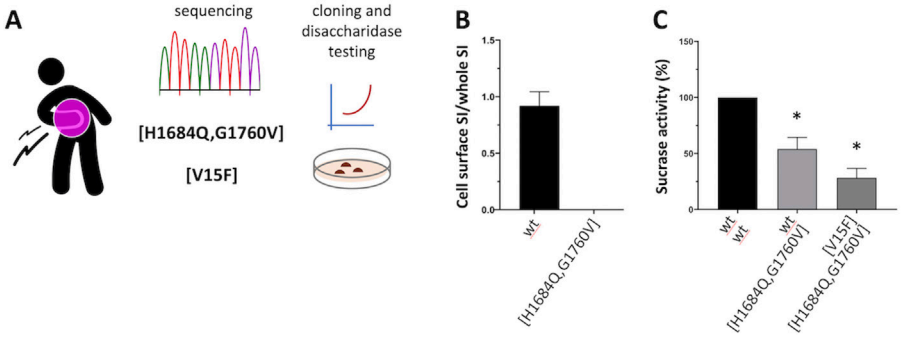


Figure 1 Patient's *SI* genetic profiling and in vitro characterisation of the enzymatic activity of corresponding DNA variants. (A) The patient's DNA was sequenced via clinical exome sequencing (Illumina) service at the Australian Genomic Research Facility (www.agrf.org.au), and confirmed via ad hoc resequencing of the SI gene (Illumina targeted assay) at IKMB in Kiel Germany; (B/C) COS-1 cells were transfected or cotransfected with cDNAs encoding *SI* variants of interest (wt, [H1684Q, G1760V] and [V15F]), and cell surface expression (B) and sucrase activity (C) determined relative to wt (set as reference 100%), upon immunoprecipitation and quantification/normalisation with appropriate antibodies as previously described.[3] *Student t-test p<0.05. SI, sucrase-isomaltase.

Adult sucrase-isomaltase deficiency masquerading as IBS

Recently in Gut, several publications reported an increased prevalence of hypomorphic (defective) sucrase-isomaltase (*SI*) gene variants in patients with irritable bowel syndrome (IBS),[1 2] and the association with impaired cell-surface expression and reduced digestive function of the corresponding enzyme.[3] In addition, hypomorphic *SI* carriers have shown reduced response compared with non-carriers in a low-FODMAP (fermentable oligo- di- mono-saccharides and polyols) trial of IBS patients with diarrhoea.[4] These and other studies,[5 6] including recent large population-based surveys,[7] raise the question whether genetic defects in the *SI* gene may be sought to explain abdominal symptoms in some patients with IBS.

A 23-year-old patient was referred with a diagnosis of IBS due to his long-standing postprandial diarrhoea associated with bloating, abdominal pain and nausea. He also had marked fatigue, headaches and mouth ulcers. He had symptoms since infancy without signs of malnutrition or failure-to-thrive. Extensive investigations excluded alternate causes of diarrhoea, including coeliac and inflammatory bowel disease, pancreatic exocrine insufficiency and bile acid diarrhoea. A low FODMAP diet worsened symptoms and psychological interventions were not helpful.

We hypothesised the involvement of *SI* defects. Resequencing of the gene identified three coding variants of interest (H1684Q, G1760V and V15F), which were assigned to a heterozygous compound combination as [H1684Q, G1760V] + [V15F] (figure 1A) based on sequencing data from additional family members (not shown). While [V15F] is known to have 35% reduced disaccharidase activity, an in vitro system was developed in order to study the [H1684Q, G1760V] variant by testing its disaccharidase activity in transfected COS cells, as previously described.[1 3] This variant showed no expression at the cell surface (figure 1B), corresponding to only residual disaccharidase activity (25%) when coexpressed with [V15F], also defective, mimicking the patient's heterozygous state (figure 1C).

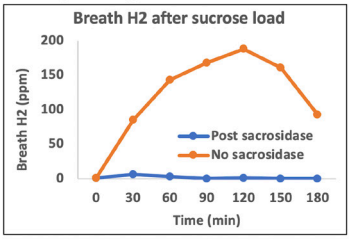
Follow-up clinical investigations of SI function showed marked impairment of sucrase and maltase activities in duodenal biopsies and, on breath hydrogen tests, a sustained hydrogen response to sucrose, which was abrogated in the presence of sacrosidase (figure 2). Formal dietary reduction of starches and sucrose was associated with a 50% symptom response, and a therapeutic trial of sacrosidase (Sucraid, QOL Medical, FL) led to complete resolution of symptoms (figure 2). Withholding then reinstituting sacrosidase verified response to it.

These results indicate that our patient has congenital SI deficiency (CSID), considered a rare autosomal recessive condition most commonly identified in infants with symptoms of diarrhoea, malabsorption and failure-to-thrive. While a few CSID cases have also been described in adults,[8] there is accumulating evidence that partial

A SI phenotype *ex vivo*

Enzyme	Duodenal activity (U/g)	Reference (U/g)
Lactase	43	>20
Sucrase	7	>50
Maltase	36	>140

B SI phenotype *in vivo*



C Therapeutic trial

Therapy	Response in symptoms
Dietary restriction of starch and sucrose	50% reduction
Sacrosidase	Resolution

Figure 2 Characterisationof SI deficiency in the studied patient. (A) Enzymatic activity ex vivo in duodenal biopsies; (B) Sucrose breath hydrogen testing with and without sucrosidase; (C) Therapeutic trials with sucrose-reducing and starch-reducing diet, and sucrosidase. SI, sucrase-isomaltase.

SI deficiency (possibly as in hypomorphic carriers) is associated with increased risk of IBS in the general population. Hence, a clinical continuum across sucrose and starch malabsorption may be envisaged, which spans a spectrum of functionally diverse DNA variations in the *SI* gene. These include homozygous and heterozygous combinations of variously defective *SI* variants, resulting in a genotype-mediated gradient of disease risk ranging from mild(er) IBS to severe CSID.

Thus, in a small fraction of patients with IBS, symptoms might be wholly or partly due to SI dysfunction associated with hypomorphic variants of the *SI* gene. Symptoms that raise the possibility of a defective *SI* gene may include onset in childhood, predominantly postprandial timing and a poor response to FODMAP restriction, which does not reduce sucrose and only partially reduces starch content. If a role for SI deficiency is suspected, it should be pursued and, while the clinical interpretation of tissue hydrolase activities and hydrogen breath tests requires further elucidation (especially in milder *SI* defects), *SI* genotyping and/or sequencing represents a valuable contribution to clinical profiling. Such findings can lead to gratifying amelioration of symptoms, although specific enzyme therapy is currently limited by cost and availability.

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Correction notice This article has been corrected since it published Online First. The author's name, Hassan Y Naim, has been updated.

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Contributors AFo, EPH, SRF and PRG patient characterisation; DMH and HN in vitro experimentation and disaccharidase assays; B-SL, AFr and MD'A genome sequence analysis and interpretation; MD'A and PRG: study conception and supervision, project planning, data interpretation, manuscript drafting; AFo, EPH, DMH, SRF, B-SL, AFr, MD'A and PRG critical revision of the manuscript.

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