko JR, Morency DT, et al. Targeting peripheral somatosensory neurons to improve tactile-related phenotypes in ASD models. Cell 2019;178(04):867–886.e24 [PubMed: 31398341]
43. James DM, Kozol RA, Kajiwara Y, et al. Intestinal dysmotility in a zebrafish (*Danio rerio*) *shank3a; shank3b* mutant model of autism. Mol Autism 2019;10:3 [PubMed: 30733854]
44. Sauer AK, Bockmann J, Steinestel K, Boeckers TM, Grabrucker AM. Altered intestinal morphology and microbiota composition in the autism spectrum disorders associated SHANK3 mouse model. Int J Mol Sci 2019;20(09):2134 [PubMed: 31052177]
45. Pfaender S, Sauer AK, Hagmeyer S, et al. Zinc deficiency and low enterocyte zinc transporter expression in human patients with autism related mutations in SHANK3. Sci Rep 2017;7:45190 [PubMed: 28345660]
46. Leblond CS, Nava C, Polge A, et al. Meta-analysis of SHANK mutations in autism spectrum disorders: a gradient of severity in cognitive impairments. PLoS Genet 2014;10(09):e1004580 [PubMed: 25188300]
47. Betancur C, Buxbaum JD. SHANK3 haploinsufficiency: a “common” but underdiagnosed highly penetrant monogenic cause of autism spectrum disorders. Mol Autism 2013;4(01):17 [PubMed: 23758743]
48. Soorya L, Kolevzon A, Zweifach J, et al. Prospective investigation of autism and genotype-phenotype correlations in 22q13 deletion syndrome and SHANK3 deficiency. Mol Autism 2013;4(01):18 [PubMed: 23758760]
49. Sarasua SM, Boccuto L, Sharp JL, et al. Clinical and genomic evaluation of 201 patients with Phelan-McDermid syndrome. Hum Genet 2014;133(07):847–859 [PubMed: 24481935]
50. Kolevzon A, Angarita B, Bush L, et al. Phelan-McDermid syndrome: a review of the literature and practice parameters for medical assessment and monitoring. J Neurodev Disord 2014;6 (01):39 [PubMed: 25784960]
51. Witmer C, Mattingly A, D’Souza P, Thurm A, Hadigan C. Incontinence in Phelan-McDermid syndrome. J Pediatr Gastroenterol Nutr 2019;69(02):e39–e42 [PubMed: 30921255]
52. Goodspeed K, Bliss G, Linnehan D. Bringing everyone to the table - findings from the 2018 Phelan-McDermid syndrome foundation international conference. Orphanet J Rare Dis 2020;15(01):152 [PubMed: 32546186]
53. Kusnik A, Vaqar S. Rumination disorder. BTI - StatPearls. May, 2023
54. Kohlenberg TM, Trelles MP, McLarney B, Betancur C, Thurm A, Kolevzon A. Psychiatric illness and regression in individuals with Phelan-McDermid syndrome. J Neurodev Disord 2020;12(01):7 [PubMed: 32050889]
55. Hussong J, Wagner C, Curfs L, von Gontard A. Incontinence and psychological symptoms in Phelan-McDermid syndrome. Neurourol Urodyn 2020;39(01):310–318 [PubMed: 31663160]

56. Yap CX, Henders AK, Alvares GA, et al. Autism-related dietary preferences mediate autism-gut microbiome associations. Cell 2021;184(24):5916–5931.e17 [PubMed: 34767757]
57. Tack J, Tornblom H, Tan V, Carbone F. Evidence-based and emerging dietary approaches to upper disorders of gut-brain interaction. Am J Gastroenterol 2022;117(06):965–972 [PubMed: 35417429]
58. Bandini LG, Curtin C, Phillips S, Anderson SE, Maslin M, Must A. Changes in food selectivity in children with autism spectrum disorder. J Autism Dev Disord 2017;47(02):439–446 [PubMed: 27866350]
59. Devi N, Madaan P, Kandoth N, Bansal D, Sahu JK. Efficacy and safety of dietary therapies for childhood drug-resistant epilepsy: a systematic review and network meta-analysis. JAMA Pediatr 2023;177(03):258–266 [PubMed: 36716045]
60. Grabrucker AM. A role for synaptic zinc in ProSAP/Shank PSD scaffold malformation in autism spectrum disorders. Dev Neurobiol 2014;74(02):136–146 [PubMed: 23650259]
61. Grabrucker S, Jannetti L, Eckert M, et al. Zinc deficiency dysregulates the synaptic ProSAP/Shank scaffold and might contribute to autism spectrum disorders. Brain 2014;137(Pt 1):137–152 [PubMed: 24277719]
62. Bruno G, Zaccari P, Rocco G, et al. Proton pump inhibitors and dysbiosis: current knowledge and aspects to be clarified. World J Gastroenterol 2019;25(22):2706–2719 [PubMed: 31235994]
63. Hojsak I, Ivković L, Trbojević T, et al. The role of combined 24-h multichannel intraluminal impedance-pH monitoring in the evaluation of children with gastrointestinal symptoms suggesting gastro-esophageal reflux disease. Neurogastroenterol Motil 2016;28(10):1488–1493 [PubMed: 27137138]
64. Rodriguez L, Morley-Fletcher A, Souza A, Rosengaus L, Nurko S. Effect of anesthesia on gastroesophageal reflux in children: a study using BRAVO wireless pH study measurements. Neurogastroenterol Motil 2015;27(11):1553–1558 [PubMed: 26264213]
65. Forootan M, Bagheri N, Darvishi M. Chronic constipation: a review of literature. Medicine (Baltimore) 2018;97(20):e10631 [PubMed: 29768326]
66. Jimenez-Gomez A, Niu S, Andujar-Perez F, et al. Phenotypic characterization of individuals with SYNGAP1 pathogenic variants reveals a potential correlation between posterior dominant rhythm and developmental progression. J Neurodev Disord 2019;11(01):18 [PubMed: 31395010]
67. Van Dijck A, Vulto-van Silfhout AT, Cappuyns E, et al. ; ADNP Consortium. Clinical presentation of a complex neurodevelopmental disorder caused by mutations in ADNP. Biol Psychiatry 2019;85(04):287–297 [PubMed: 29724491]
68. Chaidez V, Hansen RL, Hertz-Picciotto I. Gastrointestinal problems in children with autism, developmental delays or typical development. J Autism Dev Disord 2014;44(05):1117–1127 [PubMed: 24193577]
69. McCue LM, Flick LH, Twyman KA, Xian H. Gastrointestinal dysfunctions as a risk factor for sleep disorders in children with idiopathic autism spectrum disorder: a retrospective cohort study. Autism 2017;21(08):1010–1020 [PubMed: 28954536]
70. Marler S, Ferguson BJ, Lee EB, et al. Brief report: whole blood serotonin levels and gastrointestinal symptoms in autism spectrum disorder. J Autism Dev Disord 2016;46(03):1124–1130 [PubMed: 26527110]
71. Barboza JL, Okun MS, Moshiree B. The treatment of gastroparesis, constipation and small intestinal bacterial overgrowth syndrome in patients with Parkinson's disease. Expert Opin Pharmacother 2015;16(16):2449–2464 [PubMed: 26374094]
72. Bielefeldt K, Tuteja A, Nusrat S. Disorders of gastrointestinal hypomotility. F1000Res 2016;5;. Doi: 10.12688/f1000research.8658.1
73. Ramprasad C, Douglas JY, Moshiree B. Parkinson's disease and current treatments for its gastrointestinal neurogastromotility effects. Curr Treat Options Gastroenterol 2018;16(04):489–510 [PubMed: 30361854]
74. Gershon MD. 5-Hydroxytryptamine (serotonin) in the gastrointestinal tract. Curr Opin Endocrinol Diabetes Obes 2013;20(01):14–21 [PubMed: 23222853]

75. Margolis KG, Li Z, Stevanovic K, et al. Serotonin transporter variant drives preventable gastrointestinal abnormalities in development and function. J Clin Invest 2016;126(06):2221–2235 [PubMed: 27111230]
76. Fröhlich H, Kollmeyer ML, Linz VC, et al. Gastrointestinal dysfunction in autism displayed by altered motility and achalasia in *Foxp1*$^{+/-}$ mice. Proc Natl Acad Sci U S A 2019;116(44):22237–22245 [PubMed: 31611379]
77. Grubišić V, Kennedy AJ, Sweatt JD, Parpura V. Pitt-Hopkins mouse model has altered particular gastrointestinal transits in vivo. Autism Res 2015;8(05):629–633 [PubMed: 25728630]
78. Hayot G, Massonot M, Keime C, Faure E, Golzio C. Loss of autism-candidate CHD8 perturbs neural crest development and intestinal homeostatic balance. Life Sci Alliance 2022;6(01):e202201456 [PubMed: 36375841]
79. Hosie S, Ellis M, Swaminathan M, et al. Gastrointestinal dysfunction in patients and mice expressing the autism-associated R451C mutation in neuroligin-3. Autism Res 2019;12(07):1043–1056 [PubMed: 31119867]
80. Joshi S, Parmar S, Kalavant A, Shah L, Parmar D. Effectiveness of structured physiotherapy in constipation in children with neurodevelopmental disorders - a randomized trial. Physiother Theory Pract 2022. Doi: 10.1080/09593985.2022.2100299
81. Gabriele S, Sacco R, Persico AM. Blood serotonin levels in autism spectrum disorder: a systematic review and meta-analysis. Eur Neuropsychopharmacol 2014;24(06):919–929 [PubMed: 24613076]
82. Golubeva AV, Joyce SA, Moloney G, et al. Microbiota-related changes in bile acid & tryptophan metabolism are associated with gastrointestinal dysfunction in a mouse model of autism. EBioMedicine 2017;24:166–178 [PubMed: 28965876]
83. Fung TC, Vuong HE, Luna CDG, et al. Intestinal serotonin and fluoxetine exposure modulate bacterial colonization in the gut. Nat Microbiol 2019;4(12):2064–2073 [PubMed: 31477894]
84. Hsiao EY. Immune dysregulation in autism spectrum disorder. Int Rev Neurobiol 2013;113:269–302 [PubMed: 24290389]
85. Hsiao EY. Gastrointestinal issues in autism spectrum disorder. Harv Rev Psychiatry 2014;22(02):104–111 [PubMed: 24614765]
86. Yano JM, Yu K, Donaldson GP, et al. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. Cell 2015;161(02):264–276 [PubMed: 25860609]
87. Sjögren K, Engdahl C, Henning P, et al. The gut microbiota regulates bone mass in mice. J Bone Miner Res 2012;27(06):1357–1367 [PubMed: 22407806]
88. Luna RA, Oezguen N, Balderas M, et al. Distinct microbiome-neuroimmune signatures correlate with functional abdominal pain in children with autism spectrum disorder. Cell Mol Gastroenterol Hepatol 2016;3(02):218–230 [PubMed: 28275689]
89. Wang L, Christophersen CT, Sorich MJ, Gerber JP, Angley MT, Conlon MA. Elevated fecal short chain fatty acid and ammonia concentrations in children with autism spectrum disorder. Dig Dis Sci 2012;57(08):2096–2102 [PubMed: 22535281]
90. Finegold SM, Dowd SE, Gontcharova V, et al. Pyrosequencing study of fecal microflora of autistic and control children. Anaerobe 2010;16(04):444–453 [PubMed: 20603222]
91. Serra J, Pohl D, Azpiroz F, et al. ; Functional Constipation Guidelines Working Group. European society of neurogastroenterology and motility guidelines on functional constipation in adults. Neurogastroenterol Motil 2020;32(02):e13762 [PubMed: 31756783]
92. Andrews CN, Woo M, Buresi M, et al. Prucalopride in diabetic and connective tissue disease-related gastroparesis: randomized placebo-controlled crossover pilot trial. Neurogastroenterol Motil 2021;33(01):e13958 [PubMed: 32743954]
93. Carbone F, Van den Houte K, Clevers E, et al. Prucalopride in gastroparesis: a randomized placebo-controlled crossover study. Am J Gastroenterol 2019;114(08):1265–1274 [PubMed: 31295161]
94. Camilleri M, Kuo B, Nguyen L, et al. ACG clinical guideline: Gastroparesis. Am J Gastroenterol 2022;117(08):1197–1220 [PubMed: 35926490]
95. Ziessman HA. Gastrointestinal transit assessment: Role of scintigraphy: Where are we now? where are we going?. Curr Treat Options Gastroenterol 2016;14(04):452–460 [PubMed: 27682148]

96. Rodriguez L, Heinz N, Colliard K, Amicangelo M, Nurko S. Diagnostic and clinical utility of the wireless motility capsule in children: a study in patients with functional gastrointestinal disorders. Neurogastroenterol Motil 2021;33(04):e14032 [PubMed: 33184926]

97. Lee AA, Rao S, Nguyen LA, et al. Validation of diagnostic and performance characteristics of the wireless motility capsule in patients with suspected gastroparesis. Clin Gastroenterol Hepatol 2019;17(09):1770–1779.e2 [PubMed: 30557741]

98. Keller J, Hammer HF, Afolabi PR, et al. ; European 13C-Breath Test Group. European guideline on indications, performance and clinical impact of 13 C-breath tests in adult and pediatric patients: an EAGEN, ESNM, and ESPGHAN consensus, supported by EPC. United European Gastroenterol J 2021;9(05):598–625

99. Orsagh-Yentis DK, Bai S, Bobbey A, Hayes C, Pusateri A, Williams K. Spirulina breath test indicates differences in gastric emptying based on age, gender, and BMI. Neurogastroenterol Motil 2021;33(06):e14079 [PubMed: 33484210]

100. Rosen R, Garza JM, Tipnis N, Nurko S. An ANMS-NASPGHAN consensus document on esophageal and antroduodenal manometry in children. Neurogastroenterol Motil 2018;30(03):. Doi: 10.1111/nmo.13239

101. Compher C, Rubesin S, Kinosian B, Madaras J, Metz D. Noninvasive measurement of transit time in short bowel syndrome. JPEN J Parenter Enteral Nutr 2007;31(03):240–245 [PubMed: 17463151]

102. Asnicar F, Leeming ER, Dimidi E, et al. Blue poo: impact of gut transit time on the gut microbiome using a novel marker. Gut 2021;70(09):1665–1674 [PubMed: 33722860]

103. Grigg I, Ivashko-Pachima Y, Hait TA, et al. Tauopathy in the young autistic brain: novel biomarker and therapeutic target. Transl Psychiatry 2020;10(01):228 [PubMed: 32661233]

104. Ivashko-Pachima Y, Ganaiem M, Ben-Horin-Hazak I, et al. SH3- and actin-binding domains connect ADNP and SHANK3, revealing a fundamental shared mechanism underlying autism. Mol Psychiatry 2022;27(08):3316–3327 [PubMed: 35538192]

105. Kapitansky O, Giladi E, Jaljuli I, Bereswill S, Heimesaat MM, Gozes I. Microbiota changes associated with ADNP deficiencies: rapid indicators for NAP (CP201) treatment of the ADNP syndrome and beyond. J Neural Transm (Vienna) 2020;127(02):251–263 [PubMed: 32072336]

106. Karmon G, Sragovich S, Hacohen-Kleiman G, et al. Novel ADNP syndrome mice reveal dramatic sex-specific peripheral gene expression with brain synaptic and tau pathologies. Biol Psychiatry 2022;92(01):81–95 [PubMed: 34865853]

107. Amin S, Majumdar A, Mallick AA, et al. Caregiver's perception of epilepsy treatment, quality of life and comorbidities in an international cohort of CDKL5 patients. Hippokratia 2017;21(03):130–135 [PubMed: 30479474]

108. Amin S, Monaghan M, Aledo-Serrano A, et al. International consensus recommendations for the assessment and management of individuals with CDKL5 deficiency disorder. Front Neurol 2022;13:874695 [PubMed: 35795799]

109. Fehr S, Wilson M, Downs J, et al. The CDKL5 disorder is an independent clinical entity associated with early-onset encephalopathy. Eur J Hum Genet 2013;21(03):266–273 [PubMed: 22872100]

110. Leonard H, Downs J, Benke TA, Swanson L, Olson H, Demarest S. CDKL5 deficiency disorder: clinical features, diagnosis, and management. Lancet Neurol 2022;21(06):563–576 [PubMed: 35483386]

111. Mangatt M, Wong K, Anderson B, et al. Prevalence and onset of comorbidities in the CDKL5 disorder differ from Rett syndrome. Orphanet J Rare Dis 2016;11:39 [PubMed: 27080038]

112. Olson HE, Demarest ST, Pestana-Knight EM, et al. Cyclin-dependent kinase-like 5 deficiency disorder: clinical review. Pediatr Neurol 2019;97:18–25 [PubMed: 30928302]

113. Olson HE, Daniels CI, Haviland I, et al. Current neurologic treatment and emerging therapies in CDKL5 deficiency disorder. J Neurodev Disord 2021;13(01):40 [PubMed: 34530725]

114. Beighley JS, Hudac CM, Arnett AB, et al. Clinical phenotypes of carriers of mutations in CHD8 or its conserved target genes. Biol Psychiatry 2020;87(02):123–131 [PubMed: 31526516]

115. Douzgou S, Liang HW, Metcalfe K, et al. ; Deciphering Developmental Disorders Study. The clinical presentation caused by truncating CHD8 variants. Clin Genet 2019;96(01):72–84 [PubMed: 31001818]
116. Ostrowski PJ, Zachariou A, Loveday C, et al. The CHD8 overgrowth syndrome: a detailed evaluation of an emerging overgrowth phenotype in 27 patients. Am J Med Genet C Semin Med Genet 2019;181(04):557–564 [PubMed: 31721432]
117. Yasin H, Gibson WT, Langlois S, et al. A distinct neurodevelopmental syndrome with intellectual disability, autism spectrum disorder, characteristic facies, and macrocephaly is caused by defects in CHD8. J Hum Genet 2019;64(04):271–280 [PubMed: 30670789]
118. Bernier R, Golzio C, Xiong B, et al. Disruptive CHD8 mutations define a subtype of autism early in development. Cell 2014;158(02):263–276 [PubMed: 24998929]
119. Badshah N, Mattison KA, Ahmad S, et al. Novel missense CNTNAP2 variant identified in two consanguineous Pakistani families with developmental delay, epilepsy, intellectual disability, and aggressive behavior. Front Neurol 2022;13:918022 [PubMed: 35911904]
120. Gregor A, Albrecht B, Bader I, et al. Expanding the clinical spectrum associated with defects in CNTNAP2 and NRXN1. BMC Med Genet 2011;12:106 [PubMed: 21827697]
121. Mittal R, Kumar A, Ladda R, Mainali G, Aliu E. Pitt Hopkins-like syndrome 1 with novel CNTNAP2 mutation in siblings. Child Neurol Open 2021;8:X211055330
122. Smogavec M, Cleall A, Hoyer J, et al. Eight further individuals with intellectual disability and epilepsy carrying bi-allelic CNTNAP2 aberrations allow delineation of the mutational and phenotypic spectrum. J Med Genet 2016;53(12):820–827 [PubMed: 27439707]
123. Tosca L, Drévillon L, Mouka A, et al. Two new cases of interstitial 7q35q36.1 deletion including CNTNAP2 and KMT2C. Mol Genet Genomic Med 2021;9(11):e1645 [PubMed: 34582124]
124. Moreno-De-Luca D, Sanders SJ, Willsey AJ, et al. Using large clinical data sets to infer pathogenicity for rare copy number variants in autism cohorts. Mol Psychiatry 2013;18(10):1090–1095 [PubMed: 23044707]
125. Shaaya EA, Pollack SF, Boronat S, Davis-Cooper S, Zella GC, Thibert RL. Gastrointestinal problems in 15q duplication syndrome. Eur J Med Genet 2015;58(03):191–193 [PubMed: 25573720]
126. Leader G, Forde J, Naughton K, Maher L, Arndt S, Mannion A. Relationships among gastrointestinal symptoms, sleep problems, challenging behaviour, comorbid psychopathology and autism spectrum disorder symptoms in children and adolescents with 15q duplication syndrome. J Intellect Disabil Res 2021;65(01):32–46 [PubMed: 33073413]
127. Kidd SA, Lachiewicz A, Barbouth D, et al. Fragile X syndrome: a review of associated medical problems. Pediatrics 2014;134(05):995–1005 [PubMed: 25287458]
128. Talman LS, Pfeiffer RF. Movement disorders and the gut: a review. Mov Disord Clin Pract (Hoboken) 2022;9(04):418–428 [PubMed: 35586541]
129. Akol I, Gather F, Vogel T. Paving therapeutic avenues for FOXG1 syndrome: untangling genotypes and phenotypes from a molecular perspective. Int J Mol Sci 2022;23(02):954 [PubMed: 35055139]
130. McMahon KQ, Papandreou A, Ma M, et al. Familial recurrences of FOXG1-related disorder: evidence for mosaicism. Am J Med Genet A 2015;167A(12):3096–3102 [PubMed: 26364767]
131. Mitter D, Pringsheim M, Kaulisch M, et al. FOXG1 syndrome: genotype-phenotype association in 83 patients with FOXG1 variants. Genet Med 2018;20(01):98–108 [PubMed: 28661489]
132. Siper PM, Kolevzon A, Wang AT, Buxbaum JD, Tavassoli T. A clinician-administered observation and corresponding caregiver interview capturing DSM-5 sensory reactivity symptoms in children with ASD. Autism Res 2017;10(06):1133–1140 [PubMed: 28296264]
133. Lozano R, Gbekie C, Siper PM, et al. FOXP1 syndrome: a review of the literature and practice parameters for medical assessment and monitoring. J Neurodev Disord 2021;13(01):18 [PubMed: 33892622]
134. Meerschaut I, Rochefort D, Revençu N, et al. *FOXP1*-related intellectual disability syndrome: a recognisable entity. J Med Genet 2017;54(09):613–623 [PubMed: 28735298]
135. Jahromi SR, Togha M, Fesharaki SH, et al. Gastrointestinal adverse effects of antiepileptic drugs in intractable epileptic patients. Seizure 2011;20(04):343–346 [PubMed: 21236703]

136. Allen NM, Mannion M, Conroy J, et al. The variable phenotypes of KCNQ-related epilepsy. Epilepsia 2014;55(09):e99–e105 [PubMed: 25052858]
137. Beck VC, Isom LL, Berg AT. Gastrointestinal symptoms and channelopathy-associated epilepsy. J Pediatr 2021;237:41–49.e1 [PubMed: 34181986]
138. Inagaki A, Hayashi M, Andharia N, Matsuda H. Involvement of butyrate in electrogenic K^+ secretion in rat rectal colon. Pflugers Arch 2019;471(02):313–327 [PubMed: 30250967]
139. Kako H, Martin DP, Cartabuke R, Beebe A, Klamar J, Tobias JD. Perioperative management of a patient with Rett syndrome. Int J Clin Exp Med 2013;6(05):393–403 [PubMed: 23724160]
140. Konarzewski WH, Misso S. Rett syndrome and delayed recovery from anaesthesia. Anaesthesia 1994;49(04):357
141. Tofil NM, Buckmaster MA, Winkler MK, Callans BH, Islam MP, Percy AK. Deep sedation with propofol in patients with Rett syndrome. J Child Neurol 2006;21(10):857–860 [PubMed: 17005101]
142. Fu C, Armstrong D, Marsh E, et al. Consensus guidelines on managing Rett syndrome across the lifespan. BMJ Paediatr Open 2020;4(01):e000717
143. Motil KJ, Caeg E, Barrish JO, et al. Gastrointestinal and nutritional problems occur frequently throughout life in girls and women with Rett syndrome. J Pediatr Gastroenterol Nutr 2012;55(03):292–298 [PubMed: 22331013]
144. Wahba G, Schock SC, Claridge E, et al. MeCP2 in the enteric nervous system. Neurogastroenterol Motil 2015;27(08):1156–1161 [PubMed: 26031318]
145. Motil KJ, Khan N, Coon JL, et al. Gastrointestinal health questionnaire for Rett syndrome: tool development. J Pediatr Gastroenterol Nutr 2021;72(03):354–360 [PubMed: 32969958]
146. Motil KJ, Morrissey M, Caeg E, Barrish JO, Glaze DG. Gastrostomy placement improves height and weight gain in girls with Rett syndrome. J Pediatr Gastroenterol Nutr 2009;49(02):237–242 [PubMed: 19525868]
147. Motil KJ, Barrish JO, Lane J, et al. Vitamin D deficiency is prevalent in girls and women with Rett syndrome. J Pediatr Gastroenterol Nutr 2011;53(05):569–574 [PubMed: 21637127]
148. Thapa S, Venkatachalam A, Khan N, et al. Assessment of the gut bacterial microbiome and metabolome of girls and women with Rett syndrome. PLoS One 2021;16(05):e0251231 [PubMed: 33956889]
149. Castronovo P, Baccarin M, Ricciardello A, et al. Phenotypic spectrum of NRXN1 mono- and bi-allelic deficiency: a systematic review. Clin Genet 2020;97(01):125–137 [PubMed: 30873608]
150. Shaco-Levy R, Jasperson KW, Martin K, et al. Gastrointestinal polyposis in Cowden syndrome. J Clin Gastroenterol 2017;51(07):e60–e67 [PubMed: 27661969]
151. Hansen-Kiss E, Beinkampen S, Adler B, et al. A retrospective chart review of the features of PTEN hamartoma tumour syndrome in children. J Med Genet 2017;54(07):471–478 [PubMed: 28526761]
152. Innella G, Miccoli S, Colussi D, et al. Colorectal polyposis as a clue to the diagnosis of Cowden syndrome: report of two cases and literature review. Pathol Res Pract 2021;218:153339 [PubMed: 33482532]
153. Tian X, Chen J, Zhang J, et al. The efficacy of ketogenic diet in 60 Chinese patients with Dravet syndrome. Front Neurol 2019;10:625 [PubMed: 31249551]
154. Villas N, Meskis MA, Goodliffe S. Dravet syndrome: characteristics, comorbidities, and caregiver concerns. Epilepsy Behav 2017;74:81–86 [PubMed: 28732259]
155. Howell KB, McMahon JM, Carvill GL, et al. SCN2A encephalopathy: a major cause of epilepsy of infancy with migrating focal seizures. Neurology 2015;85(11):958–966 [PubMed: 26291284]
156. Wolff M, Johannesen KM, Hedrich UBS, et al. Genetic and phenotypic heterogeneity suggest therapeutic implications in SCN2A-related disorders. Brain 2017;140(05):1316–1336 [PubMed: 28379373]
157. Cammarata-Scalisi F, Callea M, Martinelli D, et al. Clinical and genetic aspects of Phelan-McDermid syndrome: an interdisciplinary approach to management. Genes (Basel) 2022;13(03):504 [PubMed: 35328058]

158. Alsufiani HM, Alkhanbashi AS, Laswad NAB, et al. Zinc deficiency and supplementation in autism spectrum disorder and Phelan-McDermid syndrome. J Neurosci Res 2022;100(04):970–978 [PubMed: 35114017]

159. Hagmeyer S, Sauer AK, Grabrucker AM. Prospects of zinc supplementation in autism spectrum disorders and shankopathies such as Phelan McDermid syndrome. Front Synaptic Neurosci 2018;10:11 [PubMed: 29875651]

160. Sgritta M, Dooling SW, Buffington SA, et al. Mechanisms underlying microbial-mediated changes in social behavior in mouse models of autism spectrum disorder. Neuron 2019;101(02):246–259.e6 [PubMed: 30522820]

161. Vlaskamp DRM, Shaw BJ, Burgess R, et al. *SYNGAP1* encephalopathy: a distinctive generalized developmental and epileptic encephalopathy. Neurology 2019;92(02):e96–e107 [PubMed: 30541864]

162. Weldon M, Kilinc M, Lloyd Holder J Jr, Rumbaugh G. The first international conference on SYNGAP1-related brain disorders: a stakeholder meeting of families, researchers, clinicians, and regulators. J Neurodev Disord 2018;10(01):6 [PubMed: 29402231]

163. Berryer MH, Hamdan FF, Klitten LL, et al. Mutations in SYNGAP1 cause intellectual disability, autism, and a specific form of epilepsy by inducing haploinsufficiency. Hum Mutat 2013;34(02):385–394 [PubMed: 23161826]

164. Lo Barco T, De Gaetano L, Santangelo E, et al. SYNGAP1-related developmental and epileptic encephalopathy: the impact on daily life. Epilepsy Behav 2022;127:108500 [PubMed: 34954508]

165. Sullivan BJ, Ammanuel S, Kipnis PA, Araki Y, Huganir RL, Kadam SD. Low-dose perampanel rescues cortical gamma dysregulation associated with parvalbumin interneuron GluA2 upregulation in epileptic Syngap1(+/−) mice. Biol Psychiatry 2020;87(09):829–842 [PubMed: 32107006]

166. von Stülpnagel C, Hartlieb T, Borggräfe I, et al. Chewing induced reflex seizures (“eating epilepsy”) and eye closure sensitivity as a common feature in pediatric patients with SYNGAP1 mutations: review of literature and report of 8 cases. Seizure 2019;65:131–137 [PubMed: 30685520]

167. Wright D, Kenny A, Eley S, McKechanie AG, Stanfield AC. Clinical and behavioural features of SYNGAP1-related intellectual disability: a parent and caregiver description. J Neurodev Disord 2022;14(01):34 [PubMed: 35655128]

168. Peippo M, Ignatius J. Pitt-Hopkins syndrome. Mol Syndromol 2012;2(3–5):171–180 [PubMed: 22670138]

169. Goodspeed K, Newsom C, Morris MA, Powell C, Evans P, Golla S. Pitt-Hopkins syndrome: a review of current literature, clinical approach, and 23-patient case series. J Child Neurol 2018;33(3):233–244 [PubMed: 29318938]

170. Moulis H, Garsten JJ, Marano AR, Elser JM. Tuberous sclerosis complex: review of the gastrointestinal manifestations and report of an unusual case. Am J Gastroenterol 1992;87(07):914–918 [PubMed: 1615951]

171. Hammad TA, Alastal Y, Khan MA, Rkaine S, Sodeman TC, Nawras A. Tuberous sclerosis complex with multiple gastrointestinal manifestations. Case report and literature review. J Gastrointest Cancer 2016;47(04):442–445 [PubMed: 26350414]

172. Williams CA, Driscoll DJ, Dagli AI. Clinical and genetic aspects of Angelman syndrome. Genet Med 2010;12(07):385–395 [PubMed: 20445456]

173. Glassman LW, Grocott OR, Kunz PA, et al. Prevalence of gastrointestinal symptoms in Angelman syndrome. Am J Med Genet A 2017;173(10):2703–2709 [PubMed: 28816003]

174. Lin JL, Rigdon J, Van Haren K, et al. Gastrostomy tubes placed in children with neurologic impairment: associated morbidity and mortality. J Child Neurol 2021;36(09):727–734 [PubMed: 33750232]

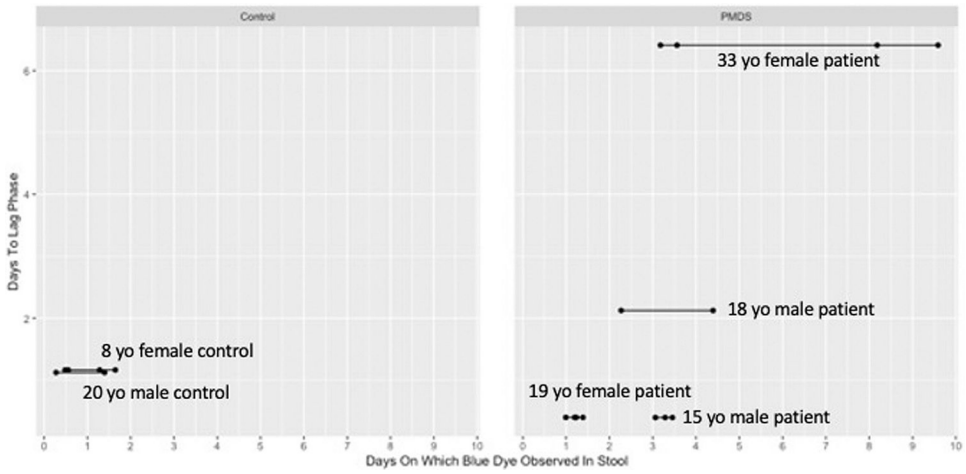

Fig. 1.

Blue muffin transit test pilot data. Figure shows days on which two or more blue stools were observed for each participant. Each dot represents a blue stool and each line connects the observations from a single individual. Y-axis shows the lag phase for each patient, i.e., the difference in time between the first and last blue stool observed. Note: PMDS indicates Phelan-McDermid syndrome patient.

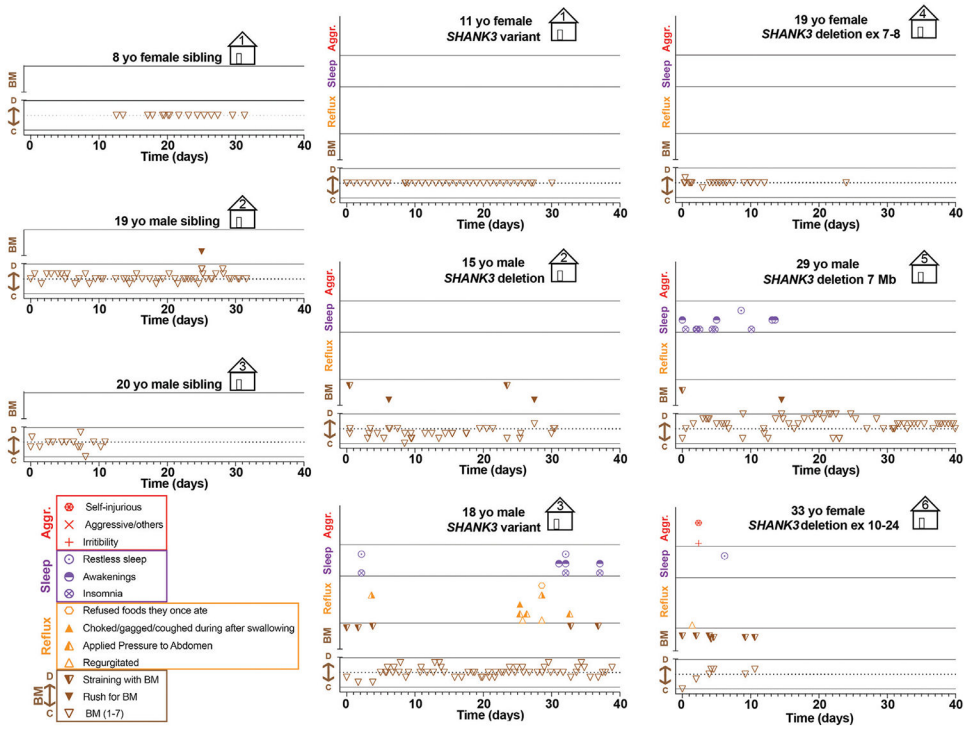

Fig. 2.

Symptom tracking indicates symptom clusters vary across time. Caregivers tracked a limited set of GI and neurological symptoms (see key, lower left: bowel movements in brown, BM with Bristol Stool Scale that ranges from 1, very hard stool, to 7, diarrhea; dashed line indicates normal BM, reflux in orange, sleep disturbances in purple, and aggression in red) using the STRIPES symptom tracker web application. Scatter plots show symptom occurrences over a period of 40 days for nine participants, three sibling controls (left), and six people with Phelan-McDermid syndrome, ranging in age from 11 to 33 (middle and right), across six households (see numbered houses).

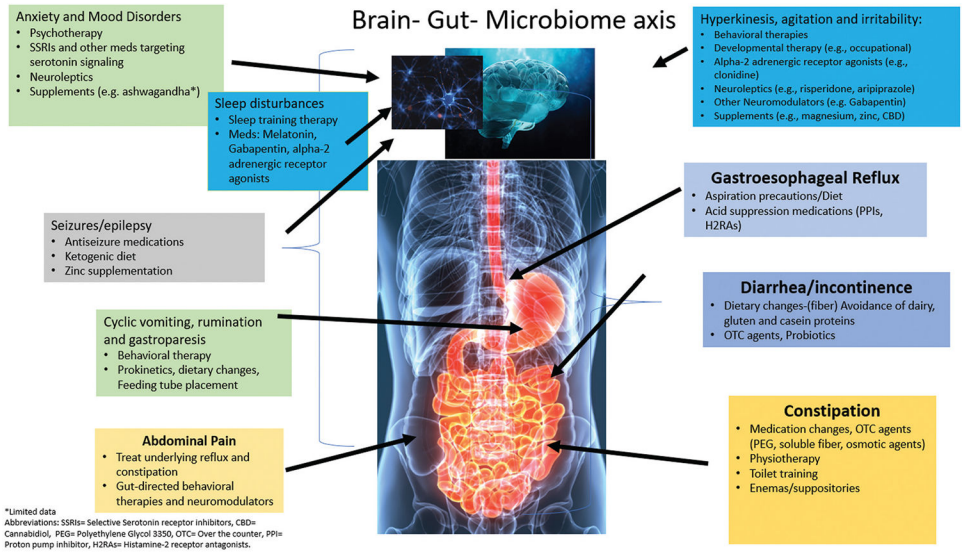

Fig. 3.

Gastrointestinal and neurological manifestations of profound autism and its current evidence and mostly non–evidence-based treatments.

Table 1

Genetic forms of ASDs/NDDs in which gastrointestinal distress has been reported by foundations and/or publications

GENE **locus** **OMIM**	**Prevalence in NDDs (Gillentine, Wang, & Eichler, 2022)**	**GI distress/clinical manifestations**	**Animal model gut phenotypes**
ADNP 20q13.13 615873	88/50,377	• ADNP disorder; Helsmoortel van der Aa syndrome; ASD/ID • GERD, reflux, cyclical vomiting, constipation common (>75%). • 10% (8/78) fed by G-tube in early childhood. • Oral movement problems especially when gene disruption occurs in the nuclear localization signal. • GI symptoms correlate with sleep disturbances[67]	Mouse models show sex-dependent alterations in the gut microbiome, relation between SHANK3 and ADNP regulation of cytoskeleton/tauopathy/ autophagy via FOXO; NAP, microtubule regulatory peptide, as a potential therapeutic target[103-106]
CDKL5 Xp22.13 300672	22/50,377	• X-linked, dominant; female:male ratio 4:1–12:1; similarities to Rett (*MECP2*)/Angelman (*UBE3A*) syndromes • Developmental and epileptic encephalopathy 2 • 10–20% of early-onset epilepsy in female infants linked to CDKL5 • Epilepsy tends to be treatment-resistant • Constipation (70.9%), reflux (64.1%), and air swallowing (27.1%); *n* = 141. • 20% ketogenic diet (improves seizure frequency, intensity, or duration) • 9/16 with vagus nerve stimulation improved seizure frequency, intensity, duration. • Gastrotomy indicated if BMI low or swallowing is dangerous • 20–40% G-tube or nasogastric tube • Nutritionist recommended[107-113]	
CHD8 16q21 615032	64/50,377	• 0.2% of people with ASD and/or developmental delay (*n* = 6,176); often *de novo* variants; haploinsufficient; macrocephaly • GI problems (~80%): constipation (40–60%), diarrhea often following constipation, reflux, vomiting[114-117]	Zebrafish model shows fewer enteric neurons and disrupted whole gut transit[78,118]
CNTNAP2 7q35-36.1 610042	4/50,377	• Pitt-Hopkins-like syndrome 1/cortical dysplasia focal epilepsy caused by homozygous variants; heterozygous variants milder, linked to various psychiatric conditions. • Constipation • Failure to thrive[119-123]	

***GENE* locus OMIM**	**Prevalence in NDDs (Gillentine, Wang, & Eichler, 2022)**	**GI distress/clinical manifestations**	**Animal model gut phenotypes**
Dup Chr 15q 608636	10/3955 with ASD; duplication most often *de novo*	• GI symptoms reported in 50–87%; $n = 50$ and $n = 38$, respectively. In $n = 38$, 10/11 females and 10/17 males reported GI symptoms • GERD and constipation each reported in 60%; severe constipation with reflux also common, 30% • Treatments for constipation included polyethylene glycol, enemas (if failed → senna and bisacodyl, Botox injection to relieve high sphincter pressure and proton pump inhibitors for GERD. • A manometry study in one patient with constipation showed high sphincter pressure and normal recto-anal inhibitory complex • Treating GI symptoms has been reported to reduce aggression • GI symptoms are most strongly correlated with ASD symptoms, sleep problems, and comorbid psychopathologies. • ~30% of patients have epilepsy; in one patient, treating GI symptoms reduced seizure frequency[124-126]	
FMR1 Xq27.3 300624	2/50,377	• Fragile X syndrome; microdeletions of *FMR1* gene (destabilized by trinucleotide repeats) ASD/ID • 11% report diarrhea and reflux[127,128]	
FOXG1 14q12 613545	5/50,377	• *De novo* variants; symptoms vary depending on variant location with most severe symptoms caused by changes in N-term DNA-binding domain • Clinically similar to RTT syndrome but recognized as a different syndrome with earlier onset; autosomal • Epilepsy common • Can show poor postnatal growth and feeding problems that call for G-tube; constipation; reflux[129-131]	
FOXP1 3p14.1 613670	40/50,377	• Speech delay, expressive language better than receptive language • Seizures reported in 7/59 • Feeding difficulties in 7/8 • Constipation in 5/60[132-134]	Mouse FoxP1 +/− model shows poor weight gain, thinner muscle layers in esophagus and colon, achalasia (high sphincter tone), and prolonged whole gut transit time[76]
KCNQ2 20q13.33 613720 121200	67/50,377	• Benign familial neonatal seizures caused by inherited dominant variants in *KCNQ2*; developmental and epileptic encephalopathy 7 (DEE 7) also inherited variants with the parent experiencing more mild symptoms—in offspring, *KCNQ2* often missense variants associated with more severe seizures that result in psychomotor difficulties. • 55/78with DEE 7 have GI symptoms including GI dysmotility and constipation (important to consider that many antiseizure medications have negative impacts on GI function[135-137]	Butyrate-dependent K-secretion through KCNQ2 in the colon[138]
MECP2 Xq28 312750	65/50,377	• Rett syndrome; X-linked *de novo* variants that cause loss-of-function • In girls: developmental delay and hypotonia <2 y followed by developmental regression and the emergence of repetitive movements, loss of language, loss of purposeful hand skills, altered gait producing life-long dependence	

GENE locus OMIM	Prevalence in NDDs (Gillentine, Wang, & Eichler, 2022)	GI distress/clinical manifestations	Animal model gut phenotypes
		• In boys: neonatal encephalopathy—developmental delay with ID • Greater sensitivity to and prolonged apnea after anesthesia[139-141] • Altered sensory processing • Growth failure/feeding problems – Yearly nutrition screening recommended – Energy-dense foods (oil, syrup, avocado) – Gastrostomy if indicated by low BMI • Dysmotility, GERD, gas, bloating, delayed stomach emptying; GI symptoms often linked to irritability • 92% prevalence of GI dysmotility/constipation – Laxatives (polyethylene glycol, magnesium hydroxide, glycerin, bisacodyl) with goal of 1 soft BM/day • GERD – Proton pump inhibitors/H_2-blockers[142-148]	
NRXN1 2p16.3 614325	12/50,377	• Pitt-Hopkins-like syndrome 2 caused by autosomal recessive variants; heterozygous variants mild linked to various psychiatric conditions/no ID. • Chronic constipation[120,149]	
PTEN 10q23.31 605309	53/50,377	• Cowden syndrome; 5–10% of people with macrocephaly and ASD/ID • Gastrointestinal hamartomas • >90% with polyps of two or more histological types[150-152]	
SCN1A 2q24.3 182389	74/50,377	• Dravet syndrome; Developmental and epileptic encephalopathy • Constipation, dysmotility • GI symptoms more prevalent in females 20/33 than in males 6/26 • ~10% with gastrostomy tube • Ketogenic diet reduced seizure frequency and interictal events in more than half of patients ($n = 60$)[137,153,154]	
SCN2A 2q24.3 613721	158/50,377	• Developmental and epileptic encephalopathy 11 or benign familial infantile seizures depending on change to gene • Episodic hyperventilation • 9/12 had GI symptoms: constipation, reflux, diarrhea	

***GENE* locus OMIM**	**Prevalence in NDDs (Gillentine, Wang, & Eichler, 2022)**	**GI distress/clinical manifestations**	**Animal model gut phenotypes**
		• 3/12 required gastrostomy tube for supplemental feeding[155,156]	
SHANK3 22q13.33 606232	2/50,377 Prevalence likely low due to GC-rich nature of the gene that makes it hard to sequence	• Phelan-McDermid syndrome; haploinsufficient; most often *de novo* deletions or mutations in *SHANK3* • Constipation, reflux, cyclical vomiting, rumination, some with G-tube • Prospective study in 17 showed 76% took medication for GI symptoms, barium swallow test was normal in 11/11, constipation (65%), reflux (59%), and choking/gagging (41%), stool incontinence in 76% and correlating with the size of the deletion and reduced intellectual function; 2/17 had abnormal colonic transit (measured using sitz markers and X-ray); regular bowel regimens recommended. • Zinc supplementation suggested given interaction between SHANK3 and Zn uptake in the gut and that SHANK3 binds Zn[31,45,47,49,51,157-159]	Zebrafish models show intestinal dysmotility and reduced numbers of enteroendocrine cells; mouse models show altered intestinal morphology and microbiome; in mouse, ASD-relevant behaviors rescued by *Limosilactobacillus reuteri* in a vagus-dependent manner[43,44,160]
SYNGAP1 6p21.32 612621	54/50,377	• Intellectual developmental disorder MRD5; most often *de novo*; one of the most prevalent forms of genetic ID • Developmental and epileptic encephalopathy • Seizures brought on by eating or other sensory stimuli • Seizures also predict sleep state transitions between REM and NREM (low-dose perampanel may help control seizures) • Constipation, reflux, links between GI and aggression, some with G-tube[66,161-167]	
TCF4 18q21.2 610954	76/50,377	• Pitt-Hopkin syndrome; often *de novo* variants; haploinsufficient. • Constipation[168,169]	
TSC 1 9q34.13 191100 *and* *TSC2* 16p13.3 613254	11/50,377 19/50,377	• Tuberous sclerosis; *de novo* variants • Hamartomas in brain, skin, heart, kidneys, lung • Rectal bleeding, papillomas in GI tract 95% (n = 21) • Also at higher risk for malignant tumors of various types • Constipation[170,171]	
UBE3A 15q11.2 105830	2/50,377	• Angelman syndrome; most commonly caused by a deletion of Chr. 15 containing the *UBE3* gene • Constipation/possibly due to low truncal tone, reflux/gagging[172,173]	

Abbreviations: ASD, autism spectrum disorder; GERD, gastroesophageal reflux disease; GI, gastrointestinal; NDD, neurodevelopmental disorder. Notes: This is not a comprehensive list but is intended to demonstrate that GI distress is widespread and found in many different genetic NDDs. It should be noted that placement of G-tubes for epilepsy medication delivery and/or nutrition can reduce mortality but

is counterindicated in cases with respiratory conditions because there is an increased incidence of severe pneumonia with G-tube placement.[174] Also, in people with epileptic encephalopathies, it is likely that GI symptoms are exacerbated by antiseizure medications.[135]

Table 2

Gastrointestinal symptoms

GI symptom or disorder	Testing category options for diagnosis	Method	Limitations in profound ASD
Dysphagia, choking, and aspiration	Radiology (fluoroscopy) Scintigraphy Endoscopy Manometry	Barium swallow (modified) Cine-esophagram Upper endoscopy Esophageal manometry	Radiation exposure Radiation exposure Sedation risk/invasive Invasive, needs cooperative patient
GERD	PPI response pH evaluation Endoscopy	PPI-pharmacy order 24-h pH catheter Catheter-less (Bravo) via endoscopy	Risk of microbiome changes, bone loss Invasive, needs cooperative patient Invasive, requires sedation
Gastroparesis (nausea and vomiting) and/or pyloric stenosis	Radiology (fluoroscopy) Scintigraphy Capsule method Endoscopy Breath test	Upper GI Gastric scintigraphy Wireless motility capsule Upper endoscopy Octanoic and spirulina	Radiation exposure and taste of barium Radiation exposure, meal taste, gluten Size of capsule, gluten bar Sedation risk, invasive Taste
Refractory constipation (rule out defecation disorder or slow transit constipation and neurogenic bowel)	Radiology Capsule Manometry (both anorectal and colon)	Radiopaque marker Wireless motility capsule Anorectal and colonic manometry	Size of capsule, radiation exposure Size of capsule, gluten bar Invasive and needs cooperative patient (colonic manometry needs colonoscopy)
Fecal incontinence	Manometry	Anorectal manometry	Needs cooperative patient but can be done with sedation (rule out Hirschsprung's)
Cyclic vomiting syndrome and rumination disorder	ROME IV diagnostic criteria	Symptom-based diagnosis with lack of pathologic findings above	Nonverbal patient cannot communicate these symptoms effectively

Abbreviations: ASD, autism spectrum disorder; GI, gastrointestinal; PPI, proton-pump inhibitor.

Note: The most relevant GI symptoms in ASD patients and the methods used to diagnose them along with the diagnostic limitations in subjects with neurodevelopment disorders.

Table 3

Nutritional components of blue muffins

	Egg white	Sugar	Jam	Flour	Protein powder	Butter/oil	Totals
Carbs		45	100	38.7			183.7
Protein	51			1.6	10		62.6
Fat						5.1	5.1
Fiber				3.2			3.2
Total	254.6						

Note: The ingredients and their respective proportions in calories/component as included in the muffin mix.