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REVIEW ARTICLE

Genetic and acquired sucrase-isomaltase deficiency: A clinical review

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Abstract

Genetic sucrase-isomaltase deficiency (GSID) is an inherited deficiency in the ability to digest sucrose and potentially starch due to mutations in the *sucrase-isomaltase* (*SI*) gene. Congenital sucrase-isomaltase deficiency is historically considered to be a rare condition affecting infants with chronic diarrhea as exposure to dietary sucrose begins. Growing evidence suggests that individuals with *SI* variants may present later in life, with symptoms overlapping with those of irritable bowel syndrome. The presence of *SI* genetic variants may, either alone or in combination, affect enzyme activity and lead to symptoms of different severity. As such, a more appropriate term for this inherited condition is GSID, with a recognition of a spectrum of severity and onset of presentation. Currently, disaccharidase assay on duodenal mucosal tissue homogenates is the gold standard in diagnosing SI deficiency. A deficiency in the SI enzyme can be present at birth (genetic) or acquired later, often in association with damage to the enteric brush-border membrane. Other noninvasive diagnostic alternatives such as sucrose breath tests may be useful but require further validation. Management of GSID is based on sucrose and potentially starch restriction tailored to the individual patients' tolerance and symptoms. As this approach may be challenging, additional treatment with commercially available sacrosidase is available. However, some patients may require continued starch restriction. Further research is needed to clarify the true prevalence of SI deficiency, the pathobiology of single *SI* heterozygous mutations, and to define optimal diagnostic and treatment algorithms in the pediatric population.

KEYWORDS

carbohydrate malabsorption, congenital sucrase isomaltase deficiency, chronic diarrhea, IBS

1 | INTRODUCTION

Congenital sucrase-isomaltase deficiency (CSID) is an autosomal recessive intestinal disorder, first described in 1960.[1] In this initial report, Weijers et al. reported a case series of three children who had diarrhea due to a "deficiency of sugar splitting enzymes." They described a condition that could be diagnosed with sugar-loading curves, the presence of lactic acid in the stools, and symptom resolution with sugar avoidance or supplementation of the deficient enzyme.[1] Such enzyme deficiencies have subsequently been characterized in more detail, and there are now at least six disorders of carbohydrate metabolism that are due to a deficiency of an enzyme on the brush border or to a defective transport system across the membrane of the enterocyte.[2]

Sucrase-isomaltase deficiency (SID), the most common and best characterized of the congenital forms of these disorders, is an inherited deficiency in the ability to hydrolyze sucrose, maltose, short 1–4

linked glucose oligomers, branched (1–6 linked) α-limit dextrins, and starch.[3] Mutations in the *SI* gene are responsible for abnormal synthesis or incorrect transport of the SI enzyme, resulting in levels of enzyme activity ranging from absent to almost normal. In affected children, symptoms typically begin with exposure to sucrose, such as when transitioning from exclusive formula or breast feeding to intake of fruits, juices, and other baby foods. Growing evidence suggests that individuals with *SI* variants may present later in life, with symptoms overlapping with those of irritable bowel syndrome. The presence of *SI* genetic variants may, either alone or in combination, affect enzyme activity and lead to symptoms of different severity. As such, a more appropriate term for this inherited condition is genetic sucrase-isomaltase deficiency (GSID), with a recognition of a spectrum of severity and onset of presentation.

What is Known

- Congenital sucrase-isomaltase deficiency is historically considered to be a rare autosomal recessive condition identified in infants with symptoms of diarrhea, malabsorption, and failure to thrive
- Single *sucrase-isomaltase* (SI) pathologic variants have been increasingly reported in children and adults with disorders of gut–brain interaction

What is New

- *SI* genetic variants, express varying degrees of enzyme activity and lead to symptoms of varying severity that may present after infancy
- SI enzyme deficiency may be an important and overlooked cause of unexplained gastrointestinal symptoms
- Given the increasing awareness of genetic *SI* variants and their association with a spectrum of gastrointestinal symptom severity, a better term is genetic sucrase-isomaltase deficiency

2 | EPIDEMIOLOGY AND VARYING CLINICAL PRESENTATION OF GSID

GSID was believed to be rare, occurring in 0.05%–0.2% of individuals of European descent and approximately 5%–10% among indigenous Greenlanders.[4] While still rare in its most severe forms, increasing evidence suggests that the phenotype of GSID can vary and that many patients present later in life, with symptoms overlapping those of irritable bowel syndrome (IBS).[5] Indeed, GSID is now considered to be a masquerader of IBS (Table 1) due to the existence of several *SI* genetic variants that, either alone or in combination, express varying degrees of enzyme activity and lead to symptoms of different severity.[6] Of note, classic symptoms of diarrhea-predominant IBS (IBS-D) also occur with secondary SID, when the intestinal mucosa has been damaged by infectious or autoimmune disorders (e.g., giardiasis, celiac disease, Crohn's disease) or there has been inhibition in SI function by medications such as miglustat, ranitidine, or codeine.[7]

When ingested sugars are not hydrolyzed and absorbed, they accumulate in the bowel, increasing the osmotic load and causing retention and secretion of water and electrolytes into the lumen. As a result of the larger intraluminal content, gut motility increases and there is an acceleration of small intestinal transit, decreasing absorption further and contributing to hyperosmolar, watery diarrhea. Once the undigested sugars reach the colon, fermentation occurs by bacterial flora with the release of hydrogen, and potentially other gases such as methane, contributing to flatulence, bloating, and abdominal cramping. When intestinal transit becomes very rapid, other nutrients may be malabsorbed, leading to a risk of failure to thrive, especially in infants and toddlers who have shorter intestines and higher metabolic needs. Stools may become very acidic and may lead to severe perianal rashes in children wearing diapers, a hallmark of impaired carbohydrate absorption. Symptoms may improve with age. Symptom severity is also believed to be modulated by the amount of ingested carbohydrates, the composition of the subject's microbiome, and most importantly, the amount of residual SI activity (Table 2).[8]

TABLE 1 Masqueraders of diarrhea-predominant IBS in children.

Inflammatory bowel disease
Celiac disease
Sucrase-isomaltase deficiency
Lactase deficiency
Small intestinal bacterial overgrowth
Microscopic colitis
Bile-acid malabsorption
Mast cell activation syndrome
Eosinophilic disorders

Abbreviation: IBS, irritable bowel syndrome.

3 | THE GENETICS BEHIND GSID

3.1 | *SI* gene and protein

The SI gene (EC 3.2.148 and 3.2.1.10) is found at chromosome 3q26.1 and is composed of 48 exons and

TABLE 2 Most common clinical presentations based on age.

Infant: FTT, diaper rash, severe diarrhea
Toddler: Abdominal distension, perianal rash, moderate to severe diarrhea
School-age child: Bloating, intermittently loose stools
Adolescent: Excessive gas, diarrhea-predominant IBS

Abbreviations: FTT, failure to thrive; IBS, irritable bowel syndrome.

encodes a protein of 1827 amino acids.[9] The SI protein is expressed in the microvillus enterocyte membrane.[10] SI is synthesized in the rough endoplasmic reticulum (ER) and then transported to the Golgi apparatus.[11] Following modification of N-linked glycans and O-glycosylation in the Golgi apparatus, 90%–95% of synthesized SI is transported to the apical membrane as pro-SI.[10] Efficient sorting of SI to the apical membrane is facilitated by associations with lipid rafts.[10] Within the apical membrane, pro-SI is cleaved by luminal pancreatic proteases (trypsin) to its two active subunits, sucrase and isomaltase.[12] The isomaltase subunit remains contiguous to the apical membrane; however, the sucrase subunit may be cleaved.[9] One study identified that before 30 weeks of gestation, SI is only present as a high molecular weight pro-SI.[13]

SI exhibits broad α-glucosidase activity with the digestion of α-1,4 glycosidically linked monosaccharides. In addition, SI digests α-1,2 and α-1,6 glycosidic linkages.[14] The two subunits, sucrase and isomaltase, are structurally similar, although they exhibit different digestive affinities towards α-1,4 and α-1,2 (sucrase) and α-1,6 (isomaltase).[14] The two subunits are associated with strong noncovalent, ionic interactions.[12] Although they are separate proteins, SI works in concert with maltase-glucoamylase to digest α-1,4 glycosidic linkages.

3.2 | Pathogenic sucrase-isomaltase genetic variants

Data from 59,533 unrelated individuals of various races/ethnicities from the legacy Exome Aggregation Consortium database evaluating 37 potential *SI* gene variants, including the four most common variants seen in GSID, demonstrated variant carrier frequencies of 1.9% in non-Hispanic Whites ($n = 32{,}726$), 0.6% in Hispanic Whites ($n = 5623$), and 0.04% in African Americans ($n = 4711$).[4,9] In one study, the four most common variants in GSID included three within the sucrase subunit (c.3218G>A, c.337OC>T, c.5234T>G) and one within the isomaltase subunit (C.1730T>G).[4,9] The location of pathogenic or likely variants associated with GSID is depicted in Figure 1.[15,16]

Pathogenic variants of *SI* may result in several different phenotypes related to altered trafficking, cellular localization, or SI function.[10] These phenotypes include accumulation and degradation of the mutant protein in the ER,[17,18] accumulation and degradation of the mutant protein in the *cis*-Golgi compartment or ER/*cis*-Golgi intermediate compartment,[19,20] defect in the sucrase catalytic site,[10] random delivery of SI to the apical and basolateral membranes (impaired trafficking),[17,21] aberrant intracellular proteolytic cleavage,[17,22] and altered SI folding resulting in aberrant trafficking.[23]

In the phenotypes where there is inadequate sucrase activity or aberrant intracellular proteolytic cleavage, isomaltase activity may still be normal if it reaches the apical membrane.[10] As such, some individuals with *SI* mutations are still able to digest starch well. Mutations of the isomaltase subunit often result in aberrant protein trafficking and therefore potential loss of both normal sucrase and isomaltase activity.[10] Compound *SI* heterozygous mutations (i.e., different variants on each gene) may also result in GSID when both parents carry different *SI* variants.[24]

The potential pathobiology of heterozygous *SI* gene variants is an area of increasing investigation. Studies in adults have highlighted that single hypomorphic (dysfunctional) *SI* variants are associated with an increased risk of IBS, particularly IBS-D.[25] Beyond an association with IBS, the presence of an *SI* variant among adults with IBS has been associated with a lower likelihood of responding to a low fermentable oligosaccharides disaccharides monosaccharide and polyol diet, which does not typically restrict sucrose.[26] A recent pilot study identified that adults with IBS who were double carriers of *SI* variants responded better to a starch and sucrose-reduced diet than single carriers and noncarriers combined.[27]

Children with disorders of gut–brain interaction (DGBI) with a primary complaint of loose stools were found to have a higher prevalence of *SI* pathologic variants, the vast majority heterozygous, compared with those in a reference consortium database (4.5% vs. 1.3%, respectively).[28] Children with DGBI who had primarily abdominal pain did not have a higher prevalence of *SI* pathologic variants compared with those in a reference consortium database, suggesting that loose stools may be an important phenotypic characteristic to help identify children with *SI* variants.[29] Personalized treatment studies based on the presence or absence of a single *SI* variant have not yet been completed in children.

Although the mechanism(s) by which single *SI* variants may contribute to underlying biological changes is unclear, growing physiologic data support the possibility that these variants can be pathobiologic. In adults, individuals with single *SI* variants and functional bloating or abdominal distension completing a two-phase (13)C-sucrose/(13)C-glucose breath test ((13)C-S/GBT) were identified to have decreased overall ^{13}C-breath enrichment compared with controls,

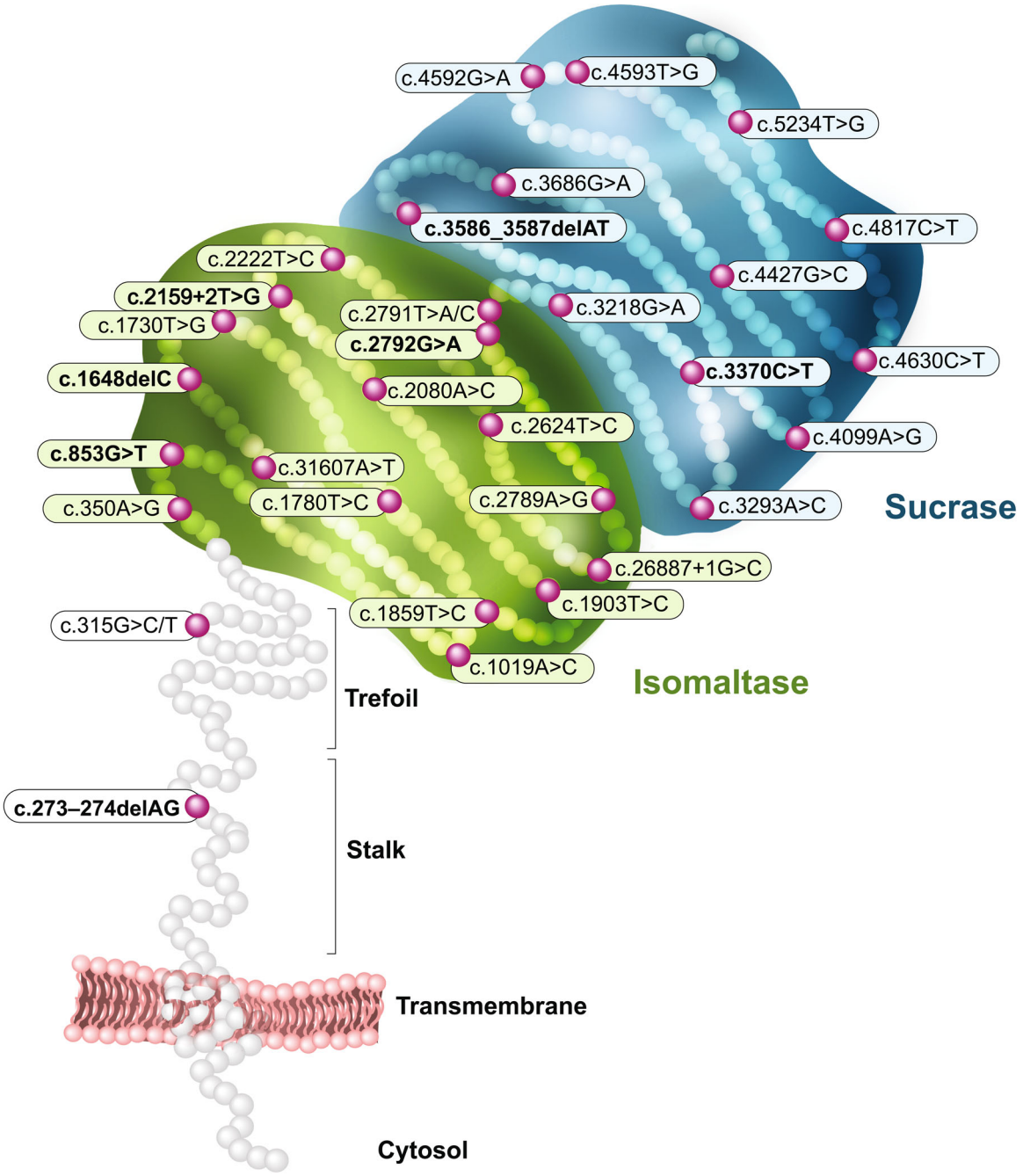

FIGURE 1 Structure of the sucrase-isomaltase enzyme and location of genetic variants associated with genetic sucrase-isomaltase deficiency. Graphical representation of the sucrase-isomaltase enzyme depicting the pathogenic or likely pathogenic variants as defined by de Leusse et al.[15] Predicted loss-of-function variants are defined as either introduction of stop-codon mutations, frameshift mutations, or disrupted splicing mutations. Adapted from Senfleber et al.[16]

suggesting sucrose malabsorption as the cause of their symptoms.[30] In vitro assessment of the potential role of a single pathogenic *SI* variant suggests that in some cases decreased overall SI activity occurs due to sequestration of the wild-type SI protein by the pathogenic SI protein into an inactive heterodimer with impairment in overall function and trafficking.[14] Further mechanistic studies within children who are single *SI* heterozygotes are needed.

4 | DIAGNOSTIC TESTING

Because long-term therapy may be required when an individual is diagnosed with GSID, it is essential that the diagnosis is based on validated tests. This is particularly important given the high placebo response in DGBI, where clinical improvement in response to dietary changes or enzyme supplements may not be reliable enough. In addition, other causes of low

disaccharidases, such as celiac disease, Crohn's disease, and other mucosal diseases, may need to be investigated.

4.1 | Indirect tests to assess disaccharidase activity

Therapeutic trials, either by avoiding sucrose for a period, taking sacrosidase, or challenging with high-dose sucrose have not been studied in a controlled manner. While in theory, deficiency can be ruled out if tolerant to a 25-g sucrose challenge, symptomatic cases would still need further study from likely high false-positive cases from osmotic load or other secondary causes.

Breath testing with sucrose allows detection of undigested sucrose by assessing breath hydrogen and methane produced by colonic bacteria. After a 24-h period on a low residue diet, 1 g/kg up to 25 g, and in some studies, up to 50 g sucrose is administered in a solution ideally 10% weight/volume. A 20 parts per million rise in breath hydrogen from baseline is considered abnormal. Results may be affected by abnormal bowel transit or the presence of small intestinal bacterial overgrowth. Furthermore, a variable percentage of healthy controls may also have some degree of malabsorption. Recent guidelines from the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) do not recommend use of breath testing for diagnosing GSID.[31]

The stable isotope-based ^{13}C-sucrose breath test, where available, offers some advantages to the sucrose hydrogen breath test, but neither test can differentiate the etiology of sucrase deficiency. Breath samples are collected after sucrose is ingested, typically 20 mg, in a solution with enough water with glucose polymer, and the amount of $^{13}CO_2$ enrichment using mass spectroscopy or infrared spectrophotometry helps identify malabsorption with those having sucrase deficiency having decreased breath $^{13}CO_2$. The mean values in patients with GSID correlate well with duodenal sucrase enzyme activity,[32] although this test has not been well validated for use in clinical practice.[33]

4.2 | Direct testing to measure disaccharidase activity

Disaccharidase assay on duodenal mucosal tissue homogenates is currently the gold standard for diagnosing overall SID. Dahlqvist initially developed a manual method to assay disaccharidase activity in homogenates of human intestinal biopsies.[34,35] Lactase, maltase, sucrase, and palatinase are reported, and some laboratories also measure glucoamylase, which further helps interpretation as well as identifying isolated glucoamylase deficiency.[36]

Liberated glucose after adding appropriate substrate to homogenates allows measurement of enzymatic activity, and automated methods are commonly used where available,[37] thereby reducing cost. A limitation of this test is that values for normal brush border enzyme activities are difficult to establish given the invasive nature of the test, and interpretation is further complicated by a highly skewed distribution.[38] Samples should be collected from the second or third part of the duodenum as activities are higher in the jejunum and sampling in the duodenal bulb may lead to reduced glucoamylase activity. Enzymatic activity is prone to destruction when exposed to formalin from forceps inadvertently dipped in specimen containers for histology, so it is recommended to collect first the samples used to measure disaccharidase activity. Repeated freeze–thaw cycles should be avoided during shipping.

Since there is significant overlap between sucrase, maltase, and glucoamylase in the digestion of maltose, maltotriose, and longer chain glucose polymers, maltase and glucoamylase activities may also be low in GSID.[39] In addition, palatinase activity can range from normal to low based on the mutation leading to GSID. One in five cases with pan-disaccharidase deficiency of all four or all five evaluated enzymes may be associated with heterozygous *SI* mutations and sucrase deficiency.[39] A ratio of sucrase to lactase at 1.0 or less has been proposed as a guide to CSID, but may miss cases.[39] Common misinterpretation in practice underscores the need for trained physician reporting of abnormal results.[8,39] While more expensive and invasive, disaccharidase testing allows for accurate measurement of enzyme activity and may help differentiate primary from secondary enzyme deficiency, though it should be noted that after an insult to the epithelia, it may take several weeks for disaccharidase activity to recover.

4.3 | Genetic tests

Genetic tests for four common mutations up to the entire *SI* gene are commercially available.[9,39] The test is typically performed using genomic DNA extracted from buccal/cheek swab and blood samples. One specialty laboratory also accepts formalin-fixed paraffin-embedded biopsy tissues and other biopsy samples. The test can also be ordered as a reflex test on duodenal mucosal biopsy specimens used for disaccharidase assays.[39] The advantages of a reflex test are reduced cost and time in obtaining and shipping a second sample. ESPGHAN recommends that the diagnosis of CSID usually be made with genetic testing in the setting of a malabsorption syndrome when first

exposed to sucrose and starch in the diet; however, this may only identify severe cases.[36]

The next-generation sequencing (NGS)-based genotyping test is suitable for subjects with clinical signs and symptoms suggestive of GSID, particularly with prior diagnosis of abnormal disaccharidase sucrase activity or familial history of GSID. The targeted regions of the entire coding sequence of the *SI* gene are sequenced via the NGS method. All single nucleotide variants or polymorphisms that are identified are reported, along with their zygosities and variance interpretation, through the ClinVar archive.[40] ClinVar is a freely accessible, public archive of reports of the relationships among human variations and phenotypes, with supporting evidence. A positive genetic test for homozygous and compound heterozygote mutations in the *SI* gene supports the diagnosis of GSID. However, not all mutations have been identified, as there is limited *SI* genetic research, especially in non-White races and ethnicities. Several databases are

TABLE 3 Foods tolerated by patients with CSID.[42]

	Tolerated by most patients with CSID		Tolerated by some patients with CSID	Not tolerated by patients with CSID	
Fruits	Avocado	Lemons	Persimmon	Apples	Peaches
	Blackberries	Limes	Plums	Apricots	Pineapple
	Blueberries	Loganberries	Raisins	Bananas	Tangelos
	Boysenberries	Olives	Watermelon	Cantaloupe	Tangerines
	Cherries	Papaya		Dates	Mandarin oranges
	Cranberries, fresh	Pears		Grapefruit	Clementines
	Currants	Pomegranates		Guava	
	Figs, raw	Prunes		Honeydew melon	
	Gooseberries	Raspberries		Mango	
	Grapes	Rhubarb		Nectarine	
	Kiwifruit	Strawberries		Oranges	
				Passion fruit	
Vegetables	Alfalfa sprouts	Endive	Edamame	Beets	Potatoes
	Artichoke, globe[a]	Green beans	Jicama	Black beans	Soybeans
	Arugula	Kale	Leek	Blackeyed peas	Split peas
	Asparagus[a]	Lettuce Mung bean sprouts	Okra	Butternut/buttercup squash	Sweet potatoes
	Bamboo shoots	Mushrooms	Pumpkin	Carrots	Yams
	Bok choy	Mustard greens	Snow peas	Cassava (yuca)	
	Broccoli[a]	Peppers (red, yellow, green)	Tempeh	Chickpeas (garbanzo beans)	
	Brussel sprouts[a]	Radishes	Tofu	Corn	
	Cabbage[a]	Rutabaga	Yellow wax beans	Garlic	
	Cauliflower[a]	Spaghetti squash		Green peas	
	Celery	Spinach		Kidney beans	
	Chard	Tomatoes		Lentils	
	Chicory	Turnips		Lima beans	
	Chives	Yellow squash		Navy beans	
	Collard greens	Zucchini (courgetti)		Onions	
	Cress			Parsnips	
	Cucumber			Pinto beans	
	Eggplant				
Sweetners	Aspartame (NutraSweet®)		Acesulfame-K	Inverted sugar syrup	Coconut sugar
	Dextrose		Agave nectar	Maltose (malt sugar)	Confectioner's sugar
	Fructose (crystalline fructose or crystalline fructose syrup)		Corn syrup	Stevia (Truvia®, Pure Via®)	Date sugar
	Glucose		Equal® (original in blue packaging)	Sucralose (Splenda®)	Maple syrup
	Lactose		High fructose corn syrup	Sugar alcohols	Molasses
			Honey	Beet sugar	Raw sugar
			Hydrogenated starch	Brown sugar	Sucanat™ (natural cane sugar)
				Cane juice	Sucrose
				Cane sugar	Sugar
				Caramel, caramel-based sauces	Turbinado sugar

Abbreviation: CSID, Congenital sucrase-isomaltase deficiency.

[a]Can cause gastrointestinal gas in all individuals.

available to assess unfamiliar mutations and characterization of likely pathogenicity. Expressions in in vitro cell cultures at the cell membrane are needed to understand the potential impact of new mutations.

Although NGS can identify known and new mutations at a lower price, these assays require careful processing as they can yield false-positive and false-negative results. A more fundamental limitation is that other rarer genetic mechanisms such as somatic mutations cannot be identified using this method. Accordingly, a negative result does not rule out GSID, and confirmatory methods as previously discussed may help confirm the diagnosis.

5 | TREATMENT OF GSID

5.1 | Dietary management

Dietary management of GSID is based on a sucrose- and starch-restricted diet. The degree of sucrose or starch intolerance can vary in each individual. Since isomaltase activity may remain intact, and because maltase accounts for 20%–40% of starch digestion, not all GSID patients are starch-intolerant. Patients should work with a registered dietician and maintain a food diary to ensure adequate nutritional intake and determine food tolerance.[41] All patients should initially be placed on a sucrose- and starch-free diet. Common foods rich in sucrose include table sugar, maple syrup, and certain fruits and vegetables (Table 3).[42] Sucrose-containing foods can be serially introduced beginning with foods with sucrose content ≤2% while monitoring gastrointestinal symptoms.[41] Some children require long-term sucrose restriction to avoid diarrheal episodes, while a minority of those identified with infant GSID may have improved sucrose tolerance over time.

After sucrose tolerance is determined, starch can be introduced into the diet. Wheat, potatoes, corn, and rice are common starch-rich foods. Starch tolerance can be improved by double-boiling while cooking, chewing slowly to maximize salivary amylase exposure, and increasing fiber content to slow gastrointestinal transit time.[42]

5.2 | Enzyme replacement therapy

Sacrosidase oral therapy was approved by the United States Food and Drug Administration for the treatment of genetically determined sucrase deficiency, which is part of CSID in 1998. In two multicenter, double-blind, randomized trials of sacrosidase treatment, 81% of patients were asymptomatic while on an unrestricted diet. Both sucrose hydrogen breath test and ^{13}C-sucrose breath tests normalized with sacrosidase administration.[43] However, additional starch restriction may be necessary for some patients as sacrosidase only aids in sucrose digestion and not in starch digestion.

Dosing of sacrosidase is weight-based, with a recommendation of 1 mL for patients weighing less than 15 kg and 2 mL for patients weighing more than 15 kg. The enzyme should be taken with each meal or snack, mixed into 2–4 ounces of room temperature liquid, and divided with half taken before the meal and half taken midway through.[43] In a postmarketing surveillance study, 65 of 69 (94%) of responders continued enzyme replacement therapy with a median duration of 3 years. The most common adverse events reported included constipation headaches, and sleep disturbances.[44] Because sacrosidase is derived from baker's yeast, it should be avoided in patients with known hypersensitivity to yeast or yeast products. Beneficial effects of *Saccharomyces cerevisiae* containing probiotics have been described as there is inherent sucrase activity; however, there is limited data on routine use and dosing.[39,45]

6 | CONCLUSIONS

Since its initial description in 1960, knowledge of the genetic basis of SID and its phenotypic expression has evolved considerably. While classic severe symptoms have been described in patients with homozygous mutations in the *SI* gene, growing evidence demonstrates that less severe presentations can occur in patients with *SI* heterozygous or homozygous variants. In particular, single *SI* pathologic variants have been increasingly noted in children with DGBI with loose stools and in adults with IBS. Given this, a more appropriate term appears to be GSID. The standard for diagnosing SI enzyme deficiency remains disaccharidase assay using intestinal biopsy; noninvasive alternatives such as sucrose hydrogen breath tests may be useful but require validation in this setting. The management of GSID involves dietary modification tailored to individual's sucrose and starch tolerance with consideration for enzyme supplementation with sacrosidase. Further studies exploring the true prevalence of GSID and the pathobiology of single *SI* heterozygous mutations are needed to inform optimal diagnostic and treatment algorithms in the pediatric population.

CONFLICT OF INTEREST STATEMENT

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