

**Dr. Kim Blake
(Canada)**

Saturday, June 19, 2021

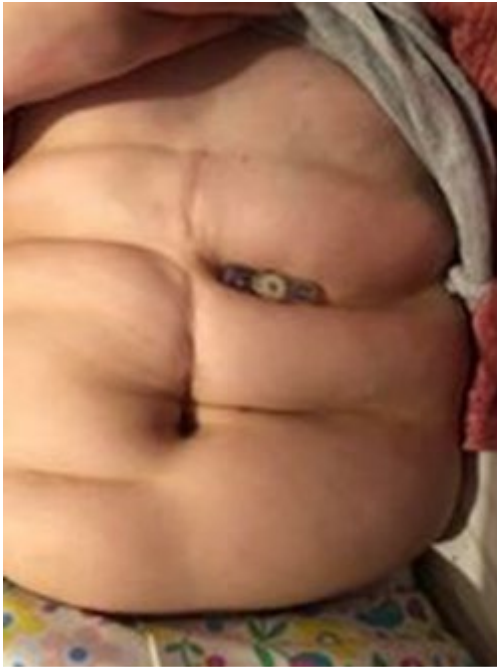
02.00 – 03.00 p.m.

**CEST- Central European Summertime
(Germany)**

***“The guts in CHARGE syndrome
Review of the gastrointestinal
tract
including motility, microbiome,
vagus nerve and POTS”***

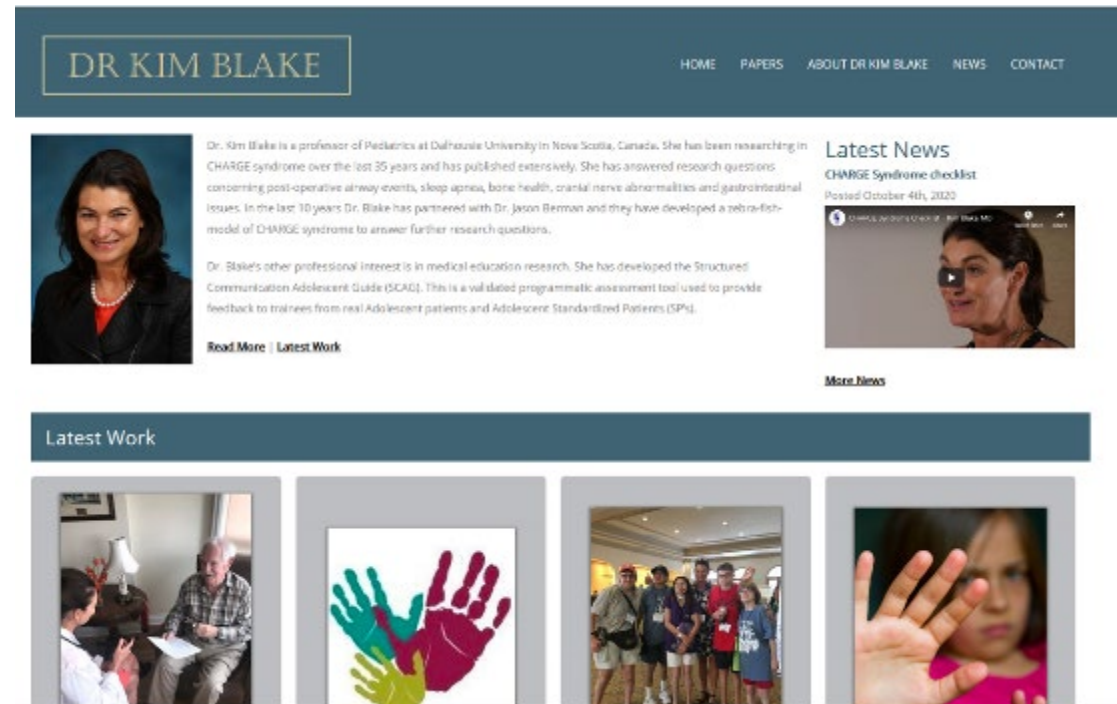
The Guts in CHARGE syndrome Review of the gastrointestinal tract including motility, microbiome, vagus nerve and POTS

German CHARGE online conference – Oberwesel, Germany
June 18th – 20th



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From my virtual lab to yours



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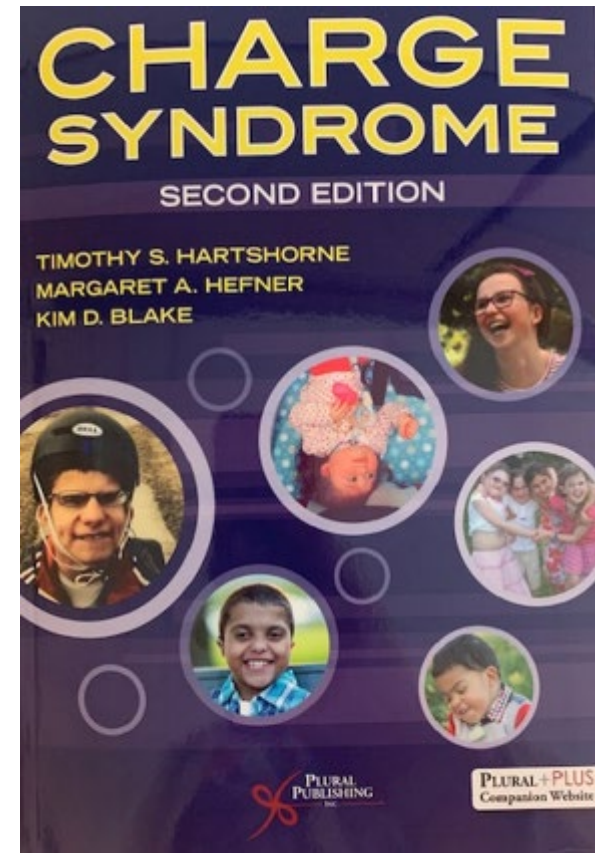
Objective

You will understand that the gut is different in
CHARGE Syndrome

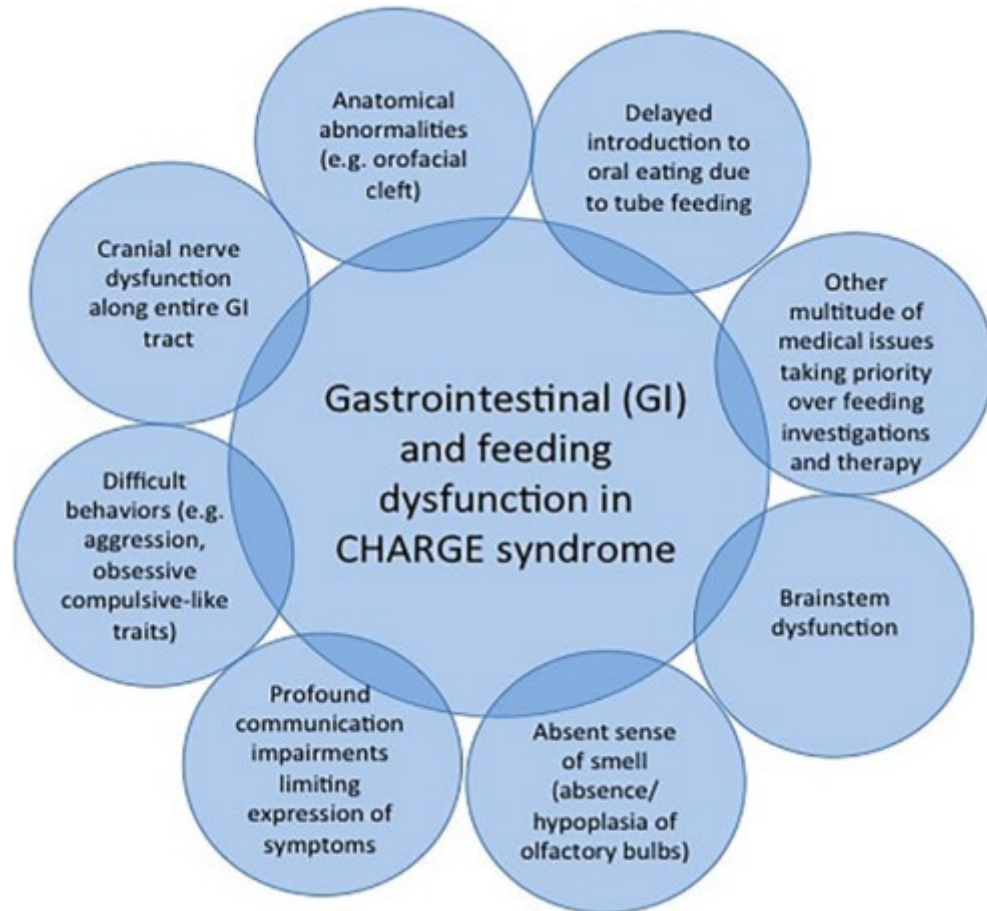
Gastrointestinal (GI) Issues arise from

- Structural abnormalities
- Motility impairments
- Sensory impairments
- Abnormal Microbiome

These are all potential targets for
treatment



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



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RESEARCH REVIEW

WILEY AMERICAN JOURNAL OF
medical genetics
Seminars in Medical Genetics

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

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CHARGE syndrome is an autosomal dominant genetic condition that is primarily diagnosed based on clinical features, with genetic testing available for confirmation. The CHARGE mnemonic stands for some of the common characteristics: coloboma, heart defects, atresia/stenosis of the choanae, retardation of growth/development, genitourinary anomalies, and ear abnormalities (CHARGE). However, many of the common clinical features are not captured by this mnemonic, including cranial nerve dysfunction, considered by some to be one of the major diagnostic criteria. Over 90% of individuals experience feeding and gastrointestinal dysfunction, which carries great morbidity and mortality. The aim of this review is to examine the nature of gastrointestinal (GI) symptoms and feeding difficulties in CHARGE syndrome, focusing on their underlying pathology, associated investigations, and available treatment options. We also provide information on available tools (for parents, clinicians, and researchers) that are important additions to the lifelong healthcare management of every individual with CHARGE syndrome. We review how cranial nerve dysfunction is

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



“Motility issues” are a key problem.

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

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 because of motility and microbiome abnormalities”



Straton, Hartshorne 2012 CHARGE non-verbal pain assessment (CNVPA)

Constipation

How many of you have problems with this?



Prevention:

- Fluids
- Exercise
- Behavioral therapy
- Diet
- Massage

Treatment:

- Polyethylene glycol PEG
MiraLAX/Ristorlax
- Senocot
- Behavioral techniques

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

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



Figure 10–3. A swallow prompt can help with oral feeding issues.



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.

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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 (LNU) / analysis, array (LNU)				
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)				
Corneal exposure – lubricating eye drops				
Photophobia – tinted glasses, sunhat				
Uvula atresia/cleft palate/tracheoesophageal fistula & ENT/Plastics consult				
Audiometry and tympanometry, monitor for recurrent ear infections				
Adaptive services for individuals with deafness/blindness				
Cochlear implant assessment if applicable				
Obstructive sleep apnea – monitor for tonsil/adenoïd hypertrophy				
Excessive secretions – consider Sialix, medication				
Dental issues – consider cleaning under anaesthetic				
CARDIOLOGY CARDIOLOGY				
Cardiac malformations common – major/minor defects, vascular ring or arrhythmias possible (echocardiogram, chest x-ray, ECG) & Cardiology consult				
Sinusitis, pneumonia, asthma & monitor				
Anesthesia risk (difficult intubations/postop airway obstruction/aspiration) – extensive preoperative assessment, combine surgical procedures				
GASTROENTEROLOGY GASTROENTEROLOGY				
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 Gastrojejunostomy tube				
Constipation – consider benha glycoside with polyethylene glycol				
Renal anomalies – abdominal u/s & EVDUG, blood pressure monitoring				
ENDOCRINOLOGY ENDOCRINOLOGY				
Hypoparathyroidism/hypoparathyroidism – LH, PTH by 3 months				
Genital hypoplasia (if undescended testes & consider orchidopexy)				
Delayed puberty – Endocrinology consult & gonadotropin levels, MRI				
Osteoporosis – DXA scan				
Poor growth – Endocrinology consult – GH stimulation test, GH therapy				
Obesity & monitor				
Fertility and contraception & discuss				
IMMUNE SYSTEM 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				
RISK RISK				
Mobility affected by ataxia, hypotonia & evaluate				
PSYCHOLOGICAL DEVELOPMENTAL				
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				
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, ArrasRebar A, van RavenwaaijSArts C, Blake K

IWK CHARGE Clinic Students & Residents Using the CHARGE Checklist



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

Subsection of feeding scale

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

Scoring of feeding scale for CHARGE syndrome

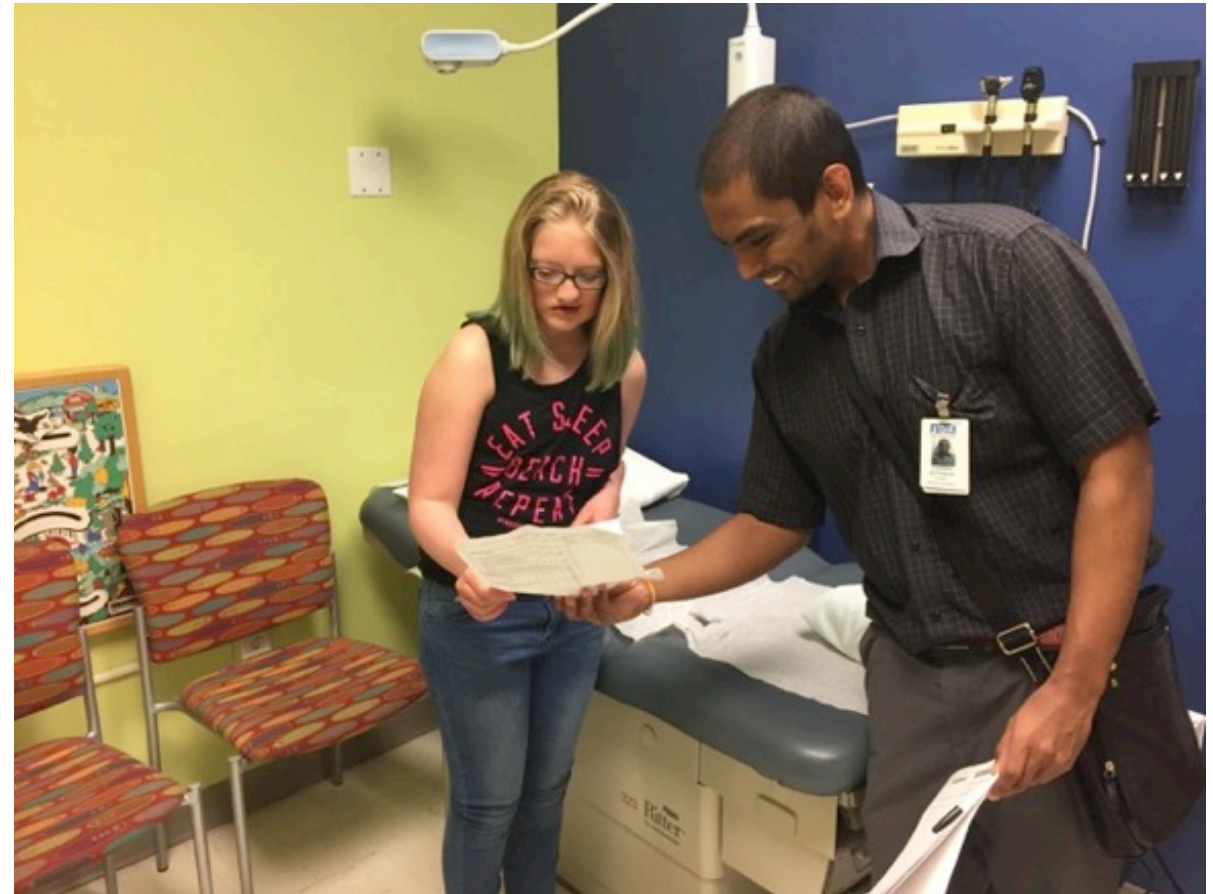
Circle one number on the scale:		Never	A Little	Sometimes	A lot	Always
16	He/she has difficulty moving food around with his/her tongue during eating.	0	1	2	3	4
17	He/she has a hard time feeling food or anything touching the inside of his/her mouth.	0	1	2	3	4
18	He/she dislikes oral eating.	0	1	2	3	4
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

Out of 100 points
Higher score = worse feeding difficulties

Three uses for the feeding scale for CHARGE Syndrome

1. To assess the severity of feeding difficulties
2. To track oral feeding progress before and after interventions
3. To warn the clinician and feeding therapist of new concerns

Hudson A, Stratton K, Hatchette J, Blake K. A new Feeding Assessment Scale (FAS) for individuals with genetic syndromes: A test of validity and reliability in the CHARGE syndrome population. *J Paediatr Child Health*. 2021 Mar: doi:10.1111/jpc.15434.



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

Loss of chd7 in zebrafish results in:

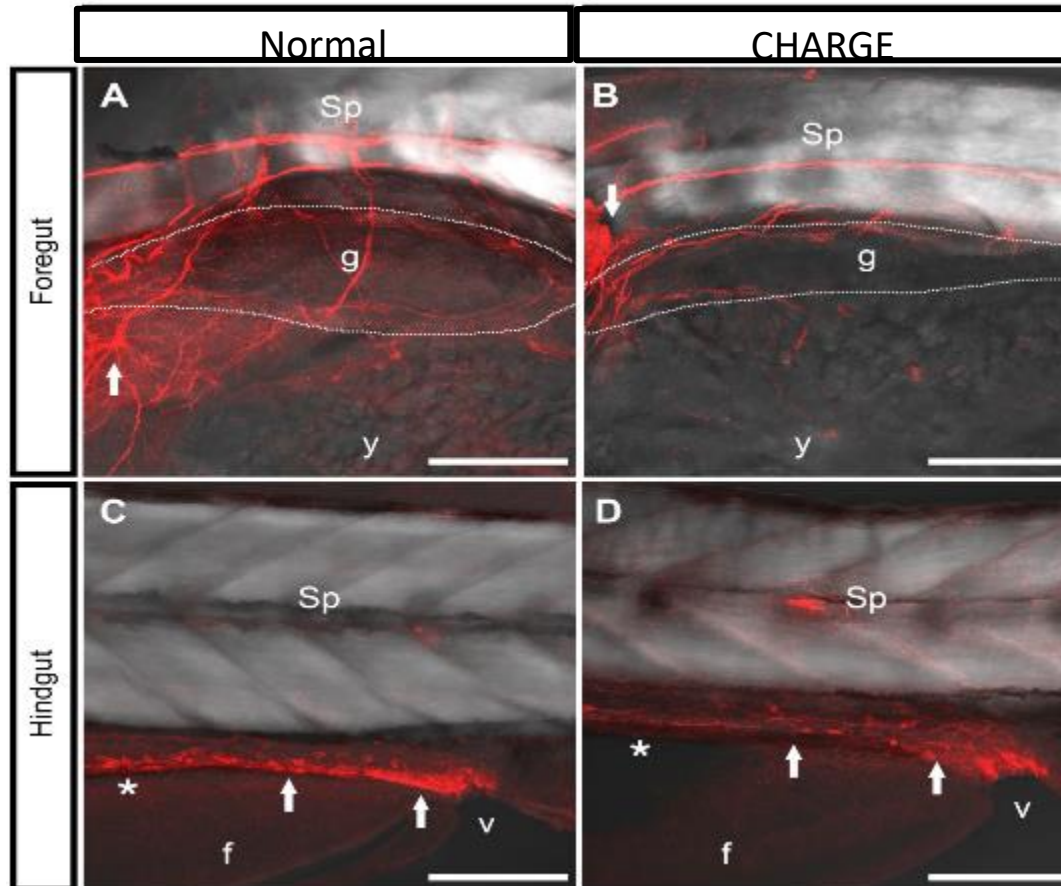
- Smaller stomachs and GI tracts with normal epithelial and muscular histology.
- Decrease and disorganized vagal nerve projections particularly in the fore gut.
- Less ability to empty their GI tract only minimally improved by pro kinetic agents.



Future

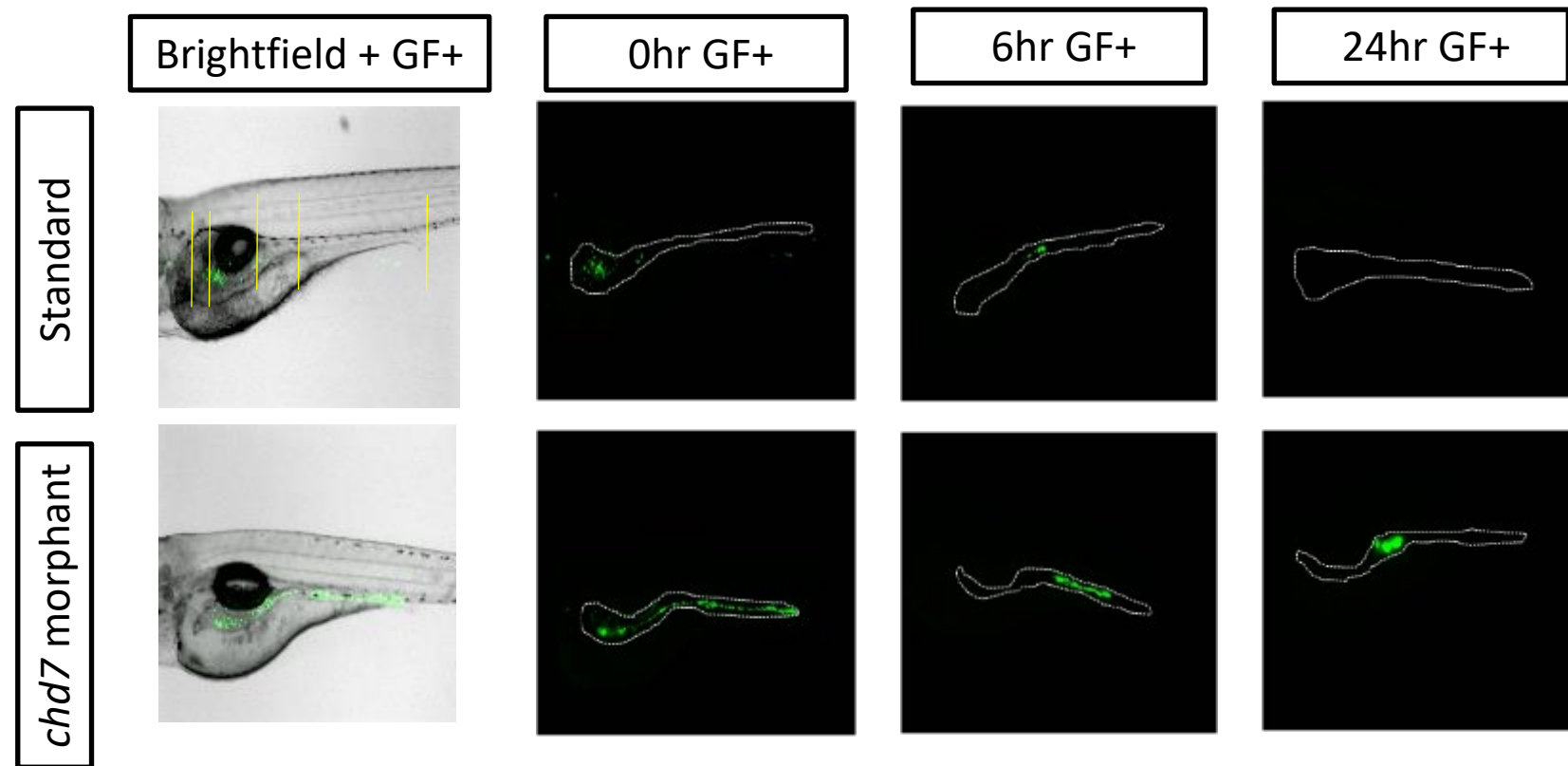
Zebrafish are an excellent model for studying compounds that improve GI motility in individuals with CHARGE syndrome.

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

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

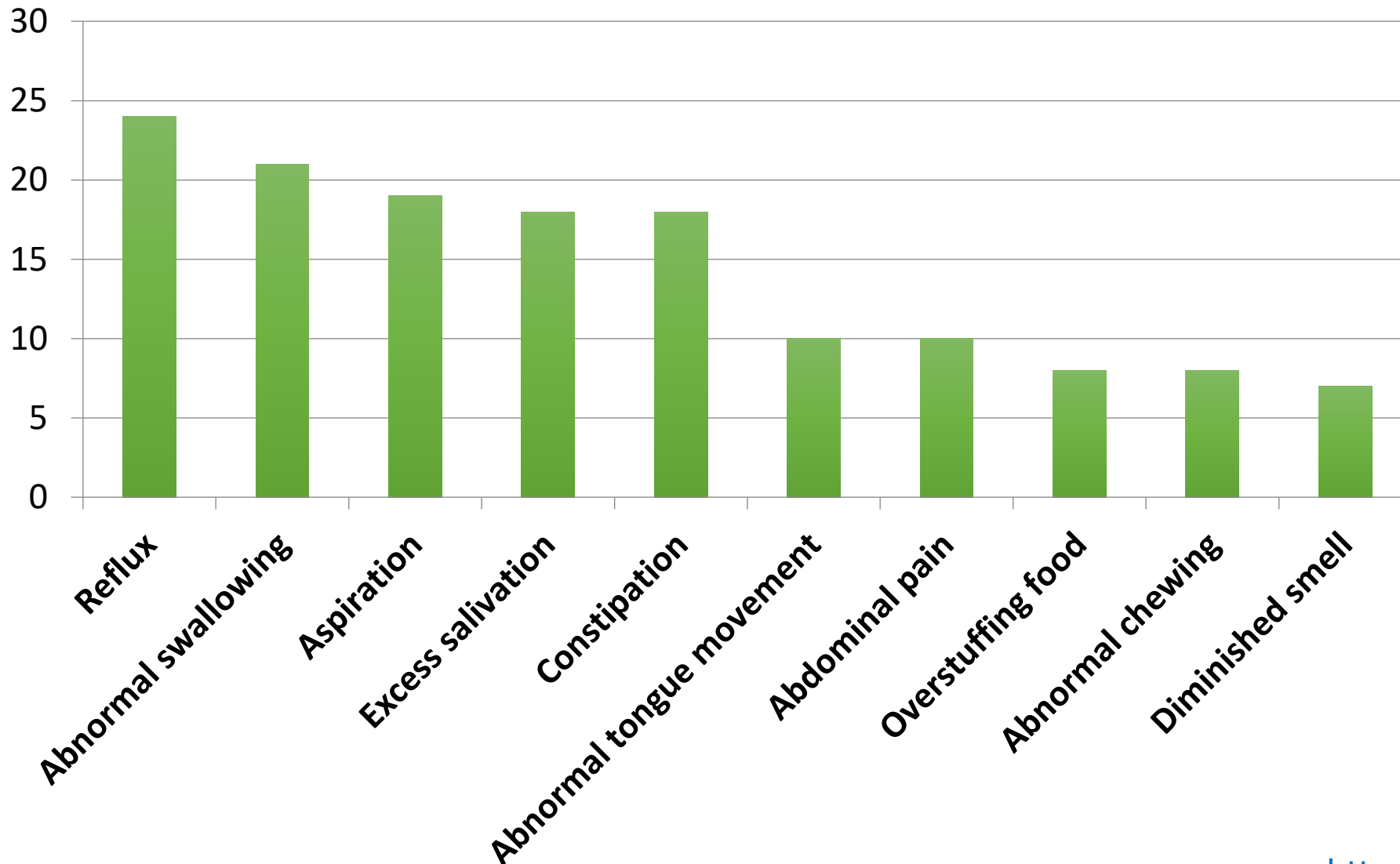


*Florescent green = tagged food travel. GI tract of zebra fish over time

GI and feeding difficulties in CHARGE syndrome: Treatments tried and parents' perceptions of their effectiveness



Top parent reported issues



- 18 males, 13 females with CHARGE syndrome
- 31 respondents (Australia, NZ, USA, UK, Sweden, Indonesia)

Treatments That Parents Think are LEAST Effective

- **Excess saliva** – Constant suctioning
- **Abdominal pain** – Acetaminophen
- **Constipation** – Movicol Jr, lactulose
- **Reflux** – Changing formula types




Treatments That Parents Think are MOST Effective

- **Excess saliva, Aspiration** – Being vertical, SLT, vitalstim therapy, botox
- **Pocketing of food, Over-stuffing, Abnormal sensation in mouth** – SLT, eating with family
- **Abnormal chewing** – Orthodontics, behavioral therapy
- **Reflux** – Fundoplication, medication
- **Abdominal pain** – Increased fibre, abdominal massage, warm baths
- **Constipation** – Less junk food, parachoc



LOW FODMAP DIET



A collage of various food items including vegetables, fruits, proteins, and grains, representing a low FODMAP diet. The items include: eggplant, red bell pepper, carrots, green leafy vegetables, cucumber, kiwi, orange, lemon, strawberries, cantaloupe, coconut, almonds, cashews, pistachios, walnuts, pecans, hazelnuts, macadamia nuts, pine nuts, sunflower seeds, pumpkin seeds, flaxseeds, chia seeds, hemp seeds, quinoa, rice, oats, barley, rye, corn, potatoes, sweet potatoes, yam, turnip, rutabaga, parsnip, carrot, beet, radish, onion, garlic, leek, shallot, scallion, chive, dill, basil, parsley, cilantro, mint, oregano, thyme, rosemary, sage, lavender, lemon balm, peppermint, spearmint, catnip, lemon verbena, and many other herbs and spices. The image is credited to @IRENAMACRI.

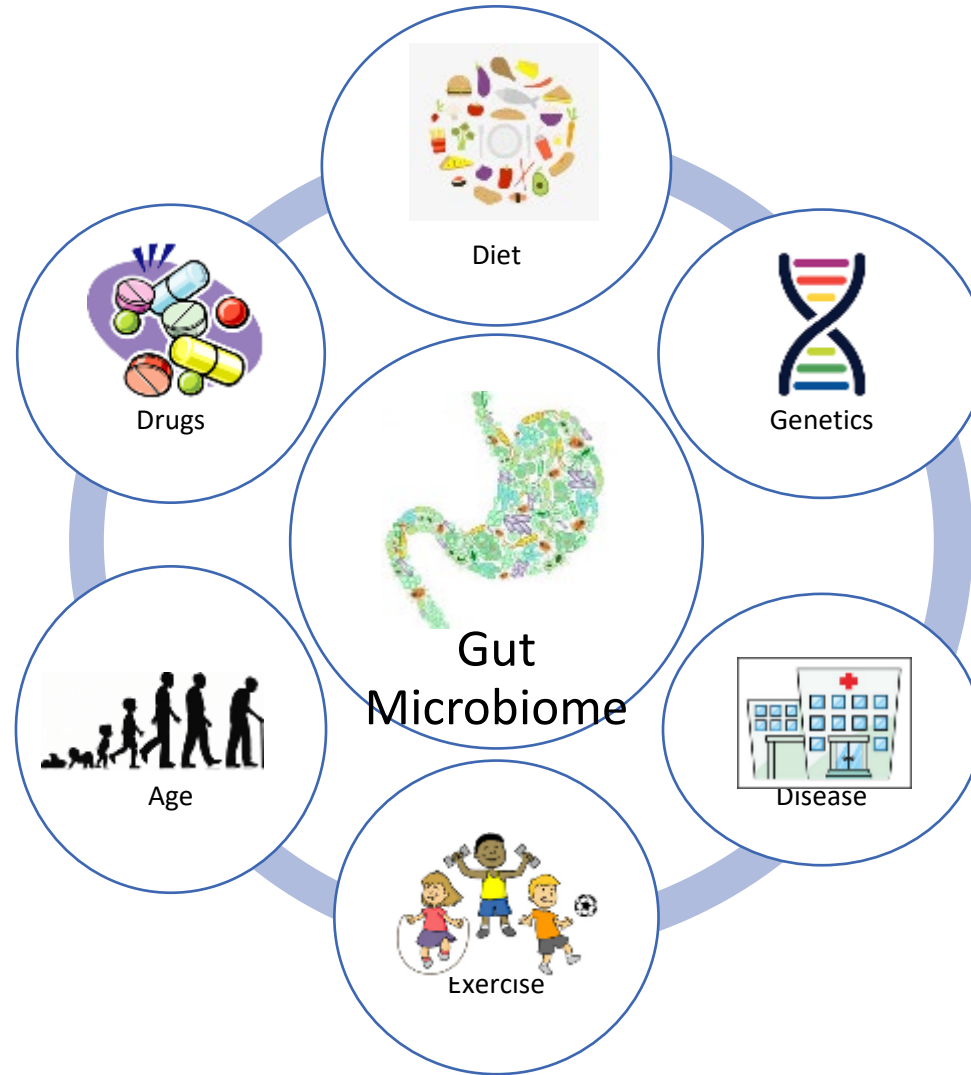
- Reduce simple carbohydrates (Bread, pasta)
- Small amounts of food regularly.
- Exercise and weight control.
- Low FODMAPP diets.



Microbiome

Gut dysbiosis

- Food travels and is digested and absorbed through the gut
- The bacteria and other organisms keep our guts healthy this is called the microbiome



- Typical microbiome contains:
 - Firmicutes
 - Actinobacteria
 - Bacteroidetes
 - Proteobacteria

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

- Gut dysbiosis is associated with:
 - Crohn's/Colitis
 - Irritable bowel syndrome
 - Obesity
 - Autism

The microbiome in CHARGE syndrome

Does the gut microbiome differ in individuals with CHARGE syndrome?

Study Design

Participants: Individuals with CHARGE syndrome from the Canadian Maritimes and their sibling.

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

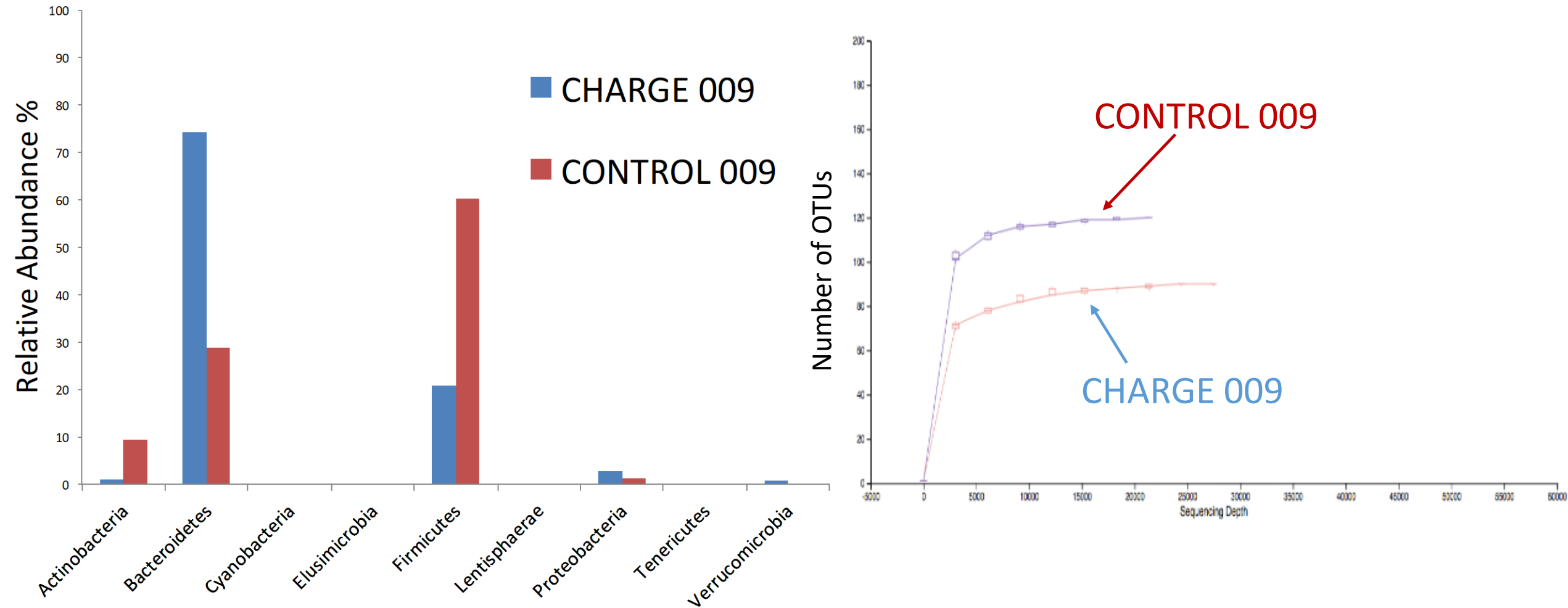
Each participant provided:

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



Results

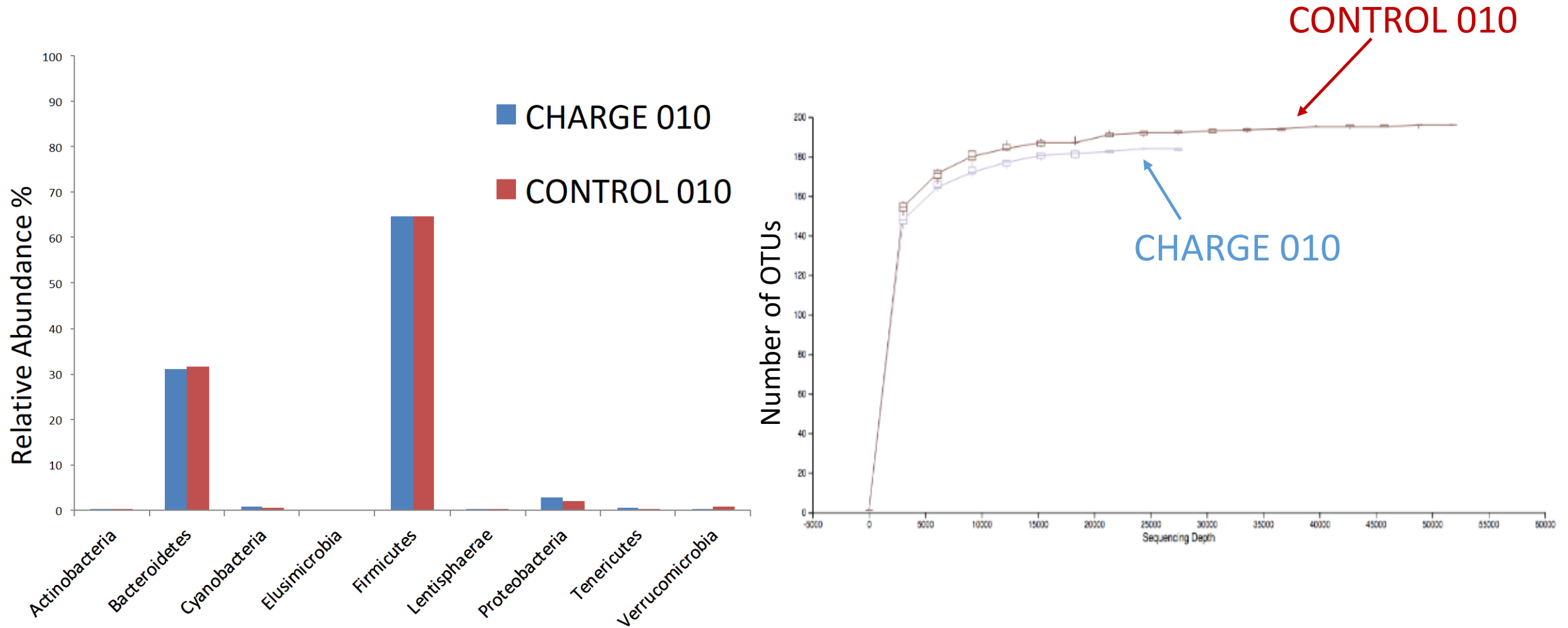
Comparing one sibling pair with different GI scores



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

Results

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
- Compare microbiome with behavioral profiles.

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
- Found effective in C. difficile infection and IBD
- Risks include transmission of infection missed during screening

Postural Orthostatic Tachycardia Syndrome (POTS)

What is POTS?

- POTS is a clinical syndrome that falls under the umbrella of dysautonomic conditions
- This means that the symptoms arise from dysregulation of the autonomic nervous system
- POTS is characterized by a rapid increase in heart rate upon standing up, and symptoms are often relieved by lying down again.
- A common “diagnostic test” is the tilt-table test



Who is vulnerable?

- Most commonly affected adolescents females.
- Can affect anyone of any age.

Patient Experience

A 17 years-old Caucasian female with a clinical diagnosis of CHARGE syndrome presented to the CHARGE clinic at the IWK with symptoms suggestive of POTS. These included:

- Physical fatigue on hot days over the last year.
- Heart rate that at times elevated to 140bpm.
- Agitation and discomfort when moving from a standing to lying position.
- Vomiting, loss of color in the face, sweatiness, pre-syncope and diarrhea following standing up



One instance severe enough that prompted a visit to the Emergency Department.

At a follow-up appointment, a tilt-table test was performed to investigate the possibility of POTS. Heart rate and blood pressure were recorded throughout the test. The blood pressure did not change, but the heart rate increased by 40 beats per minute when she was positioned to 90°. Lowering her to a supine position returned the heart rate to normal.

Provisional Results



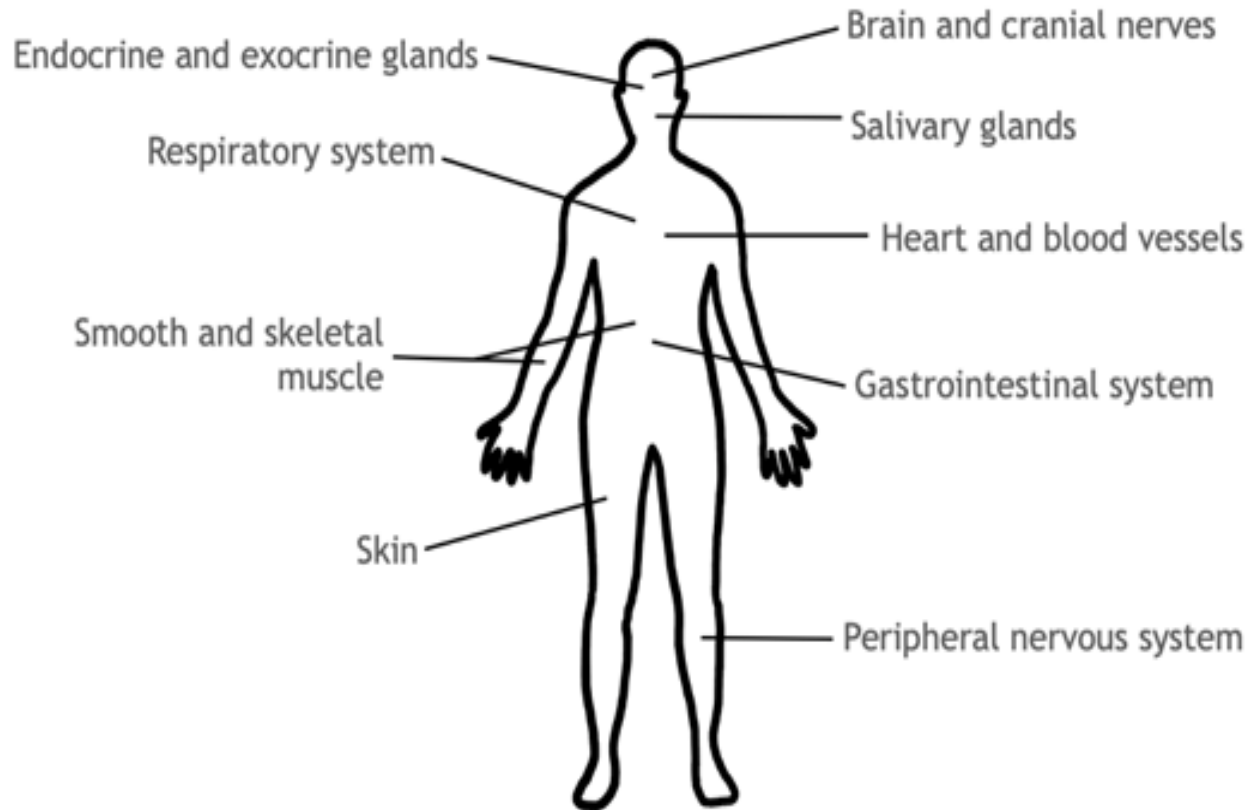
A "POTS" questionnaire was piloted at the 2019 International CHARGE Syndrome Conference (n=12) individuals took part in the study.

- 4/12 reported increased heart rate, or a racing heart.
- 3/12 reported light-headedness.
- 7/12 reported fatigue.
- 6/12 reported upset stomach
- 8/12 reported trouble passing stool
- 10/12 reported that being in the heat makes them feel sick

Data analysis of our total of 30 participants is currently underway.

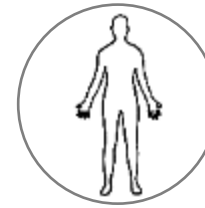
POTS What to watch for

Why should we care?



CHARGE Syndrome has an impact on many organs in the body that are related to the autonomic nervous system (ANS), which is the system that gets dysregulated in dysautonomic conditions like POTS.

Signs and Symptoms



Fatigue, weakness
Muscle pain, exercise intolerance
Poor temperature regulation
Increased or decreased sweating



Feeling worried, anxious or depressed
“Brain fog”
Headache, dizziness



Increased heart rate, especially when standing up
+/- Rapid breathing



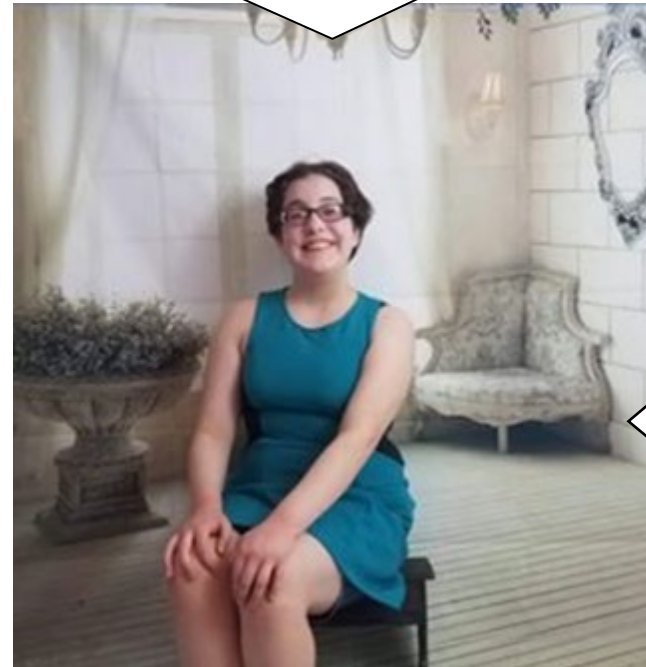
Feeling nauseous/diarrhea or constipation
Feeling bloated
+/- cramps in your belly

Patient Experience

- Onset: older childhood to early adolescent
- Experiencing symptoms especially rapid increase in heart rate, difficulty breathing, feeling incredibly fatigue and feeling nauseous

In their own words:

"It's awful & we have to go to the hospital regularly for fluids to help her come out the the episodes. She can't walk, talk, eat, or drink & feels like she's falling even when she is laying down. She misses 2-3 days of school a week & sleeps most of the time she is there."



"...At this point we were using a wheel-chair every time we went to the store because she was so fatigued just from walking to the car to the inside of the store and was getting dizzy."

Summary and Recommendations

1. POTS is difficult to diagnose – especially with individuals who have multi-sensory impairment
 - Awareness of what to look for is important
2. Treatment is difficult!
 - Treatment recommendation included awareness of the condition and associated triggers, monitoring fluid and salt intake, and taking breaks during periods of activity
3. POTS falls under the umbrella of “dysautonomia”, which includes several other similar conditions
 - There is likely more overlap with CHARGE syndrome than we currently understand



If interested in this study contact:

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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
- **Recommended 1000 iu Vit D**



What next?

- More participants in adolescent study
- The adult microbiome

Are you interested?

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- micaela.sabean@dal.ca



Questions and Answers

www.drkimblake.com

