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Research Article

Fructose, a naturally occurring monosaccharide, is increasingly used as an added sweetener in processed foods in the form of high fructose corn syrup. Increased fructose intake combined with the identification of children with clinical evidence of isolated fructose malabsorption (IFM) has stimulated interest in possible disorders of fructose absorption. The intestinal absorption of fructose is carried out by the facilitative hexose transporter, which has been designated as GLUT5. Functional properties and tissue distribution of GLUT5 suggest that IFM might be due to mutations in the GLUT5 gene. To test this hypothesis, we screened the GLUT5 gene for mutations in a group of eight patients with IFM and in one subject with global malabsorption, as compared with 15 healthy parents of subjects and up to 6 unrelated controls. No mutations were found in the protein coding region of this gene in any of the subjects. A single G to A substitution in the 5' untranslated region of exon 1 was identified in the subject with global malabsorption. This subject and her healthy mother were heterozygous for the variant sequence, suggesting that it was unlikely to be clinically significant. In addition, sequence analysis of each of the 12 GLUT5 exons was performed in the index case and confirmed the negative single-strand conformation polymorphism findings. These studies demonstrate that IFM does not result [...]

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Molecular Analysis of the Fructose Transporter Gene (*GLUT5*) in Isolated Fructose Malabsorption

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Abstract

Fructose, a naturally occurring monosaccharide, is increasingly used as an added sweetener in processed foods in the form of high fructose corn syrup. Increased fructose intake combined with the identification of children with clinical evidence of isolated fructose malabsorption (IFM) has stimulated interest in possible disorders of fructose absorption. The intestinal absorption of fructose is carried out by the facilitative hexose transporter, which has been designated as GLUT5. Functional properties and tissue distribution of GLUT5 suggest that IFM might be due to mutations in the *GLUT5* gene. To test this hypothesis, we screened the *GLUT5* gene for mutations in a group of eight patients with IFM and in one subject with global malabsorption, as compared with 15 healthy parents of subjects and up to 6 unrelated controls. No mutations were found in the protein coding region of this gene in any of the subjects. A single G to A substitution in the 5' untranslated region of exon 1 was identified in the subject with global malabsorption. This subject and her healthy mother were heterozygous for the variant sequence, suggesting that it was unlikely to be clinically significant. In addition, sequence analysis of each of the 12 *GLUT5* exons was performed in the index case and confirmed the negative single-strand conformation polymorphism findings. These studies demonstrate that IFM does not result from the expression of mutant GLUT5 protein. (*J. Clin. Invest.* 1996. 98:2398–2402.) Key word: carbohydrate malabsorption

Introduction

Fructose, a naturally occurring monosaccharide, is present in fruits and natural sweeteners. Low expense, easy availability, and extreme sweetness have made high fructose corn syrup al-

most ubiquitous in processed foods (1–4). The use of fructose sweeteners results in a sharp increase in mean daily fructose intake after weaning (1). Isolated fructose malabsorption (IFM)¹ is a rare pediatric clinical entity that has been reported as isolated case reports from several different countries (5–7). The inheritance pattern of IFM is unknown, but there are no known families with multiple affected individuals, which suggests autosomal recessive inheritance. The patients have pronounced symptoms after ingestion of low amounts of free fructose including colicky abdominal pain and diarrhea. The symptoms of IFM patients resolve on a fructose free diet, with relapse upon rechallenge. In cases where small bowel biopsy has been performed, the histology and disaccharidase activities have been normal. Breath hydrogen testing is performed by administering a known dose of test carbohydrate to an individual. Malabsorbed carbohydrate reaches the colonic flora and undergoes bacterial fermentation producing hydrogen, short-chain fatty acids, methane, and carbon dioxide. The hydrogen produced by this reaction is expired; an elevated breath level after ingestion of a given sugar suggests the inappropriate delivery of that sugar to the colon (8, 9). In an IFM patient, increased breath hydrogen during fructose breath testing is associated with symptoms, whereas breath hydrogen is not elevated after ingestion of other test sugars and symptoms do not occur. IFM is clinically distinct from chronic nonspecific diarrhea (10, 11) in that symptoms occur after ingestion of small amounts of fructose and colicky abdominal pain is a prominent complaint. The recognition of the clinical entity of IFM stimulated our interest in possible specific abnormalities of fructose absorption in these children.

GLUT5 is a high affinity fructose transporter located on the luminal surface of absorptive epithelial cells in the small intestine of humans and rodents (12–19). The levels of GLUT5 mRNA and protein are regulated by fructose intake (20).

Single-strand conformational polymorphism (SSCP) analysis has become a common method of screening for mutations (21–23). Sequence changes as small as a single nucleotide substitution can alter the secondary structure and allow resolution of wild-type and mutant strands. To evaluate a possible association between mutations in human GLUT5 protein and the clinical entity of IFM, we performed SSCP analysis of the human *GLUT5* gene in IFM patients.

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1. Abbreviations used in this paper: IFM, isolated fructose malabsorption; SSCP, Single-strand conformational polymorphism.

Table I. Summary of Clinical Data

Patient number	Sex	Age at onset of symptoms	Age at diagnosis	FBT ΔH_2 (symptoms)	SBT ΔH_2 (symptoms)	SB biopsy histology	SB biopsy disaccharidase
1	F	5 mo	8 mo	95 (bloating, crying)	60 (none)	Normal	Normal
2	F	5 mo	5 yr	100 (diarrhea, crying)	27 (none)	Normal	Normal
3	F	12 mo	2.5 yr	51 (diarrhea, pain)	37 (loose stool)	Normal	Normal
4	M	6 mo	2.75 yr	13 (diarrhea)	-7 (none)	Normal	Normal
5	F	6 mo	3.5 yr	75 (flatus, pain)	ND	ND	ND
6	M	6 mo	1.6 yr	10 (diarrhea, pain)	3 (none)	Normal	ND
7	M	20 mo	2.75 yr	82 (diarrhea, pain)	ND	Normal	Normal
8	M	9 mo	2.25 yr	73 (diarrhea)	64 (none)	ND	ND
9	F	newborn	newborn	ND	ND	Partial blunting	ND

Methods

Subjects. Eight probands with IFM were identified through case reports in the medical literature and national and international Pediatric Gastroenterology conferences (patients 1–8). The diagnosis of IFM was confirmed by review of clinical data, breath hydrogen testing, and histologic and enzyme analysis where available (Table I). Probands presented with complaints of abdominal pain, gas, and diarrhea after ingestion of fruits and fruit juice and underwent evaluation by a Pediatric Gastroenterologist. IFM probands and their parents were enrolled under an institutional review board–approved protocol at the Children’s Hospital of Philadelphia. A ninth patient with clinical symptoms compatible with global carbohydrate malabsorption was also included along with her parents (patient 9). Genomic DNA was extracted from whole blood leukocytes following a standard protocol (24).

Polymerase chain reaction. The human *GLUT5* gene has 12 exons designated 1–3, 4a, 4b, 5–8, 9a, 9b, and 10 (J. Takeda, and G.I. Bell, GenBank accession numbers U05344 and U11839 to U11843). The gene encodes a protein of 501 amino acids. Using the DNA sequence of the human *GLUT5* gene and the known intron-exon structure as a guide, primers were constructed to amplify each of the 12 exons by PCR. Primers range from 17–24 bp in length, the exons range in length from 99 to 294, and the predicted PCR products range in length from 159–387 bp (Table II). Primers were selected from intronic sequences such that splice sites were amplified and the closest primer begins 19 bp outside of the exon. Individual PCR reactions were performed for each exon in each patient using standard components with 100–150 ng of genomic template DNA. In addition, a genomic λ -phage clone (lambda-151) containing exons 4a–10 was used as a positive control for those exons. Water served as a negative control for each of the PCR reactions. PCR was performed in the pres-

Table II. PCR Primer Pairs and Product Lengths For *GLUT5* Exons

Primer name	Primer sequence	Exon length	Product length
		<i>base pairs</i>	
Exon 1F	AAGACCAGGTTCTGAAAGG	129	249
Exon 1R	TGGCAGCCAAGCCTGCTCTT		
Exon 2F	ACTCGCCTTGATCTCTGCAG	99	224
Exon 2R	GACCCACTGCGTGAACAGCC		
Exon 3F	GGTGTCCCTAACAGCTAATGT	161	335
Exon 3R	ATCTTAGTCTCATGGTAAGG		
Exon 4aF	CTGATATTTGTCTCTGCAG	132	187
Exon 4aR	CTCACAGAATGGCAATACAGC		
Exon 4bF	TACTTGAAGACAGCTTGTC	153	241
Exon 4bR	CCGAGATGTCCTGAACTCAC		
Exon 5F	AGGCCGCTGGTGCCAGCTCG	105	255
Exon 5R	CGCGCAGCGTCTGTAGGGCT		
Exon 6F	CGGCCGCAAGAAAGAAAGGTAAC	188	309
Exon 6R	CCAGCTCCCGAGCCGAGCC		
Exon 7F	CCGCGCTTGCCTTGCG	111	159
Exon 7R	TGGAGGCTGTGGGAGCT		
Exon 8F	CATGTGAATGTGAGGTGCG	102	387
Exon 8R	ACACGGTCCCCAGATGTCTG		
Exon 9aF	CCGTCCTACGCTTTGTCTGC	128	158
Exon 9aR	TGACACCCTGAGGCCAGCTT		
Exon 9bF	GCTCTGCCTTCAGGGAGGCT	128	223
Exon 9bR	GCTCGCACTGTACTGCATGG		
Exon 10F	CACGTCCCACAGTGTACCT	294	359
Exon 10R	GACTGCATTCCACATCAGAG		

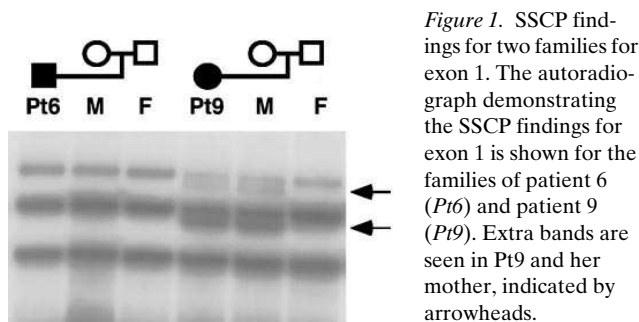


Figure 1. SSCP findings for two families for exon 1. The autoradiograph demonstrating the SSCP findings for exon 1 is shown for the families of patient 6 (Pt6) and patient 9 (Pt9). Extra bands are seen in Pt9 and her mother, indicated by arrowheads.

ence of ^{32}P - α -dCTP. Cycling conditions in each case started with an initial 4-min denaturation at 92°C followed by 45 cycles of 94°C for 1 min, 60 or 63°C for 1 min, and 72°C for 1 min.

SSCP analysis. Radiolabeled PCR products were resolved on various nondenaturing polyacrylamide gels and visualized by autoradiography. Various SSCP conditions were used including: 10% glycerol-5% polyacrylamide at room temperature, 4°C; 10% glycerol-7.5% polyacrylamide at room temperature, 4°C; and Hydrolink MDE (J.T. Baker, Inc., Phillipsburg, NJ) (0% glycerol) at 4°C. Table III summarizes the conditions completed for each exon.

Sequence analysis. Abnormal patterns observed by SSCP were selected for analysis by direct sequencing. Nonradioactive PCR products were gel isolated using GeneClean (BIO 101 Corp., Vista, CA) as per manufacturer's instructions. Resulting fragments were directly sequenced using direct thermocycle sequencing protocol Amplicycle (Perkin-Elmer Corp., Branchburg, NJ) in the presence of ^{35}S - α -dATP and were visualized by autoradiography. Alternatively, sequencing was performed by the Children's Hospital of Philadelphia Nucleic Acid/Protein Research Core Facility using a Dye Terminator Cycle Sequencing Kit with AmpliTaq DNA polymerase, FS (Perkin Elmer/Cetus Instruments, Foster City, CA).

Results

Subjects. The 28 subjects studied were 8 probands, 13 unaffected parents of IFM patients, 1 patient with global malabsorption (patient 9), her 2 parents, and up to 6 healthy controls. Clinical data is summarized in Table I. In addition, a GLUT5 genomic phage clone λ -151 and water were used as positive and negative controls (see Methods). The eight IFM probands fulfilled the criteria for isolated fructose malabsorption defined by a clinical constellation of gas, diarrhea, and colicky abdominal pain associated with ingestion of dietary fructose. Symptoms were replicated during breath hydrogen testing with 1 g/kg fructose. Sucrose breath testing was performed in six patients with elevated breath hydrogen occurring in four; however, no clinical symptoms were observed after sucrose administration. All other breath hydrogen tests were normal, and intestinal biopsies (when performed) demonstrated normal epithelial histology and disaccharidase activities. Patient 9, with global malabsorption, has also been screened for mutations in the sodium-glucose cotransporter gene, *SGLT1*, and no abnormalities were found (Martin G. Martin, UCLA, Los Angeles, CA, personal communication).

SSCP analysis and sequencing. SSCP revealed two distinct band patterns occurring in exon 1 (Fig. 1). A single pattern for exon 1 was observed in each of the eight IFM probands and their parents as well as in the healthy controls, and a second pattern was observed in patient 9 and her mother. Direct sequencing of nonradioactive PCR products generated from genomic DNA from this patient and her mother revealed a G to

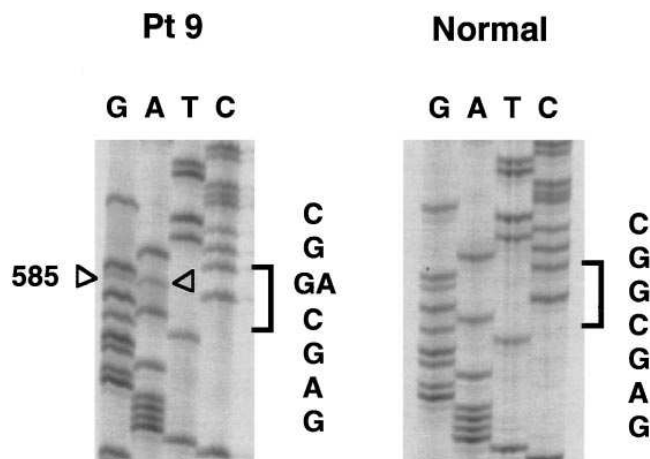


Figure 2. Sequence analysis of variant vs. normal SSCP patterns for exon 1. The autoradiograph demonstrating the sequencing results for exon 1 comparing patient 9 with a healthy control. Patient 9 has 50% G and 50% A at nucleotide position 585 (open arrowheads), demonstrating a G to A substitution on one allele. Identical findings were observed in the mother of this child.

A replacement at nucleotide 585, in the 5' untranslated area of exon 1 (shown in Fig. 2). Exon 1 extends from nucleotide 514 to 642 with the 5' untranslated region from 514 to 609. As this substitution does not alter the protein sequence, it is likely to be a polymorphism. Although not significant for the purposes of this study, this polymorphism may be useful for linkage analysis in other settings.

Extensive SSCP analysis as summarized in Table III demonstrated only single patterns at exons 2–10 in the probands (data not shown). To confirm the absence of variation demonstrated by SSCP, we elected to compare the sequence of each amplified exon of the index literature case of IFM (patient 1) to that of amplified products from the genomic phage clone (where available), to our sequencing of other patients and control subjects, and to the published cDNA sequence (25). Sequencing of each exon amplified from patient 1 and other individuals (Table III) was identical to that of the published cDNA sequence.

Genome database analysis revealed inconsistencies between the reported cDNA and genomic clone sequences; however, we were able to resolve the inconsistencies in favor of the cDNA sequence by our repeat sequencing of the genomic phage clone as compared with the corresponding region of three unrelated control individuals and the cDNA sequence. Additional sequencing was performed on patient samples for consistency. The corrections in the genomic clone involved exon 5 and intron 8 and have been entered into the Genbank/EMBL/DBJ genome database (accession number pending).

Discussion

The identification of a specific facilitative fructose transporter and the existence of individuals with isolated fructose malabsorption prompted us to evaluate the potential occurrence of mutations of human *GLUT5* in patients with IFM. SSCP screening methods were used and negative findings were confirmed by sequence analysis in the index case (patient 1). We have shown that there are no detectable protein-altering muta-

Table III. Summary of Alleles Screened and SSCP Conditions for each Exon

Exon	Number of patients with IFM screened	Number of parents screened	Number of siblings screened	Number of healthy controls screened	Number of alleles screened	Number of alleles sequenced	SSCP conditions used*
1	9	13	3	4	58	8	A, B, C
2	9	15	0	3	54	4	B, C
3	9	15	3	5	64	6	A, B, C
4a	9	15	3	4	62	6	B, C
4b	9	15	3	6	66	6	B, C
5	9	14	0	4	54	10	B, C
6	9	14	0	4	54	2	C
7	9	14	0	4	54	2	C
8	9	14	3	3	58	4	B, C
9a	9	13	0	5	54	12	B, C
9b	9	15	0	5	58	2	B, C
10	9	15	0	4	56	2	B, C

*A, 10% glycerol/5% acrylamide at room temperature, 4°C; B, 10% glycerol/7.5% acrylamide at room temperature, 4°C; C, MDE gel at room temperature, 4°C.

tions in *GLUT5* in the most rigorously characterized individuals with isolated fructose malabsorption, including the index case for this disorder.

Failure of the SSCP method is unlikely to be the cause of our inability to identify significant mutations. First, SSCP performed simultaneously under various electrophoresis and temperature conditions has had proven efficiency in numerous other screening efforts. For example, screening of the sodium-glucose transporter gene in patients with glucose-galactose malabsorption revealed numerous mutations (23). Furthermore, we were able to detect a single base pair substitution in patient 9 and her mother, demonstrating a functional methodology. In addition, sequence analysis of all 12 exons demonstrated the absence of mutations in the index case, patient 1. This confirms the negative SSCP findings in this patient, and, within the limitations of SSCP, the findings for each of the seven additional patients studied who had identical patterns.

If *GLUT5* mutations are not responsible for the manifestation of isolated fructose malabsorption, other explanations are needed. One possibility is that depressed (or absent) *GLUT5* protein levels could result in failure to transport fructose normally. *GLUT5* gene expression appears to be regulated transcriptionally by fructose, and it is possible that IFM results from abnormal regulation of *GLUT5* by fructose. The nature of the *cis*-acting elements and *trans*-acting factors responsible for mediating the effects of fructose on *GLUT5* expression are unknown; efforts are underway to elucidate the molecular basis of fructose's effects on *GLUT5* message and protein levels. It is possible that mutations in the "fructose regulatory element" of the *GLUT5* gene or the protein(s) that mediate the transcriptional effects of fructose are responsible for IFM. Once these are identified it will be possible to test their role in IFM directly. We did not evaluate upstream sequences of *GLUT5* in our patients, nor have direct studies of *GLUT5* message or protein levels been performed.

An alternative explanation is to hypothesize that other avenues for fructose absorption into the enterocyte exist and are abnormal in IFM patients. For example, fructose absorption is stimulated by the presence of glucose in a dose-dependent

fashion leading to speculation that there are additional fructose transport mechanisms (4, 26). As the proportion of glucose to fructose increases, fructose absorption is enhanced with maximal absorption at equimolar concentrations (4, 26). Delivery of fructose in the form of sucrose also leads to augmented fructose absorption (26). However, in the presence of Acarbose, an inhibitor of brush-border sucrase-isomaltase, glucose facilitated fructose transport is normal (4, 27). This demonstrates that sucrase-isomaltase is not necessary for glucose-enhanced fructose absorption. Another possibility might be that one or more additional proteins is necessary for proper functioning or positioning of the *GLUT5* transporter within the enterocyte membrane, and that one of these proteins is the site of the abnormality in IFM patients.

A final (and perhaps most likely) explanation is that IFM patients have abnormal handling of overflow carbohydrate in the colon as compared with normal individuals. As the result of variations in intestinal flora, some individuals produce more gas, hydrogen, and short chain fatty acids than others, thereby altering the symptoms produced by malabsorption of carbohydrates in the small bowel (28). This hypothesis is supported by the observations that elevated breath hydrogen after fructose ingestion is common but generally not associated with the diarrhea, flatus, or abdominal pain that are characteristic of IFM. Elevated breath hydrogen levels were observed in all 57 healthy children < 6 yr of age after a 2 g/kg oral dose of fructose, and in 25 of 57 children with a 1 g/kg dose, but no symptoms were observed with either dose (9). The limited capacity for ingestion of fructose in these patients may be similar to that of the general population, but symptoms may be caused by other factors.

In summary, we used SSCP analysis to evaluate the *GLUT5* gene exons in patients with isolated fructose malabsorption. While SSCP detected a single base substitution in the 5' untranslated region of exon 1, this replacement occurred in a global malabsorption patient and her healthy mother rather than an IFM proband, and the substitution was not predicted to alter protein sequence. Sequence analysis of each of the *GLUT5* exons was performed in the index case and confirmed

the negative SSCP findings. These studies demonstrate that GLUT5 mutations are not responsible for the clinical entity of isolated fructose malabsorption.

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