

30. Chantret I, Lacasa M, Chevalier G, et al. Sequence of the complete cDNA and the 5' structure of the human sucrase-isomaltase gene. Possible homology with a yeast glucoamylase. *Biochem J* 1992; 285:915–23.
31. Nichols BL, Eldering J, Avery S, et al. Human small intestinal maltase-glucoamylase cDNA cloning. Homology to sucrase-isomaltase. *J Biol Chem* 1998;273:3076–81.
32. Nichols BL, Avery S, Sen P, et al. The maltase-glucoamylase gene: common ancestry to sucrase-isomaltase with complementary starch digestion activities. *Proc Natl Acad Sci U S A* 2003;100:1432–7.
33. Quezada-Calvillo R, Robayo-Torres C, et al. Luminal substrate “brake” on mucosal maltase-glucoamylase activity regulates total rate of starch digestion to glucose. *J Pediatr Gastroenterol Nutr* 2007;45:32–43.
34. Quezada-Calvillo R, Sim L, Ao Z, et al. Luminal starch substrate “brake” on maltase-glucoamylase activity is located within the glucoamylase subunit. *J Nutr* 2008;138:685–92.
35. Quezada-Calvillo R, Robayo-Torres C, Opekun AR, et al. Contribution of mucosal maltase-glucoamylase activities to mouse small intestinal starch alpha-glucogenesis. *J Nutr* 2007;137:1725–33.
36. Nichols BL, Quezada-Calvillo R, Robayo-Torres CC, et al. Mucosal maltase-glucoamylase plays a crucial role in starch digestion and prandial glucose homeostasis of mice. *J Nutr* 2009;139:684–90.
37. Jones K, Sim L, Mohan S, et al. Mapping the intestinal alpha-glucogenic enzyme specificities of starch digesting maltase-glucoamylase and sucrase-isomaltase. *Bioorg Med Chem* 2011;19:3929–34.
38. Eskandari R, Jones K, Rose DR, et al. Selectivity of 3'-O-methylponkoranol for inhibition of N- and C-terminal maltase glucoamylase and sucrase isomaltase, potential therapeutics for digestive disorders or their sequelae. *Bioorg Med Chem Lett* 2011;21:6491–4.
39. Sim L, Willemsma C, Mohan S, et al. Structural basis for substrate selectivity in human maltase-glucoamylase and sucrase-isomaltase N-terminal domains. *J Biol Chem* 2010;285:1763–70.
40. Sim L, Quezada-Calvillo R, Sterchi EE, et al. Human intestinal maltase-glucoamylase: crystal structure of the N-terminal catalytic subunit and basis of inhibition and substrate specificity. *J Mol Biol* 2008;375:782–92.
41. Krasilnikoff PA, Gudman-Hoyer E, Moltke HH. Diagnostic value of disaccharide tolerance tests in children. *Acta Paediatr Scand* 1975; 64:693–8.
42. Perman JA, Barr RG, Watkins JB. Sucrose malabsorption in children: noninvasive diagnosis by interval breath hydrogen determination. *J Pediatr* 1978;93:17–22.
43. Douwes AC, Fernandes J, Jongbloed AA. Diagnostic value of sucrose tolerance test in children evaluated by breath hydrogen measurement. *Acta Paediatr Scand* 1980;69:79–82.
44. Lifschitz CH, Irving CS, Gopalakrishna GS, et al. Carbohydrate malabsorption in infants with diarrhea studied with the breath hydrogen test. *J Pediatr* 1983;102:371–5.
45. Davidson GP, Robb TA. Detection of primary and secondary sucrose malabsorption in children by means of the breath hydrogen technique. *Med J Aust* 1983;2:29–32.
46. Robayo-Torres CC, Opekun AR, Quezada-Calvillo R, et al. ¹³C-breath tests for sucrose digestion in congenital sucrase isomaltase-deficient and sacrosidase-supplemented patients. *J Pediatr Gastroenterol Nutr* 2009;48:412–8.

hydrolyze sucrose, maltose, short 1–4 linked glucose oligomers, branched (1–6 linked) α -limit dextrins, and starch (1). Exposure to these nutrients provokes osmotic diarrhea with pain, bloating, and abdominal distention; rapid small bowel transit and malabsorption of other nutrients; excessive bacterial fermentation of malabsorbed carbohydrate with colonic gas production and acidification of the stools; and at times, chronic malnutrition and failure to thrive (2). After the sucrase-isomaltase (SI) gene was identified on chromosome 3 (3q25–26) and was cloned in 1992 by Chantret and colleagues, more than 25 mutations in the gene responsible for the synthesis of SI have been discovered (3–6). These mutations result in a variety of defects in the folding of the synthesized propeptide chain; the initial high mannose and then complex glycosylation; the sequential export from the endoplasmic reticulum to the Golgi apparatus, and eventually to the apical membrane; the anchoring of the N-terminal aspect of the isomaltase subunit in the enterocyte microvillus membrane; and the normal architecture of the sucrase and isomaltase catalytic sites, which are independent of each other and can be affected separately, leading to isolated deficiencies (5,6). The intracellular phenotypic heterogeneity is reflected in a range of enzymatic capability ranging from completely absent sucrase activity to low but present residual activity and from completely absent isomaltase activity to normal activity. Because SI is responsible for approximately 60% to 80% of the maltase activity in the brush border of the enterocyte, maltase activity is also significantly reduced in almost all cases.

In addition to the degree of enzyme deficiency, the appearance of overt clinical manifestations of CSID is partially determined by the amount of sugar and starch being consumed. Approximately 60% of the total calories consumed in the average diet in the United States originate from carbohydrates, with 30% of carbohydrate calories deriving from sucrose (7). The typical adult consumes about 150 lb of sugar per year and 65 lb of sucrose. The influence of the dietary consumption of sucrose is best illustrated by the natural history of CSID in Greenland, where approximately 5% to 10% of Greenland Eskimos are affected (8). Before the introduction of a Western diet in the middle part of the last century provoked by the settlement of Greenland by northern Europeans from Denmark and other European countries, CSID was unknown among the indigenous population, who consumed a fish-and-marine mammal-based diet, relatively high in fat and protein and low in carbohydrates and sucrose. A marked increase in diarrhea and other gastrointestinal symptoms in the indigenous population led to studies in the 1970s that delineated the prevalence of CSID. The early introduction of sucrose and starch in the form of baby juices, baby food fruits and certain vegetables, and sucrose- and maltodextrin-containing infant formulas also plays a role in the timing of clinical manifestations of CSID.

Other hormonal and dietary factors and micronutrients also influence small intestinal sucrase activity. Unlike lactase activity

Clinical Aspects and Treatment of Congenital Sucrase-Isomaltase Deficiency

William R. Treem

Congenital sucrase-isomaltase deficiency (CSID) was first described by Weijers and colleagues in 1960 and has subsequently been defined as an inherited deficiency in the ability to

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that is unresponsive to lactose consumption, sucrase activity is inducible by a high-sucrose, high-carbohydrate diet and reduced by a high-protein, low-carbohydrate diet (9). Both thyroxine and corticosteroids induce the expression of SI on the brush border of the enterocyte (10). In animal models, dietary-induced iron deficiency results in decreased small-bowel disaccharidase activity, with lactase affected more than SI (11). This appears to be the result of decreased gene expression caused by overexpression of PDX-1, a repressor of the lactase and sucrase promoter regions. PDX-1 overexpression can be reversed with restoration of a normal iron-containing diet and replenishment of iron stores. Naturally occurring phytochemicals in the diet (eg, cinnamon extract, onions, garlic, certain spices, mushrooms, chamomile tea) can act as inhibitors of amylase and intestinal α -glucosidases, thus influencing luminal sucrase activity (12). In patients with CSID and mutations allowing some residual SI activity, these hormonal and dietary factors may influence the onset and severity of symptoms.

PREVALENCE OF CSID

The actual prevalence of CSID is still a matter of debate. Substantial progress in cloning disease-causing mutations has opened the possibility of conducting large-scale population-based screening. In a recent study by Scott and colleagues, all 48 exons of the 100-kb SI gene on chromosome 3 were sequenced in 31 biopsy-proven patients with CSID and 55 different mutations were identified, with at least 1 of the 4 most common mutations found on 32 (59%) of the affected alleles (4). If one assumes the Hardy-Weinberg equilibrium for mutations in the population, then there is an 83% probability that an individual with severe clinical manifestations of CSID will have at least 1 of these 4 mutations. The results of this study raise the possibility in the near future of a genetic screening test both for population prevalence studies and to aid in the diagnosis of new cases. With the availability of DNA harvesting from buccal mucosa, the feasibility of genetic testing in young infants and children increases substantially. Studies are in progress to determine whether genetic testing also can be done on intestinal epithelial biopsy specimens opening the possibility of simultaneously determining disaccharidase levels and genetic mutations for CSID.

Clinical studies of relatively homogenous selected populations have yielded high rates of CSID, ranging from 5% to 10% in Greenland Eskimos, 3% to 7% in Canadian native peoples, and about 3% in Alaskans of native ancestry (13,14); however, estimates of the prevalence of CSID in other North American and European populations generally range from 1 in 500 to 1 in 2000 among non-Hispanic whites, with a lower prevalence in African Americans and whites of Hispanic descent. These studies evolved from older studies of intestinal disaccharidase levels in adult patients undergoing endoscopy for gastrointestinal symptoms (15,16). The estimates have shown low levels of sucrase activity >1 standard deviation (SD) below the mean in mucosal biopsy specimens from 2% to 9% of patients, even in the absence of overt mucosal injury. If one assumes that some of these patients represent heterozygotes for CSID, then the prevalence quoted above seems plausible; however, the diagnosis of CSID is rarely made even in infants and young children, suggesting the possibility that the phenotype of CSID may be much broader and more variable than previously thought and that a large proportion of affected adult and pediatric patients are not being tested and diagnosed.

This hypothesis receives support from the analysis of recently released whole exome sequence data (Exome Variant Server, <http://evs.gs.washington.edu/EVS>). Belmont and colleagues at the Children's Nutrition Research Center at the Baylor College of

Medicine reviewed the SI gene sequence data in a population of approximately 3500 North American white adults ascertained as controls or with atherosclerosis and no known bias for gastrointestinal disease. These data showed 271 rare missense variants with an aggregate allelic frequency of 0.03864. Based on this allele frequency, and assuming that the alleles segregate independently, Hardy-Weinberg proportions were used to estimate the frequency of homozygotes and compound heterozygotes for rare alleles. Although it is not known whether all of these variants result in decreased enzyme activity, the large number of variants could be consistent, with an estimated frequency of 1:670 affected patients and 7% carriers in this population (personal communication, Dr John Belmont, February 28, 2012; public data at the Exome Variant Server).

There are several pieces of clinical evidence that support the view that CSID is more prevalent than previously believed. Studies of disaccharidase levels from intestinal biopsy specimens sent to 2 pediatric reference laboratories have shown surprisingly frequent results for a pattern suggesting CSID. In 2 studies of almost 1000 biopsies each, sucrase deficiency was defined as >1 SD below the mean activity level in 1 study and $<10\%$ of the mean in another (17,18). As defined, sucrase deficiency was found in 11% and 13% of biopsy specimens in the 2 studies. Included were specimens with isolated sucrase or SI deficiency only (1.0% and 1.1%, respectively), SI and maltase-glucoamylase (MGAM) deficiency only (3.0% and 2.4%, respectively), and pandisaccharidase deficiency (5.8% in both studies). Pandisaccharidase deficiency was more likely accounted for by acquired diffuse intestinal villous injury. Although correlation with histology was not provided, the surprisingly high numbers of isolated SI and combined SI-MGAM deficiencies without lactase deficiency suggest that specific genetically determined enzyme deficiencies may be playing a role.

Although small intestinal disaccharidases are most often investigated in the clinical setting of diarrhea in infants and young children, the role of disaccharidase deficiencies and specifically SI deficiency in other gastrointestinal syndromes also has been entertained. Small series of patients with CSID have revealed a subgroup of adolescents and even adults who present with dyspepsia, gas, and/or irritable bowel syndrome (IBS) rather than the classic presentation of watery diarrhea, failure to thrive, diaper rash, irritability, and acidic stools in infancy (2,19,20). Karnsakul and colleagues studied 44 children and adolescents with dyspepsia, only 4 of whom had intermittent diarrhea (21). Patients underwent endoscopy with small bowel biopsies and disaccharidases and one-third had low sucrase activity (>1 SD from the mean), including 4 of 44 with isolated low sucrase activity, and 11 of 44 with sucrase and pandisaccharidase deficiency, but no significant villous atrophy. In addition, in preliminary follow-up studies of families with index cases of CSID uncovered in a child, parents with a long-term diagnosis of IBS were subsequently identified as having CSID (22).

After the sequencing of all of the exons of the CSID gene, most patients with CSID studied by Scott and colleagues have been found to be homozygous or compound heterozygotes for disease-causing mutations (4). Kerry and Townley showed that the parents of 4 children with CSID had intestinal sucrase activity below the lower limits of normal and a sucrase:lactase ratio <0.8 , both consistent with the heterozygous state and supporting an autosomal recessive pattern of inheritance (23); however, 3 patients in Scott and colleagues' study who presented with classical symptoms and biopsy-proven absent sucrase activity with absent or low isomaltase activity, and 2 others with milder decreases in both enzymes, appeared to be heterozygote carriers with a mutation on 1 allele and a wild-type gene on the other. These small studies lend credence to the hypothesis that CSID is more prevalent than previously

thought; manifests with milder phenotypes that may even omit diarrhea as a prominent symptom; and may be transmitted in ways other than strict autosomal recessive inheritance. The combination of the “heterozygous” state with other genetic and/or dietary and nutritional interactions may provoke gastrointestinal symptoms in certain patients.

PRESENTATION AND NATURAL HISTORY OF CSID

The classical presentation of CSID is severe watery diarrhea, failure to gain weight, irritability, and diaper rash in a 9- to 18-month-old infant who has been exposed to sucrose and starch in the form of baby juices, baby food fruits, teething biscuits, crackers, and other starches. Factors that contribute to the predilection for a presentation during infancy include the shorter length of the colon and a decreased capacity for colonic reabsorption of fluid and electrolytes, more rapid small intestinal transit, a high carbohydrate diet, and the ontogeny of amylase activity that does not reach “adult” levels until the second year of life (24); however, clinical studies during the last 20 years and a retrospective review of 65 patients with CSID have revealed a variety of presentations that defy the conventional view (5,22,25,26). Table 1 describes the symptoms at presentation in these 65 patients. Although most have presented with the classic symptoms, a significant minority have only been diagnosed between 2 to 8 years old after normal growth and a previous diagnosis of chronic nonspecific diarrhea of childhood (“toddler’s diarrhea”), or even later during adolescence or young adulthood carrying a diagnosis of diarrhea-predominant IBS. Up to one-third have had vomiting as a prominent symptom, suggesting again that dyspepsia, gas, bloating, and even reflux-like symptoms may predominate in some patients. Other anecdotal reports have mentioned hypercalcemia and nephrocalcinosis in infants with CSID, and even renal calculi in 2 adults with CSID (27,28).

In a follow-up study of 65 patients with CSID who responded to a questionnaire after being identified by a record of prescriptions for enzyme replacement therapy, 53 of 65 reported the onset of symptoms before 1 year of age, 7 between 1 and 10 years old, and 5 after 10 years of age (22); however, the age at which a diagnosis was made was shifted to the right, with only 17 of 65 diagnosed in the first year, 30 between 1 and 5 years, 10 between 5 and 10 years, and 8 after 10 years of age. The potential reasons for this delay in diagnosis include a mistaken diagnosis of protein intolerance in infancy with multiple formula changes and the elimination of glucose oligomers (maltodextrin) that are partially hydrolyzed by sucrase in favor of glucose monomers in amino acid-based formulas (29). A diagnosis of food allergy often also leads to the elimination of juices and baby foods that may have a high sucrose load, further masking the true underlying cause of diarrhea in patients with CSID. Later in childhood, a diagnosis of chronic

nonspecific diarrhea often will result in a lower carbohydrate, higher fat diet, and the elimination of all juices with improvement in symptoms of patients with CSID (30). Older children and adolescents with CSID and diarrhea-predominant IBS may learn which foods trigger their symptoms and avoid those foods, thus masking their true diagnosis. In addition, chronic carbohydrate malabsorption may act as a prebiotic stimulus to colonic bacterial growth, creating a significant increase in the capacity to ferment and salvage malabsorbed carbohydrate, and stimulate colonic short-chain fatty acid synthesis and sodium and fluid reabsorption by the colonocyte (31). Colonic bacterial flora “adaptation” may thus contribute to a decrease in diarrhea symptoms over time in some patients with CSID.

DIAGNOSIS OF CSID

At present, the gold standard for the diagnosis of CSID remains small intestinal biopsy specimens assayed for lactase, sucrase, isomaltase (palatinase), and maltase activity. In general, the criteria applied to make the diagnosis of CSID include normal small bowel morphology in the presence of absent or markedly reduced sucrase activity, isomaltase activity varying from 0 to full activity, reduced maltase activity, and normal lactase activity, or in the setting of reduced lactase, a sucrase:lactase ratio of <1.0. Table 2 summarizes the disaccharidase activities in 36 patients with CSID; all were included in 2 pivotal clinical trials included as part of the new drug application (NDA) for sacrosidase submitted to the Food and Drug Administration (FDA; NDA 20-772/S-011, 1998). Sucrase activity was absent in 24 of 36 (66%) patients, and in all but 3, activity was less than the third percentile of 977 values in “controls,” which consisted of unselected small bowel biopsies from children with diarrhea and other gastrointestinal symptoms (18). All sucrase activity values in patients with CSID were <10th percentile of controls. Almost two-thirds (23/35) had absent palatinase (isomaltase) activity, and all but 2 were <10th percentile, with 1 of those in the normal range and 1 with elevated activity. Maltase activity was variable. No patient had absent activity, but the mean equaled 41.5 U/g protein and the majority (25/36, 69%) exhibited reductions >2 standard deviations from the mean in controls. All but 2 patients demonstrated <10% of control activity. Two patients exhibited normal activity. There was no clear correlation between absent or residual sucrase activity with the spectrum of decreased maltase activity. Because the brush border enzyme MGAM is responsible for at least 20% of maltase activity, those patients with low maltase activity may be examples of combined deficiencies of SI and MGAM (32,33). Elevated lactase enzyme activity levels were found in 3 of our patients and have been found in a small minority of patients with CSID in most studies to date.

Recent studies of the SI gene in symptomatic patients with intestinal disaccharidase deficiency have identified compound

TABLE 1. Presenting symptoms in 65 patients with CSID (22)

Symptom	No. patients (%)
Diarrhea	62 (95)
Bloating/gas	55 (85)
Abdominal pain	43 (66)
Irritability	43 (66)
Diaper rash	40 (62)
Failure to thrive	39 (60)
Nausea/vomiting	22 (34)
Irritable bowel syndrome	12 (18)

TABLE 2. Intestinal biopsy disaccharidase activities in 36 patients with CSID (U/g protein) (42,43)

	Sucrase (n = 36)	Isomaltase (palatinase) (n = 35)	Maltase (n = 36)	Lactase (n = 36)
Mean	2.3	1.9	41.5	30.5
Standard deviation	4.4	5.8	34.7	19.2
Median	0	0	29.2	27.6
Minimum	0	0	10.9	5.2
Maximum	15.4	33.3	166.7	101.5

heterozygotes with less severely reduced sucrase and isomaltase and even what appears to be true heterozygotes with 1 normal allele and what appears to be a more severe mutation on the other allele (4–6,34). One patient in the cohort studies by Scott et al appeared to have normal wild-type genes on both alleles with moderately reduced sucrase activity and symptoms provoked by sucrose consumption, which suggested acquired sucrase deficiency even in the presence of normal small intestinal morphology (4). Other causes of false-positive results come from biopsies taken in the proximal duodenum, where disaccharidase levels are often only approximately two-thirds of the levels found in the proximal jejunum (35). In addition, mishandling of biopsy specimens resulting in inadequate rapidity of freezing and premature thawing can result in a diffuse reduction in disaccharidase activity. Studies of replicate intestinal biopsy disaccharidase assays have demonstrated a coefficient of variation of 27%, stressing the variability of the assay (18). This variation emphasizes the role of clinical judgment in making the diagnosis of CSID from mucosal disaccharidase assay values.

Other less invasive methods of diagnosis include the sucrose breath hydrogen study and differential urinary disaccharides (36,37). Although relatively easy to accomplish, the sucrose breath hydrogen study is compromised by significant contamination from both false-positives (secondary sucrase deficiency from villous injury, dumping syndrome, and bacterial overgrowth) and false-negatives (nonhydrogen producers, antibiotic interference, delayed gastric emptying). Also, this test can provoke severe symptoms as a result of the 2-g/kg oral sucrose load given to patients with CSID. The differential urinary disaccharide test examines the ratio of urinary sucrose:lactulose, which should approach 1.0 in patients with CSID; however for accurate results, this test relies on obtaining an accurate 10-hour urine collection that is difficult in many infants and young children and the presence of normal intestinal permeability.

Figure 1 summarizes data from studies of the utility of a ^{13}C -sucrose breath test to diagnose CSID (38). This test requires the administration of a small dose of uniformly labeled ^{13}C -sucrose mixed in unlabeled maltodextrin in water as a carrier and the subsequent collection of $^{13}\text{CO}_2$ -enriched breath samples every 15 minutes for 2 hours. The separate administration of ^{13}C -glucose mixed in maltodextrin and collection of $^{13}\text{CO}_2$ allows ^{13}C -sucrose hydrolysis and digestion to be expressed as a coefficient of glucose oxidation (CGO). As Figure 1 shows, the mean percent CGO of ^{13}C -sucrose in 10 patients with CSID is $25\% \pm 21\%$ compared with $146\% \pm 45\%$ in 10 age-matched controls. A cutoff of 79% CGO yields 100% sensitivity and specificity for CSID. Although the test

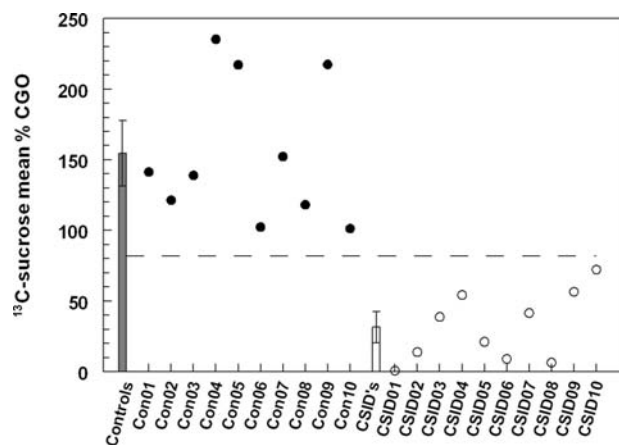


FIGURE 1. Data summary from studies of the utility of a ^{13}C -sucrose breath test to diagnose CSID.

requires 2 breath tests and infrared spectrophotometry, it has several advantages: it is noninvasive, has excellent sensitivity and specificity, and avoids provocation of gastrointestinal symptoms because of an excessive sucrose load.

TREATMENT OF CSID

Previous follow-up studies of children with CSID treated with sucrose- and starch-restricted diets have demonstrated that only 10% of patients remain consistently asymptomatic, and 60% to 75% still experience diarrhea, gas, and/or abdominal pain, with a lower proportion (20%) complaining of nausea. Only approximately half of these children are compliant with the prescribed diet (39,40). Harms and colleagues described the amelioration of both hydrogen production and gastrointestinal symptoms in 8 children with CSID treated with Baker's yeast (*Saccharomyces cerevisiae*) cakes before a sucrose breath hydrogen test (41). *S cerevisiae* contains a β -fructofuranoside fructohydrolase with sucrase but not maltase or isomaltase activity. By using specific growing conditions to promote increased enzyme activity and belt drying to preserve this activity, the food industry has for many years been using this enzyme to convert sugarcane (sucrose) to molasses and keep the centers of cream-filled candies liquid. Preclinical studies on a liquid preparation derived from the *S cerevisiae* (sacrosidase) grown under these conditions showed that 1 mL of this preparation contained approximately 8500 U of sucrose-hydrolyzing activity (8500 μmol glucose formed per minute per milliliter) (42). Sacrosidase was free of lactase, isomaltase, or maltase activity; rich in mannose glycosylation; maintained stable activity with refrigeration; and did not lose significant activity with a pH down to 1.0. Incubation of the enzyme with pepsin at or near the pH optimal for pepsin activity (1.5), however, produced a rapid loss of activity. Preincubation of the pepsin with bovine serum albumin provided a decoy for the pepsin and allowed preservation of sacrosidase activity even at a pH of 1.5.

Figure 2 shows the results of sucrose breath hydrogen studies on the first child with CSID treated with sacrosidase under an orphan drug grant from the FDA. Two breath tests with 2 and 4 g/kg sucrose loads produced a marked rise in breath hydrogen and gastrointestinal symptoms; however, breath tests accompanied by sacrosidase treatment prevented the rise in breath hydrogen and the symptoms. Subsequent pivotal trials in >40 subjects between the ages of 5 months and 29 years were conducted, with the diagnosis of CSID based on chronic watery diarrhea with an acid pH, a tissue

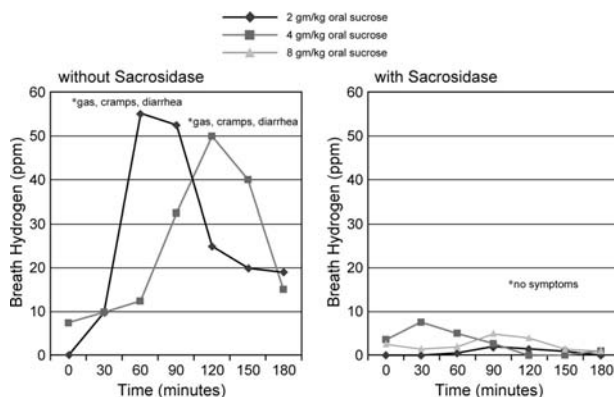


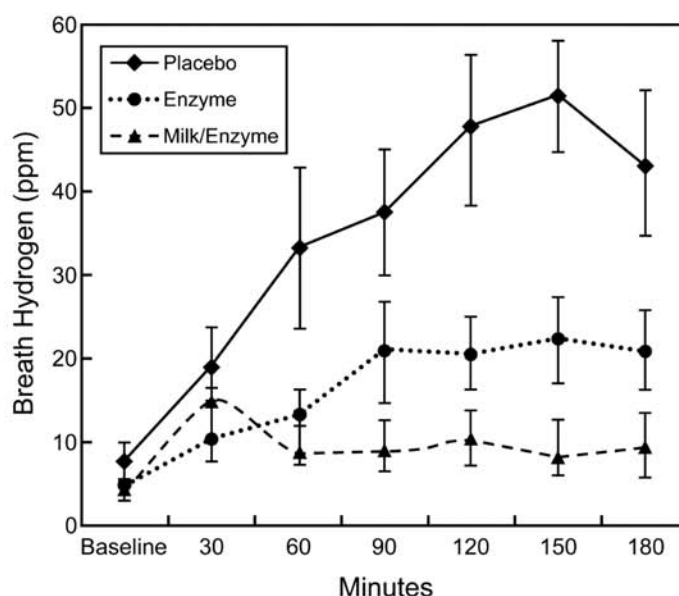
FIGURE 2. Results of sucrose breath hydrogen studies on the first child with CSID treated with sacrosidase under an orphan drug grant from the Food and Drug Administration.

sucrase activity level of <10% of the mean of controls, a normal lactase level, and a normal lactose breath hydrogen test (42,43). These multicenter, double-blind, randomized studies used 3 increasing dilutions of sacrosidase and an undiluted form in 4 arms given to each subject in random order during a 10-day period in which time the subjects consumed a normal sucrose-containing (approximately $1.75\text{--}2.5\text{ g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$) and starch-containing ($5.2\text{--}5.8\text{ g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$) diet. Two breath hydrogen studies (with and without sacrosidase) were performed in the first study and 3 (with and without sacrosidase and with sacrosidase plus cow's milk acting as a pepsin decoy) in the second pivotal study.

The results of these studies can be summarized as follows. All dilutions of sacrosidase reduced symptoms of sucrose

malabsorption provoked by both the breath tests and the period of unrestricted diet; the undiluted preparation most significantly reduced watery stools, gas, cramps, and bloating. Full-strength (undiluted) sacrosidase normalized these symptoms and the stool frequency in comparison with the baseline period of a sucrose-free, starch-restricted diet and no sacrosidase treatment. Full-strength sacrosidase resulted in 81% of patients, consuming an unrestricted diet, remaining asymptomatic, compared with 78% untreated during the baseline, diet-restricted period. Excessive breath hydrogen production was blocked by the double-blind administration of sacrosidase compared with placebo and was further reduced by consuming milk before sucrose ingestion (Fig. 3A). A study of the ^{13}C -sucrose breath test with and without sacrosidase administration

A



B

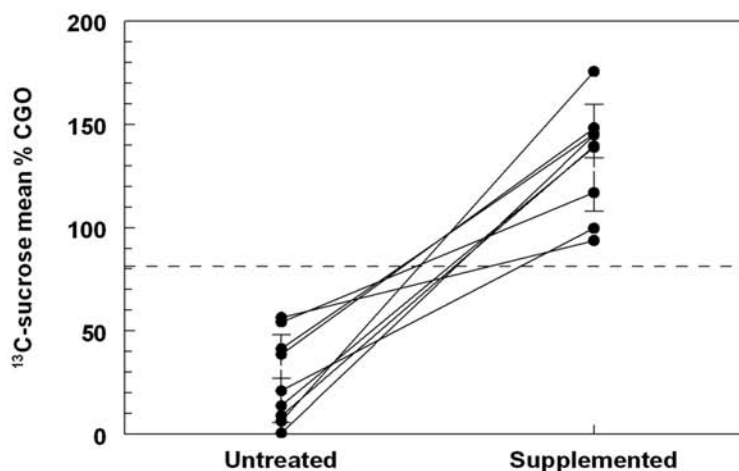


FIGURE 3. A, Excessive breath hydrogen production blocked by the double-blind administration of sacrosidase compared with placebo and was further reduced by consuming milk before sucrose ingestion. B, A study of the ^{13}C -sucrose breath test with and without sacrosidase administration confirmed these results and shows that all of the subjects had normalized CGO with therapy.

TABLE 3. Persistence of symptoms in 65 patients with CSID treated with Sucraid (22)

Symptom frequency	Diarrhea, %	Bloating/gas, %	Nausea/vomiting, %	Abdominal pain, %
0 times per week	46	43	96	91
1 time per week	28	18	4	9
2–3 times per week	12	13	0	0
>3 times per week	14	26	0	0

confirmed these results and shows that all of the subjects had normalized CGO with therapy (Fig. 3B) (37). Adverse events were limited to unrelated episodes of vomiting, pallor, and dehydration, each in a single subject, and a possibly related event of wheezing in a young child with known asthma, who was later found to have a positive skin test for sacrosidase (43). This incident led to the recommendation on the label to perform skin tests on patients with asthma before sacrosidase is administered. No other patients have been described with this adverse effect. These studies resulted in the submission of an NDA to the FDA and approval of Sucraid (sacrosidase) as treatment for CSID in 1998. Treatment was covered by Medicaid, after which private insurance coverage was approved. Recommendations for dosing on the label suggest using 1 mL with meals or snacks for patients <15 kg and 2 mL with meals or snacks for those >15 kg. Doses are to be split, with half the dose given at the onset of a meal and the other half midway through, when the intragastric environment is buffered to a higher pH and pepsin may be partially decoyed by other proteins.

A preliminary postmarketing surveillance study was conducted involving 229 patients with CSID who received prescriptions for Sucraid (sacrosidase) between 2004 and 2009. Results are summarized in a published abstract and in the proceedings of this symposium (22). Sixty-nine of 229 questionnaires were returned from 60 of 69 patients in 27 states in the United States and from 9 patients in 4 other countries. Included were 39 male patients and 66 of 69 patients younger than 18 years old. Sixty-five patients continued taking Sucraid; 2 had abandoned it because of lack of efficacy and 2 because of its cost. The median duration of therapy was 3 years and one-third had been treated continuously for >5 years. Nine of 65 (14%) patients were exceeding the maximum recommended dose per meal (2 mL) to try to control symptoms. Either a normal diet or a mild sucrose- and starch-restricted diet was consumed by 41 of 65 (65%) patients, but in 27%, strict sucrose restriction with either mild or strict starch restriction was necessary to maintain acceptable suppression of symptoms, even while taking Sucraid. Table 3 summarizes symptoms while patients are being treated with Sucraid. The majority (59/65, 92%) had <3 bowel movements per day, and 74% experienced either no diarrhea or diarrhea once per week, 12% had diarrhea 2 to 3 times per week, and 14% had diarrhea >3 times per week. In 74%, bloating occurred <3 times per week. Abdominal pain and nausea/vomiting were not seen in any patients >1 time per week and were completely absent in >90% of patients. The most common adverse events reported included constipation in 6 of 65, headaches in 5 of 65, and sleep disturbances in 8 of 65. None of these events resulted in discontinuing Sucraid.

CONCLUSIONS

Both clinical studies and molecular/genetic investigations suggest that CSID is a more common disease than previously believed and that genetically modified small intestinal SI digestion accounts for a broad spectrum of clinical phenotypes, including some potentially hidden in large cohorts of patients with IBS, chronic nonspecific diarrhea, and perhaps even dyspepsia (44).

The advent of noninvasive breath tests with excellent sensitivity and specificity and genetic tests of relatively common mutations in the CSID gene hold out the promise of more accurate population prevalence studies and diagnosis of less classic cases, even in adults who are believed to have lifelong functional bowel disorders. The recent approval of an enzyme replacement therapy has allowed liberalization of the previously mandatory sucrose restrictive diet and restored a more normal lifestyle, particularly to infants and young children exposed to a high carbohydrate diet (45). Further modifications of this therapy with the possible additions of enzymes geared to supplement higher maltase and glycoamylase activity may be in the offing to help patients cope with the continued problem of starch malabsorption. Research has demonstrated that additional amylase activity amplifies the effect of SI and MGAM on starch digestion and offers another potential addition to enzyme replacement therapy (18,46).

REFERENCES

1. Weijers H, Va De Kamer J, Mossel D, et al. Diarrhoea caused by deficiency of sugar-splitting enzymes. *Lancet* 1960;6:296–7.
2. Treem W. Congenital sucrose-isomaltase deficiency. *J Pediatr Gastroenterol Nutr* 1995;21:1–14.
3. Chantret I, Lacasa M, Chevalier G, et al. Sequence of the complete cDNA and the 5' structure of the human sucrose-isomaltase gene. Possible homology with a yeast glucoamylase. *Biochem J* 1992;285:915–23.
4. Uhrich S, Wu Z, Huang J, et al. Four mutations in the SI gene are responsible for the majority of clinical symptoms of CSID. *J Pediatr Gastroenterol Nutr* 2012;55(Suppl 2):S34–5.
5. Alfalah M, Keiser M, Leeb T, et al. Compound heterozygous mutations affect protein folding and function in patients with congenital sucrose-isomaltase deficiency. *Gastroenterology* 2009;136:88–92.
6. Naim HY, Heine M, Zimmer KP, et al. Congenital sucrose-isomaltase deficiency: heterogeneity of inheritance, trafficking, and function of an intestinal enzyme complex. *J Pediatr Gastroenterol Nutr* 2012;55(Suppl 2):000–000.
7. Codain L, Eaton SB, Sebastian A, et al. Origins and evolution of the Western diet: health implications for the 21st century. *Am J Clin Nutr* 2005;81:341–54.
8. Gudmand-Hoyer E, Fenger H, Kern-Hansen P, et al. Sucrase deficiency in Greenland. *Scand J Gastroenterol* 1987;22:24–8.
9. Goda T, Koldovsky O. Dietary regulation of small intestinal disaccharidases. *World Rev Nutr Diet* 1988;57:275–329.
10. Yeh KY, Yeh M, Holt PR. Differential effects of thyroxine and cortisone on jejunal sucrose expression in suckling rats. *Am J Physiol* 1989;256:604–12.
11. West A, Oates P. Decreased sucrase and lactase activity in iron deficiency is accompanied by reduced gene expression and upregulation of the transcriptional repressor PDX-1. *Am J Physiol Gastrointest Liver Physiol* 2005;289:G1108–14.
12. Tundis R, Loizzo R, Menichini F. Natural products as alpha-amylase and alpha-glucosidase inhibitors and their hypoglycaemic potential in the treatment of diabetes: an update. *Mini Rev Med Chem* 2010;10:315–31.
13. Bell R, Draper H, Bergan JG. Sucrose, lactose, and glucose intolerance in northern Alaskan Eskimos. *Am J Clin Nutr* 1973;26:1185–90.

14. Ellestad-Sayad J, Haworth J, Hildes J. Disaccharide malabsorption and dietary patterns in two Canadian Eskimo communities. *Am J Clin Nutr* 1978;31:1473–8.
15. Peterson M, Herber R. Intestinal sucrase deficiency. *Trans Assoc Am Physicians* 1967;80:275–83.
16. Welsh J, Poley J, Bhatia M, et al. Intestinal disaccharidase activities in relation to age, race, and mucosal damage. *Gastroenterology* 1978;75:847–55.
17. Gupta S, Chong S, Fitzgerald J. Disaccharidase activities in children: normal values and comparison based on symptoms and histological changes. *J Pediatr Gastroenterol Nutr* 1999;28:246–51.
18. Quezada-Calvillo R, Robayo-Torres C, Ao Z, et al. Luminal substrate “brake” on mucosal maltase-glucoamylase activity regulates total rate of starch digestion to glucose. *J Pediatr Gastroenterol Nutr* 2007;45:32–43.
19. Muldoon C, Maguire P, Gleeson F. Onset of sucrase-isomaltase deficiency in late adulthood. *Am J Gastroenterol* 1999;94:2298–9.
20. Ringrose R, Preiser H, Welsh J. Sucrase-isomaltase (palatinase) deficiency diagnosed during adulthood. *Dig Dis Sci* 1980;25:384–7.
21. Karnsakul W, Luginbuel U, Hahn D, et al. Disaccharidase activities in dyspeptic children: biochemical and molecular investigations of maltase-glucoamylase activity. *J Pediatr Gastroenterol Nutr* 2002;35:551–6.
22. Treem WR, Douglas M, Duong S, et al. Congenital sucrase-isomaltase deficiency (CSID) in the era of Sucraid. *J Pediatr Gastroenterol Nutr* 2009;53(Suppl 1):E85.
23. Kerry K, Townley R. Genetic aspects of intestinal sucrase-isomaltase deficiency. *Aust Paediatr J* 1965;1:223–35.
24. Auricchio S, Ciccimarra F, Moauro L, et al. Intraluminal and mucosal starch digestion in congenital deficiency of intestinal sucrase and isomaltase activities. *Pediatr Res* 1972;6:832–9.
25. Baudon J, Veinberg F, Thioulouse E, et al. Sucrase-isomaltase deficiency: changing pattern over two decades. *J Pediatr Gastroenterol Nutr* 1996;22:284–8.
26. Treem WR. Clinical heterogeneity in congenital sucrase-isomaltase deficiency. *J Pediatr* 1996;128:727–9.
27. Belmont J, Reid B, Taylor W, et al. Congenital sucrase-isomaltase deficiency presenting with failure to thrive, hypercalcemia, and nephrocalcinosis. *BMC Pediatr* 2002;2:1–7.
28. Starnes C, Welsh JD. Intestinal sucrase-isomaltase deficiency and renal calculi. *N Engl J Med* 1970;282:1023–4.
29. Newton T, Murphy M, Booth IW. Glucose polymer as a cause of protracted diarrhea in infants with unsuspected congenital sucrase-isomaltase deficiency. *J Pediatr* 1996;128:753–6.
30. Treem WR. Chronic non-specific diarrhea of childhood. *Clin Pediatr* 1992;31:413–20.
31. Treem WR, Ahsan N, Kastoff G, et al. Fecal short-chain fatty acids in patients with diarrhea-predominant irritable bowel syndrome: in-vitro studies of carbohydrate fermentation. *J Pediatr Gastroenterol Nutr* 1996;23:280–6.
32. Skovbjerg H, Krasilnikoff P. Maltase-glucoamylase and residual isomaltase in sucrose-intolerant patients. *J Pediatr Gastroenterol Nutr* 1986;5:365–71.
33. Lebenthal E, U KM, Zheng BY, et al. Small intestinal glucoamylase deficiency and starch malabsorption: a newly recognized alpha-glucoamylase deficiency in children. *J Pediatr* 1994;124:541–6.
34. Sander P, Alfalah M, Keiser M, et al. Novel mutations in the human sucrase-isomaltase gene (SI) that cause congenital carbohydrate malabsorption. *Hum Mutat* 2006;27:119.
35. Smith J, Mayberry J, Ansell ID, et al. Small bowel biopsy for disaccharidase levels: evidence that endoscopic forceps biopsy can replace the Crosby capsule. *Clin Chim Acta* 1989;183:317–21.
36. Perman J, Barr R, Watkins JB. Sucrose malabsorption in children: noninvasive diagnosis by interval breath hydrogen determination. *Pediatrics* 1978;93:17–22.
37. Bjarnason I, Batt R, Catt S, et al. Evaluation of differential disaccharide excretion in urine for non-invasive investigation of altered intestinal disaccharidase activity cause by (-glucosidase inhibition, primary hypolactasia, and celiac disease. *Gut* 1996;39:374–81.
38. Robayo-Torres C, Opekun A, Quezada-Calvillo R, et al. 13C-breath tests for sucrose digestion in congenital sucrase isomaltase-deficient and sacrosidase-supplemented patients. *J Pediatr Gastroenterol Nutr* 2009;48:412–8.
39. Antonowicz I, Lloyd-Still J, Khaw KT, et al. Congenital sucrase-isomaltase deficiency. Observations over a period of 6 years. *Pediatrics* 1972;49:847–53.
40. Kilby A, Burgess E, Wigglesworth S, et al. Sucrase-isomaltase deficiency. A follow-up report. *Arch Dis Child* 1978;53:677–9.
41. Harms H, Bertele-Harms R, Bruer-Kleis D. Enzyme-substitution therapy with the yeast *Saccharomyces cerevisiae* in congenital sucrase-isomaltase deficiency. *N Engl J Med* 1987;316:1306–9.
42. Treem WR, Ahsan N, Sullivan B, et al. Evaluation of liquid yeast-derived sucrase enzyme replacement in patients with sucrase-isomaltase deficiency. *Gastroenterology* 1993;105:1061–8.
43. Treem WR, McAdams L, Stanford L, et al. Sacrosidase therapy for congenital sucrase-isomaltase deficiency. *J Pediatr Gastroenterol Nutr* 1999;28:137–42.
44. Rahhal R, Bishop W. Sacrosidase trial in chronic non-specific diarrhea in children. *Open Pediatr Med J* 2008;2:35–8.
45. Lucke T, Keiser M, Illsinger S, et al. Congenital and putatively acquired forms of sucrase-isomaltase deficiency in infancy: effects of sacrosidase therapy. *J Pediatr Gastroenterol Nutr* 2009;49:485–7.
46. Liakopoulou-Kyriakides M, Karakatsanis A, Stamatoudis M, et al. Synergistic hydrolysis of crude corn starch by α -amylases and glucoamylases of various origins. *Cereal Chem* 2001;78:603–7.

Congenital Sucrase-Isomaltase Deficiency: Heterogeneity of Inheritance, Trafficking, and Function of an Intestinal Enzyme Complex

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Brush border membranes are the largest exposed surfaces in tissues. They constitute the interface between the “milieu exterieur” and the “milieu interieur” of the body in a variety of organs such as the gastrointestinal tract and bile canaliculi, where hydrolytic, absorptive, and secretory processes take place. The intestinal mucosa is the exclusive site for nutrient metabolism and subsequent uptake of the generated products, such as monosaccharides and amino acids. The hydrolysis and absorption of micronutrients are achieved by the concerted action of hydrolases and transporters that are predominantly located in the brush border membranes (BBMs) (1).

The hydrolases are divided into 2 major families, the peptidases and the disaccharidases (2). The peptidases, such as aminopeptidases N (CD13), A, and W, carboxypeptidases P and M, dipeptidylpeptidase IV, or α -glutamyl transpeptidase, are expressed in many tissues, including the intestine and the kidney (3,4). The

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