Fig. 5B), results in an inactive protein. Proline is added in the middle of an α-helix and likely disrupts the helix and associated secondary structure. The mutation is 21.2 Å away from the catalytic nucleophile, but it is in the interior of the protein where proline is found only infrequently because this residue typically lies on the surface of globular proteins. The disorder of the active site caused by this mutation likely affects function and causes the inactivity of the protein.

In addition to the specifics of inhibitor-enzyme interactions, there are some important questions that can be addressed by future structural analyses. The roles of portions of the enzyme module structures that are distal to the active sites have not been investigated. In particular, the structure identified a β-trefoil region, a fold that has been associated with both carbohydrate-binding modules of microbial glycoside hydrolases and protein–protein interactions. Furthermore, although studies of individual modules have been critical in studying their characteristics, MGAM and SI both exist physiologically as dienzyme complexes. How do the modules interact within the intact complex? To what extent is this interaction important for their activities? Finally, what is the basis for the altered activity or trafficking of mutated SI domains in patients with CSID? Structural studies of intact MGAM and SI enzymes can contribute to answering these questions.

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REFERENCES

1. Nichols B, Eldering J, Avery S, et al. Human small intestinal maltase-glucoamylase cDNA cloning. *J Biol Chem* 1998;273:3076–81.
2. Cantarel BL, Coutinho PM, Rancurel C, et al. The carbohydrate-active enzymes database (CAZy): an expert resource for glycogenomics. *Nucleic Acids Res* 2009;37:D233–8.
3. Henrissat B, Bairoch A. New families in the classification of glycosyl hydrolases based. *Biochem J* 1993;293:781–8.
4. Henrissat B. A classification of glycosyl hydrolases. *Biochem J* 1991; 280:309–16.
5. Nichols B, 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.
6. Alfalah M, Keiser M, Leeb T, et al. Compound heterozygous mutations affect protein folding and function in patients with congenital sucrase-isomaltase deficiency. *Gastroenterology* 2009;136:883–92.
7. Ritz V, Alfalah M, Zimmer K-P, et al. Congenital sucrase-isomaltase deficiency because of an accumulation of the mutant enzyme in the endoplasmic reticulum. *Gastroenterology* 2003;125:1678–85.
8. Rossi EJ, Sim L, Kuntz DA, et al. Inhibition of recombinant human maltase glucoamylase by salacinol and derivatives. *FEBS J* 2006;273: 2673–83.
9. 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.
10. 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.
11. Chen W, Kuntz D, Hamlet T, et al. Synthesis, enzymatic activity, and X-ray crystallography of an unusual class of amino acids. *Bioorg Med Chem* 2006;14:8332–40.
12. 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;285:17763–70.
13. Balfour JA, McTavish D. Acarbose: an update of its pharmacology and therapeutic use in diabetes mellitus. *Drugs* 1993;46:1025–54.
14. Johnston PS, Coniff RF, Hoogwerf BJ, et al. Effects of the carbohydrase inhibitor miglitol in sulfonylurea-treated NIDDM patients. *Diabetes Care* 1994;17:20.
15. Ghavami A, Johnston B, Pinto B. A new class of glycosidase inhibitor: synthesis of salacinol and its stereoisomers. *J Org Chem* 2001;66:2312–7.
16. Chandrasena JPC. The Chemistry and Pharmacology of Ceylon and Indian Medicinal Plants. Colombo, Sri Lanka: H and C Press; 1935.
17. Eskandari R, Jones K, Rose DR, et al. Probing the active-site requirements of human intestinal N-terminal maltase glucoamylase: the effect of replacing the sulfate moiety by a methyl ether in ponkoranol, a naturally occurring (-glucosidase inhibitor. *Bioorg Med Chem Lett* 2010;20:5686–9.
18. Keiser M, Alfalah M, Propsting MJ, et al. Altered folding, turnover, and polarized sorting act in concert to define a novel pathomechanism of congenital sucrase-isomaltase deficiency. *J Biol Chem* 2006;281: 14393–9.
19. Spodsberg N. Molecular basis of aberrant apical protein transport in an intestinal enzyme disorder. *J Biol Chem* 2001;276:23506–10.
20. Jacob R, Zimmer K, Schmitz J, et al. Congenital sucrase-isomaltase deficiency arising from cleavage and secretion of a mutant form of the enzyme. *J Clin Invest* 2000;102:281–7.
21. Ren LI, Qin X, Cao X, et al. Structural insight into substrate specificity of human maltase-glucoamylase. *Protein Cell* 2011;2:827–36.

Starch Digestion and Patients With Congenital Sucrase-Isomaltase Deficiency

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Starch is the major carbohydrate storage type found in plant seeds and tubers in a semicrystalline form. Starch is consumed by humans as a major glucose source of dietary energy and it can supply as much as 70% to 80% of the calories in the overall average human diet (1–3). Starch has 2 main molecular structures: amylose, which consists of long linear chains of glucose associated by α-1,4 glucosidic linkages and occasional branching with α-1,6 linkages, and amylopectin consisting of relatively short α-1,4 bound glucose chains of variable length with a relatively high content of α-1,6 branching chains (Fig. 1, top left). Amylopectin, in particular, is an extremely large molecule containing approximately 1 million glucosyl units that lead to a complexity of branched structures that differs among genetic backgrounds (4–6). The proportion of amylose versus amylopectin, the average length of α-1,4-linked linear chains, and the frequency of α-1,6 branching vary considerably among starches. Such differences lead to variation in the digestion rate and production of α-amylase digestion products (7–9). These products, known as α-limit dextrins (Fig. 1, bottom), can modulate catalytic activities of the mucosal α-glucosidases.

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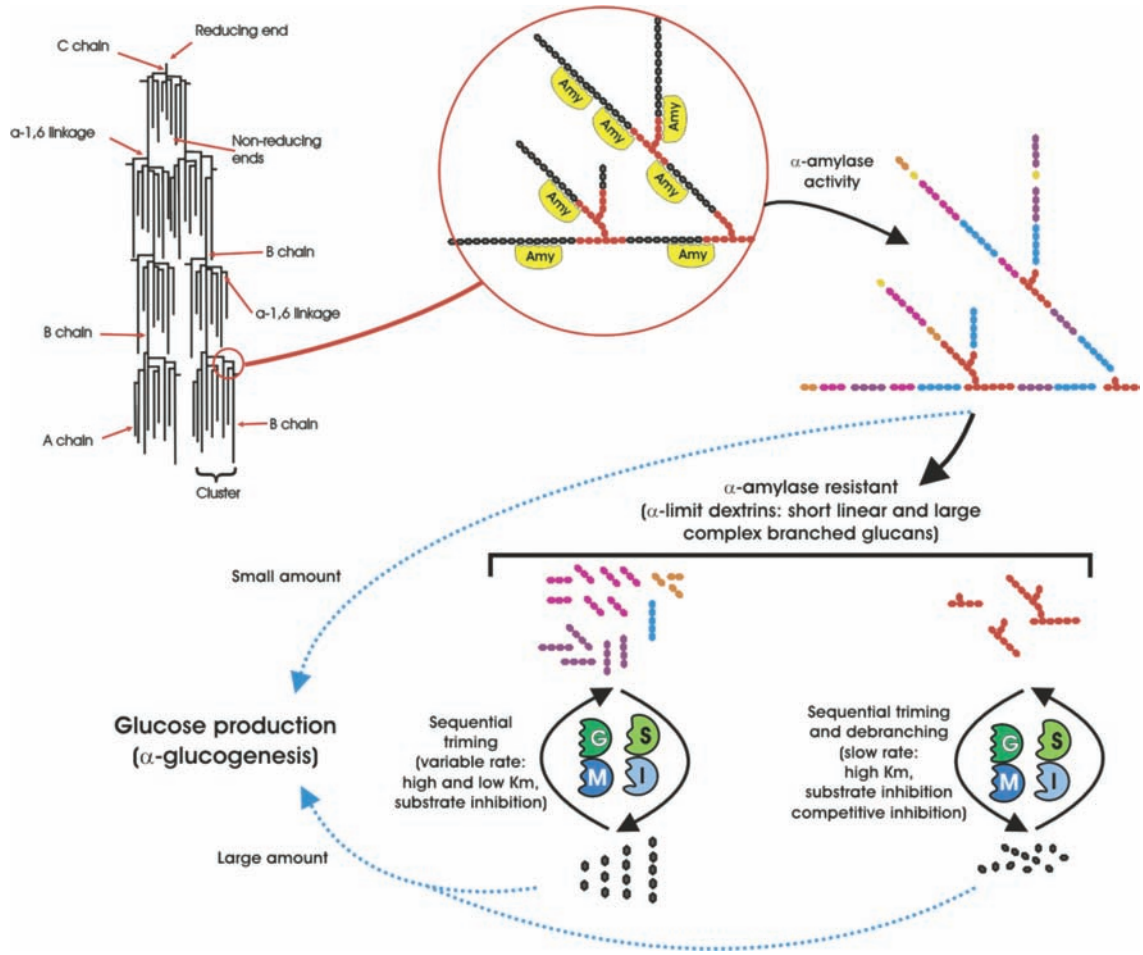

FIGURE 1. Schematic representation on the digestion process of starch, beginning with starch branched molecule (top left), digestion by α-amylase (top middle), susceptibility of segments of the branched molecule to α-amylase (top right) (red = nondigestible, blue = digestible, purple = slowly digestible, magenta and orange = poorly or nondigestible), digestion of α-amylase products by mucosal intestinal enzymes showing variability in digestion rates and kinetics to produce glucose (bottom). Amy = α-amylase, G = glucoamylase (C-terminal), M = maltase (N-terminal), S = sucrase (C-terminal), I = isomaltase (N-terminal).

COOKING RELATED TO HUMAN EVOLUTION

A new view on the human diet and evolution proposes that evidence of cooking up to 1.8 million years ago (10), and its accompanying gelatinization of starch in tubers and cereals, increased energy availability in prehistoric humans and was an evolutionary force for the development of modern humans. The importance of extracting maximum glucose from starchy foods for our ancestors cannot be overstated. What on cursory glance seems like a redundancy of enzymes to digest starch to glucose instead is an efficient, if not elegant, system for obtaining energy for the body.

PROCESS OF STARCH DIGESTION

In humans, the digestion of starch occurs by enzymatic hydrolysis during its transit through the gastrointestinal tract and requires the participation of 6 different α-glucosidic activities. Two luminal α-1,4 endoglucosidases, namely salivary and pancreatic α-amylases, hydrolyze linear unbranched starch segments with $\geq\geq 5$ glucose residues, releasing oligomers with from 2 (maltose, the simplest glucose oligomer) to 5 glucose residues, but with minimal production of free glucose (Fig. 1, top middle and right) (11). The segments containing α-1,6-linked branches are resistant to these α-amylase activities. To attain the effective release of free glucose, linear and branched glucose oligomers resulting from α-amylase digestion must be further hydrolyzed by 4 exohydrolases present in the mucosal epithelial cells of the small intestine (Fig. 1, bottom). These hydrolases comprise sucrase-isomaltase (SI) and maltase-glucoamylase (MGAM) complexes with C- and N-terminal enzymes, each composed of 2 α-glucosidases containing catalytic sites that act on the nonreducing ends of linear and branched glucose oligomers, with substantial release of free glucose monomers (12,13). All 4 enzymes have α-1,4 glucosidic activity and 1 enzyme, isomaltase, has substantial α-1,6 glucosidic activity that cleaves the linkages present in the branch points of α-limit dextrins. Individual MGAM and SI subunits share high sequence identity, approximately 40% to 60%. C-terminal enzymes have approximately 60% sequence identity, as do the N-terminal enzymes; however, sequence identity was relatively lower (approximately 40%) between C- and N-terminal α-glucosidases (Fig. 2) (14–16).

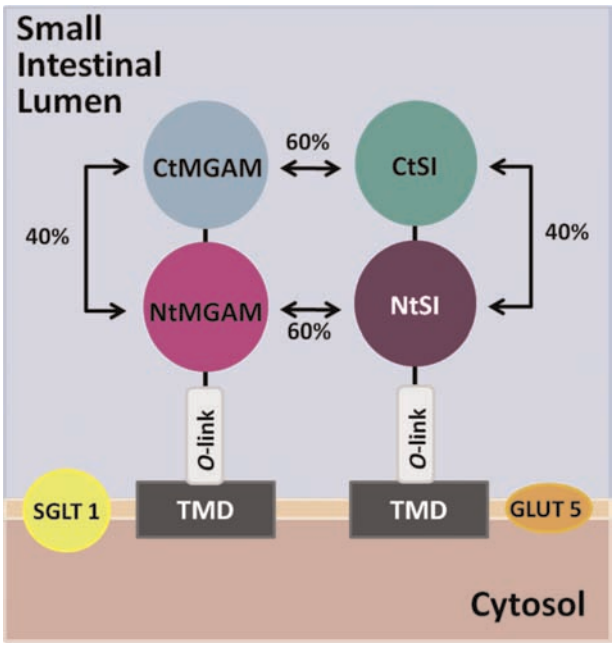

FIGURE 2. MGAM and SI protein complexes linked to the transmembrane domain (TMD) via the O-glycosylated linkage. Percentages among mucosal α-glucosidases represent sequence identity. SGLT1 = sodium dependent glucose transporter 1; GLUT5 = glucose transporter 5.

α-GLUCOSIDASES OF THE GASTROINTESTINAL TRACT

α-Amylase

Salivary and pancreatic α-amylases are synthesized as approximately 78 kDa and are coded by the genes *AMY1* and *AMY2*, respectively, located in the human chromosome 1. The typical human haploid genome contains 2 copies of *AMY2* (*AMY2 A* and *B*) (17), but the presence of multiple copies of the segment containing both genes, *AMY1* and *2*, is common among normal human populations and seems to be associated with the amounts of starch ingested by particular human ethnic groups, suggesting that multiple copies of amylase genes is an adaptative feature for efficient digestion of high starch diets (18). The human α-amylases have specificity for the α-1,4 linked straight-chain regions of α-glucosyl polysaccharides. Human α-amylases have maximal specificity for the interior links, and the active sites bind 5 consecutive glucose residues at specific subsites, cleaving between the second and third subsites to form 2 smaller polymers (Fig. 1, top middle and right). Products that are smaller than the linear maltopentaose are unable to bind at all subsites, have low affinity for the active site of α-amylases, and the productive cleavage of these smaller oligosaccharides by α-amylases is markedly hampered. In addition, α-1,6 branching linkages interfere with the activity of α-amylases and may contribute to a slow digestion fraction observed in the hydrolysis products of starch. The sequential action of α-amylases promotes the release of linear glucose oligomers with 2 to 5 glucose residues together with larger and highly branched molecules, usually termed α-limit dextrins, as the main final products of luminal starch digestion.

MGAM

Human MGAM contains 1857 amino acid residues, which after glycosylation and insertion in the apical membrane, displays a total molecular weight of close to 335 kDa (19,20). The cDNA sequences for the human enzyme have revealed the presence of 2 α-glucosidases in the mature protein (ct-MGAM and nt-MGAM), which display high sequence identity to the respective α-glucosidases of the SI complex and contain 1 potential active site (WIDMNE) in each. MGAM was originally described as 2 relatively thermoresistant maltase activities present in the human intestinal mucosa, and experimental evidence shows the existence of at least 2 subunits in the MGAM complex (21,22). Research has demonstrated that substantial differences in catalytic properties exist between the N- and C-terminal α-glucosidases of the enzyme (19,20). The C-terminal α-glucosidase shows a faster glucoamylase activity than the N-terminal α-glucosidase, but experiences substrate inhibition by the 3 to 5 series of glucose oligomers (maltotriose to maltopentaose) (Fig. 1, bottom middle). In contrast, the N-terminal α-glucosidase displays slower catalytic α-glucogenesis than the C-terminal α-glucosidase, but it shows much lower substrate inhibitory effect by the same glucose oligomers (11,23). In addition, clear differences of up to 2 orders of magnitude were observed in their degree of susceptibility to inhibition by acarbose, with the C-terminal α-glucosidase being more sensitive than the N-terminal α-glucosidase (24). The human MGAM gene (National Center for Biotechnology Information reference sequence NM_004668.2) is located in chromosome 7 (7*q*34). The human and mouse genomic projects have shown that the genomic region coding for MGAM of most mammalian species contains paralogous replications (4,5) of the 3′ segment coding for the C-terminal α-glucosidase of MGAM, each with potential for its transcription and alternative splicing. The recombinant mouse and human MGAM cDNA sequences show that the corresponding mRNAs are spliced alternatively in the segment corresponding to exons 22 to 44. In addition, the respective recombinant C-terminal proteins display variations in catalytic properties. These observations suggest that MGAM may be considered as a family of closely related proteins rather than a single unimodal protein and suggest that the catalytic properties of MGAM molecules may display variations depending on developmental stage, nutritional status, or diet. Its individual role in starch digestion, therefore, may require independent analysis and determination of the relative proportions of at least the most prominent splicing isoforms.

SI

The gene coding for the human SI complex is located on chromosome 3*q*16, producing a protein with a predicted size of nearly 210 kDa (25,26). The mature SI is a complex composed of 2 α-glucosidases, sucrase and isomaltase (National Center for Biotechnology Information reference sequence NP_001032.2). After synthesis, the fully active proenzyme is transported and inserted in the apical membrane of the enterocytes through its N-terminus (27). Subsequently, SI is subjected to extracellular processing by pancreatic proteolytic enzymes in the intestinal lumen cleaving the complex and generating free sucrase and membrane-bound isomaltase subunits (28). The cleaved molecules remain associated to each other through noncovalent interactions. Both α-glucosidases display considerable α-glucosidic activity on starch-derived glucose oligomers. Human SI complex has an overall contribution of 60% to 80% of the total human intestinal maltase activity because of the amount of protein in the small intestine (29,30); however, the apparent K_m values calculated for sucrase and

isomaltase in association is at least 10 times higher than the apparent K_m values calculated for the same activities of ct-MGAM (glucoamylase). The α-glucosidic activities of SI are, therefore, predominant in the human intestine but are a much slower glucose producer from glucose oligomers than is MGAM. The α-1,6 glucosidic linkage of the branched α-limit dextrins is hydrolyzed by the isomaltase of the SI complex. Although these branched linkages may contribute to the generation of ''slow-digesting'' products of starch digestion, SI displays approximately 50% as much debranching (isomaltase) activity as its maltase activity, which provides enough activity to cope with the total branched linkages that may be present during the starch digestive process (Fig. 1, bottom right).

Production of glucose from dietary starch depends on the orchestrated activities of SI and MGAM. Rates of substrate digestion depend on their specific interaction with 4 mucosal α-glucosidases. Control of glucogenesis can be obtained both through types of available substrates and inhibitory effects of oligomers on the different α-glucosidases.

GLYCEMIC RESPONSE DURING STARCH DIGESTION

Digestion of starch in the small intestine can occur rapidly, slowly, or not at all, and accordingly it has been nutritionally categorized in vitro as rapidly digestible starch (RDS), slowly digestible starch (SDS), and resistant starch (RS). In the in vitro Englyst et al (31) assay, RDS is digested within 20 minutes and correlated to the high glycemic index in that it leads to a sudden increase in the blood glucose level. In contrast, SDS is hydrolyzed at a much slower rate, and in the in vitro method is measured as glucose released from 20 to 120 minutes. RS, unlike RDS and SDS, cannot be digested in the small intestine and is used as dietary fiber in the large intestine (31,32). SDS has drawn interest because foods containing SDS are considered to have a glycemic index. Low glycemic index foods including SDS provide a moderated postprandial glucose response and extended glucose release and the possibility of reducing the risk of common chronic diet-related metabolic diseases (eg, type 2 diabetes mellitus, obesity, cardiovascular diseases) (33–38).

CSID ISSUES

In patients with congenital sucrase-isomaltase deficiency (CSID), the only α-glucosidases present are the 2 MGAM subunits, commonly termed maltase and glucoamylase. Although these enzymes have the function of digesting α-amylase digestion products of starch to glucose, it is the full complement of MGAM and SI that efficiently accomplishes starch digestion. For starch digestion, that which is most missing in patients with CSID, is the debranching activity of isomaltase that is responsible for removing branches of the α-limit dextrins to linear maltooligosaccharides for rapid digestion by MGAM. Also missing is the abundance of the SI enzyme complex and its proposed role in slower digestion of starch-degradation products. The well-known sucrose malabsorption in CSID is often coupled with a problem of starch malabsorption. Undigested starch and sucrose molecules can also cause chronic diseases of the colon (eg, chronic osmotic diarrhea, abdominal pain) (39,40).

Possibilities of Increasing Starch Digestion by MGAM

One strategy for reducing starch malabsorption in patients with CSID would be to find ways to increase starch digestibility by MGAM so that undigested starch does not cause abdominal distress. A recent finding by our group shows that glucoamylase, also referred to as ct-MGAM, has high hydrolytic activity toward native starch molecules, so much so that it has been proposed to assist α-amylase in digesting starch (41). Starchy foods designed to be better digested by ct-MGAM would thus result in more complete digestion and glucose absorption in the small intestine. Such foods may include those with dispersed starch molecules that are found in well-gelatinized foods that include shear processes to break apart swollen starch granules (eg, purees, puddings, porridges). Maltodextrins, which are partially hydrolyzed starch-based products, would also likely be well digested by the MGAM enzymes, as would maltooligosaccharides (smaller breakdown products of starch).

Could Slowly Digestible Starchy Foods Be Better for Patients With CSID?

Another strategy for reducing abdominal distress experienced by some patients with CSID after consumption of starchy foods may be to consume slowly digestible, low-glycemic-response starchy foods. The reasoning here is that such starches digest slowly in the small intestine and can slow gastric emptying and motility of food (40), thus slowing starch delivery to the small intestine, where it would be better able to digest it, and that starch which enters the colon would do so in smaller amounts and during a longer postprandial period. As a result, bloating and osmotic effects of maltooligosaccharides in the bowel that can cause diarrhea would be reduced.

Slowly digestible starches can be found in a number of foods that have slowly digestible matrices (eg, al dente pasta, some whole-grain foods) and slowly digestible starch types (eg, moderately higher amylose cereals, partially gelatinized) (42). Consumption of these foods would represent a somewhat restrictive diet, which in the case of consumption of sucrose has been alleviated by supplementation with sacrosidase (43,44). Still, there is a fairly wide range of foods with slow digestible starch property. Other approaches that may be less restrictive in achieving slow starch digestion would include the addition of glucoamylase as a supplement or partial inhibition of α-amylase or MGAM, and disaccharides or maltooligosaccharides with α-linkages other than the 1,4 and 1,6 linkages found in starch molecules (eg, kojibiose, nigerose, isomaltulose).

REFERENCES

1. French D. Chemistry and biochemistry of starch. In: Whelan WJ, ed. *Biochemistry of Carbohydrates.* London: Butterworth & Co; 1975: 267–335.
2. Lee PC. Digestibility of starches and modified food starches. *J Pediatr Gastroenterol Nutr* 1983;2:227–32.
3. Whistler RL, BeMiller JN. Carbohydrate Chemistry for Food Scientists. St. Paul, MN: American Association of Cereal Chemists; 1997.
4. Mua JP, Jackson DS. Fine structure of corn amylose and amylopectin fractions with molecular weights. *J Agric Food Chem* 1997;45:3840–7.
5. Buleon A, Colonna P, Planchot V, et al. Starch granules: structure and biosynthesis. *Int J Biol Macromol* 1998;23:85.
6. Biliaderis CG. Structure and phase transitions of starch polymers. In: Walter RJ, ed. *Polysaccharide Association Structures in Food.* New York: Marcel Dekker; 1998:57–168.
7. Ao Z, Simsek S, Zhang G, et al. Starch with a slow digestion property produced by altering its chain length, branch density, and crystalline structure. *J Agric Food Chem* 2007;55:4540–7.
8. Zhang G, Ao Z, Hamaker BR. Nutritional property of endosperm starches from maize mutants: a parabolic relationship between slowly digestible starch and amylopectin fine structure. *J Agric Food Chem* 2008;56:4686–94.

9. Zhang G, Sofyan M, Hamaker BR. Slowly digestible state of starch: mechanism of slow digestion property of gelatinized maize starch. *J Agric Food Chem* 2008;56:4695–702.
10. Wrangham R. Catching Fire: How Cooking Made Us Human New York: Basic Books; 2009.
11. Quezada-Calvillo R, Robayo-Torres CC, 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.
12. Jones BJ, Brown BE, Loran JS, et al. Glucose absorption from starch hydrolysates in the human jejunum. *Gut* 1983;24:1152–60.
13. Gray GM. Starch digestion and absorption in nonruminants. *J Nutr* 1992;122:172–7.
14. Ernst HA, Lo Leggio L, Willemoës M, et al. Structure of the *Sulfolobus solfataricus* α-glucosidase: implications for domain conservation and substrate recognition in GH31. *J Mol Biol* 2006;358: 1106–24.
15. Heymann H, Breitmeier D, Günther S. Human small intestinal sucrase-isomaltase: different binding patterns for malto- and isomaltooligosaccharides. *Bio Chem Hoppe-Seyler* 1995;376:249–53.
16. Robayo-Torres CC, Quezada-Calvillo R, Nichols BL. Disaccharide digestion: clinical and molecular aspects. *Clin Gastroenterol Hepatol* 2006;4:276–87.
17. Zabel BU, Naylor SL, Sakaguchi AY, et al. High-resolution chromosomal localization of human genes for amylase, proopiomelanocortin, somatostatin, and a DNA fragment (D3S1) by in situ hybridization. *Proc Natl Acad Sci* 1983;80:6932–6.
18. Iafrate AJ, Feuk L, Rivera MN, et al. Detection of large-scale variation in the human genome. *Nat Genet* 2004;36:949–51.
19. 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.
20. 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.
21. Kelly JJ, Alpers DH. Properties of human intestinal glucoamylase. *Biochim Biophys Acta* 1973;315:113–22.
22. Dahlqvist A. The separation of intestinal invertase and three different intestinal maltases on TEAE-cellulose by gradient elution, frontal analysis and mutual displacement chromatography. *Acta Chem Scand* 1958;13:1817–27.
23. 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.
24. 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.
25. Alpers DH, Helms D, Seetharam S, et al. In vitro translation of intestinal sucrase-isomaltase and glucoamylase. *Biochem Biophys Res Commun* 1986;134:37–43.
26. Chandrasena G, Osterholm DE, Sunitha I, et al. Cloning and sequencing of a full-length rat sucrase-isomaltase-encoding. *Gene* 1994;150:355–60.
27. Brunner J, Wacker H, Semenza G. Sucrase-isomaltase of the small-intestinal brush border membrane: assembly and biosynthesis. *Methods Enzymol* 1983;96:386–406.
28. Naim HY, Sterchi EE, Lentze MJ. Biosynthesis of the human sucrase-isomaltase complex. Differential O-glycosylation of the sucrase subunit correlates with its position within the enzyme complex. *J Biol Chem* 1988;263:7242–53.
29. Semenza G, Auricchio S, Rubino A. Multiplicity of human intestinal disaccharidases I. Chromatographic separation of maltases and of two lactases. *Biochim Biophys Acta* 1965;96:487–97.
30. Semenza G, Auricchio S, Mantei N. Small intestinal disaccharidases. In: Scriver CR, et al., eds. *Metabolic Basis of Inherited Disease.* New York: McGraw-Hill; 2001: 1623–50.
31. Englyst HN, Kingman SM, Hudson GJ, et al. Measurement of resistant starch in vitro and in vivo. *Br J Nutr* 1996;75:749–55.
32. Englyst HN, Kingman SM, Cummings JH. Classification and measurement of nutritionally important starch fractions. *Eur J Clin Nutr* 1992;46:S33–50.
33. Ludwig DS. The glycemic index. *JAMA* 2002;287:2414–23.
34. Jenkins DJA, Kendall CWC, Augustin LS, et al. Glycemic index: overview of implications in health and disease. *Am J Clin Nutr* 2002;76:266S–73S.
35. Jenkins DJA, Kendall CWC, McKeown-Eyssen G, et al. Effect of a low-glycemic index or a high-cereal fiber diet on type 2 diabetes. *JAMA* 2008;300:2742–53.
36. Muir J, O'Dea K. Validation of an in vitro assay for predicting the amount of starch that escapes digestion in the small intestine of humans. *Am J Clin Nutr* 1993;57:540–6.
37. Opperman AM, Venter CS, Oosthuizen W, et al. Meta-analysis of the health effects of using the glycaemic index in meal-planning. *Br J Nutr* 2004;92:367–81.
38. Wolever TMS. Carbohydrate and the regulation of blood glucose and metabolism. *Nutr Rev* 2003;61:S40–8.
39. Karnsakul W, Luginbuehl 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.
40. Treem WR. Congenital sucrase-isomaltase deficiency. *J Pediatr Gastroenterol Nutr* 1995;21:1–14.
41. Lin AH-M, Nichols BL, Quezada-Calvillo R, et al. Unexpected high digestion rate of cooked starch by the ct-maltase-glucoamylase small intestine mucosal α-glucosidase subunit. *PLoS One* 2012;7: e35473.
42. Zhang G, Hamaker BR. Slowly digestible starch: concept, mechanism, and proposed extended glycemic index. *Crit Rev Food Sci* 2009; 49:852–67.
43. 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.
44. Treem WR, McAdams L, Stanford L, et al. Sacrosidase therapy for congenital sucrase-isomaltase deficiency. *J Pediatr Gastroenterol Nutr* 1999;28:137–42.

Frequency of Sucrase Deficiency in Mucosal Biopsies

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Carbohydrates, sugars, and starches are an important source of energy, especially for the brain, which is completely dependent on glucose for energy (1). The US Department of Agriculture recommends that carbohydrates provide 45% to 65% of daily energy units (2) and the dietary reference intakes set the adequate

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