



Professional Day

Friday, August 2, 2019

Gastrointestinal (GI) and Feeding Difficulties in CHARGE Syndrome; the Guts of It

Kim Blake, MD, Professor, Dalhousie University

Presenter Information

Dr. Kim Blake is a professor of pediatrics at Dalhousie University in Nova Scotia, Canada. She has been researching CHARGE syndrome over the last 35 years and has published extensively. She has explored post-operative airway events, sleep apnea, bone health, cranial nerve abnormalities, and gastrointestinal issues. In the last 10 years Dr. Blake has partnered with Dr. Jason Berman and they have developed a zebrafish model of CHARGE syndrome to answer further research questions. With this model we have been able to understand about the abnormalities of the vagus nerve and gut mobility in CHARGE syndrome which has influenced our knowledge of gut motility. Anesthesia and sedation risk has also been researched in our zebrafish model. This supports the clinical findings that individuals with CHARGE syndrome have increased risk following anesthesia and should have combined procedures where possible, in one anesthesia. Kim is very proud of the CHARGE syndrome checklist which has been developed both for families, individuals, and professionals to use as a guide and a teaching tool for anybody dealing with CHARGE syndrome.

Presentation Abstract

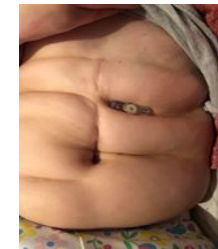
The aim of this presentation is to discuss the gastrointestinal (GI) symptoms and feeding difficulties in CHARGE syndrome.

Over 95% of individuals with CHARGE syndrome experience feeding and gastrointestinal (GI) dysfunction. The structural abnormalities, motility impairment and sensory impairment all contribute to the GI issues and are potential treatment targets. I will describe how cranial nerve abnormalities underlines the pervasive GI dysfunction and the need for further research on gut motility and the microbiome. Much of the work has come from Dr. Blake's laboratory/team at Dalhousie University in Canada. She will describe the clinical and basic science research that has been completed over the last 10 years. A recent publication titled "Etiology and functional validation of gastrointestinal motility dysfunction in a zebrafish model of CHARGE syndrome" will be discussed. Dr. Blake will also touch on the microbiome and preliminary data from her students.

Learning Objectives

- To leave you more knowledgeable and inspire you to ask questions about the forgotten gastrointestinal (GI) issues in CHARGE syndrome.
- To share with you and your family the CHARGE syndrome checklist (Trider et al 2017) and the feeding assessment scale (Hudson et al).
- To be an advocate for the CHARGE "gut" and move the research forward in gut motility and the microbiome.

Gastrointestinal (GI) and feeding difficulties in CHARGE syndrome; the guts of it.



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Dr. Blake's virtual lab



<http://www.drkimblake.com>

IWK Health Centre 2019

The gut is different in CHARGE syndrome

Gastrointestinal (GI) issues arise from

- Structural abnormalities
- Motility impairment
- Sensory impairment

These are all potential targets for treatment

Gastrointestinal and feeding difficulties in CHARGE syndrome: A review from head-to-toe

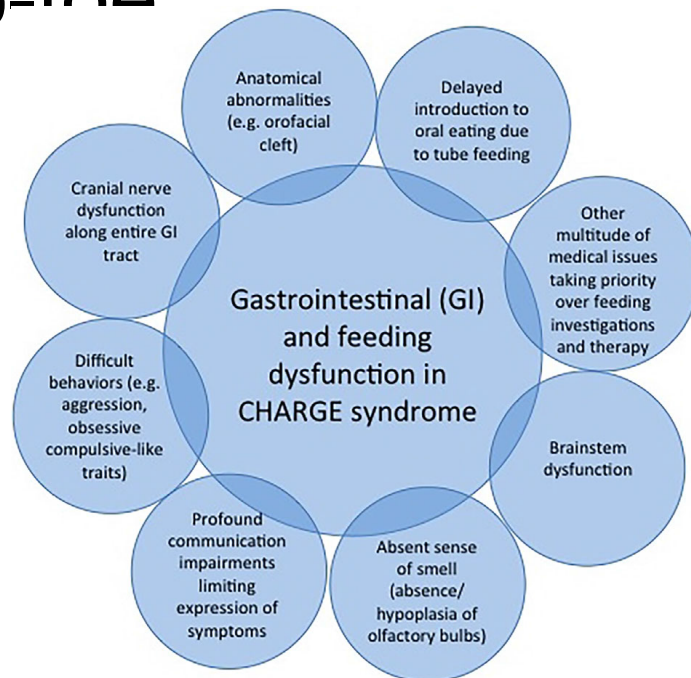


TABLE 1 CHARGE syndrome characteristics and resulting feeding and gastrointestinal manifestations

Phenotypic consequence	Frequency in the CHARGE syndrome population Bergman et al. (2011); Hale et al. (2016)	Feeding and gastrointestinal manifestations
Coloboma of the iris, retina, choroid or disc (unilateral or bilateral)	75–89%	<ul style="list-style-type: none"> Interfere with feeding process Poor hand-eye coordination when feeding
Choanal atresia/stenosis (unilateral or bilateral)	38–61%	<ul style="list-style-type: none"> Disturbance and incoordination of respiration during sucking
Cranial nerve (CN) dysfunction		
CN I (olfactory)	86–100%	<ul style="list-style-type: none"> Decreased interest in food Reduced taste
CN V (trigeminal)	86–100%	<ul style="list-style-type: none"> Abnormal chewing Decreased sensation around mouth can cause food falling out of mouth
CN VII (facial)	86–100%	<ul style="list-style-type: none"> Interference with chewing ability Decreased taste Inability to retain salivary secretions or

TABLE 2 A summary of currently available treatment options for gastrointestinal and feeding difficulties, from head to toe, in CHARGE syndrome

Gastrointestinal/feeding dysfunction	Currently available treatment options
Absent/decreased sense of smell	<ul style="list-style-type: none"> Use of strong tasting foods
Anatomical anomalies (choanal atresia/stenosis, cleft palate/lip, larynx/pharynx defects, vascular rings, etc.)	<ul style="list-style-type: none"> Surgical repair
Overcrowded oral cavity	<ul style="list-style-type: none"> Tonsillectomy and adenoidectomy
Excess salivation	<ul style="list-style-type: none"> Botulinum toxin A (Botox) injection into salivary glands Combining multiple surgeries at one time to minimize use of anesthetic and risk of postoperative airway events
Aspiration	<ul style="list-style-type: none"> Tube feeding (nasogastric, gastrostomy, jejunostomy) Texture limited diet (e.g., puree only) Feeding therapy to improve oral feeding skills Treatment of gastroesophageal reflux disease
Packing (pocketing food into cheeks) and mouth over-stuffing	<ul style="list-style-type: none"> Avoidance of bread/pasta type foods Liquid chasers (e.g., water, puree) after taking bites of food Cutting food into small pieces
Choking	<ul style="list-style-type: none"> Checking cheeks for any left over food Using a timer to pace swallowing and eating during meal time Close supervision during eating Texture limited diets
Cranial nerve dysfunction (CN V, VII, VIII, IX, X, XI)	<ul style="list-style-type: none"> Feeding therapy to re-learn feeding process if neurological function improves with age Potential for nerve stimulation (further research is needed)

ANN NY MED J.
2017;1-11

The upper GI tract

Cranial nerve innervations and structural abnormalities are key issues

- Cranial facial abnormalities can interfere with feeding particularly in infancy.
- Children with choanal atresia/stenosis have significantly more GI symptoms than those without.#
- Excessive salivation secretion can be a problem
- Mouth over stuffing and pocketing is prevalent.*



Gastroesophageal Reflux (GER) and tube feeding



- Gastroesophageal Reflux is often severe and difficult to treat.
- Tube feeding is highly prevalent and can be protracted
- Tube feeds vs. oral feeders have more
 - Stomach pain
 - Discomfort when eating
 - Food and drink limits
 - Trouble swallowing
 - Nausea and vomiting
 - Constipation

“Motility issues” are a key problem.

Macdonald et al 2016 AJMG

Abdominal Pain

- Prevalent and difficult to assess and the underlining diagnosis is often missed.
- Digestion issues are clinically present. There has been very little research in this area.

“The gut is different in CHARGE syndrome”



Hartsthorn and Straton,
Research on pain scale

Constipation

How many of you have problems with this?



Prevention:

- Fluids
- Exercise
- Behavioral therapy
- Diet
- Massage

Treatment:

- Polyethylene glycol / MiraLAX
- PEG
- Senocot (motility agents)
- Behavioral techniques

Risk factors for poor bone health in adolescents and adults with CHARGE syndrome.

Key Findings

- 87% of individuals are not getting enough vitamin D
- 41% not getting enough calcium

Recommendations:

- Increase in the amount of calcium and vitamin D
- Replace sex hormones.
- Increase in weight bearing activity
- # 1000 iu Vit D



Forward 2007 AJMG

Conditions that are missed and need to be on the differential diagnosis

- Abdominal colic
- Pocketing/
Overstuffing
- Gall stones
- Dumping syndrome



Letter to the Editor | [Free Access](#)

Late Dumping Syndrome in a 17-Year-Old Female With Charge Syndrome

Mr Angus Morgan, Ms Alexandra Hudson, Professor Angela Arra-Robar, Dr Kim Blake

First published: 04 December 2017 | <https://doi.org/10.1111/jpc.13724>

Conflict of interest: None declared.

PDF TOOLS SHARE

IWK CHARGE Clinic Students & Residents Using the CHARGE Checklist

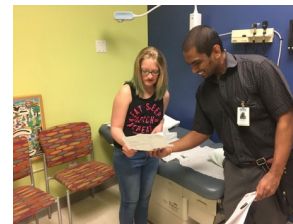
**CHARGE SYNDROME CHECKLIST: HEALTH SUPERVISION ACROSS THE LIFESPAN
(FROM HEAD TO TOE)**

**Shaded boxes indicate key assessment points*

		INFANCY (0-2 years)	CHILDHOOD (3-11 years)	ADOLESCENCE (12-17 years)	ADULTHOOD (18+ years)
GENETICS	Clinical diagnosis (Blake et al. or Verloes or Hale et al. criteria)				
	Genetic testing – Genetics consult (CNU/ analysis, array CNU) Genetic counselling				
NEUROLOGY	CNS malformations/hypoplasia olfactory bulb/temporal bone (semicircular canal) malformations – requires MRI/CT				
	Seizures – more common at older ages – consider EEG Cranial nerve problems – monitor for absent sense of smell, facial nerve palsy, sensorineural hearing loss, vertigo, swallowing problems				
EYES, EARS, NOSE AND THROAT	Coloboma, risk of retinal detachment & Ophthalmology consult (dilated eye exam in infancy, vision assessments) Lacrimal exposure – lubricating eye drops Photophobia – tinted glasses, sunhat Laryngeal atresia/cleft palate/tracheoesophageal fistula & TBI/Plastics consult Adaptive services for individuals with deafness/blindness Uchlear implant assessment if applicable Obstructive sleep apnea – monitor for tonsil/adenoid hypertrophy Excessive secretions – consider botox, medication Dental issues – consider desling under anesthetic				
	Cardiac malformations common – major/minor defects, vascular ring or arrhythmias possible (echocardiogram, chest x-ray, ECG) & Cardiology consult Tumours, pneumonia, asthma & monitor Anesthesia risk (difficult intubations/postop airway obstruction/aspiration) – extensive preoperative assessment, combine surgical procedures				
GASTROENTEROLOGY Gastrointestinal	Gastroesophageal reflux – Gastroenterology consult – consider motility agents with proton pump inhibitor Poor suck/chew/swallow & feeding team assessment/intervention Aspiration risk, tracheoesophageal fistula – swallowing studies May need supplemental feeds – frequently requires gastrostomy tube or Gastro-jejunostomy tube Constipation – consider Jenna glyceride with polyethylene glycol				
	Renal anomalies – abdominal u/s +/- VUUG, blood pressure monitoring Hypogonadotropic hypogonadism – LH, FSH by 3 months Genital hypoplasia (if undescended testes & consider orchiopexy) Delayed puberty – Endocrinology consult & gonadotropin levels, MRI Uterovaginal anomalies – Uterine scan Poor growth – Endocrinology consult – GH stimulation test, GH therapy Liberty & monitor Fertility and contraception & discuss				
IMMUNE SYSTEM	Note presence of thymus at open heart surgery Routine immunizations/antibody titres to immunizations in adolescence Recurrent infections – Immunology consult Scoliosis/kyphosis monitor				
	Mobility (affected by ataxia, hypotonia) & evaluate Assess gross and fine motor skills – Occupational Therapy, Physiotherapy Communication, language, writing abilities – Speech Language Therapy Consider deafblind consultant Prepare for transitions to school, situations, places, systems Psychoeducational assessment, Individualized Education Plan Sleep disturbances – consider melatonin Behavior management – self regulation, impulse control, anxiety, obsessions, compulsions, anger Learning skills & support Life skills/adaptive behaviour/social skills/social play Address sexuality Family stress – offer supports and resources Medical self-management – work on managing medications, understanding conditions, seeing healthcare provider independently				

**Abbreviations listed on page 2*

Trider C, ArraRobar A, van RavenswaayJArts C, Blake K



<http://www.drkimblake.com>

A feeding scale for CHARGE syndrome

Date: _____

Name of Individual: _____

Age: _____ Gender (Circle one): Male Female Not Disclosed

Completed By (Circle one): Mother Father Feeding Therapist Nurse/Physician Other: _____

What percentage of your child/adult's daily fluid/nutrition intake is by G/I tube feeding? (Circle one percentage):

0%	25%	50%	75%	95%
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Circle one number on the scale:		Never	A Little	Sometimes	A lot	Always
1	He/she will refuse food when eating orally.	0	1	2	3	4
2	He/she takes longer than 45 minutes to eat orally.	0	1	2	3	4
3	He/she takes less than 15 minutes to eat orally.	0	1	2	3	4
4	He/she needs close supervision when eating orally.	0	1	2	3	4
5	He/she needs someone in the room when eating orally.	0	1	2	3	4
6	He/she has problems cutting food when eating orally.	0	1	2	3	4
7	He/she has problems feeding him/herself when eating orally.	0	1	2	3	4
8	He/she chokes or coughs when eating orally.	0	1	2	3	4
9	He/she has trouble chewing food.	0	1	2	3	4
10	He/she has trouble swallowing food.	0	1	2	3	4
11	He/she has to be told or reminded to chew.	0	1	2	3	4
12	He/she has to be told or reminded to swallow.	0	1	2	3	4
13	He/she does not like to mix food textures when eating (e.g. mixing puree and solid food).	0	1	2	3	4
14	He/she accidentally loses food out of his/her mouth during eating.	0	1	2	3	4
15	He/she will over-stuff his/her mouth with food during eating.	0	1	2	3	4

16	He/she has difficulty moving food around with his/her tongue during eating.	0	1	2	3	4
17	He/she has a hard time feeling food or anything touching the inside of his/her mouth.	0	1	2	3	4
18	He/she dislikes oral eating.	0	1	2	3	4
19	He/she lets food sit in his/her cheeks or palate during eating (on purpose or not).	0	1	2	3	4
20	He/she will have food hidden in his/her cheeks or palate after the meal has ended (on purpose or not).	0	1	2	3	4
21	The Parent/Caregiver gets worried about their child/adult's ability to eat orally.	0	1	2	3	4
22	The Parent/Caregiver has difficulties feeding their child/adult. (e.g. preparing food the right way, getting enough information about helping them eat/drink)	0	1	2	3	4
Does the child/adult have problems with:		No		Yes		
23	Cold foods	0		1		
24	Room temperature foods	0		1		
25	Warm foods	0		1		
26	Thin liquids (e.g. water)	0		1		
27	Pureed foods (e.g. applesauce)	0		2		
28	Mashed lumpy food (e.g. mashed potatoes or mashed vegetables)	0		2		
29	Soft chewable foods (e.g. bread, crackers)	0		2		
30	Tough chewable foods (e.g. meat)	0		1		
31	Hard vegetables and fruit (e.g. raw apples)	0		1		
Total Score (sum of all items)		/100 total points				
Circle one:		Feeding difficulties: Mild (0-25 points) Moderate (26-50 points) Severe (51-100 points)				

Subsection of Feeding Scale

Circle one number on the scale:		Never	A Little	Sometimes	A lot	Always
16	He/she has difficulty moving food around with his/her tongue during eating.	0	1	2	3	4
17	He/she has a hard time feeling food or anything touching the inside of his/her mouth.	0	1	2	3	4
18	He/she dislikes oral eating.	0	1	2	3	4
19	He/she lets food sit in his/her cheeks or palate during eating (on purpose or not).	0	1	2	3	4
20	He/she will have food hidden in his/her cheeks or palate after the meal has ended (on purpose or not).	0	1	2	3	4

Scoring of feeding scale for CHARGE syndrome

<http://www.drkimblake.com>

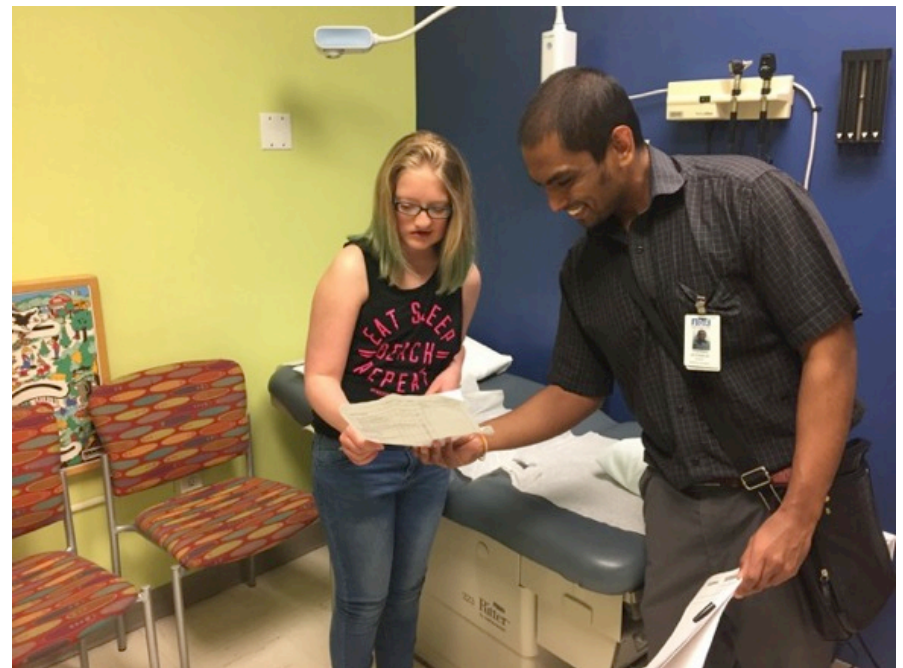
29	Soft chewable foods (e.g. bread, crackers)	0	2
30	Tough chewable foods (e.g. meat)	0	1
31	Hard vegetables and fruit (e.g. raw apples)	0	1
Total Score (sum of all items)			/100 total points

Out of 100 points
Higher score = worse feeding difficulties



The feeding scale for CHARGE Syndrome; used to

1. Assess the severity of feeding difficulties
2. Track oral feeding progress before and after interventions
3. Warn the clinician and feeding therapist of new concerns



Etiology and functional validation of Gastrointestinal motility dysfunction in a zebra fish model of CHARGE syndrome

Loss of chd7 in zebrafish results in:

- Smaller stomachs and GI tracts with normal epithelial and muscular histology.
- Decrease and disorganized vagal nerve projections particularly in the fore gut.
- Less ability to empty their GI tract only minimally improved by pro kinetic agents.



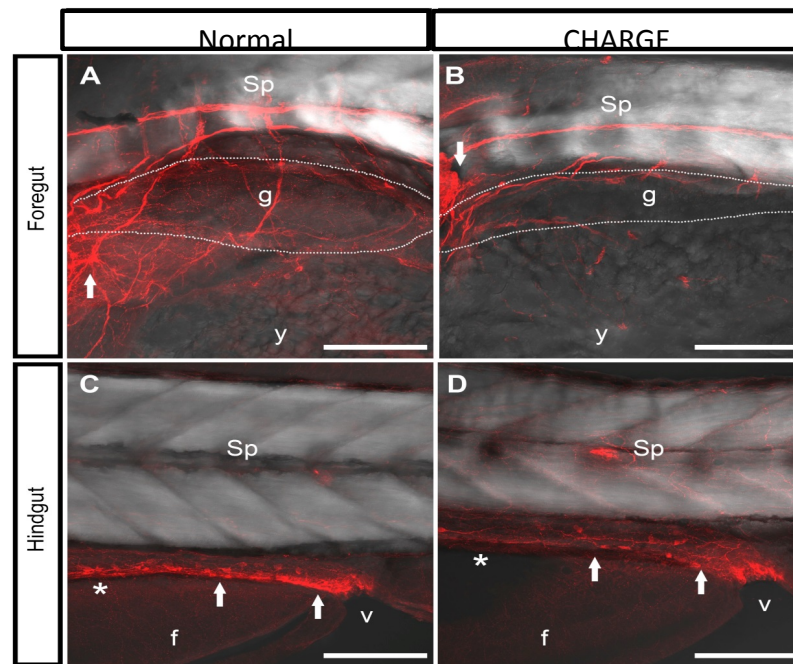
Future

Zebrafish are an excellent model for studying compounds that improve GI motility in individuals with CHARGE syndrome.

International Journal of Pediatric Otorhinolaryngology V82, March 2016, pgs. 107-115

Clooney et al FEEBS 285,11, 2018

Innervation of the CHARGE Zebrafish (*chd7*) and normal controls in the gut



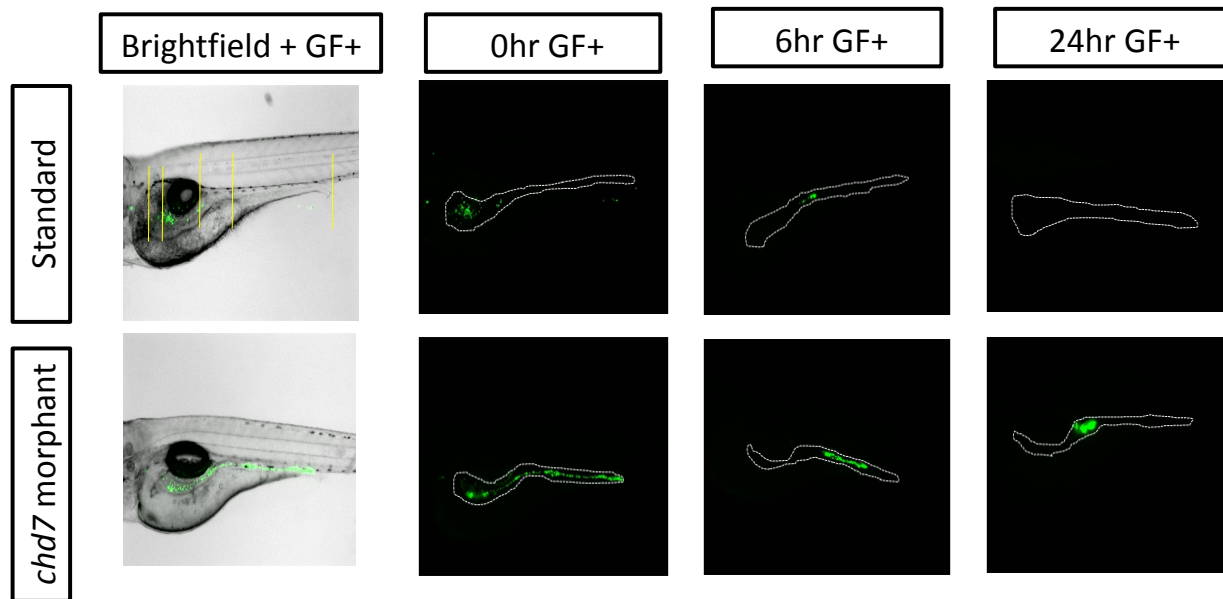
- Decreased enteric nerve branches around the fore gut (Compare A & B)
- Difference in size and shape of the gut in the CHARGE fish.

Sp = spine, F = ventral fin, V = vent, G = gut (outlined in hashed line), arrow = vagal nerve plexus, y = yolk

Clooney et al FEEBS
285,11, 2018

International Journal of Pediatric
Otorhinolaryngology V82, March
2016, pgs. 107-115

Decreased motility shown in CHARGE zebrafish by delayed emptying of GI tract



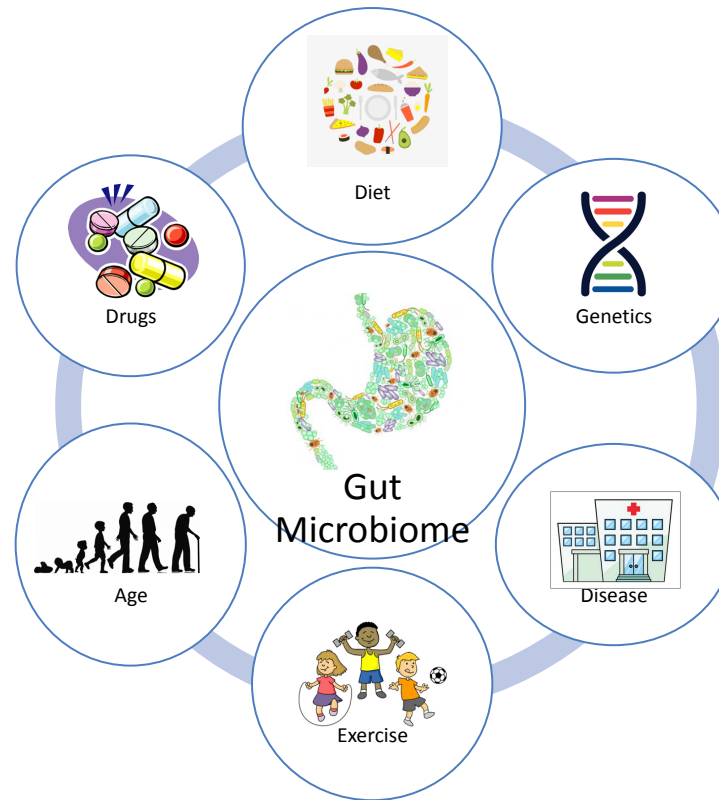
*Florescent green = tagged food travel. GI tract of zebra fish over time

Microbiome

Background

- Food travels from mouth to anus through the *gastrointestinal tract (GI tract)*
- Food is digested and excreted along the way by chemicals and precise movements in the GI tract

BUT... there are also trillions of *bacteria* and other organisms that help keep our guts healthy = **GUT MICROBIOME**



Gut dysbiosis

Typical microbiome contains:

- Firmicutes
- Actinobacteria
- Bacteroidetes
- Proteobacteria

When these change in *type* or *number* and cause GI distress → **dysbiosis**

Gut dysbiosis is associated with GI disorders and extra-intestinal disorders:

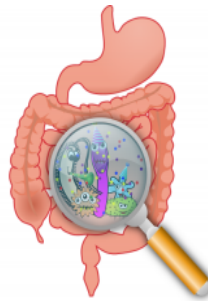
- Crohn's/Colitis
- Irritable bowel syndrome
- Obesity
- Autism
- Etc....

Research Question

1) Does the gut microbiome differ in individuals with CHARGE syndrome compared to individuals who are not affected with CHARGE?

2) If so, does the change in gut microbiome correlate with the severity of GI symptoms?

3) And does the CHARGE gut microbiome correlate with dietary factors?



Study Design

Participants: Individuals with CHARGE syndrome from the Canadian Maritimes and if possible, their sibling who is unaffected by CHARGE

- 7 individuals with CHARGE (proband)
- 4 sibling controls (subject)

Each participant provided:

- a stool sample
- a Block Food Screener
- a PedsQL GI symptom severity questionnaire

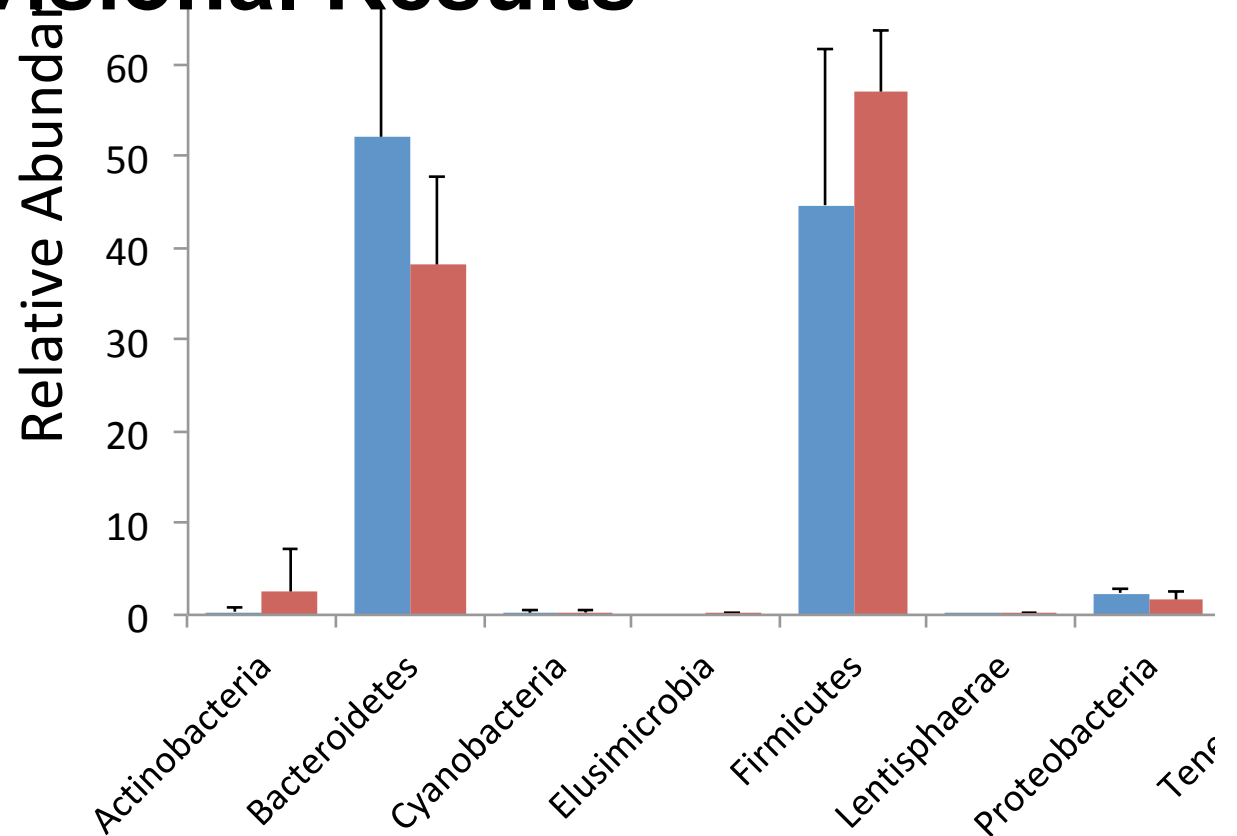
Provisional Results

N = 11

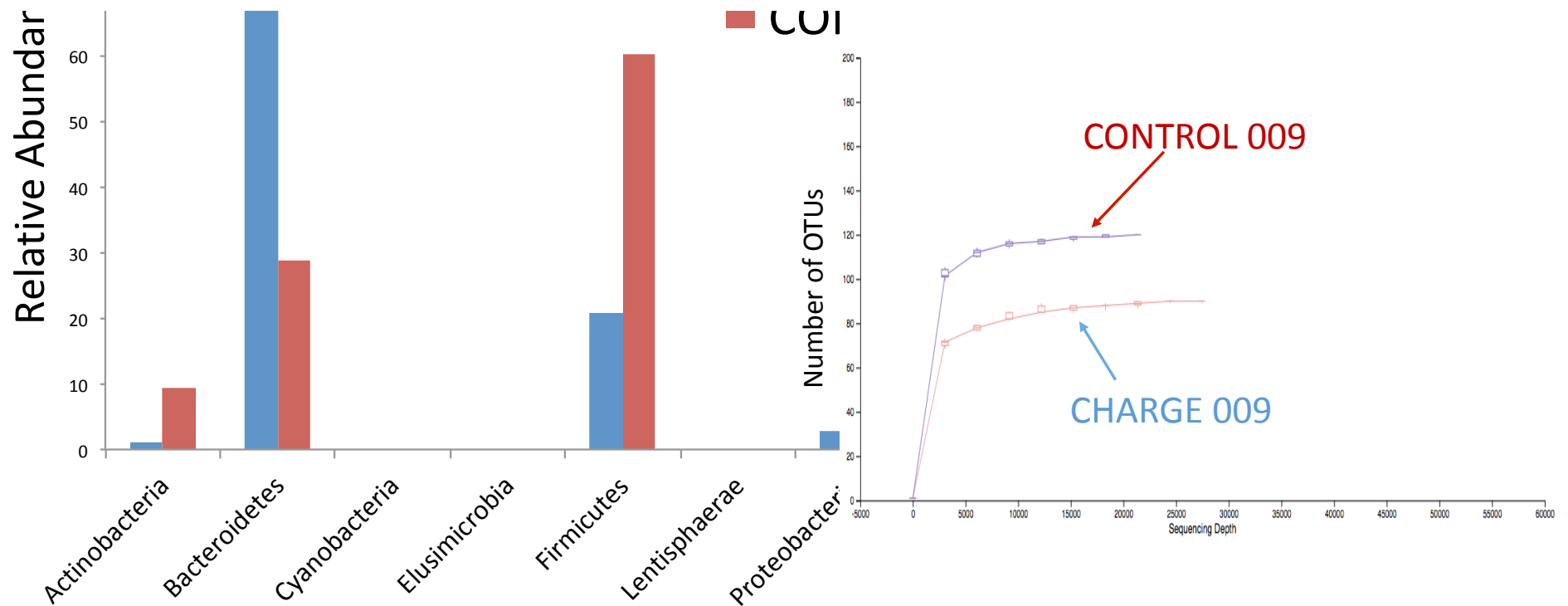
- CHARGE n=7
- Control n=4

Figure 1: Average relative abundance of bacteria phyla found in the gut microbiome of individuals with CHARGE (blue) and sibling control (red)

No significant differences

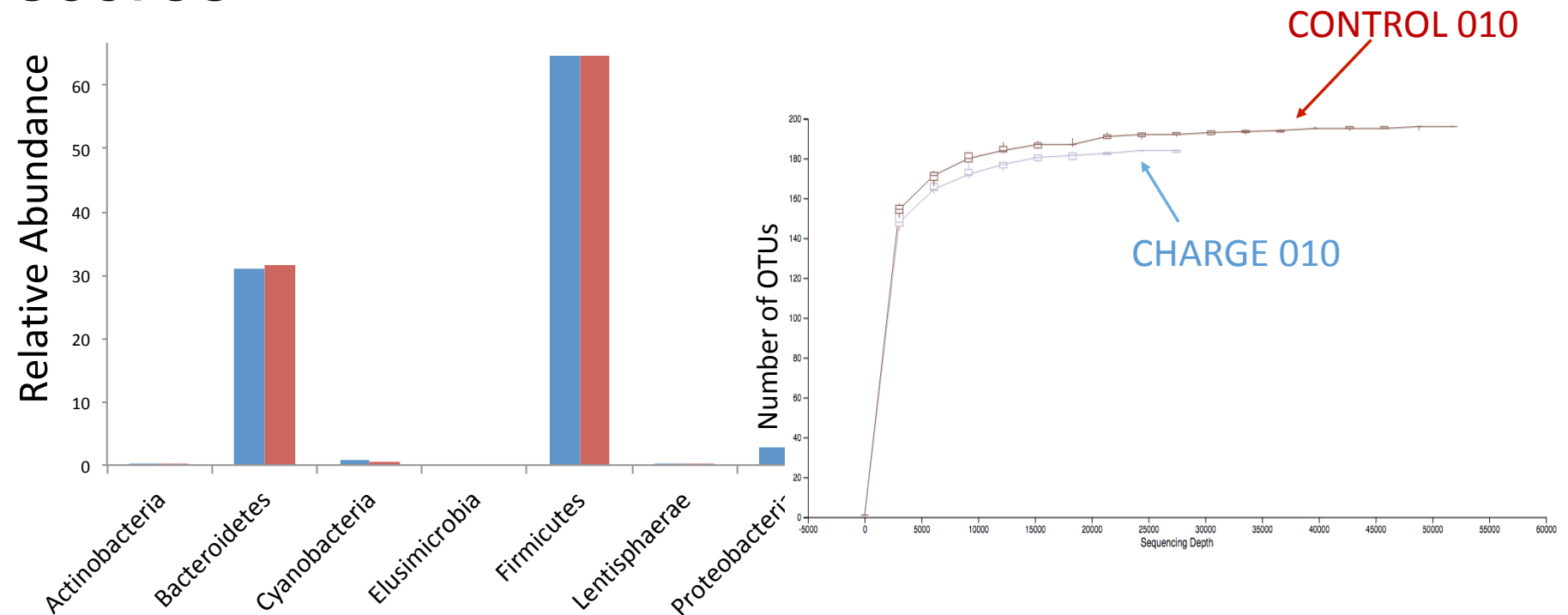


Comparing one sibling pair with different GI scores



The sibling with CHARGE had moderate feeding difficulties according to PASSFP; the control sibling had no feeding difficulties

Comparing one sibling pair with similar GI scores



The sibling pair scored within low range of feeding difficult and GI symptoms for the PASSFP and PEDSQL questionnaires

Discussion and Conclusion

- The CHARGE microbiome is different in our provisional results
- Trend: ↑ Bacteroidetes ↓ Firmicutes and ↓ diversity
 - Bacteroidetes are important for maintaining a healthy gut, regulating the immune system and the gut-brain axis
 - Firmicutes ferment carbohydrates in the gut. Decrease also seen in IBD.
 - Decreased diversity is also seen in IBD, IBS, obesity and autism and is related to increased susceptibility to diseases
- Next steps: increase study population, compare microbiome according to feeding types and specific GI symptoms, use software to assess functional impact of the altered bacteria

Novel Therapies for dysbiosis

Fecal Transplantation



- Stool from a healthy donor → screening → transplant to patient
- Some formulas are being made in labs instead of needing donor
- Transplant can be per rectum or orally
- Found effective in *C. difficile* infection and IBD
- Risks include transmission of infection missed during screening and risks associated with colonoscopy

Questions and Answers

