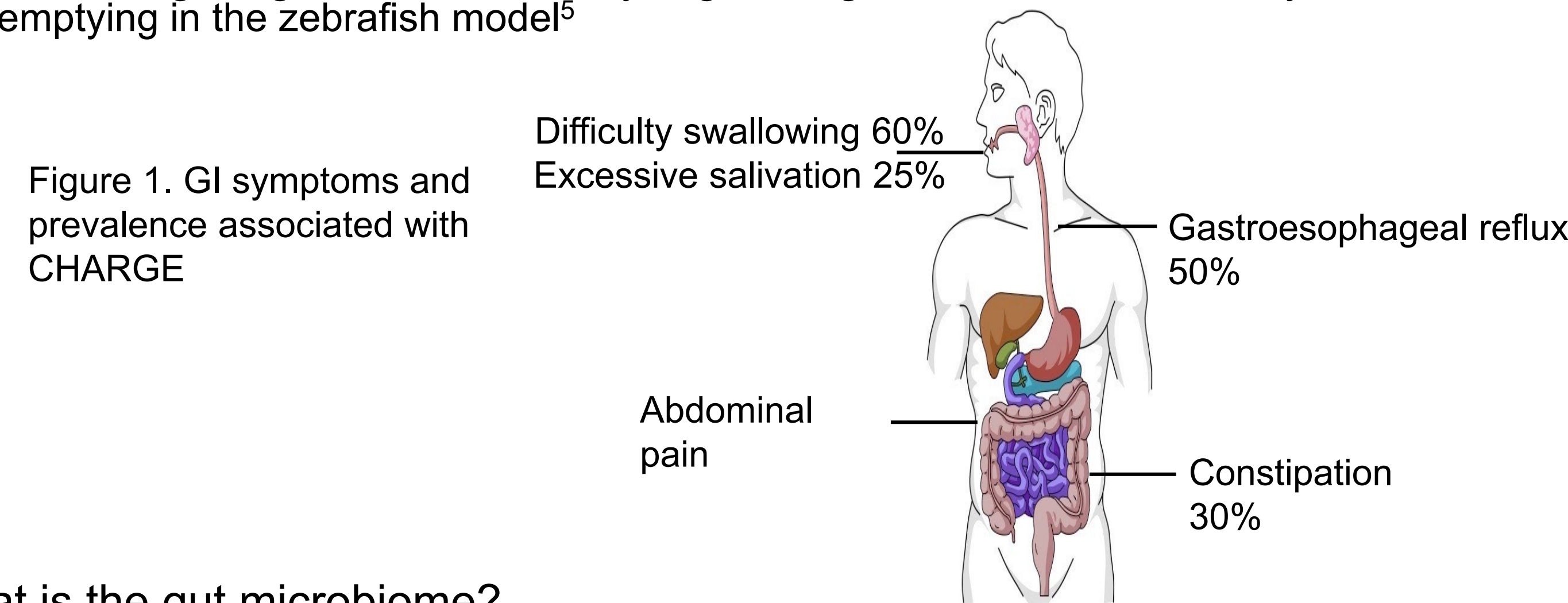


Background Information

- What is CHARGE Syndrome?
 - Congenital syndrome associated with Chd7 gene mutation
 - Leads to abnormal neural crest development
- What do we know about gastrointestinal (GI) symptoms in CHARGE?
 - Common GI symptoms and prevalence^{2,3} depicted in Figure 1.
 - The impact of gastrointestinal (GI) distress is considered similar in severity to patients with inflammable bowel disease (IBD)¹
 - Zebrafish with chd7 mutations also have fewer enteric and vagus nerves innervating the gut⁴. This leads to dysregulated gut contractions and delayed emptying in the zebrafish model⁵



- What is the gut microbiome?
 - Gut health is regulated by the colonies of bacteria that inhabit the GI tract called the gut microbiome.
 - Aids in metabolism, regulate the immune system and influence cognitive behaviour through the gut-brain axis.
 - Imbalances in the type and number of bacteria, called gut dysbiosis, has been implicated in health conditions such as IBD, IBS, autism, obesity, and cancer^{6,7}.

Question

- Does the gut microbiome in individuals with CHARGE syndrome differ compared to their unaffected sibling?
- Are there any characteristics that are common in the gut microbiome of people with CHARGE syndrome?

Methods

Participants: Pediatric patients across Canada with a confirmed genetic diagnosis of CHARGE syndrome, and when possible their unaffected sibling

Stool collection

-
- one time stool sample
 - DNA isolated and bacteria identified by 16S rRNA sequencing

PASSFP

-
- Measures severe feeding problems
 - Scored from 0-64

PEDSQL

-
- Gastrointestinal symptoms scale
 - Scores 10 domains of GI symptoms

Results

Total of 11 participants: 7 with CHARGE, 4 sibling controls

No significant difference between relative bacterial abundance at the phyla taxonomic level for individuals with CHARGE compared to sibling controls.

However, when individuals with CHARGE and severe GI symptoms (n=3) were compared to participants with normal GI scores (n=8) according to the PEDSQL questionnaire there was a **significant difference in Bacteroidetes and Firmicutes**.

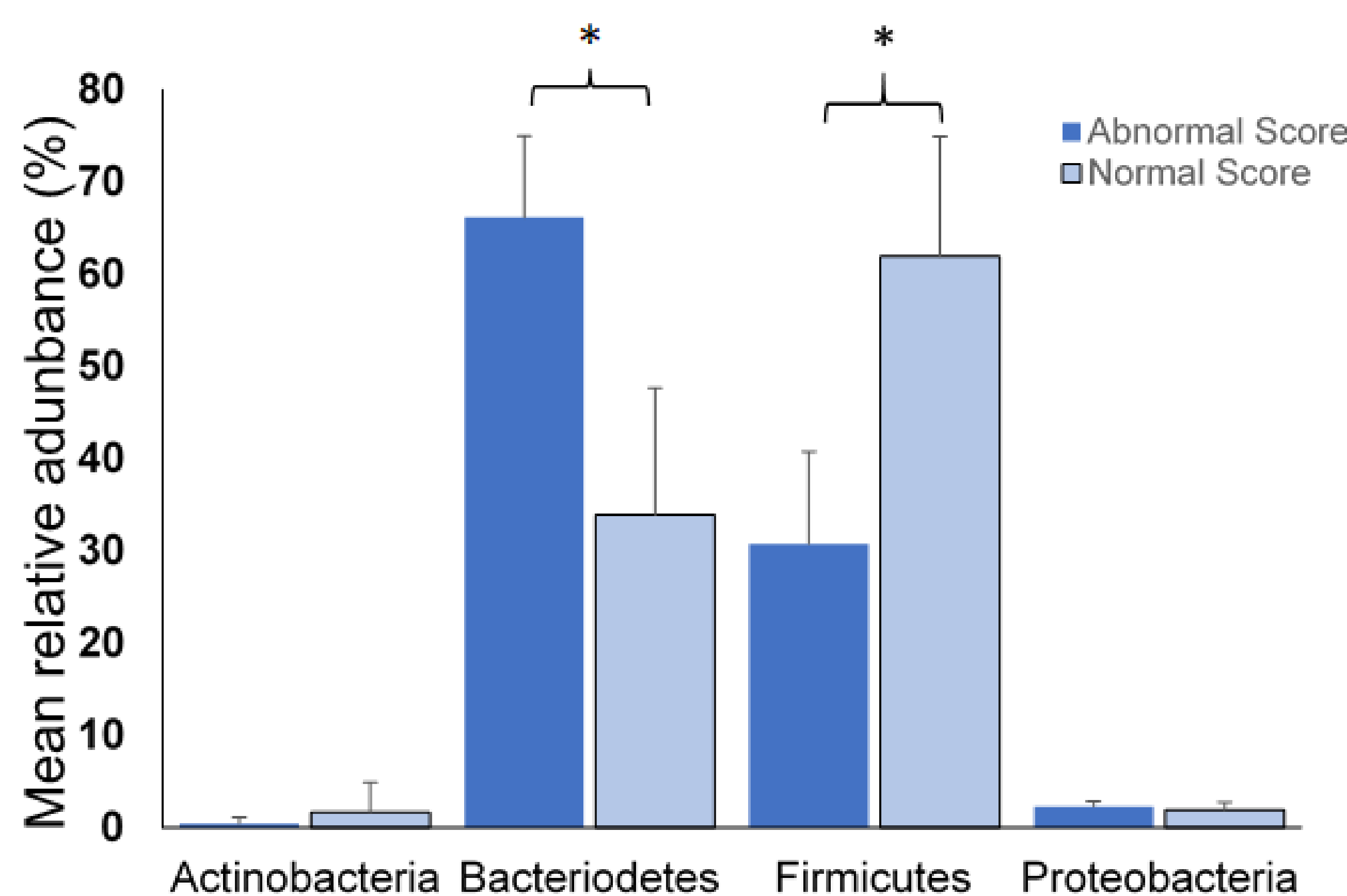


Figure 2. Mean relative abundance of the four most abundant bacterial phyla determined through 16S DNA sequencing of stool samples for participants with severe PEDSQL GI symptom score (less than 77) versus normal GI scores. There were 3 individuals with CHARGE in the abnormal score group and the 8 other participants had normal GI scores.

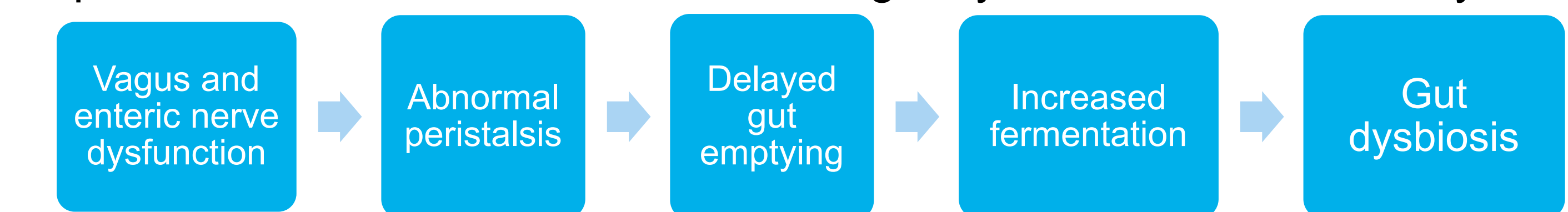
Table 1. **PEDSQL gastrointestinal symptom scale scores** for 10 different domains. Average score out of 100 and p-value given for participants with CHARGE syndrome versus the sibling control group.

	Mean Score		
	CHARGE	control	p-value
Stomach pain and hurt	82.14	100.00	0.099
Stomach discomfort when eating	88.57	100.00	0.135
Food and drink limits	73.81	100.00	0.042
Trouble Swallowing	72.62	100.00	0.009
Heartburn and Reflux	83.93	100.00	0.017
Nausea and Vomiting	91.07	100.00	0.082
Gas and Bloating	66.84	97.32	0.023
Constipation	54.08	85.71	0.015
Blood in bowel movement	100.00	100.00	-
Diarrhea	80.10	100.00	0.005
Total	76.80	95.44	0.002

Conclusion

- CHARGE syndrome displays a large phenotypic range and the gut microbiome is influenced by a number of possible confounding factors
- Our data showed a significant ↑Bacteroidetes and ↓Firmicutes abundances in the CHARGE gut microbiome when individuals had more severe GI symptoms
 - Firmicutes and Bacteroidetes are responsible for carbohydrate fermentation
 - A similar trend was observed in similar experiment done in Autism⁷
 - ↓Firmicute: often seen in IBD⁶
 - ↑Bacteroidetes: reported in IBS and chronic constipation⁸
 - Probiotic therapy has been shown to reduce anxiety-related behaviours in animals with vagus nerve dysfunction⁹
- This is preliminary research, however there may be a role for probiotic therapy or fecal microbiota transplantation as a last resort in this population with severe GI distress

Proposed mechanism for GI distress and gut dysbiosis in CHARGE Syndrome



Future Directions

- Awaiting metabolomic study results for an expanded population of 20 participants
- Stay tuned for a gut-brain axis study in the adult CHARGE population coming from our research group!

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