



Hereditary fructose intolerance in Brazilian patients



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ABSTRACT

Introduction: Hereditary fructose intolerance (HFI) is a rare inborn error of carbohydrate metabolism, autosomal recessive, caused by mutations in the gene ALDOB, leading to deficiency of aldolase B. Symptoms begin in the first months of life with the introduction of complementary foods containing fructose, sucrose or sorbitol, often with vomiting, feeding problems and failure to thrive. Prolonged exposure may cause liver and kidney failure, which can lead to death. Treatment consists in removing the toxic sugars of diet.

Materials and methods: Clinical and molecular characterization of four unrelated patients from the State of Minas Gerais, Brazil, all children from non-consanguineous parents.

Results and discussion: Age at diagnosis was between 10 and 32 months and the severity of the disease correlated with the increasing of age at diagnosis. The predominant symptoms were vomiting, weight loss, and hepatomegaly. Severe renal tubular acidosis manifested in one child. All patients had remission of symptoms after dietary modification. The sequencing of the ALDOB gene identified one homozygous patient for the mutation c.524C>A (p.A175D), while the others were compound heterozygous for c.360_363delCAA (p.N120KfsX32), c.178C>T (p.R60X) mutations, c.448G>C (p.A150P) and c.524C>A (p.A175D). Clinical improvement of patients after dietary treatment is suggestive of the diagnosis, confirmed by molecular analysis. The prevalence of mutations found in our Brazilian patients is different from those of international literature.

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1. Introduction

The hereditary fructose intolerance (HFI; MIM 229600) is an inborn error of carbohydrate metabolism caused by mutations in the gene encoding the aldolase B liver enzyme [1] (ALDOB; EC 4.1.2.13; GenBank accession no. AH002597). The p.A150P mutation, followed by the p.A175D, is the most prevalent in the international literature [2,3,4,5,6]. The incidence of HFI is around 1/10,000 to 1/100,000 newborns and varies according to the ethnic group studied [4,6,7,8]. This data result in a predicted carrier frequency between 1:55 and 1:120 [6]. There is no data of HFI in the Brazilian population. Fructokinase phosphorylates the fructose obtained in the diet to fructose-1-phosphate, substrate for aldolase B. The aldolase B deficiency leads to fructose-1-

phosphate accumulation primarily in cells of the liver, intestine and proximal renal tubule, leading to phosphate depletion, deficient energy metabolism and impairment of gluconeogenic/glycolytic pathway [2,9,10,11]. In general, the individual with HFI has normal growth and development during exclusive breastfeeding. The introduction of fructose, sucrose (disaccharide formed by fructose and glucose) or sorbitol can cause mainly vomiting, feeding difficulties and failure to thrive. More acutely symptoms are gastrointestinal distress, hypoglycemia, shock and hepatomegaly, pallor, bleeding, tremor and jaundice. Without treatment, liver and kidney failure can occur, leading to death [12,13]. The clinical response to dietary treatment strongly suggests the diagnosis of HFI. Patients may present fructose elimination in the urine, identified by various techniques, such as thin-layer chromatography, and quantified enzymatically [14]. The diagnosis can be confirmed by the decrease of enzymatic activity of aldolase B, measured in samples from liver, kidney and intestinal mucosa biopsies [15] or by sequencing the gene ALDOB [2]. The treatment is the complete removal of all sources of fructose, sucrose and sorbitol of the diet, eliminating the

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consumption of fruits and sucrose and restricting the intake of vegetables. One should be aware of the labels of dietary products that may contain sorbitol and also medicines, in which fructose and sucrose may be used in vehicles [1]. This restriction is sufficient to stop the symptoms and restore normal growth, even though hepatomegaly may persist for months or even years, for still unknown reasons [13].

We report four non-related Brazilian patients with HFI, attempting for recognition of this potentially severe disease that has an excellent prognosis since it is treated.

2. Methodology

2.1. Clinical data

The clinical data of four non-related patients were collected from their medical records, with the consent of parents and/or guardians.

2.2. Molecular analysis

Blood samples were collected in anticoagulant tube containing EDTA, followed by DNA extraction [7]. For patient 1, allele-specific oligonucleotide hybridization for targeted mutations of ALDOB was performed at Boston University [6]. Sequencing of all exons and intron/exon junction regions of ALDOB, in forward and reverse directions, by fluorescent automated dideoxy DNA sequencing [7] was performed for patients 2, 3 and 4.

The analysis of the results was performed using the reference sequences NG_012387.1 (DNA), NM_000035.3 (cDNA) and NP_000026.2 (protein) [16] and the previous description of mutations provided by the Human Gene Mutation Database (HGMD) [17].

3. Results

3.1. Clinical and biochemical data

Data from four patients with HFI is presented below and summarized in Table 1.

3.1.1. Patient 1

Second daughter of non-consanguineous couple. Cesarean section at 37 weeks of gestation, weight 2610 g and length of 49 cm, appropriate for gestational age. She received breast milk and infant formula from birth. At 6 months of age the complementary feeding started with aversion to fruits, juices and yogurts. She presented vomiting after eating these foods, and also after administration of drugs in the form of sweet syrup. She held the 15th percentile for weight until 6 months, but it decreased after eight months of age. At 13 months, with weight = 6500 g (percentile < 3, 50th percentile for 4 months) and length = 69 cm (percentile < 3), she was admitted in the hospital for investigation. There was a remarkable hepatomegaly, with liver palpable 8 cm below the right costal margin. Laboratory tests showed liver and renal

dysfunction: STGO: 316 U/L (13–49), STGP: 114 U/L (10–37), direct bilirubin level: 0.8 mg% (0 to 0.3) and proteinuria ++ (100 mg/dL). Dietary treatment for HFI started, leading to progressive remission of symptoms. Sugar chromatography of urine was normal, result attributed to the lack of fruit intake. After 10 days she gained 480 g and laboratory improvement was noticed (SGOT: 173 U/L, SGPT: 92 U/L and normal 24-hour proteinuria, 38.92 mg). Abdominal ultrasound at 15 months showed liver with normal dimensions. Urine tests, blood count and liver function were always normal in later controls. Anthropometric data at 18 months: weight = 8950 g (15th percentile), length = 74.5 cm (3rd percentile) and PC = 45.2 cm (below the 10th percentile), and at 25 months, weight = 10,820 g (15–50th percentile), length = 82.2 cm (3–15th percentile) and PC = 46.3 cm (below the 10th percentile). The parents noticed that, despite the rejection to fruits in general, she always looked for green acerola to ingest. Her psychomotor development was always appropriate for her age.

3.1.2. Patient 2

First son of non-consanguineous parents. Born at term of cesarean delivery, indicated by maternal hypertension and fetal macrosomia, without complications. Birth weight = 3940 g, length = 52 cm and Apgar 9. Healthy until 5 months old, receiving breast milk and infant formula. After the first vegetable soup he presented crisis of vomiting, hypotonia, lethargy and grunting. He developed severe aversion to fruits and vegetables and had sweating, malaise and prostration after lunch, dinner, and fruit. Because of a reduction in growth velocity and weight gain, renal tubular acidosis was investigated and confirmed: pH: 7.30 (7.39 ± 0.03); HCO₃⁻: 12.2 mEq/L (21 ± 2); BE: -12.6 mEq/L (-2 + 2); pCO₂: 25.1 mm Hg (34 ± 4); Cl: 106 mEq/L (96–106); K: 4.2 mEq/L (3.5–5.0); Na: 136 mEq/L (137–145); proteinuria ++; urine pH: 7.1 (5.5–7.0); and calcium/creatinine in urine: 4.67 mg/dL (<0.25). Other blood results: normal glycemia, urea and creatinine, hypochromic microcytic anemia, high triglycerides: 162 mg/dL (<100) and abnormal liver function: SGOT: 239 U/L (16–57); and SGTP: 242 U/L (24–59). Urinary tract ultrasound was normal. An alkalizing formula (30 mEq citrate/kg/day) was prescribed in an attempt to control acidosis with a gradual increase in dose, without effect. At 2 years and 8 months the patient came to the metabolic specialist in anasarca, malnourished and with hepatomegaly (liver 6 cm below the xiphoid process, increased consistency) and liver dysfunction. Lab results: STGO: 168 U/L, SGTP: 190 U/L, GGT: 25 U/L (5–27); prothrombin activity: 80%, albumin 2.8 g/dL (3.4–4.2); globulin: 2.1 g/dL (1.4–3.2); P: 2.4 mg/dL (3.8–5.5), alkaline phosphatase: 1173 U/L (104–345); decompensated metabolic acidosis (pH: 7.30, HCO₃⁻ 16 mEq/L), increased lactate: 5.2 mmol/L (0.7–2.1). Ammonia, blood glucose, cholesterol, triglycerides, serum copper, alpha-1-antitrypsin, urea and creatinine were normal. Due to the clinical suspicion of HFI dietary treatment was initiated and medicines containing sucrose and sorbitol were excluded. In 21 days the patient became completely asymptomatic, with regression of liver size (3 cm below the xiphoid

Table 1
Summary of the clinical history of patients with HFI.

Patient	P1	P2	P3	P4
Parental consanguinity	No	No	No	No
Age of onset of symptoms	6 months	5 months	6 months	3 months
Age at diagnosis	1 year	2 years and 8 months	1 year and 6 months	10 months
Initial symptoms	Vomiting, aversion to fruits, hepatomegaly, insufficient weight gain	Vomiting, lethargy crisis, insufficient weight gain, renal tubular acidosis, hepatomegaly, anasarca	Vomiting, irritability, sleep disorders, abdominal distension, hepatomegaly,	Vomiting, lethargy crisis, hepatomegaly
Laboratory findings	Proteinuria ++, ↑transaminases	Metabolic acidosis, ↑urine calcium, proteinuria ++, ↑transaminases, ↓P, ↑triglycerides	↑cholesterol and triglycerides, liver biopsy with glycogen storage and steatosis	↑transaminases

process), without edema, with good nutritional status and laboratory tests and without the need for medications. At 3 years and 9 months of age, in the last evaluation, the child had normal psychomotor development, weight: 15,400 g (25–50th percentile) and height: 1.0 m (25–50th percentile). He grew 18 cm in the first year of treatment.

3.1.3. Patient 3

Second daughter of non-consanguineous parents, cesarean delivery at term, with adequate birth weight. Healthy until 6 months of age on exclusive breastfeeding. Bloating, irritability and sleep disorder started with the introduction of complementary feeding. She developed aversion to fruits and preference for salty foods. There was a decrease in growth rate and hepatomegaly after 1 year old. At age 19 months laboratory tests were done: urinalysis with density: 1020 (1015–1025), pH: 5 (5.5–7.0), unusual elements absent, regular sediment analysis; total cholesterol: 230 mg/dL (desirable <170); HDL cholesterol: 42 mg/dL (desirable >40); LDL: 152 mg/dL (desirable <110); VLDL: 36 mg/dL; triglycerides 182 mg/dL (<100 mg/dL); SGTO: 50 U/L (16–57); SGTP: 57 U/L (24–59); total bilirubin: 0.5 mg% (0.2–1.3); direct bilirubin: 0.1 mg% (0.0–0.3); GGT: 27 U/L (5–27); prothrombin time 93% (70–110), and INR: 1.05. Other tests: normal uric acid, lactate and CK. Liver biopsy showed sharp and diffuse macrovacuolar steatosis, interspersed with small areas of hepatocytes with aspect of plant cell by cytoplasmic accumulation of glycogen, evidenced by periodic acid–Schiff (PAS) stain, with and without diastase, and sinusoid compression due to accumulation of these substances; absence of fibrosis; conclusion: histopathology compatible with glycogen storage disease. HFI was suspected and diet initiated with complete remission of symptoms.

3.1.4. Patient 4

First son of non-consanguineous parents, cesarean delivery at term, without complications. Healthy until 3 months of life, then he began vomiting after ingestion of coconut water, fruits and vegetables. The patient received treatment for gastroesophageal reflux without improvement of vomiting. Hepatomegaly was noted at 5 months old, when liver impairment was also detected: SGTO: 194.8 U/L (16–57); SGTP: 236 U/L (24–59); total bilirubin: 0.68 mg% (0.2–1.3); and direct bilirubin: 0.39 mg% (0.0–0.3). Serology tests for hepatitis A, rubella and toxoplasmosis were negative, but positive for cytomegalovirus (IgG); the blood gases were normal. Admitted at the hospital with 10 months old because during sleep he was found lethargic, with vomiting and in apnea. Due to the clinical HFI suspicion, dietary treatment was initiated and the symptoms disappeared, suggesting the disease. At age 12 months his liver function normalized, but his liver continued to enlarge (5 cm below the right costal margin). Only at age 18 months the hepatomegaly reduced. His weight was maintained in the 15th percentile.

3.2. Molecular analysis.

The DNA sequencing of the subjects showed p.A150P, p.A175D, p.N120KfsX32, p.R60X and p.N120KfsX32 mutations in the ALDOB

gene, all already reported in the literature [18,19,20,21]. Patient 1 was homozygous for p.A175D and the other were compound heterozygous (Table 2).

4. Discussion and conclusion

All four patients initiated symptoms after ingestion of food or medications containing fructose, sucrose or sorbitol. Vomiting and hepatomegaly occurred in all patients, two of them had lethargy crisis, possibly due to not registered hypoglycemia. One of these received treatment for renal tubular acidosis, but liver dysfunction presented in this case should be a clue for the missed HFI diagnosis. Age at diagnosis of the four patients ranged from 10 to 32 months, with more severe impairment of the disease related with increased age at diagnosis.

The presence of hepatomegaly in patients with HFI is a consequence of the accumulation of lipids in the liver [18]. The literature reports that after the fructose consumption the concentration of fatty acids in circulation increases more than two times in patients with HFI compared to healthy subjects, which can explain the increase in serum triglyceride levels observed in patients 2 and 3 [22,23,24].

Glycogen accumulation in the liver, such as observed in patient 3 is unusual, and can work as a confounding factor for the diagnosis of patients with HFI. Cain and Ryman [25] report a case of a 2-year-old patient diagnosed with HFI after death by enzyme dosage in liver cells. Liver biopsy had previously revealed the presence of increased amounts of glycogen (11.6%, normal: 1–4%), suggesting storage of glycogen. The reasons of this accumulation are poorly understood, but the authors suggest that there is reduction of glycogenolysis by phosphoglucomutase inhibition, that catalyzes the conversion of glucose-1-phosphate to glucose-6-phosphate, or due to deficiency of intracellular inorganic phosphate diverted to the formation of fructose-1-phosphate [25,26].

Before the HFI suspicion and start of treatment all patients had liver function tests because of hepatomegaly (abnormal in patients 1, 2 and 4), only patient 2 had results of blood phosphate (low) and glucose (normal); other analytes as blood fructose and magnesium were not requested for any patient.

Molecular analysis of the gene ALDOB is the least invasive diagnostic method to confirmation of suspected patients. It is important mainly when there is partial response to treatment in order to prevent children who do not have the disease to submit to a restrictive diet.

According to the international literature, the most prevalent mutant alleles are p.A150P (44% in the US and 30 to 50% in Italy), followed by p.A175D (9% in the US and 19 to 50% in Italy) [5,6,27,28]. We observed that in the four reported patients of Minas Gerais State, Brazil, the mutant allele p.A150P was the least frequent (12.5%), and the most frequent mutations were p.A175D (37.5%), p.N120KfsX32 (25%), and p.R60X (25%).

Previous studies have demonstrated the pathogenicity of mutations found in our patients. The p.A150P mutation causes the exchange of alanine for proline at the domain of the enzyme for substrate binding. Structural and functional investigations of this substitution have shown that the mutation leads to losses in thermal stability, quaternary structure, and activity. X-ray crystallography is used to reveal the structural basis of these perturbations [29]. The p.A175D mutation results in the substitution of an alanine residue, highly conserved among aldolase enzymes of various species, for aspartic acid resulting in changes of the load and conformation in a critical region of the enzyme. The mutant protein was found to be extremely labile and is possibly rapidly degraded in situ as a result of denaturation [30]. The alteration in the reading frame in p.N120KfsX32 and the creation of a premature stop codon by mutation p.R60X both result in truncated proteins, which lack essential sites for enzymatic action [20,21]. The fact that patients 1 and 2 were homozygous for missense alleles and patients 3 and 4 were homozygous for null alleles doesn't seem to have correlation with their clinical outcomes.

Table 2
Summary of the molecular changes observed in ALDOB gene of the patients.

Patient	Presentation	cDNA	Protein	Description
P1	Homozygous	c.524C>A	p.A175D	[18]
P2	Compound heterozygous	c.448G>C	p.A150P	[19]
		c.524C>A	p.A175D	[18]
P3	Compound heterozygous	c.360_363 delCAA	p.N120KfsX32	[20]
		c.178C>T	p.R60X	[21]
P4	Compound heterozygous	c.360_363 delCAA	p.N120KfsX32	[20]
		c.178C>T	p.R60X	[21]

We believe that HFI is underdiagnosed because of the wide and non-specific spectrum of symptoms. Patients without diagnosis can survive if they learn to reject foods that cause them discomfort, and so protect themselves. The preference of the patient 1, for example, for consuming green fruit is a demonstration of this fact, since these fruits have a lower amount of free fructose which is released during the ripening process through degradation of complex carbohydrates [31,32].

The differential diagnosis should be centered on other inborn errors of metabolism as tyrosinemia, galactosemia, glycogen storage disorders, Wilson's disease [12] and respiratory chain disorders. Hepatitis, toxic hepatitis, liver tumor, intrauterine infection and sepsis are also considered [12].

The HFI should be distinguished from other diseases with the same treatment, as food protein-induced enterocolitis syndrome [33] and fructose malabsorption [34].

Compliance with ethics guidelines

Conflict of interest: Eugênia Ribeiro Valadares, Ana Facury da Cruz, Talita Emile Ribeiro Adelino, Viviane de Cássia Kanufre, Lais Maria Santos Valadares e Valadares, Maria do Carmo Ribeiro, Maria Goretti Moreira Guimarães Penido, Luciano Amedee Peret Filho declare that they have no conflict of interest.

Informed consent: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

References

- Steinman B, Gitzelmann R, van den Berghe G. Disorders of fructose metabolism. In: Scriver CR, Beaudet AL, Valle D, Sly WS, editors. *The Metabolic and Molecular Bases of Inherited Disease*. New York: McGraw-Hill; 2001:1489–1520.
- N. Bouteldja, D.J. Timson, The biochemical basis of hereditary fructose intolerance, *J Inher Metab Dis* 33 (2010) 105–112, <http://dx.doi.org/10.1007/s10545-010-9053-2>.
- D.R. Tolan, Molecular basis of hereditary fructose intolerance: mutations and polymorphisms in human aldolase B gene, *Hum Mutat* 6 (1995) 210–218, <http://dx.doi.org/10.1002/humu.1380060303>.
- C.L. James, P. Kellos, M. Ali, T.M. Cox, Neonatal screening for hereditary fructose intolerance: frequency of the most common mutant aldolase B allele (A149P) in the British population, *J Med Genet* 33 (1996) 837–841, <http://dx.doi.org/10.1136/jmg.33.10.837>.
- L. Ferri, A. Caciotti, C. Cavicchi, M. Rigoldi, R. Parini, M. Caserta, et al., Integration of PCR sequencing analysis with multiplex ligation-dependent probe amplification for diagnosis of hereditary fructose intolerance, *JIMD Rep* 6 (2012) 31–37, http://dx.doi.org/10.1007/8904_2012_125.
- E.M. Coffee, L. Yerkes, E.P. Ewen, T. Zee, D.R. Tolan, Increased prevalence of mutant null alleles that cause hereditary fructose intolerance in the American population, *J Inher Metab Dis* 33 (2010) 33–42, <http://dx.doi.org/10.1007/s10545-010-9192->.
- R. Santer, J. Rischewski, M. von Weihe, et al., The spectrum of aldolase B (ALDOB) mutations and the prevalence of hereditary fructose intolerance in central Europe, *Hum Mutat* 25 (2005) 594 PubMed: 15880727.
- J. Gruchota, E. Pronicka, L. Korniszewski, et al., Aldolase B mutations and prevalence of hereditary fructose intolerance in a Polish population, *Mol Genet Metab* 87 (2006) 376–378 PubMed: 16406649.
- R. Herman, Z.D. Fructose, Metabolism IV. Enzyme deficiencies: essential fructosuria, fructose intolerance, and glycogen-storage disease, *Am J Clin Nutr* 21 (1968) 693–698 PubMed: 4875257 <http://ajcn.nutrition.org/content/21/6/693.long>.
- T.M. Cox, Aldolase B and fructose intolerance, *The FASEB J* 8 (1994) 62–71 0892-6638/94/00080062/\$01.50. © FASEB.
- T.M. Cox, The genetic consequences of our sweet tooth, *Nat Rev Genet* 3 (2002) 481–487, <http://dx.doi.org/10.1038/nrg815>.
- K. Baerlocher, R. Gitzelmann, B. Steinmann, N. Gitzelmann-Cumarasamy, Hereditary fructose intolerance in early childhood: a major diagnostic challenge. Survey of 20 symptomatic cases, *Helv Paediatr Acta* 33 (1978) 465–487 PubMed: 738900.
- M. Odièvre, C. Gentil, M. Gautier, D. Alagille, Hereditary fructose intolerance in childhood. Diagnosis, management, and course in 55 patients, *Am J Dis Child* 132 (1978) 605–608, <http://dx.doi.org/10.1001/archpedi.1978.02120310069014>.
- Steinmann B, Santer R, Disorders of fructose metabolism. In: Saudubray JM, van den Berghe G, Walter JH, editors. *Inborn Metabolic Diseases: Diagnosis and Treatment*. Berlin: Springer-Verlag; 2012: 157–165.
- B. Steinmann, R. Gitzelmann, The diagnosis of hereditary fructose intolerance, *Helv Paediatr Acta* 36 (1981) 297–316.
- National Center For Biotechnology Information (NCBI). Retrieved from <http://www.ncbi.nlm.nih.gov>. Accessed March 13, 2015.
- The Human Gene Mutation Database (HGMD). Cardiff University, Institute of Medical Genetic in Cardiff. Retrieved from <http://hgmdbtrial.biobase-international.com/hgmd/pro/trial.php>. Accessed March 13, 2015.
- N.C. Cross, R. de Franchis, G. Sebastio, C. Dazzo, D.R. Tolan, C. Gregori, et al., Molecular analysis of aldolase B genes in hereditary fructose intolerance, *Lancet* 335 (1990) 306–309, [http://dx.doi.org/10.1016/0140-6736\(90\)906033](http://dx.doi.org/10.1016/0140-6736(90)906033).
- N.C. Cross, D.R. Tolan, T.M. Cox, Catalytic deficiency of human aldolase B in hereditary fructose intolerance caused by a common missense mutation, *Cell* 53 (1988) 881–885, [http://dx.doi.org/10.1016/S0092-8674\(88\)90349-2](http://dx.doi.org/10.1016/S0092-8674(88)90349-2).
- C. Dazzo, D.R. Tolan, Molecular evidence for compound heterozygosity in hereditary fructose intolerance, *Am J Hum Genet* 46 (1990) 1194–1199 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1683824/pdf/ajhg00103-0191.pdf>.
- C.C. Brooks, D.R. Tolan, A partially active mutant aldolase B from a patient with hereditary fructose intolerance, *The FASEB J* 8 (1994) 107–113 <http://www.fasebj.org/content/8/1/107.full.pdf>.
- J. Perheentupa, E. Pitkanen, E.A. Nikkila, O. Somersalo, J. Hakosalo, Hereditary fructose intolerance. A clinical study of four cases, *Ann Paediatr Fenn* 8 (1962) 221–235 PubMed: 13942402.
- M. Cornblath, I. Rosenthal, R. Sh, W. Sh, C. Rk, Hereditary fructose intolerance, *N Engl J Med* 269 (1963) 1271–1278, <http://dx.doi.org/10.1056/NEJM196312122692401>.
- Nikkila Ea, Perheentupa J. Non-esterified fatty acids and fatty liver in hereditary fructose intolerance. *Lancet*. 1962;2:1280. DOI: [http://dx.doi.org/10.1016/S0140-6736\(62\)92857-X](http://dx.doi.org/10.1016/S0140-6736(62)92857-X)
- A.R. Cain, B.E. Ryman, High liver glycogen in hereditary fructose intolerance, *Gut* 12 (1971) 929–932 PubMed: 5289293 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1411945/>.
- E.R. Froesch, Disorders of fructose metabolism, *Clin Endocrinol Metab* 5 (1976) 599–611 <http://jcp.bmj.com/content/s1-2/1/7.full.pdf>.
- R. Santamaria, M.I. Scarano, G. Esposito, L. Chiandetti, P. Izzo, F. Salvatore, The molecular basis of hereditary fructose intolerance in Italian children, *Eur J Clin Chem Clin Biochem* 31 (1993) 675–678 <http://jmg.bmj.com/content/33/9/786.full.pdf>.
- G. Sebastio, R. de Franchis, P. Strisciuglio, G. Andria, C. Dionisi Vici, G. Sabetta, Aldolase B mutations in Italian families affected by hereditary fructose intolerance, *J Med Genet* 28 (1991) 241–243, <http://dx.doi.org/10.1136/jmg.28.4.241>.
- A.D. Malay, K.N. Allen, D.R. Tolan, Structure of the thermostable mutant aldolase B, A149P: molecular basis of hereditary fructose intolerance, *J Mol Biol* 347 (2005) 135–144 PMID:15733923.
- P. Kellos, J. Sygusch, T.M. Cox, Expression, purification, and characterization of natural mutants of human aldolase B. Role of quaternary structure in catalysis, *J Biol Chem* 275 (2) (2000) 1145–1151 PMID: 10625657.
- R.C. Adão, M.B.A. Glória, Bioactive amines and carbohydrate changes during ripening of 'Prata' banana (*Musa acuminata* × *M. balbisiana*), *Food Chem* 90 (2005) 705–711, <http://dx.doi.org/10.1016/j.foodchem.2004.05.020>.
- R.V. Mota, F.M. Lajolo, B.R. Cordenunsi, Carbohydrate composition of some banana's cultivars (*Musa* spp.) during ripening, *Food Science and Technology* 17 (1997) 94–97 <http://dx.doi.org/10.1590/S0101-20611997000200005> (Campinas).
- A. Fiocchi, C. Dionisi-Vici, G. Cotugno, P. Koch, L. Dahdah, Fruit-induced FPIES masquerading as hereditary fructose intolerance, *Pediatrics* 134 (2014) 602–605, <http://dx.doi.org/10.1542/peds.2013-2623>.
- M. Lentze, Congenital diseases of the gastrointestinal tract, *Georgian Med News* 230 (2014) 46–53 PubMed: 24940857 <http://europepmc.org/abstract/med/24940857>.