GI Alliance

Advancing GI Patient Care 2021

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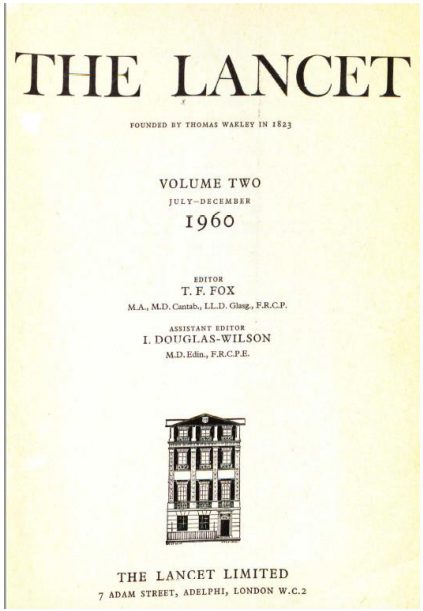
Congenital Sucrase Isomaltase Deficiency

Daksesh Patel, DO

Disclosures

- Honorarium: QOL
- Speaker: QOL

Congenital Sucrase-Isomaltase Deficiency (CSID)


THE LANCET

FOUNDED BY THOMAS WAKLEY IN 1823

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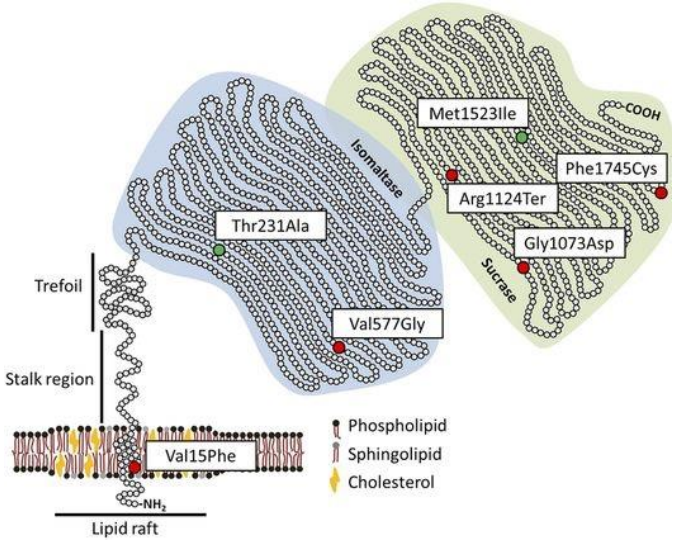
- The first report of an autosomal recessive Congenital Sucrase-Isomaltase Deficiency (CSID) was published in 1960
- **“Diarrhoea Caused by Deficiency of Sugar-Splitting Enzymes”**

Weijers HA, Van De Kamer JH, Mossel DAA, Dicke WK. Diarrhoea Caused by Deficiency of Sugar-Splitting Enzymes. *Lancet*. 1960; 276 (7145): 296-7.

Sucrase-Isomaltase Gene (SI)

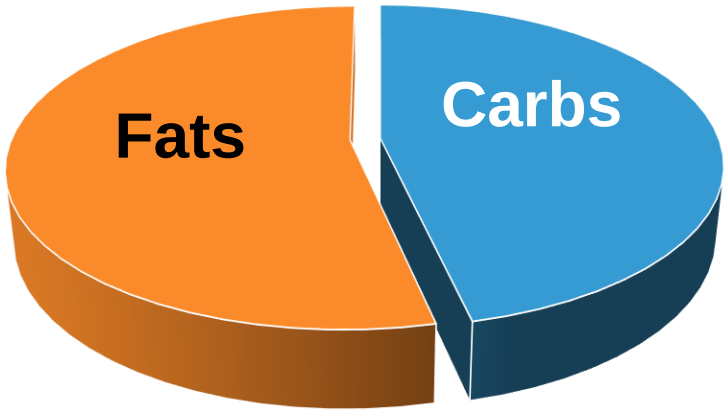
- Encodes a heterodimer with 2 active sites, sucrase and isomaltase[1]
  - Very large, approximately 100 kilobases
  - Located on chromosome 3, position 26.1
  - 48 exons encoding 1827 amino acids
- 880 SI rare pathogenic variants (SI-RPVs)[2]
- 4 SI variants account for ~60% of the patients' of European descent
- Sucrase-isomaltase is synthesized in the enterocyte as a single glycoprotein chain and, after insertion in the brush-border membrane, is cleaved by pancreatic proteases into sucrase and isomaltase



1. Uhrich S et al. *J Pediatr Gastroenterol Nutr*. 2012; 55 (suppl 2): S34-5; 2. Garcia-Etxebarria K et al. *Clin Gastroenterol Hepatol*. 2018; 16 (10): 1673-6; 3. Henström M et al. *Gut*. 2018; 67 (2): 263-70.

Carbohydrates: More Than Your Daily Bread…

~ 46% of 2,000 calorie western diet[1,2]

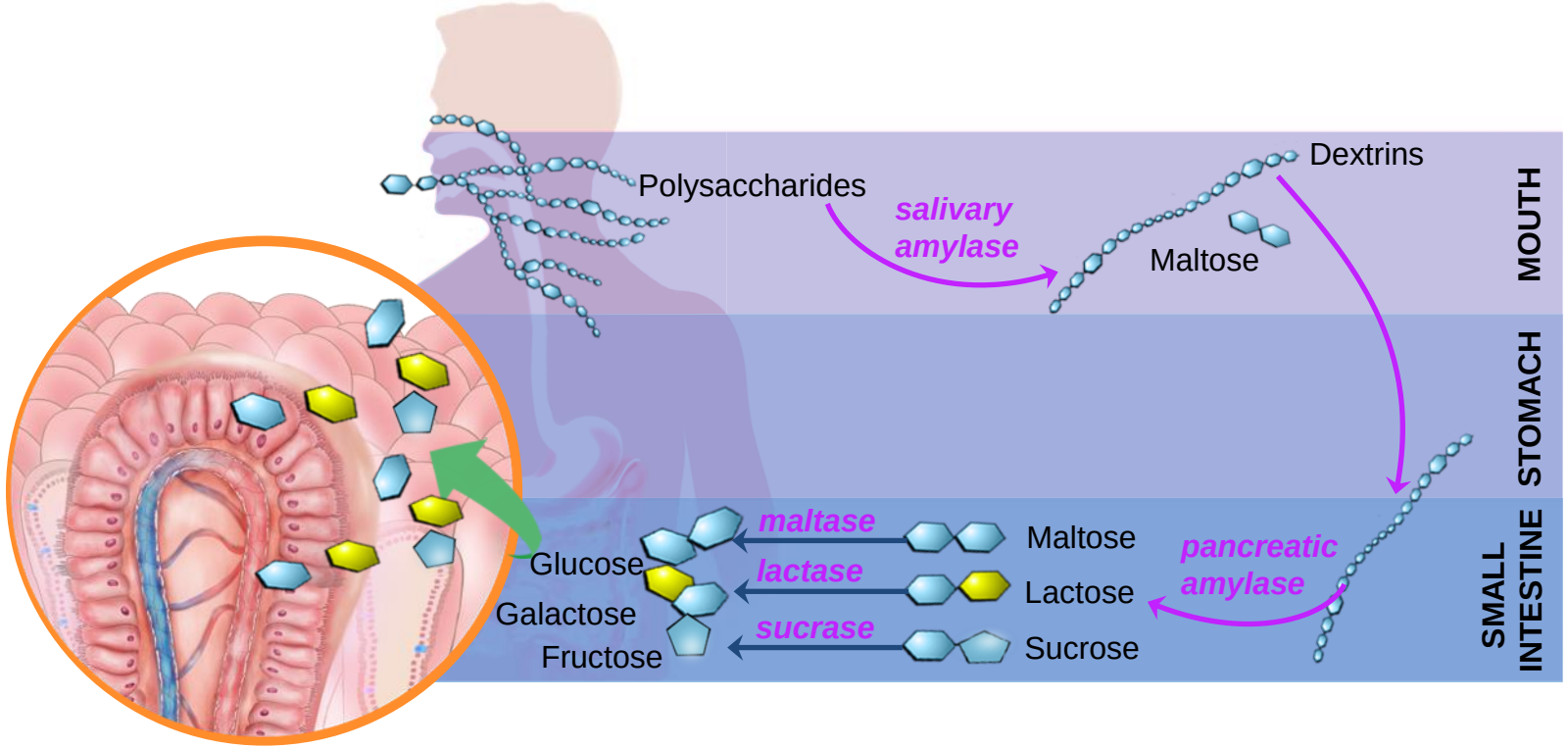


Disaccharides

- Lactose
- Sucrose
- Maltose
- Trehalose

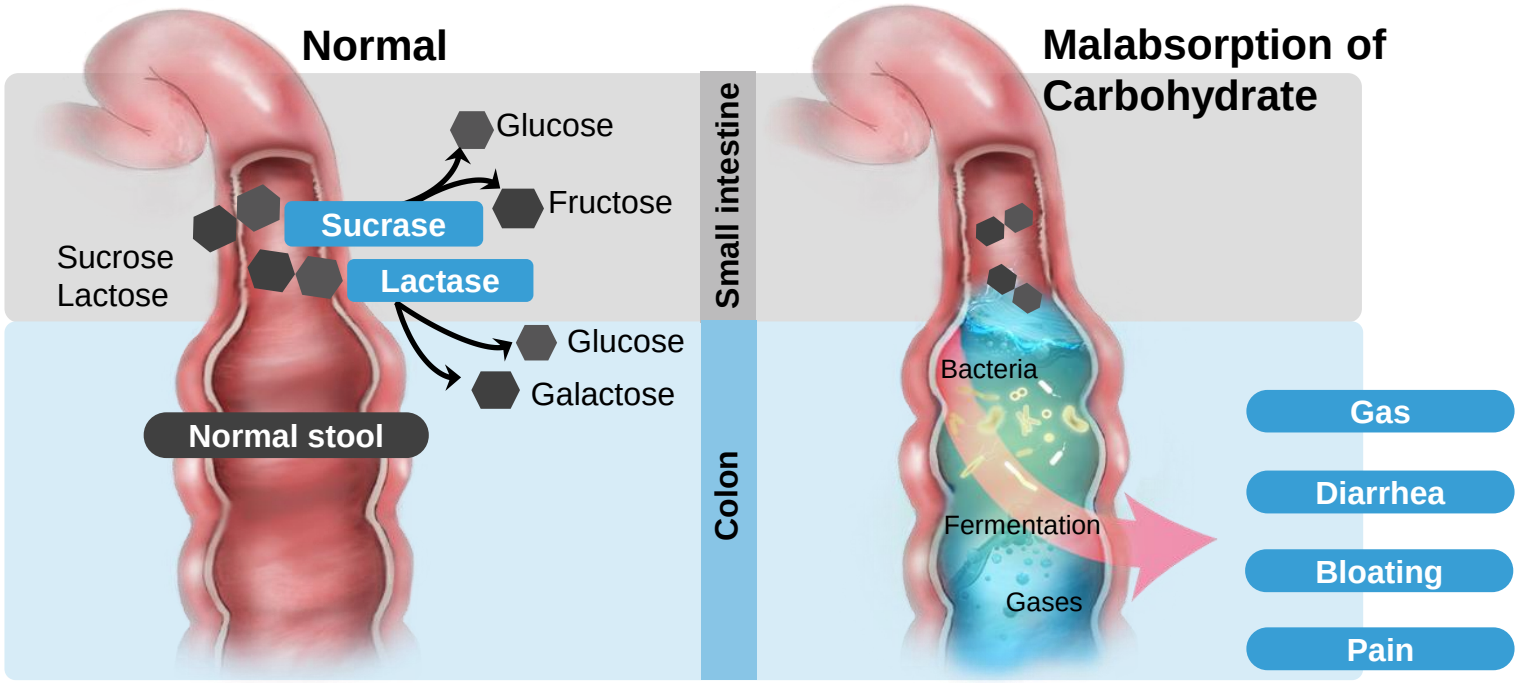
1. U.S. Department of Agriculture. https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/1516/Table_1_NIN_GEN_15.pdf. Accessed September 13, 2019; 2. U.S. Department of Agriculture. https://www.nal.usda.gov/fnic/how-many-calories-are-one-gram-fat-carbohydrate-or-protein. Accessed September 13, 2019.

Carbohydrate Digestion and Absorption
The Road to Monosaccharides



Sitrin MD. *The Gastrointestinal System*. Digestion and Absorption of Carbohydrates and Proteins. 137-158.

Clinical Consequences of Carbohydrate Malabsorption



1. Treem WR. *J Pediatr Gastroenterol Nutr*. 2012; 55 (Suppl 2): S7-S13; 2. Canani RB et al. *Nutrients*. 2016; 8: 157.

Etiologies of Key Disaccharidase Deficiencies: Lactase and Isomaltase-Sucrase

Congenital[1,2]

- **Congenital Lactase Deficiency (rare)**
- **Congenital Sucrase-Isomaltase Deficiency (CSID)**
  - Autosomal recessive (CSID)
  - Symptomatic heterozygous carriers
  - Compound heterozygotes

Secondary Causes[2]

- Celiac sprue
- Chemo/XRT enteropathy
- Crohn's disease
- Allergic enteropathy
- Acute gastroenteritis
- Giardiasis
- SIBO

CSID, congenital sucrase isomaltase deficiency; IBD, inflammatory bowel disease.

1. Cohen S. *Molecular Cellular Pediatr*. 2016; 3: 5; 2. Naim HY et al. *J Pediatr Gastroenterol Nutr*. 2012; 55 (Suppl 2): S13-S20.

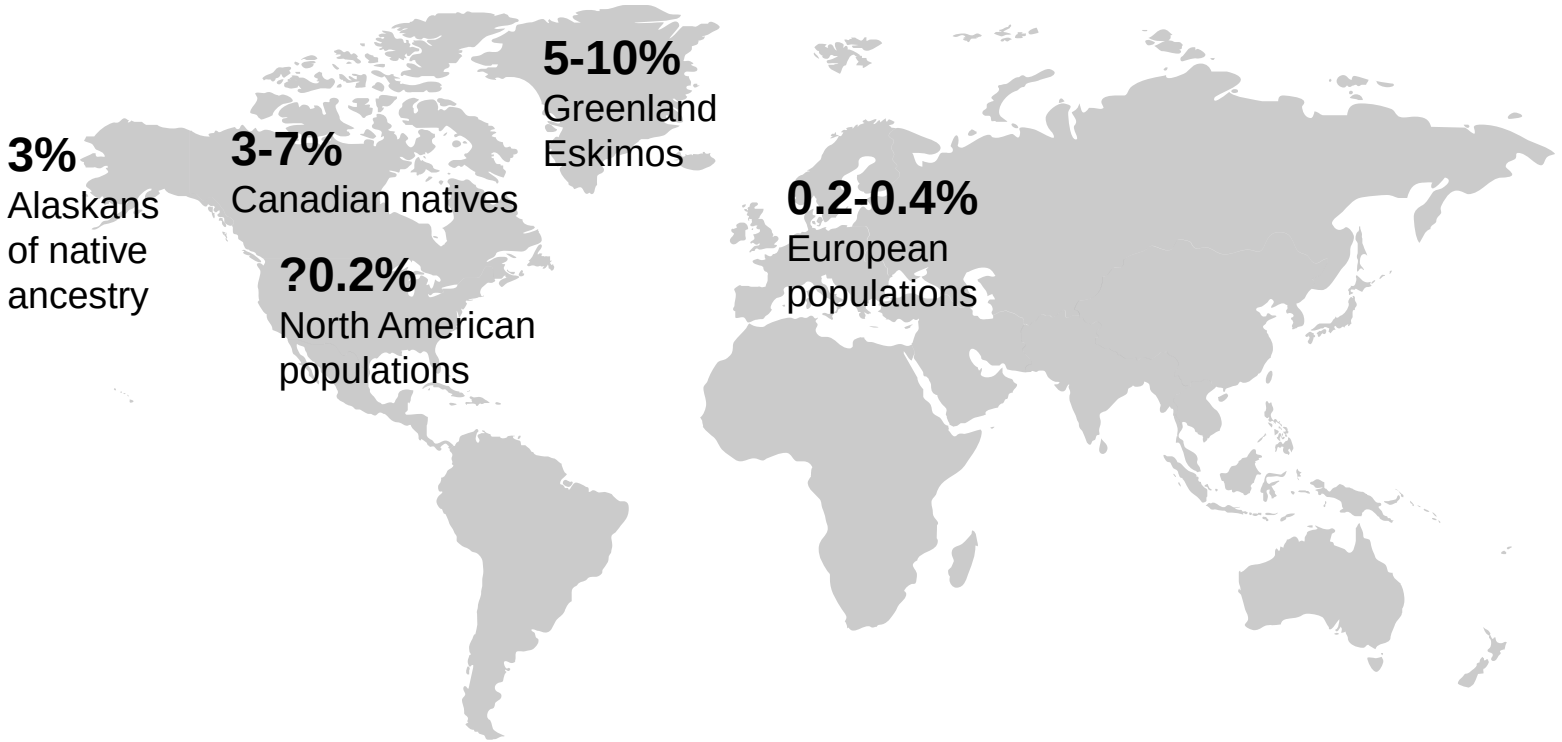
CSID Signs and Symptoms

- Frequent, lifelong, and postprandial diarrhea, loose stools, gas, bloating
- Other potential signs
  - Family history
  - Avoidance of carbohydrates, sweet foods
  - Low BMI
- IBS symptoms not responding to therapy

BMI, body mass index.

1. Kim SB et al. *Dig Dis Sci*. 2020; 65 (2): 534-540; 2. Puertolas MV, Fifi AC. *Nutrients*. 2018; 10: 1835;
3. Treem WR. *J Pediatr Gastroenterol Nutr*. 2012; 55 (Suppl 2): S7-S13; 4. Cohen SA. *Mol Cell Pediatr*. 2016; 3: 5.

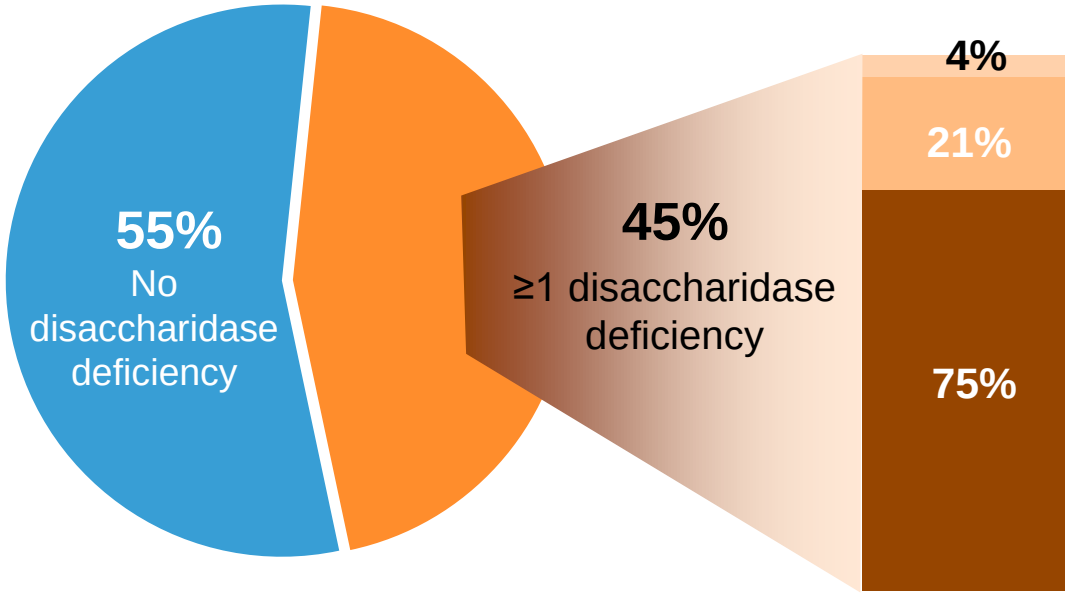
Historic Prevalence of Sucrase Deficiency



Treem WR. *J Pediatr Gastroenterol Nutr.* 1995; 21 (1): 1-14.

How Common Is Disaccharidase Deficiency?

Analysis of Mucosal Biopsies (N=27,875)



9.3%
were sucrase deficient overall

Nichols BL et al. *J Pediatr Gastroenterol Nutr.* 2012; (Suppl 2):S28-S30.

Incidence of Sucrase-Isomaltase Rare Pathogenic Variants (*SI*-RPV) in GI Patients

	Chronic diarrhea[1]	Patients with IBS-D diagnosis
Subjects (N)	308	952
With rare CSID variants (n)	14	40
Incidence	4.5%	4.2%

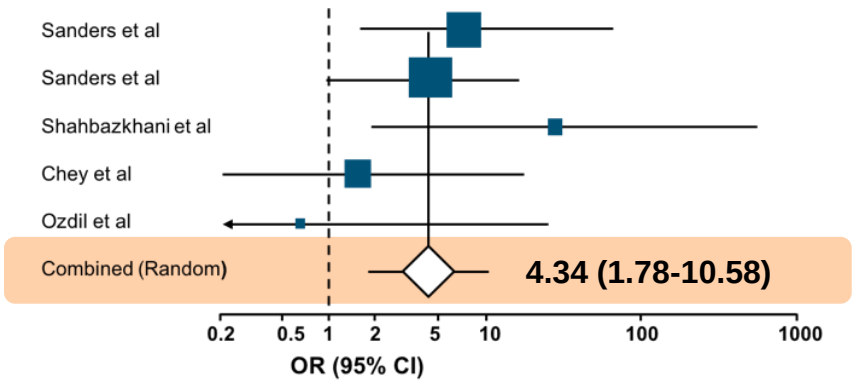
- Genetic evidence suggests link between SI variations and IBS susceptibility
- *SI*-RPV does not always cause CSID, but is highly correlated

1. QOL Medical. Data on file; 2. Garcia-Extebarria K et al. *Clin Gastroenterol Hepatol.* 2018; 16 (10): 1673-1676. doi: 10.1016/j.cgh.2018.01.047

Celiac Disease is Not Common in IBS

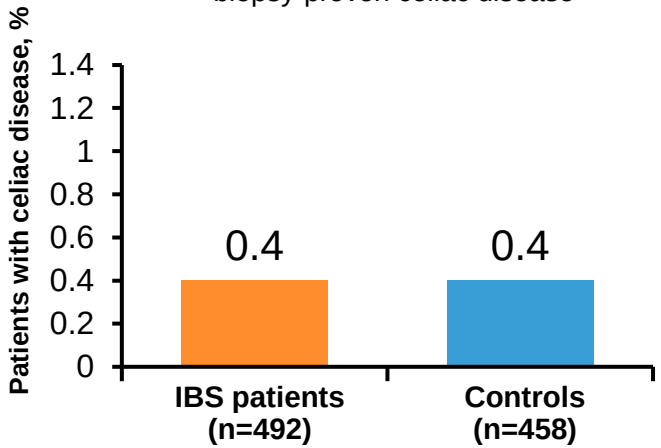
International Meta-analysis[1]

Prevalence of biopsy-proven celiac disease in IBS vs controls



US Prospective Study[2]

Non-constipated IBS patients (Rome II)
biopsy-proven celiac disease



1. Ford et al. *Archives Int Med.* 2009; 169: 651; 2. Cash BD, Chey WD. *Gastroenterology*. 2011; 141: 1187.

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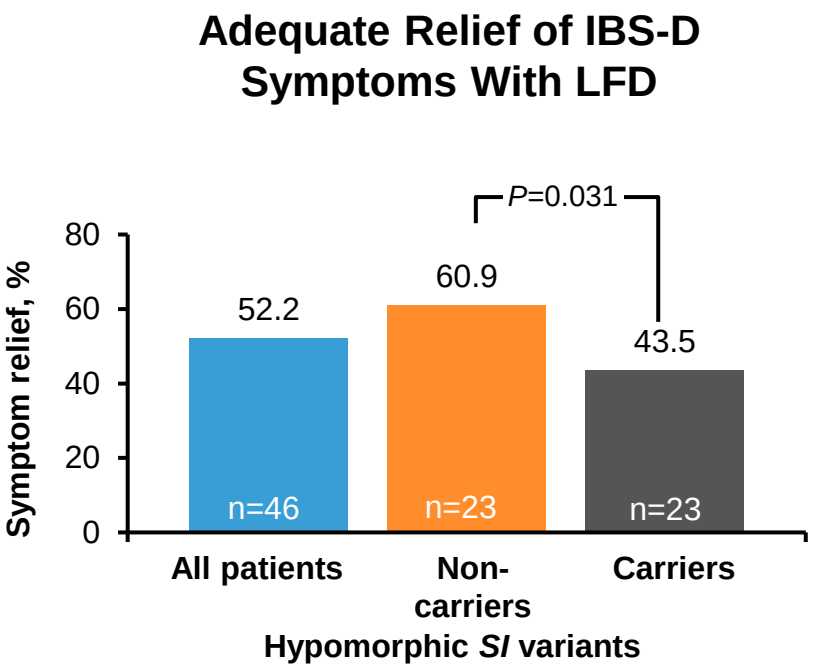
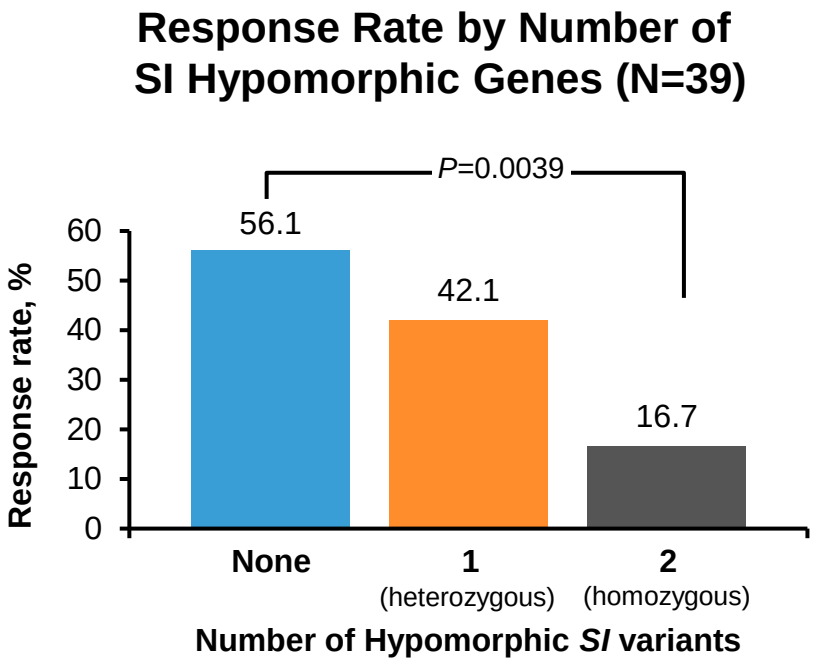
Consider CSID in Low FODMAP Diet Failures

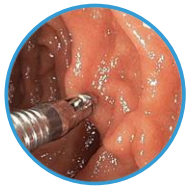




LFD, low FODMAP diet; mNICE, modified National Health and Care Excellence; RCT, randomized controlled trial.

Zheng T et al. *Gut*. 2020; 69 (2): 397-398.

Tests That Aid in Diagnosing CSID



Small bowel biopsy[1,2]

- Considered gold standard
- Specimens sent to specialty lab

Genetic test[2]

- Buccal swab, saliva, or blood
- Detects 37 polymorphisms in *SI* gene

Breath tests[2]

- Hydrogen-methane
- ^{13}C-sucrose

Sucrose challenge[3]

- Simple test, but not validated

SI, sucrase isomaltase

1. Treem WR. *J Pediatr Gastroenterol Nutr*. 2012; 55 (Suppl 2): S7-S13; 2. Cohen S et al. *Molecular Cellular Pediatr*. 2016; 3: 5; 3. Puntis JW, Zamvar V. *Arch Dis Child*. 2015; 100 (9): 869-871.

Enzyme Function via Disaccharidase Assay Is the Gold Standard for CSID Diagnosis

Collect

- First biopsies
- 2-3 biopsies obtained from distal duodenum/proximal jejunum
  - Disaccharidase levels decreased by ≥33% in proximal duodenum
- Place samples in empty eppendorf tube
  - Do not place the tissue on gauze, filter paper, or use any type of support medium, not even saline

Freeze

- Place eppendorf tube with collected sample immediately on ice (dry or wet ice) and freeze within 2 hours of collection at -20° C to -70 ºC.

Ship

- Ship frozen on dry ice. Forward to appropriate lab promptly on the same day
- Turn around time is typically 3-7 days

1. Burke M. *Clin Biochem Rev*. 2019; 40 (4): 167-174; 2. Treem WR. *J Pediatr Gastroenterol Nutr*. 2012; 2: 55: S7-S13.

Enzyme Function via Disaccharidase Assay Is the Gold Standard for CSID Diagnosis

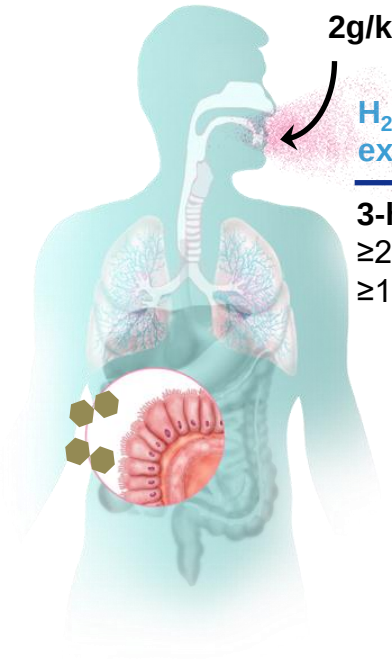
Disaccharidase Reference Intervals

Enzyme	Normal range (U/min/g protein)[a]
Lactase	15 – 46
Sucrase	25 – 70
Maltase	100 – 224
Palatinase	5 – 26

Advantages
• Only test to differentiate primary from secondary sucrase-isomaltase deficiency • Ability to determine enzyme activity for all disaccharidases • Increasingly, insurance payors are requiring DA prior to covering enzyme replacement therapy
Limitations
• Invasive and expensive and time consuming • Assay variability (27%) • False positives with obtaining samples from the proximal duodenum and due to patchy distribution of disaccharidases in the brush border • False positives with mishandling specimens

1. Burke M. *Clin Biochem Rev*. 2019; 40(4):167-174; 2. Treem WR. *J Pediatr Gastroenterol Nutr*. 2012; 2: 55: S7-S13.

Sucrose Hydrogen Methane Breath Test for CSID



2g/kg sucrose solution

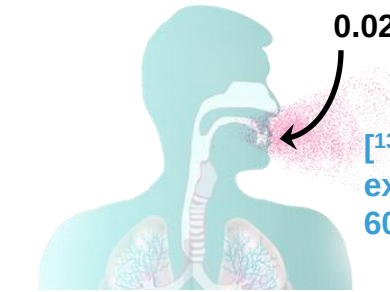
H_2 and/or methane exhalation over 3 hours

3-hr breath test positive:
≥20 ppm H_2 from baseline
≥10 ppm CH_4 from baseline

Advantages
• Safe and non-invasive
• Patient can do at home
Limitations
• Time consuming (3 hours)
• Not specific
• False positives due to Dumping Syndrome, SIBO
• False negatives due to delayed gastric emptying, recent antibiotic use, and non-hydrogen producers
• May cause symptoms in patients with CSID due to large sucrose load

1. Robayo-Torres CC et al. *J Ped Gastroenterol Nutr*. 2009; 48 (4): 412-8; 2. Rezaie A et al. *Am J Gastroenterol*. 2017; 112 (5): 775-84; 3. Treem WR. *J Pediatr Gastroenterol Nutr*. 2012; 55 (Suppl 2): S7-S13.

^{13}C Sucrose Breath Test for CSID/SID



Normal sucrase activity[a]
Females: >5.10%
Males: >3.91%

Advantages	Limitations
• Safe (stable isotope) and non-invasive • Better tolerated and more specific than hydrogen/methane test	• False positives with Dumping Syndrome • False negatives with delayed gastric emptying • Need for further validation

[a]90-minute sucrose digestion.

1. Robayo-Torres CC et al. *J Ped Gastroenterol Nutr*. 2009; 48 (4): 412-8; 2. Rezaie A et al. *Am J Gastroenterol*. 2017; 112 (5): 775-84; 3. Treem WR. *J Pediatr Gastroenterol Nutr*. 2012; 55 (Suppl 2): S7-S13.

Discordance Between ^{13}C-Sucrose Breath Test and Disaccharidase Assays Results

- Biopsy sample location
- Handling sample
- Assay variability
- Cut-off at 25 mMol/min/g protein may be too low
- Dumping syndrome
- Gastroparesis

1. Treem WR. *J Pediatr Gastroenterol Nutr*. 2012; 55 (Suppl 2): S7-S13; 2. Rahaal RM, Bishop WP. *Open Pediatr Med J*. 2008; 2: 35-38.

Genetic Testing for CSID

- Buccal swab (2) or blood (5-6cc for adults and 2-3cc for infants)
- Tests 37 common pathogenic variants of the SI gene
- Positive genetic test
  - Same pathogenic SI gene variant in both alleles
  - Different pathogenic SI gene variant in each allele
  - Pathogenic SI gene variant in one allele only

Advantages
• Simple procedure • Noninvasive • If positive, confirms CSID regardless of genotype
Limitations
• Costly • Lengthy turnaround time (1 month) • Tests only 37 of >2000 *SI* variants – normal test does not rule out CSID

Chumpitazi BP et al. *J Pediatr Gastroenterol Nutr*. 2012; 55 (2): S36.

4-4-4 Sucrose Challenge

Stir 4 tablespoons of ordinary table sugar into a 4-ounce glass of water and mix until completely dissolved

Drink on empty stomach

Monitor for symptoms (bloating, gas, and diarrhea) during subsequent 4-8 hours

Advantages
• Simple and easy • Inexpensive • Theoretically sensitive; high likelihood of symptoms in CSID
Limitations
• Not validated • Unknown NPV and PPV • May result in severe symptoms

CSID Disease Information. Available at http://www.csiddiseaseinfo.com. Accessed June 16, 2020.

Dietary Management of CSID

- Treat with a low sucrose diet
- Consider reducing dietary starch consumption if moderate symptoms remain
  - If maltase or isomaltase activities are low
  - If patient reports symptoms after starch consumption
- All CSID patients are sucrose intolerant; some may also be starch intolerant

McMeans AR. *J Pediatr Gastroenterol Nutr*. 2012; 55 (Suppl 2): S37-S38.

Limit or Avoid High Carbohydrate Ingredients

Eliminate Sugar First

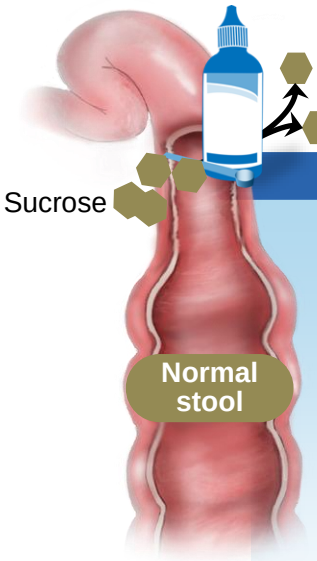
- Table sugar
- Beet sugar
- Brown sugar
- Cane sugar
- Caramel sugar
- Coconut sugar
- Confectioner’s sugar
- Date sugar
- Raw sugar

Reduce Starch If Still Symptomatic

- Potatoes
- Rice
- Bread
- Pasta
- Limit dextrins
- Maltodextrin
- Modified tapioca starch
- Glucose polymers
- Maltose (brown rice syrup, corn syrup solids, malt)

McMeans AR. *J Pediatr Gastroenterol Nutr*. 2012; 55 (Suppl 2): S37-S38.

Sacrosidase Oral Solution



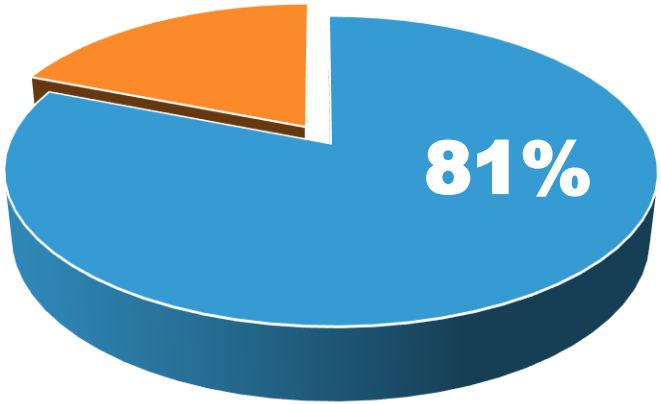
Sacrosidase

- Derived from *Saccharomyces cerevisiae*[1]
- Contains ~8500 IU sucrase activity/mL[2]
- Hydrolyzes sucrose[1]
- No activity against starches[1]
  - 1 mL if ≤15 kg (≤33 lbs) = 28 drops = 8,500IU
  - 2 mL if >15 kg (>33 lbs) = 56 drops = 17,000IU
- Mix dose in 2 to 4 ounces of water, milk, or infant formula. Do not dissolve it or take with fruit juice.
- Administer before and during meals or snacks[2]

1. Treem WR et al. *J Pediatr Gastroenterol Nutr.* 1999; 28 (2): 137-42; 2. Sucraid® (sacrosidase) [prescribing information]. QoL Medical, LLC; Vero Beach, FL; 2019.

Overall Symptomatic Response to Oral Sacrosidase

Post-hoc Responder Analysis[a] (N=28 children with CSID)



of patients (N=28) became asymptomatic with sacrosidase during a 10-day period[a]

[a]Asymptomatic defined as symptom-free for ≥7 of the 10 study days.
Treem WR et al. *J Pediatr Gastroenterol Nutr.* 1999; 28 (2): 137-42.

Sacrosidase Oral Solution

- May cause an allergic reaction so avoid in those with a known hypersensitivity to yeast or yeast products, papain, or glycerin
- Most common adverse events reported are constipation, insomnia, and headaches
- Caution in patients with poorly controlled diabetes since sacrosidase can raise blood glucose levels by hydrolyzing sucrose
  - Do not heat solution or mix in hot or acidic beverages (juice)
  - Keep refrigerated at 36°F to 46°F (2°C - 8°C) to protect it from heat and light

Sucraid® (sacrosidase) [prescribing information]. QoL Medical, LLC; Vero Beach, FL; 2019.

Conclusions

- The majority of dietary carbohydrates are digested by sucrase-isomaltase
- CSID is likely more common than previously believed. Current literature suggests an overall CSID prevalence of 4-5%
- Optimal diagnostic strategy for CSID remains unclear
  - While disaccharidase assay is the current gold standard, the ^{13}C sucrose breath test offers a noninvasive, practical strategy to help establish the diagnosis
- Although current evidence is insufficient to recommend early testing, CSID should be included in the differential diagnosis of patients with presumed IBS, particularly in those that are not responding to dietary modifications
- Treatment of CSID should be individualized based on patient preferences, using an iterative approach that incorporates dietary management and/or enzyme replacement therapy