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Phenotypic variability and gastrointestinal manifestations/interventions for growth in *NAA10*-related neurodevelopmental syndrome

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Abstract

Our study of 61 children with *NAA10*-related neurodevelopmental syndrome, an X-linked disorder due to *NAA10* gene variants, demonstrated a high prevalence of growth failure, with weight and height percentiles often in the failure-to-thrive diagnostic range; however, dramatic weight fluctuations and phenotypic variability is evidenced in the growth parameters of this population. Although never previously explored in depth, the gastrointestinal pathology associated with *NAA10*-related neurodevelopmental syndrome includes feeding difficulties in infancy, dysphagia, GERD/silent reflux, vomiting, constipation, diarrhea, bowel incontinence, and presence of eosinophils on esophageal endoscopy, in order from most to least prevalent. Additionally, the gastrointestinal symptom profile for children with this syndrome has been expanded to include eosinophilic esophagitis, cyclic vomiting syndrome, Mallory Weiss tears, abdominal migraine, esophageal dilation, and subglottic stenosis. Although the exact cause of poor growth in *NAA10*-related neurodevelopmental syndrome probands is unclear and the degree of contribution to this problem by GI symptomatology remains uncertain, an analysis including nine G-tube or GJ-tube fed probands demonstrates that G/GJ-tubes are overall efficacious with respect to improvements in weight gain and caregiving. The choice to insert a gastrostomy or gastrojejunal tube to aid with weight gain is often a challenging decision to make for parents, who may alternatively choose to

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AUTHOR CONTRIBUTIONS

Gholson J. Lyon was responsible for all videoconferencing and primary data collection, with secondary summaries performed by Elaine Marchi. Data analysis was performed by Katherine Sandomirsky and Gholson J. Lyon. Maureen Gavin and Karen Amble assisted with in-person visits at the Jervis clinic. The first draft of the manuscript was written by Katherine Sandomirsky, with editing thereafter by Gholson J. Lyon, with input from all other authors.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

rely on oral feeding, caloric supplementation, calorie tracking, and feeding therapy. In this case, if *NAA10*-related neurodevelopmental syndrome children are not tracking above the failure to thrive (FTT) range past 1 year of age despite such efforts, the treating physicians should be consulted regarding possibly undergoing G-tube placement to avoid prolonged growth failure. If G-tubes are not immediately inducing weight gain after insertion, recommendations could include altering formula, increasing caloric input, or exchanging a G-tube for a GJ-tube by means of a minimally invasive procedure.

Keywords

NAA10; *NAA15*; Ogden syndrome; gastrointestinal

1 | INTRODUCTION

The purpose of this study is to explore the clinical gastrointestinal phenotype of *NAA10*-related neurodevelopmental syndrome (Lyon et al., 2022). Current scientific literature documents the following GI-related complications associated with this syndrome: poor feeding, dysphagia, aspirations, umbilical hernia, diarrhea (Rope et al., 2011), multiple gastrointestinal infections (Wu & Lyon, 2018), vomiting requiring hospitalization (Gogoll et al., 2021), anteriorly displaced anus (Afrin et al., 2020), oversized liver (Maini et al., 2021), chronic constipation (Rasmus Ree et al., 2019), eosinophilic gastritis (Gupta et al., 2019), esophageal and gut dysmotility syndrome, esophagitis, fecal incontinence, silent reflux, and gastric reflux (Cheng et al., 2019). Such gastrointestinal symptoms may play a role in the commonly documented growth findings of postnatal growth failure observed in children with *NAA10*-related syndrome; parallel findings of growth retardation were observed in *NAA10* knock-out yeast (Mullen et al., 1989; Polevoda & Sherman, 2003), zebrafish (*Danio rerio*) (R. Ree et al., 2015), and mice (Kweon et al., 2021; Lee et al., 2019). However, *NAA10*-related neurodevelopmental syndrome is phenotypically variable in humans (Wu & Lyon, 2018), with certain probands experiencing normal weights and stature (Støve et al., 2018). Multiple probands analyzed in the literature required feeding tube placement to treat feeding difficulties and/or FTT (Afrin et al., 2020; Bader et al., 2020; Cheng et al., 2019; Gogoll et al., 2021; Gupta et al., 2019; Maini et al., 2021; Saunier et al., 2016), but the efficacy of tube feeding is only discussed in two publications, albeit very briefly. According to one such study by Rope et al. (2011), a male with a c.109T>C p. (Ser37Pro) variant (Proband 60 in our study) “was able to build up subcutaneous fat stores, presumably because of G tube feeding” in infancy (Rope et al., 2011). A separate study refers to a female de novo c. 384T>G p.(Phe128Leu) variant whose early feeding difficulties were improved by G-tube placement at 2 months old, as per her parent, who also stated that, at 1.5 years old, this child’s weight was lower than that of age-matched females (Cheng et al., 2019). However, this was the extent of the discussion regarding the direct benefits or detriments of G-tube feeding, and neither of these studies included growth parameters immediately preceding and following tube insertion. This study aims to explore the effectiveness of nasogastric, gastric, and gastro-jejunal tubes on the growth trajectories of *NAA10*-related syndrome probands.

2 | METHODOLOGY

Our methods consisted of mining medical records and data from interviews conducted by Dr. Gholson Lyon (in-person or via videoconferencing with the families of probands analyzed), recently reported in a preprint on MedRxiv (Lyon et al., 2022). Oral and written consent was obtained for research and publication, with approval of protocol #7659 for the Jervis Clinic by the New York State Psychiatric Institute—Columbia University Department of Psychiatry Institutional Review Board. Excel and Prism software were utilized for creating graphs and tables. SimulConsult was used to determine weight percentiles and standard deviation values of height and weight parameters. In an effort to exclude identifying information, the term “parent” was used in lieu of “mother” or “father,” “sibling” was used instead of “brother” or “sister,” and age ranges, rather than exact ages, were included throughout this text. Of note, certain probands included in our study have already been described in the literature. Refer to Table S1 to determine which probands in our study correspond to previously published *NAA10*-related syndrome children. Probands 2, 3, 5, 7–9, 12, 17–19, 22, 25, 27–29, 32–35, 37–50, 52, and 54 have not heretofore been published. These individuals have been described in more detail in a preprint related to the phenotypic spectrum of *NAA10*-related neurodevelopmental syndrome (Lyon et al., 2022).

3 | RESULTS

The probands investigated in this study possess varying *NAA10* variants (Tables 1 and S1).

According to the plotted weight percentile trajectories of our study’s probands, there exists a great deal of variability in the growth of children with *NAA10*-related neurodevelopmental syndrome (Figure 1). However, upon closer analysis 58% are at or below the 10th percentile and 47% are at or below the 5th percentile for weight (Figure S10B). 76% of data points between 0 and 30 months of age fall below the 20th percentile. Also, of note, 72% of probands included in our study had at least one weight percentile value in the FTT range. Such weight percentile values confirm the previous findings of low weights among children with *NAA10*-related neurodevelopmental syndrome. Similarly, although height percentile values demonstrate variability, 61% of data points are at or below the 10th percentile for height and 29% of data points are at or below the 5th percentile for height, indicating that the majority of analyzed probands are of small stature as compared to healthy age-matched children.

Please refer to Figures S13–S18 for growth data grouped by pathogenic variants, which show that growth variability exists even among probands with the same variant. Although, Ser37Pro probands all uniformly demonstrated poor growth (Figure S14).

While variability of height and weight percentiles exists between probands (Figure S11 and Table S10), a substantial amount of variability is also seen on an individual basis (Figure S12). Healthy children typically remain in the same height and weight percentile throughout the majority of childhood. WHO growth charts are divided into the 0.1, 3rd, 15th, 50th, 85th, 97th, and 99.9th percentiles. Although increases or decreases in height and weight percentile around 2–3 years of age may still indicate normal growth, before

the age of 3, a height or weight percentile change that crosses two divisions (from the 3rd to 50th weight percentile for example) is deemed abnormal. After 3 years of age, healthy children should not experience growth percentile differences on a monthly or yearly basis until puberty (Marchand and Canadian Paediatric Society, Nutrition and Gastroenterology Committee, 2012). However, our probands demonstrated dramatic height and weight percentile fluctuations during the first 3 years of life (Figure 1a,c) and between 3 years of age and 11 years of age (Figure 1b,d).

3.1 | Gastrointestinal symptom analysis

The following gastrointestinal symptoms were found in our probands: feeding difficulties in infancy (90%), dysphagia (75%), GERD (54%), vomiting (44%), constipation (34%), diarrhea/loose stools (24%), bowel incontinence (12%),and eosinophils noted on endoscopy (10%) (Figure 2), according to parental reports during interviews or physician reports found in medical records. Table S2 shows which symptoms each individual proband demonstrated. Less commonly reported gastrointestinal symptoms included: bowel incontinence, esophageal or gastric dysmotility, delayed gastric emptying, bloating, recurrent abdominal distension (gaseous), celiac disease, cyclical bacterial overgrowths of small intestine, Giardia and C. diff infections, abdominal pain, celiac artery stenosis, dilated esophagus, severe subglottic stenosis, posterior glottic granulation tissue, vascular ring wrapped around esophagus, suspected abscess in caudate lobe of liver, and eosinophilic esophagitis. For more information pertaining to how all of these symptoms varied in severity, frequency, and nature, refer to the Section A of Supplementary Text.

3.2 | Tube feeding

Of the 61 children analyzed in our study, 9 children were G-tube fed at some point in life: four females and five males. All G-tube fed female probands demonstrated benefit from G-tube use as evidenced by parental testimonial or by increases in weight percentiles after tube insertion. Of note, four male G/GJ-tube-fed probands had died—Probands 25 and 28 (before 12 months of age) and Probands 30 and 60 (between 1 and 5 years of age). G-tubes were shown to be efficacious in four of the five male probands, whereas the fifth male proband demonstrated benefit from transitioning from a G tube to a GJ tube (which extends into the jejunal segment of the small intestine).

For details regarding the weight trajectories of each tube-fed patient and his/her parent's testimonials, refer to the Section B of Supplementary Text.

For the children in this study who had variants in the *NAA10* gene but did not receive a G-tube or GJ-tube, there is no way of knowing whether their weight trajectories would have been more favorable had they been tube fed. Of the 9 G or GJ tube fed probands, 7 probands showed weight improvements while the tube was used for nutrition according to weight trajectory data (Figure 3a, Figures S1 and S2, Figure 4E) and 2 probands demonstrated weight benefits or general improvements according to parental testimonials (parental testimonial section of Table S6). However, there is tremendous variability in the weight percentiles corresponding to males and females who were not G or GJ tube fed with

a sizeable portion of children localized in the FTT range (on or directly above the *x*-axis) (Figure S9).

The efficacy of G-tubes and GJ-tubes with respect to growth poses a stark contrast to that of lack of efficacy of nasogastric (NG) tubes (Figure 3). For more information concerning the effects of NG-tube feeding on probands described in this study, refer to the Section C of Supplementary Text.

4 | DISCUSSION

Our weight data substantiates previous reports of children with *NAA10*-related neurodevelopmental syndrome being small in terms of weight and stature, as evidenced by low percentile values (Lyon et al., 2022; Rope et al., 2011). We also found that these values fluctuated dramatically on an individual level, often to an abnormal extent according to WHO criteria, suggesting that growth is disordered in multiple ways for this patient population. Additionally, we further confirmed that the phenotypic spectrum of *NAA10*-related neurodevelopmental syndrome includes gastrointestinal pathology; almost every analyzed proband had at least one GI-related symptom. Just as the height and weight percentiles demonstrated variability, the GI symptom profile was heterogenous among our probands with respect to symptom frequency, severity, and nature. The clinical profile of *NAA10*-related neurodevelopmental syndrome was expanded to include findings that had not been previously described in the literature such as eosinophilic esophagitis, cyclic vomiting syndrome, Mallory Weiss tears, abdominal migraine, esophageal dilation, and subglottic stenosis. Previous studies have listed gastrointestinal findings in children with *NAA10*-related neurodevelopmental syndrome, but there has been no mention of which symptoms were most prevalent. In our analysis, the five most common symptoms in order from most to least frequent were feeding difficulties in infancy, dysphagia, GERD/silent reflux, vomiting, and constipation. Although dysphagia among *NAA10*-related neurodevelopmental syndrome children has been reported in the literature, there has never been a specification of dysphagia type. We found that the three probands who had both dysphagia and abnormal findings on barium swallow imaging all had oropharyngeal dysphagia in particular.

We readily acknowledge that the decision to insert a G-tube or GJ-tube for feeding is a complex one, and this should be evaluated on a case-by-case basis. With this in mind and with the caveat that our data is limited by the small quantity of probands available for analysis, all boys and girls with *NAA10* variants displayed benefits from G-tube or GJ-tube feedings. For some of these children, G-tubes or GJ tubes were particularly helpful as a relatively quick method of raising weight percentiles out of the FTT range. For others who were tracking above the third to fifth percentiles, G-tubes helped to increase weights to healthier percentile ranges, at times crossing multiple growth chart divisions. Since the G-tubes or GJ-tubes were shown to be efficacious in some form for each child analyzed, it is recommended that parents of children with *NAA10*-related neurodevelopmental syndrome strongly consider, in consultation with their physicians, to conduct G-tube insertion in case of low weight or severe feeding difficulty and to not give up on tube feeding if immediate, obvious growth benefits are not demonstrated. For two probands, although the G-tube

was not showing clear growth improvements on one formula, after switching formulas (to Peptamen Jr. or Nutren Jr.) or increasing caloric intake (depending on caloric demands) they began to benefit in terms of growth values and/or parental testimonies. Caregivers should transition to a different formula or adjust caloric input through the tube and then closely monitor growth values before determining G-tube efficiency. If these changes do not yield improvements in weights, parents should consider G to GJ tube exchange, a minimally invasive procedure that extends a catheter to the jejunum from the stoma that was already created for G-tube insertion (Kim et al., 2010), as the only two probands who underwent this exchange demonstrated increases in weight following this conversion.

With respect to children who did not show growth improvements from NG-tubes, although we cannot know how these children would have fared without these tubes (perhaps, theoretically they may have done worse without them), due to the growth benefits witnessed among children while being G-tube fed and the lack of improvements seen in weight among NG-tube fed children, another recommendation may be to forgo NG-tube placement and insert G-tubes during times of growth failure or severe feeding difficulties.

Although G-tube feeding had led to improvements in weight and caregiving in a number of our probands, it is important to note that there are risks associated with G-tube insertion, as described in Section E of the Supplementary Text. These risks must be weighed against the benefits of rescuing children from the failure to thrive range, which are explained in Section F of the Supplementary Text.

According to the case of Proband 3, intensive parental intervention involving consistent feeding, calorie tracking, and dietary supplementation as an alternative to tube-feeding may successfully treat growth failure, as further discussed in Section G of the Supplementary Text. If such early efforts are not sufficient to raise an *NAA10*-related neurodevelopmental syndrome child's weight above the 5th percentile by 6–12 months of age, parents should be strongly encouraged to consider G or GJ tube placement because continued caregiver efforts and enrollment in feeding therapy after this age have not been shown to engender weights above the FTT zone, as further discussed in Section H of the Supplementary Text. For many probands in our study, weight data in the first year of life was not available. However, for four probands (13, 17, 32, and 43) who were not G/GJ-tube fed, weight data in the first year of life demonstrated that if parental efforts were not enough to supersede the FTT zone by 6 months of age, then FTT persisted for months to years afterward (Figure S5). For more information on this topic, refer to Section I of the Supplementary Text.

A subject for further research should be the root of growth failure in *NAA10*-related neurodevelopmental syndrome children. Perhaps in children with *NAA10*-related neurodevelopmental syndrome, growth failure is partially a consequence of absorption issues, as Proband 60 demonstrated his most substantial growth increases while on NJ and GJ tubes as compared to only NG and G-tubes (Figure S2A), further discussed in Section J of Supplementary text. As evidenced by our data, poor growth cannot be attributed to inadequate caloric intake, inability to properly chew or swallow, growth hormone deficiency, or low appetite; past the age of 6–12 months, calorie tracking, caloric supplementation, and using feeding therapy to successfully teach children how to chew, swallow, and no longer

choke on food did not induce adequate weight gain. Low appetite was also not an observable cause of poor growth, as multiple proband parents claimed that their children had great appetites, were constantly hungry, and that "desire to eat has never been a problem." Growth hormone deficiency was treated with growth hormone administration in two of our probands (11 and 13), but these efforts kept these probands in the FTT range, although they did lead to weight improvements. For more information regarding impact of GH treatment in our probands, refer to the Section D of the Supplementary Text, including Figures S7 and S8.

One limitation of our study is that only the first nine research participants were interviewed in-person and physically examined by medical doctors, including by one medical geneticist, one neurologist, and one psychiatrist. After this time, all interviews were converted to videoconferencing starting in March 2020, with the onset of the COVID19 pandemic, and the families met with the psychiatrist only (GJL). However, we did not observe any major differences in the information obtained from the in-person visits as compared to the videoconference visits.

During peer review, we were asked to evaluate whether cardiac pathology in our study's probands had affected growth. This has been addressed in Table S11 and Figures S18 and S19. Conclusions from this analysis suggest that cardiac insufficiency is not responsible for growth deficiency; these are likely two separate phenomena, as further discussed in Section K of the Supplementary Text.

A first draft of the manuscript was published as a preprint on MedRxiv (Sandomirsky et al., 2022) and circulated to the parents of our probands, four of whom responded. This cannot be included here due to space limitations, but to learn more about their feedback and updates, please refer to the Section L of Supplementary Text.

Lastly, during peer review, the editor stipulated that we should refer to this condition in this paper as *NAA10*-related neurodevelopmental syndrome, instead of also referring to it as Ogden syndrome. We have done this, and further discussion of this can be found in Section M of Supplementary Text.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY STATEMENT

Summary data is included in supplementary information. The human subject data that support the findings of this study are available on request from the corresponding author, as the underlying phenotype data are not publicly available due to privacy restrictions.

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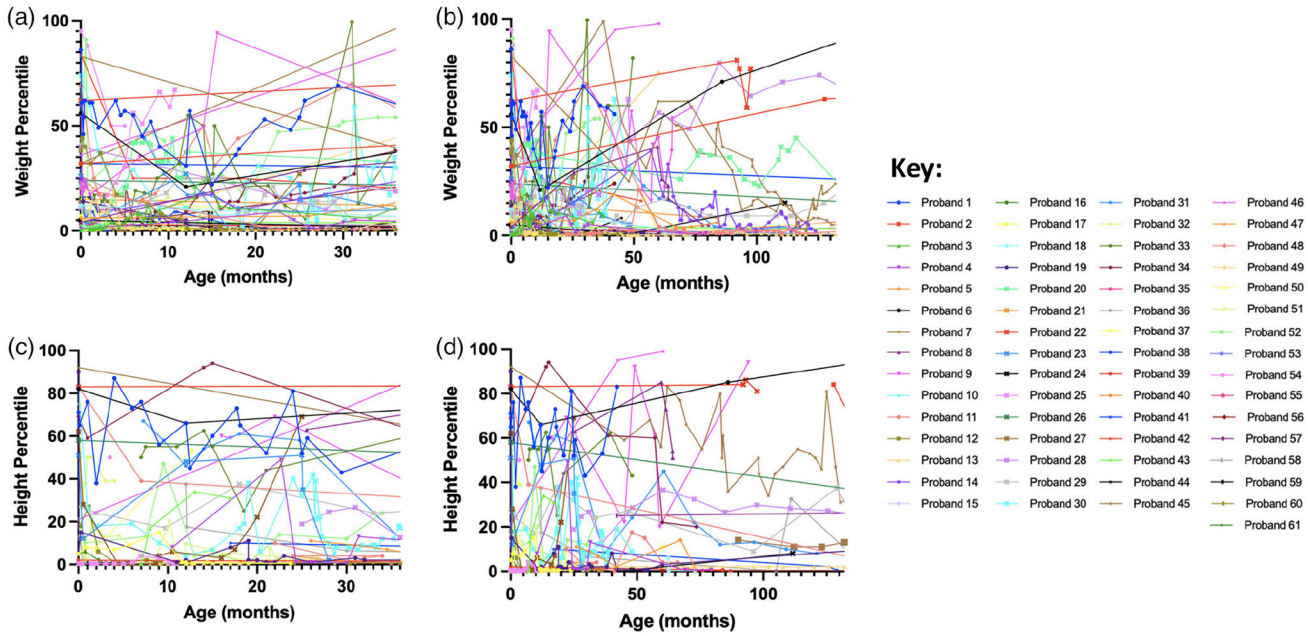

FIGURE 1.

Height and weight percentiles at different age ranges, to improve readability. (a). Weight percentiles during first 3 years of life. (b). Weight percentiles between 3 and 11 years old. (c). Height percentiles during first 3 years of life. (d). Height percentiles between 3 and 11 years old. If either weight or height data were not available for a particular proband, then this proband number was excluded from the graph. Of note, there is no available weight data for Proband 61 and no available height data for the following probands: 21, 44, 47, 49, 55, and 60.

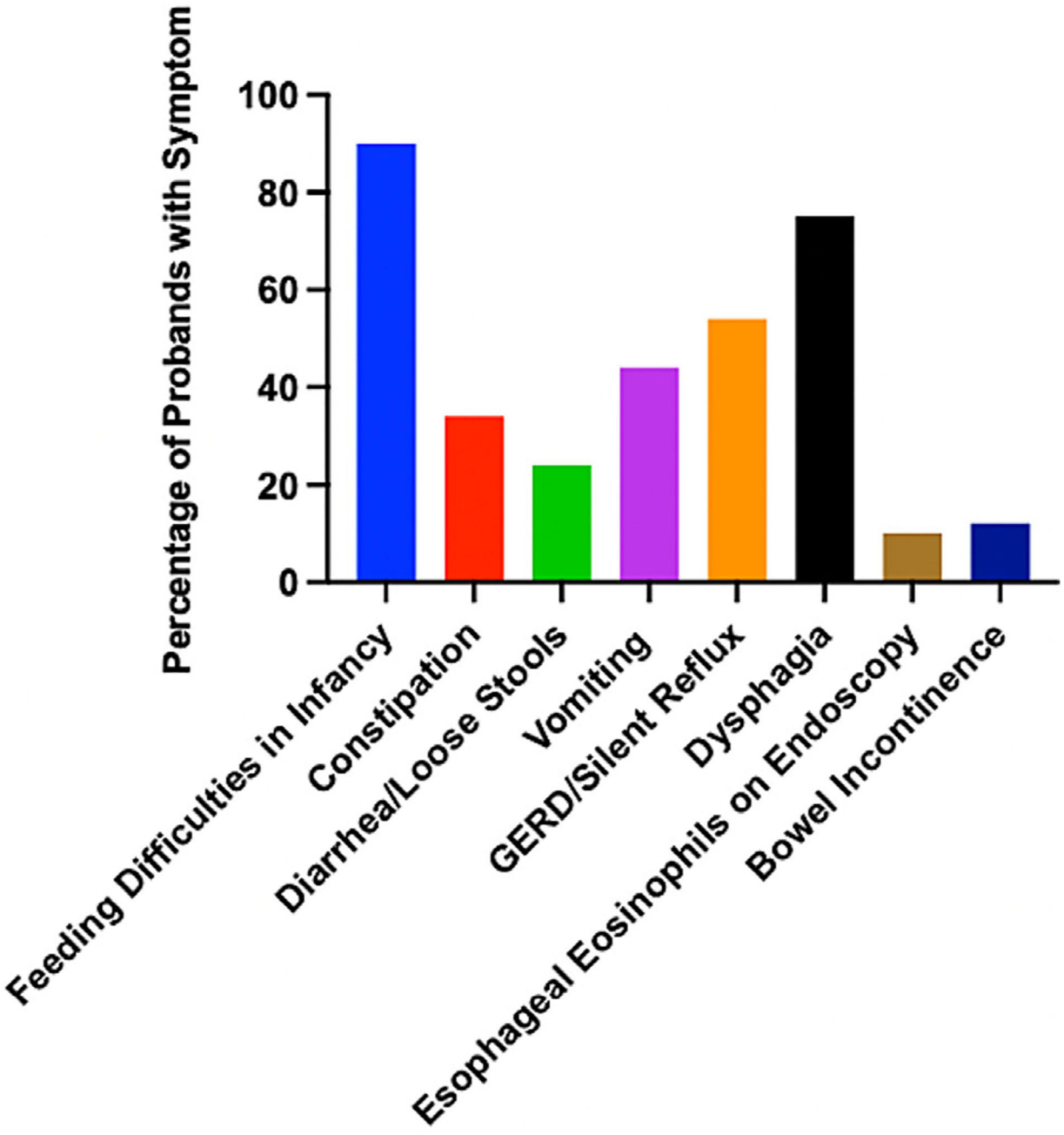

FIGURE 2.
Prevalence of gastrointestinal symptoms in analyzed probands.

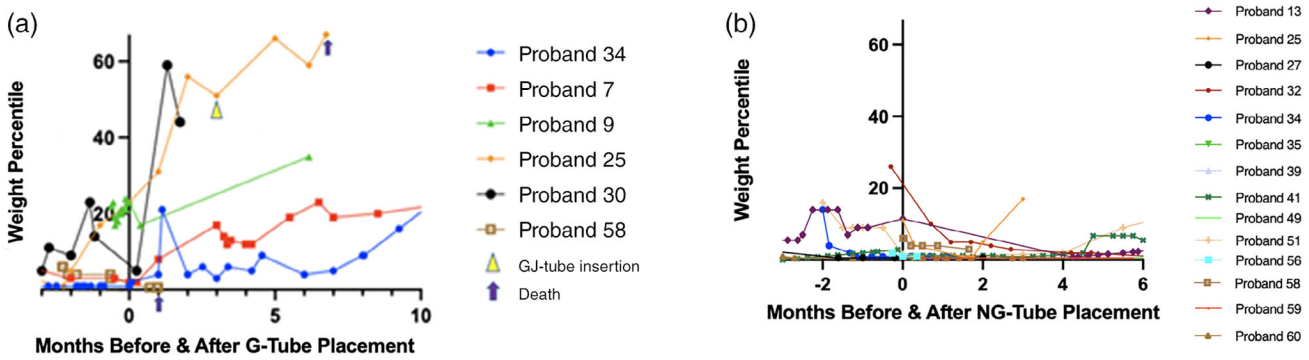

FIGURE 3.

Gastrostomy and nasogastric tube efficacy. (a) Weight percentiles of male and female probands before and after G-tube insertion. G-tube was inserted at $x = 0$ for probands in this figure. All points to the left of zero on the x-axis correspond to weight percentiles prior to G-tube insertion, and all points to the right of zero on the x-axis correspond to weight percentiles following G-tube insertion, while the G-tube was in place (and while utilized for nutrition by each respective proband). (b) Weight percentiles of male and female probands before and after NG-tube insertion. NG tube was inserted at $x = 0$ for probands in this figure. All points to the left of zero on the x-axis correspond to weight percentiles prior to NG-tube insertion, and all points to the right of zero on the x-axis correspond to weight percentiles following NG-tube insertion.

TABLE 1

Probands.

Proband assigned #	cDNA pathogenic variant	Protein variant	Sex of proband
1	c.259G>T	p.Ala087Ser	F
2	c.247C>T	p.Arg083Cys	F
3	c.247C>T	p.Arg083Cys	F
4	c.247C>T	p.Arg083Cys	F
5	c.215T>C	p.Ile072Thr	M
6	c.361C>G	p.Leu121 Val	F
7	c.384T>G	p.Phe128Leu	F
8	c.384T>G	p.Phe128Leu	F
9	c.384T>G	p.Phe128Leu	F
10	c.259G>T	p. Ala087Ser	F
11	c.311C>A	p. Ala104Asp	F
12	c.247C>T	p.Arg083Cys	F
13	c.247C>T	p.Arg083Cys	F
14	c.247C>T	p.Arg083Cys	F
15	c.247C>T	p.Arg083Cys	F
16	c.247C>T	p.Arg083Cys	F
17	c.247C>T	p.Arg083Cys	F
18	c.247C>T	p.Arg083Cys	F
19	c.247C>T	p.Arg083Cys	F
20	c.247C>T	p.Arg083Cys	F
21	c.247C>T	p.Arg083Cys	F
22	c.247C>T	p.Arg083Cys	F
23	c.247C>T	p.Arg083Cys	F
24	c.259G>T	p.Arg083Cys	F
25	c.247C>T	p.Arg083Cys	M
26	c.247C>T	p.Arg083Cys	F
27	c.542_551del	p.Glu181Alafs*67	M
28	c.047A>C	p.His016Pro	F
29	c.359A>C	p. His120Pro	F

Proband assigned #	cDNA pathogenic variant	Protein variant	Sex of proband
30	c.215T>C	p. Ile072Thr	M
31	c.440T>C	p. Met147Thr	F
32	c.384T>G	p. Phe128Leu	F
33	c.384T>G	p. Phe128Leu	F
34	c.367T>C	p.Ser123Pro	F
35	c.455_458del	p.Thr152Argfs*6	M
36	c.259G>T	p.Ala087Ser	F
37	c.247C>T	p.Arg083Cys	F
38	c.247C>T	p.Arg083Cys	F
39	c.247C>T	p.Arg083Cys	F
40	c.247C>T	p.Arg083Cys	F
41	c.247C>T	p.Arg083Cys	F
42	c.247C>T	p.Arg083Cys	F
43	c.247C>T	p.Arg083Cys	F
44	c.247C>T	p.Arg083Cys	F
45	c.346C>T	p.Arg116Trp	F
46	c.445C>T	p. Arg149Trp	M
47	c.30C>G, c.22C>T	p. Asp010Gly, p. Pro08Ser	F
48	c.440T>C	p.Met147Thr	F
49	c.440T>C	p.Met147Thr	F
50	c.384T>G	p.Phe128Leu	F
51	c.384T>G	p.Phe128Leu	F
52	c.383T>C	p.Phe128Ser	F
53	c.109T>C	p.Ser037Pro	M
54	c.92A>G	p.Tyr31Cys	F
55	c.128A>C	p.Tyr43 Ser	F
56	c.128A>C	p.Tyr43 Ser	M
57	c.128A>C	p.Tyr43 Ser	M
58	c.109T>C	p.Ser37Pro	M
59	c.109T>C	p.Ser37Pro	M
60	c.109T>C	p.Ser37Pro	M

Proband assigned #	cDNA pathogenic variant	Protein variant	Sex of proband
61	c.029A>G	p. Asp10Gly	M