

Congenital Sucrase-Isomaltase Deficiency: Summary of an Evaluation in One Family

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Evaluation for congenital sucrase-isomaltase deficiency (CSID) historically has been performed using duodenal enzyme disaccharidase assays, in which the Dahlqvist method is used to assess the activities of the disaccharidases in vitro (1,2). Meanwhile, noninvasive means have been developed to test for CSID (3). One of these methods is the ^{13}C -based breath test, the results of which have been found to correlate well with duodenal mucosal enzyme analysis (4). Another approach is SI exome genetic sequencing, which has identified both homozygous mutations and compound heterozygote mutations that cause CSID (5–7).

METHODS

We present our evaluation of 3 siblings from the same biological parents who were confirmed to have CSID via disaccharidase enzyme testing. Full details of this study and the testing results will be described in a subsequent, complete manuscript. A brief symposium summary is presented here. All 3 siblings developed diarrhea with sucrose intake and all eventually developed poor weight gain. With institutional review board approval, an effort was undertaken in which all 3 siblings and several family members from both paternal and maternal sides completed ^{13}C -sucrose breath testing and SI genetic sequencing.

RESULTS

^{13}C -sucrose digestion and oxidation were expressed as a percent coefficient of glucose oxidation (%CGO), as previously described (4). Using the ^{13}C -sucrose breath test, we determined that all 3 siblings had abnormally low ^{13}C -sucrose oxidation, based on previously established cutoff values. In addition, the father of the siblings also had abnormally low %CGO values after a ^{13}C -sucrose breath test. When questioned about his gastrointestinal health, the father was under the incorrect impression that having several loose bowel movements per day was normal. In general, the paternal side of the family appeared to have lower %CGO as compared with the maternal side. Since this experiment was

completed, we have determined that the best %CGO for lower-limit ^{13}C -sucrose oxidation is 80% (unpublished data), using a well-characterized control population.

Based on SI genetic sequencing, we determined that 2 of the siblings with CSID had a previously described compound heterozygote mutation combination (5) based on mutations on exon 16 and exon 27; however, the third sibling with CSID had a novel compound heterozygote mutation combination, based on the mutation previously described, on exon 27 and a new mutation found on exon 38. The exon 16 and exon 38 mutations were inherited from the maternal side, and the exon 27 mutation was inherited from the paternal side. Interestingly, although the mother had both exon 16 and 38 mutations, she had no gastrointestinal symptoms; her %CGO after a ^{13}C -sucrose breath test was normal.

The identified novel heterozygous novel mutation was introduced into the SI complementary DNA, and the mutant gene was expressed in COS cells. The effects were assessed at the protein and subcellular levels. An earlier evaluation conducted in a similar fashion had shown that the previously described compound heterozygote mutations on exons 16 and 27 blocked the SI trafficking from the endoplasmic reticulum to the Golgi apparatus (5). Similarly, analysis of the novel compound heterozygote mutation resulted in delayed trafficking of SI from the endoplasmic reticulum, suggesting an implication of this SI variant in the onset of CSID.

DISCUSSION

Our study showed that the combination of disaccharidase enzyme testing, ^{13}C -sucrose breath testing, genetic SI exome sequencing, and subsequent protein and subcellular analyses has established the compatibility between the in vitro (disaccharidase enzyme analysis) and in vivo (^{13}C breath test) methods. The results enabled us to identify compound heterozygote mutations in 3 siblings with CSID. The reason for the lack of symptoms in the mother who had both exon 16 and exon 38 heterozygote mutations may derive from incomplete penetrance or possibly having mutations that were of an epistatic orientation (eg, *cis* and *cis*) that would not result in disease.

In summary, we demonstrated a novel pattern of inheritance of CSID in the same family, in which 2 different combinations of compound heterozygote mutations are responsible for the onset of an intestinal malabsorption disorder.

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