








Genetic Loss of Sucrase-Isomaltase Function: Mechanisms, Implications, and Future Perspectives

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Abstract: Genetic variants causing loss of sucrase-isomaltase (SI) function result in malabsorption of sucrose and starch components and the condition congenital sucrase-isomaltase deficiency (CSID). The identified genetic variants causing CSID are very rare in all surveyed populations around the globe, except the Arctic-specific c.273_274delAG loss-of-function (LoF) variant, which is common in the Greenlandic Inuit and other Arctic populations. In these populations, it is, therefore, possible to study people with loss of SI function in an unbiased way to elucidate the physiological function of SI, and investigate both short-term and long-term health effects of reduced small intestinal digestion of sucrose and starch. Importantly, a recent study of the LoF variant in Greenlanders reported that adult homozygous carriers have a markedly healthier metabolic profile. These findings indicate that SI inhibition could potentially improve metabolic health also in individuals not carrying the LoF variant, which is of great interest considering the massive number of individuals with obesity and type 2 diabetes worldwide. Therefore, the objectives of this review, are 1) to describe the biological role of SI, 2) to describe the metabolic impact of the Arctic *SI* LoF variant, 3) to reflect on potential mechanisms linking reduced SI function to metabolic health, and 4) to discuss what knowledge is necessary to properly evaluate whether SI inhibition is a potential therapeutic target for improving cardiometabolic health.

Keywords: sucrase-isomaltase, congenital sucrase-isomaltase deficiency, loss-of-function variants, cardiometabolic health, sucrose, Greenland, Inuit

Sucrase-Isomaltase – Function and Loss-of-Function

Intake of added sugars has during the past decade received increasing attention as a potential contributing factor to the global epidemic increase in body weight and obesity-related comorbidities.¹ The sugar most commonly added to processed foods is sucrose, but sucrose is also naturally present in eg fruits and vegetables. Sucrose is a disaccharide consisting of one glucose and one fructose molecule, bound together by a glycosidic linkage. Intestinal absorption of sucrose as well as other carbohydrates requires that the saccharide chains are digested into monosaccharides. This digestion starts with the α -amylases in the mouth and is finalized by the α -glucosidases, maltase-glucoamylase and sucrase-isomaltase (SI), in the small intestine.²

The SI enzyme consists of two domains, sucrase and isomaltase, and is anchored to the brush-border membrane in the small intestine (Figure 1A). The isomaltase domain hydrolyzes α -1,6-glycosidic linkages in isomaltose and oligosaccharides derived from amylase-cleaved starch and glycogen. The sucrase domain cleaves the α -1,2-glycosidic linkages in sucrose to form glucose and fructose, and contributes to the cleavage of the α -1,4-glycosidic linkage in maltose to form two glucose monosaccharides.³ In humans, SI is responsible for 60–80% of the maltase activity in the intestine and almost all sucrase activity due to its high abundance and low substrate specificity.⁴ Thus, SI is an essential enzyme for the

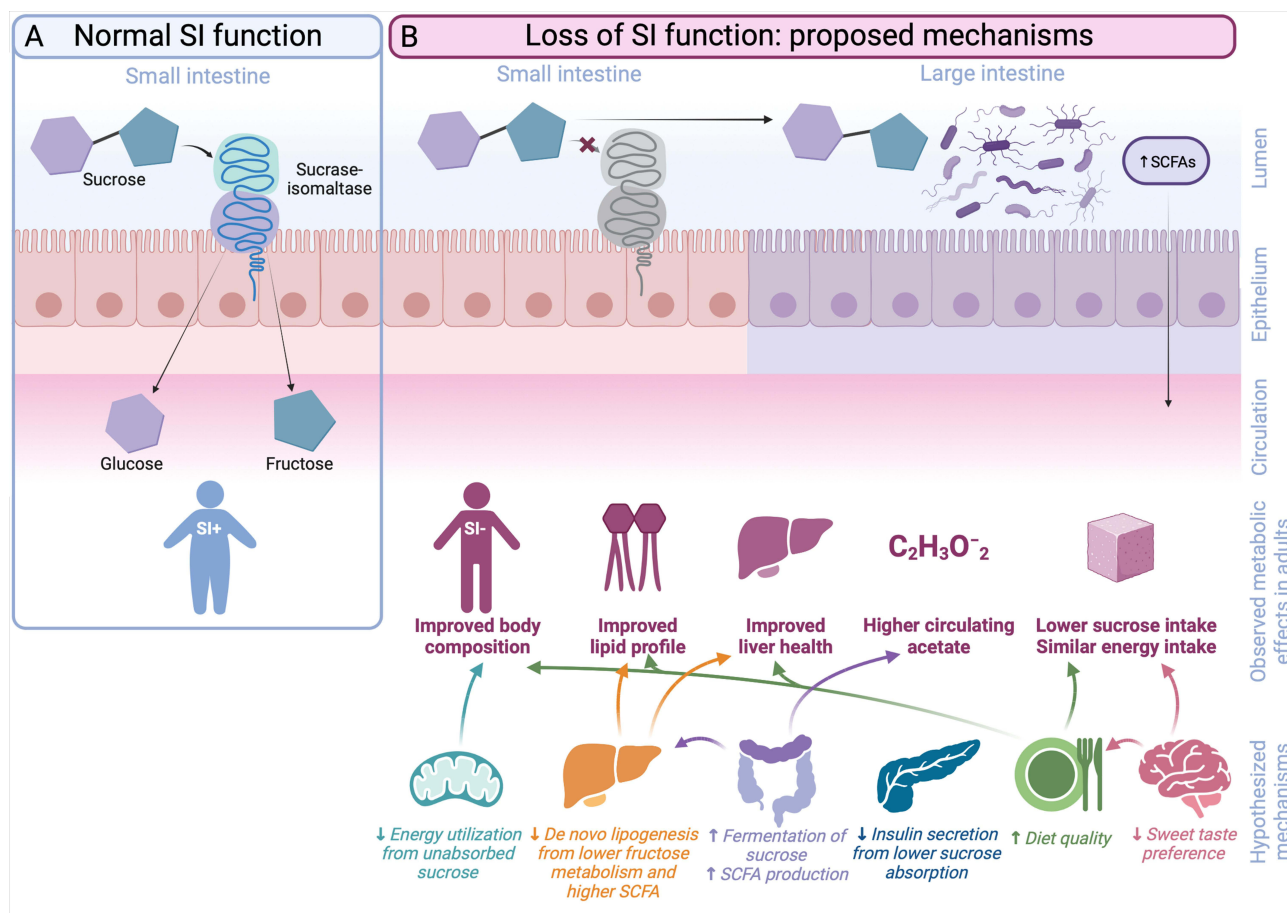


Figure 1 Overview of sucrase-isomaltase function and implications of loss of sucrase-isomaltase function. Illustration of (A) normal sucrase-isomaltase (SI) function and (B) the proposed mechanisms of loss of SI function in the intestine, observed metabolic effects in adult homozygous carriers of the Arctic-specific SI LoF variant,²⁸ and the hypothesized mechanisms that may contribute to these metabolic effects. SCFAs, short-chain fatty acids; SI+, normal SI function; SI-, loss of SI function. Created with BioRender.com.

digestion of starchy foods and foods containing sugars, which are major components of the diet in most populations across the world.^{5,6}

Loss of SI function results in malabsorption of sucrose, isomaltose, maltose, and other undigested starch components. These carbohydrates continue along the gastrointestinal (GI) tract where they increase the osmotic pressure and are metabolized by gut bacteria rather than by the host.³ This condition is called congenital sucrase-isomaltase deficiency (CSID). In children, CSID is characterized by a range of GI symptoms, such as stomach pain, flatulence, and diarrhea, similar to symptoms of lactose intolerance. These symptoms generally become evident when children start consuming foods containing sucrose and are relieved when following dietary recommendations to consume a sucrose-free diet,⁷ while restriction of starch generally is not necessary.⁸ Besides GI symptoms, children with CSID may become malnourished, underweight, and dehydrated, leading to hospitalization in some cases.⁷ Even though the condition persists in adulthood, symptoms seem to be reduced with age; hence, in adults the symptoms range from none, to increased bowel movement, flatulence, and diarrhea. Therefore, the condition may be misdiagnosed as eg, irritable bowel syndrome.^{3,9} Given a correct diagnosis, some individuals with CSID are treated with enzymatic replacement therapy, allowing them to consume sucrose-containing meals with fewer GI symptoms.¹⁰

The diagnosis of CSID can be made either based on clinical investigations including assessment of symptoms, endoscopies, biopsies, and sucrose breath hydrogen tests, or genetic screening. Studying genetically diagnosed loss of SI function is the most robust and unbiased way of studying the health effects of impaired SI function, compared to studying

CSID diagnosed based on clinical investigations, where the specific cause and degree of reduction in SI function is unknown.

In this review, we will, therefore, focus on the effects of impaired SI function as a consequence of deleterious genetic variants at the *SI* gene.

Genetic Variation in the Sucrase-Isomaltase Gene

The *SI* gene, which encodes the SI enzyme, is located on chromosome 3 and harbors a number of rare pathogenic mutations across functional domains, including the sucrase domain, the isomaltase domain, the cytosolic tail, the transmembrane domain, the stalk region, and the trefoil 1 domain (Figure 2).^{11–25} These variants are predicted to result in reduced SI function or complete loss of SI function,²⁶ and thereby CSID.

Prevalence of Loss of Sucrase-Isomaltase Function Across the World

The prevalence of CSID is often reported to range between about 0.05–0.2% in European populations, and to be even lower in populations with African and Hispanic ancestry.⁴ These prevalence numbers are based on clinical assessment of patients with GI symptoms. However, using a genetic definition of CSID, estimated as the proportion of homozygous carriers of *SI* variants categorized as pathogenic, likely pathogenic, or LoF, the prevalence is much lower across different populations with a prevalence of only 0.0005% to 0.013% in European populations²⁶ (Figure 3). Hence, the variants causing loss of SI function are very rare in large populations like Europeans, Africans, and south Asians, and most of them have only been observed in the heterozygous state or in a single homozygous carrier.^{26,27} Therefore, it is not feasible to study the health effects of loss of SI function in these populations.

Prevalence of Loss of Sucrase-Isomaltase Function in the Arctic

In contrast to most populations across the world, CSID is relatively common in Arctic populations, with a reported prevalence of 3–7% in Canadians and Alaskans based on clinical diagnosis.⁴ Recently, the *SI* c.273_274delAG variant was identified in a Canadian individual with CSID symptoms.¹⁸ This variant is located in the stalk region of the enzyme (Figure 2) and is predicted to result in complete loss of SI function in homozygous individuals.¹⁸ The allele frequency was found to be 17% in Canadian Inuit, 14% in the general Greenlandic population, and 20% in the Inuit ancestry

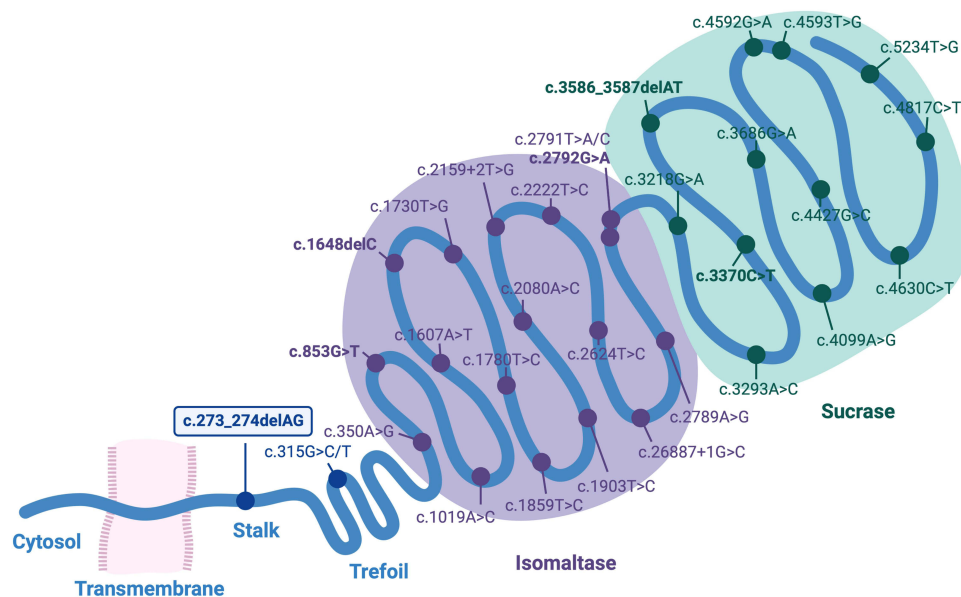


Figure 2 Structure of the sucrase-isomaltase enzyme and location of genetic variants associated with congenital sucrase-isomaltase deficiency. Graphical representation of the SI enzyme depicting the pathogenic or likely pathogenic variants as defined by Leusse et al²⁶ Predicted LoF variants are defined as either introduction of stop-codon mutations, frameshift mutations, or disrupted splicing mutations, and are shown in bold. The Arctic-specific c.273_274delAG variant is highlighted. Created with BioRender.com.

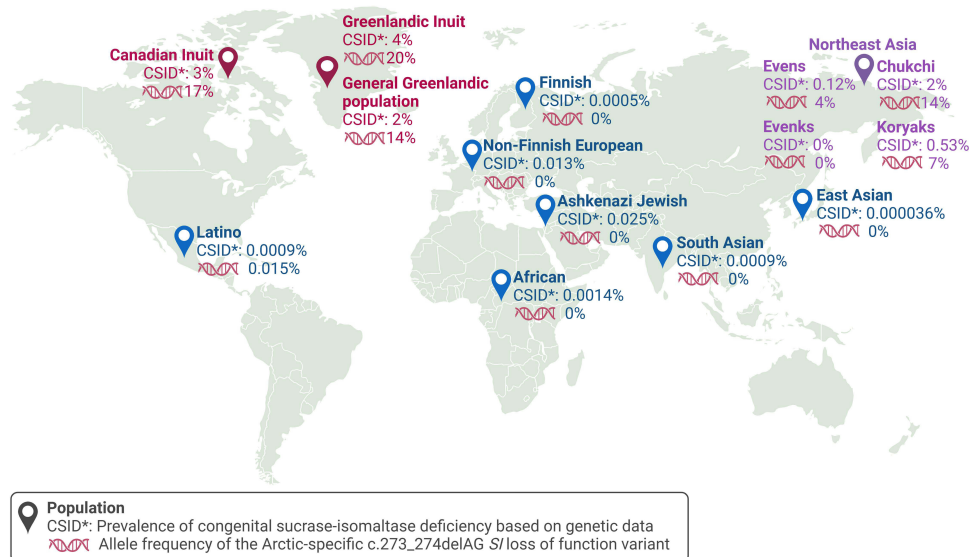


Figure 3 Prevalence of CSID and allele frequencies of the c.273_274delAG *SI* variant across populations. The prevalence of congenital sucrase-isomaltase deficiency estimated based on expected numbers of homozygous carriers (CSID*) of 1) the Arctic-specific *SI* c.273_274delAG loss-of-function (LoF) variant in Canadian Inuit (red), Greenlanders (red), and Northeast Asians (purple)^{18,28,29} or 2) pathogenic, likely pathogenic, or predicted LoF variants in GnomAD populations (blue).²⁶ The allele frequency of the Arctic-specific *SI* c.273_274delAG LoF variant for each population is indicated with .^{18,27–29} Created with BioRender.com.

proportion of the Greenlandic population, corresponding to a CSID prevalence of 3%, 2%, and 4%, respectively.^{18,28} This *SI* LoF variant is almost absent in all populations except in Inuit populations and Siberians^{18,28,29} (Figure 3) and overall, the differences in frequency of the *SI* c.273_274delAG variant between populations explain the large variation in the prevalence of CSID across the world.

Despite the fact that the c.273_274delAG variant is only in high frequency in Arctic populations, no signs of positive selection in the region near the variant have been reported. Hence, this variant could likely have reached a high frequency in Arctic populations due to genetic drift, which has a particularly large impact in small and isolated populations, and lack of negative selection.²⁸ The lack of negative selection is likely explained by the high content of protein and fat and low content carbohydrates and sugar, in the traditional Inuit diet.³⁰ This diet may have allowed carriers of the genetic variant to remain asymptomatic, until a few decades ago when western foods high in sucrose and starch were introduced to Greenland. Hence, lack of negative selection together with genetic drift likely resulted in c.273_274delAG being common in Arctic populations including the Greenlandic Inuit.²⁸

Health Effects of *SI* Loss-of-Function or Inhibition

The Arctic-specific *SI* variant is the only known *SI* LoF variant that is sufficiently common to enable studies of the potential health impact of loss of *SI* function, by comparing homozygous carriers of the variant, who have no *SI* function, with the rest of the population. Alternatively, insights can be gained by studying the impact of the α -glucosidase inhibitors, acarbose, voglibose, and miglitol. These α -glucosidase inhibitors are anti-diabetic drugs, which reduce the degradation of carbohydrates by inhibiting different combinations of digestive enzymes, including *SI*.³¹ The α -glucosidase inhibitors are unspecific in their inhibition but have the advantage of the possibility to study large sample sizes.

A recent study showed that Greenlandic adults who are homozygous carriers of the Arctic-specific *SI* LoF variant had a markedly healthier metabolic profile compared to the rest of the Greenlandic population.²⁸ They had a healthier body composition, with a 2 kg/m² lower BMI and almost 5 kg lower body weight. These effect sizes are much larger than those reported for any common genetic variant associated with BMI in Europeans.³² The homozygous variant carriers also had a healthier lipid profile, particularly with 0.3 mmol/L lower levels of serum triglycerides. This effect size is substantial and of similar magnitude as the effect of the lipid-lowering drugs statins.³³ Interestingly, the homozygous variant carriers had twice as high levels of serum acetate compared to heterozygous and wild-type individuals (0.056

mmol/L higher) (Figure 1B). These observations seemed to be independent of the lower intake of added sugar, which was also observed among homozygous carriers.²⁸ Interestingly, the healthy phenotype was confirmed by a *SI* knock-out mouse model, but only when their diet included sucrose. The mouse model also supported the link between sucrose intake and markedly higher levels of plasma acetate.²⁸ The healthier metabolic phenotype could be expected to result in a lower risk of cardiometabolic diseases, but no significant effects were seen on measures of glucose homeostasis, type 2 diabetes, or cardiovascular disease.²⁸ However, a larger sample size and/or longer follow-up time is required to determine these potential relationships.

To our knowledge, only Andersen et al²⁸ have currently assessed cardiometabolic effects of loss of SI function, likely due to the rarity of LoF variants outside the Arctic. Additionally, this study also provided potential explanations for the healthier phenotype observed among the homozygous carriers of the *SI* LoF variant.

Contributing Mechanisms to Health Effects of SI Loss-of-Function or Inhibition

Increased Gut Fermentation of Undigested Carbohydrates

It was hypothesized that the healthy metabolic effects associated with the loss of SI function were mediated through increased gut bacterial fermentation and possible alterations in gut microbiome composition, leading to increased production of short-chain fatty acids such as butyrate, propionate, and acetate.²⁸ Consistent with this, the circulating level of acetate was twice as high in homozygous carriers of the Arctic-specific *SI* LoF variant compared to the rest of the Greenlandic population and increased in response to a sucrose load in the *SI* knock-out mouse model as previously mentioned.²⁸ This hypothesis suggests that undigested sucrose serves as a type of dietary fiber, which tends to have beneficial effects on gut microbiome composition.³⁴ However, it is unknown if the health-promoting effects are mediated by acetate alone, or by a combination of acetate, propionate, and butyrate, as all these short-chain fatty acids have been linked to modulation of metabolic health through a wide range of mechanisms.³⁵

Two studies have directly assessed the association between reduced SI function and gut bacterial composition, by studying the effect of a relatively common variant in European populations estimated to result in a modest reduction in SI enzyme activity of about 35%.³⁶ This variant was associated with a lower abundance of *Parabacteroides*,³⁶ a genus that is potentially linked to body weight and inflammation,^{37,38} and with nominally significant altered abundance of certain carbohydrate-digesting genera, including higher abundance of *Blautia*,³⁹ a genus that might play a role in metabolic and inflammatory diseases.⁴⁰ As the studied European variant only results in a modest reduction in SI activity, the effect of the Arctic-specific complete LoF variant on microbiome composition could potentially be greater.

The link between maldigestion of carbohydrates and alterations in gut bacterial composition is also supported by genome-wide association studies, showing that variants affecting the expression of the lactase gene, which causes lactase persistence, are among the host genetic variants most strongly associated with microbiome composition, particularly with the abundance of the *Bifidobacterium* genus.^{41–44} Species within the *Bifidobacterium* genus have repeatedly been observed to increase in abundance following fiber and prebiotic supplementation and have been suggested to contribute to reducing body weight and metabolic risk markers after such interventions.⁴⁵ *Bifidobacteria* can metabolize saccharides via a unique pathway using fructose-6-phosphoketolase, the so-called “bifid shunt.”⁴⁶ Considering the similarities between lactose intolerance and CSID, effects on the microbiome from loss of SI function could be expected. Interventions with α -glucosidase inhibitors have also demonstrated alterations in the gut microbiome, many of which also point to an effect on increased *Bifidobacterium* abundance among many other microbial changes,^{47–51} as well as an increase in total fecal output of short-chain fatty acids.⁵²

On the contrary, adverse metabolic effects of changes in the gut bacterial composition, due to a high intake of dietary sugars have been the topic of many recent studies.^{53,54} However, these studies are generally performed in rodents with normal digestion of sucrose or focus particularly on the intake of fructose. Hence, whether these findings are relevant for understanding the effects of loss of SI function on the gut bacterial composition is uncertain. Nevertheless, the research linking SI function to gut microbiome composition is at present very limited, and the few

identified associations with single genera are difficult to interpret as it remains elusive what actually constitutes healthy gut microbiome changes.

Improved Diet Quality

It is also likely, that the GI symptoms caused by intake of sucrose-rich foods in homozygous carriers of the Arctic-specific *SI* LoF variant, could result in a generally healthier diet in these individuals, as a result of increased dietary awareness, as well as sucrose-rich foods being replaced by healthier, less energy-dense alternatives. Greenlandic homozygous carriers of the *SI* LoF variant reported on average 29 g/day lower intake of added sucrose and an overall lower intake of carbohydrates,²⁸ thus supporting this hypothesis. There was no difference in self-reported total energy intake. However, the intake estimations were based on a relatively short semi-quantitative food frequency questionnaire. Although there are dietary recommendations for individuals with CSID,⁵⁵ the literature on the actual dietary patterns of these individuals is very limited. Therefore, it would be of interest to study the dietary intake in greater detail.

Reduced Nutrient and Energy Utilization

Lower body weight could potentially be expected among individuals with loss of SI function owing to unutilized energy from maldigestion of carbohydrates. When particularly fast-digesting carbohydrates are unabsorbed, a lower postprandial glycemic load can also be expected, which may be metabolically beneficial. Although no effect of loss of SI function was observed on markers of glucose and insulin homeostasis in the fasted state in Greenlanders,²⁸ children with CSID have a reduced plasma glucose response following a sucrose load.^{56,57} Furthermore, based on studies on α -glucosidase inhibitors, one might expect a lower glycemic response to a carbohydrate-rich mixed meal when SI function is inhibited.^{35,58}

Future Perspectives

Taken together, previous studies of genetic loss of SI function, as well as studies on α -glucosidase inhibitors, suggest that SI inhibition could be a treatment target for obesity and general metabolic health. However, there are still a number of questions related to the underlying mechanisms and long-term effects that remain to be addressed. In particular, longitudinal investigations of cardiometabolic disease incidence warrant further study in larger sample sizes. Moreover, it would also be of interest to study incidence data of other conditions such as cancer, as a meta-analysis found that treatment with α -glucosidase inhibitors was associated with a reduced risk of cancer in type 2 diabetes patients, particularly GI cancer (OR = 0.83, 95% CI = 0.71–0.97).⁵⁹

Understanding the Underlying Mechanisms

In future studies, it will be interesting to investigate the path of sucrose in individuals with loss of SI function. Specifically, it will be interesting to investigate the impact of undigested sucrose in the distal gut on the composition of the gut bacteria and the fecal and circulating metabolome, including the concentration of short-chain fatty acids. If the hypothesized link between undigested sucrose in the distal gut and increased levels of short-chain fatty acids in circulation can be verified, it would be important to follow the metabolic path and identify the specific target tissues of short-chain fatty acids, as well as other metabolites, identified to be altered in concentration in individuals with loss of SI function.

Interestingly, previous studies have indicated that some sucrose enters the circulation as an intact disaccharide and well-controlled biomarker validation studies have demonstrated that the excreted amount of sucrose and fructose in urine over 24 hr is highly proportional to the intake of total sugars, although only around 0.05% of ingested sucrose and fructose are excreted.^{60–62} Understanding how and why sucrose can enter systemic metabolism, and if this is affected by the loss of SI function, is crucial to fully understand the potential metabolic benefits of inhibiting SI.

Taste Preferences and Perceptions

Limited evidence exists on taste and food preferences in individuals with loss of SI function. Children with fructose intolerance quickly develop a strong aversion to sweet foods in response to symptoms caused by these.^{63,64} Though not

investigated thoroughly in individuals with loss of SI function, this appears to be rarer in children with decreased intestinal SI levels.⁶⁵

In a mouse study, SI as well as other disaccharide-hydrolyzing enzymes like maltase-glucoamylase have been found to be expressed in the taste cells that hold the major sweet taste receptors for sugars in both humans and mice (T1R2 and T1R3). Interestingly, when treating the tongue in mice with the α -glucosidase inhibitors miglitol or voglibose, the gustatory nerve response to sucrose decreased by 40% and to maltose by 25% for both inhibitors.⁶⁶ This indicates that SI could play a role in perception of sweet taste from sucrose. Individuals with loss of SI function might, therefore, be less sensitive towards sweet taste from sucrose and maybe carbohydrates in general. Alterations in sweet taste perception in individuals with loss of SI function might affect dietary intake if sweet foods appear less sweet and thereby less appealing, thus potentially contributing to the healthier phenotype observed among Greenlandic homozygous *SI* LoF variant carriers.²⁸

Assessment of Possible Adverse Effects of SI Inhibition

The potential of inhibiting SI as a drug target for prevention and management of cardiometabolic disease must, of course, be evaluated in perspective of adverse effects, eg GI discomfort. An SI-inhibiting drug could have similar GI side effects as the α -glucosidase inhibitors, resulting in diarrhea and bloating when consuming carbohydrates. The α -glucosidase inhibitors are therefore generally not well tolerated by patients.⁶⁷ However, an SI-inhibiting drug would target one specific enzyme, and fewer GI side effects may therefore be expected than from α -glucosidase inhibitors. This is in line with observations in Greenlanders, where no significant differences were reported for GI symptoms or overall health perception in homozygous carriers of the Arctic-specific *SI* LoF variant compared to the rest of the population.²⁸

These potential side effects and other long-term effects of an SI-inhibiting drug can be studied further in Inuit populations, where the frequency of the *SI* LoF variant is high. However, it would require a relatively large study population and long follow-up time to identify rare, as well as long-term, side effects. Therefore, studies on α -glucosidase inhibitors might also provide insights.

Concluding Remarks

CSID is rare in most populations but prevalent in Arctic populations due to the Arctic-specific c.273_274delAG *SI* LoF variant. In children, CSID is associated with GI symptoms, which are often treated with dietary modifications or enzyme replacement to restore SI function. However, studies of Greenlandic adult carriers of the Arctic-specific *SI* LoF variant indicate that inhibition of SI could be a possible treatment of metabolic diseases, including obesity. Additional studies are needed to understand the underlying mechanisms, potential benefits, and side effects of SI inhibition. Moreover, there is a great potential of obtaining a deeper understanding of carbohydrate metabolism through the unique Arctic-specific *SI* LoF variant.

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