Sucrase-isomaltase genotype and response to a starch-reduced and sucrose-reduced diet in IBS-D patients

Recently in Gut, several reviews and reports have highlighted hypomorphic (dysfunctional) variants of the sucrase-isomaltase (*SI*) gene in relation to increased risk of irritable bowel syndrome (IBS), particularly the diarrhoea-predominant type (IBS-D).[1–4] Similar to congenital (rare recessive) and acquired forms of SI deficiency, impaired SI enzymatic activity is expected to lead to colonic accumulation of undigested disaccharides, thus triggering IBS manifestations via gut microbiota fermentation, gas production and osmotic diarrhoea. Reduced efficacy of a diet low in FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) is also observed for *SI* hypomorphic IBS-D carriers,[4] as this intervention may be suboptimal for individuals with possible defects in the digestion of carbohydrates other than FODMAPs (the lowFODMAP diet does not specifically restrict sucrose and starch, the substrates of SI disaccharidase activity). These results hold strong potential for personalising therapeutic (dietary) interventions in subgroups of IBS patients, though the eventual relevance of *SI* genotype has not been tested in the optimal dietary context, that is when patients are challenged with reducing the amount of SI substrates, like in a sucrose and starch-restricted diet (SSRD).

Aiming to generate specific hypothesis that may be tested in future trials, we conducted a pilot investigation and

retrospectively evaluated data from two previous SSRD studies from Sweden and Spain[5 6]: we assessed the relation between *SI* genotype and symptom amelioration in a total of 50 IBS-D patients of European ancestry, defined according to consensus gold standard Rome IV Criteria (table 1).[7] High-quality *SI* targeted sequencing data were obtained for all subjects using an Illlumina AmpliSeq DNA assay with optimal coverage of the region of interest (>99% 30× coverage of 48 *SI* exons). To identify hypomorphic variants, the functional relevance of *SI* non-synonymous (coding) changes was computationally predicted as previously described.[4 8–10] Seven *SI* hypomorphic variants were identified, namely Val15Phe (dbSNP database https://www.ncbi.nlm.nih.gov/snp entry rs9290264), Pro348Leu (rs77546399), Val371Met (rs138434001), Ile799Val (rs150246328), Tyr975His (rs146785675), Gly1073Asp (rs121912616) and Arg1367Gly (rs143388292), most of which already described in previous studies.[4 8–10] Based on available genotype and functional data, IBS-D patients were stratified into *SI* hypomorphic variant double-carrier, single-carrier and non-carrier groups, and cumulative analyses of *SI* genotype were performed, as previously done,[4 8–10] in relation to SSRD response. A valid hypothesis is that *SI* carriers, especially double-carriers, would benefit more from a diet (SSRD) that restricts dietary intake of carbohydrates that may be inefficiently digested when SI disaccharidase activity is reduced (as in *SI* carriers). A logistic regression based on sex-adjusted and age-adjusted additive genetic model did not disclose any direct correlation between *SI* genotype and SSRD response (not shown). However, as shown in figure 1 where SSRD response after 2 and 4 weeks are reported, all *SI* hypomorphic double-carriers consistently improved with the diet at both timepoints, while the response in other *SI* genotype groups varied. Despite the small sample size, this gave rise to a significant p value when SSRD results for IBS-D double-carriers were specifically compared with the remainder of the cohort in a Fisher's exact test ($p<0.05$). Hence, while other mechanisms are certainly at play (also non-carriers respond to SSRD treatment), our results suggest that *SI* hypomorphic variants may affect the response to carbohydrate-focused diets.

Altogether from this and previous studies,[3 4 8–10] compelling evidence is accumulating for a role of *SI* variants in IBS, which holds potential for the management of IBS-D patients based on their genotype.

Table 1 Demographics and clinical characteristics of the patients included in this study

Characteristics*	Sweden	Spain	Total†
IBS-D patients	20	30	50
Females (%)	12 (60.0)	19 (63.3)	31 (62.0)
Age, mean±SD	48.9±13.4	42.8±13.9	45.2±13.9
IBS-SSS (mean±SD) at baseline	282.4±69.3	293.8±71.1	289.2±69.9
IBS-SSS (mean±SD) at 2 weeks	194.1±100.3	183.8±89.7	187.9±93.2
IBS-SSS (mean±SD) at 4 weeks	157.3±93.2	142.5±99.0	148.4±94.1
Responders at 2 weeks (%)‡	15 (75.0)	20 (66.7)	35 (70.0)
Responders at 4 weeks (%)‡	17 (85.0)	25 (83.3)	42 (84.0)
SI hypomorphic genotype (0/1/2)§	12/4/4	15/11/4	27/15/8

*Demographic, IBS symptom severity scores (IBS-SSS) and SSRD response during the observation period, at 2 and 4 weeks (standard deviation (SD)).
†Swedish and Spanish patients did not significantly differ for age, sex, IBS-SSS scores or SSRD response rates.
‡A positive SSRD response was defined as a drop of 50 IBS-SSS points, compared with baseline.
§*SI* hypomorphic genotype (non-carriers/single-carriers/double-carriers).
IBS, irritable bowel syndrome; SI, sucrase-isomaltase; SSRD, sucrose and starch-restricted diet.

In line with this and previous observations, a strategy may be envisaged to treat *SI* hypomorphic (double) carriers with SSRD, while non-carriers may actually benefit more from a low-FODMAP diet. Our results provide rationale for testing this hypothesis in future trials.

Andreea Zamfir-Taranu ,[1]
Britt-Sabina Löscher ,[2] **Diab M. Husein**,[3]

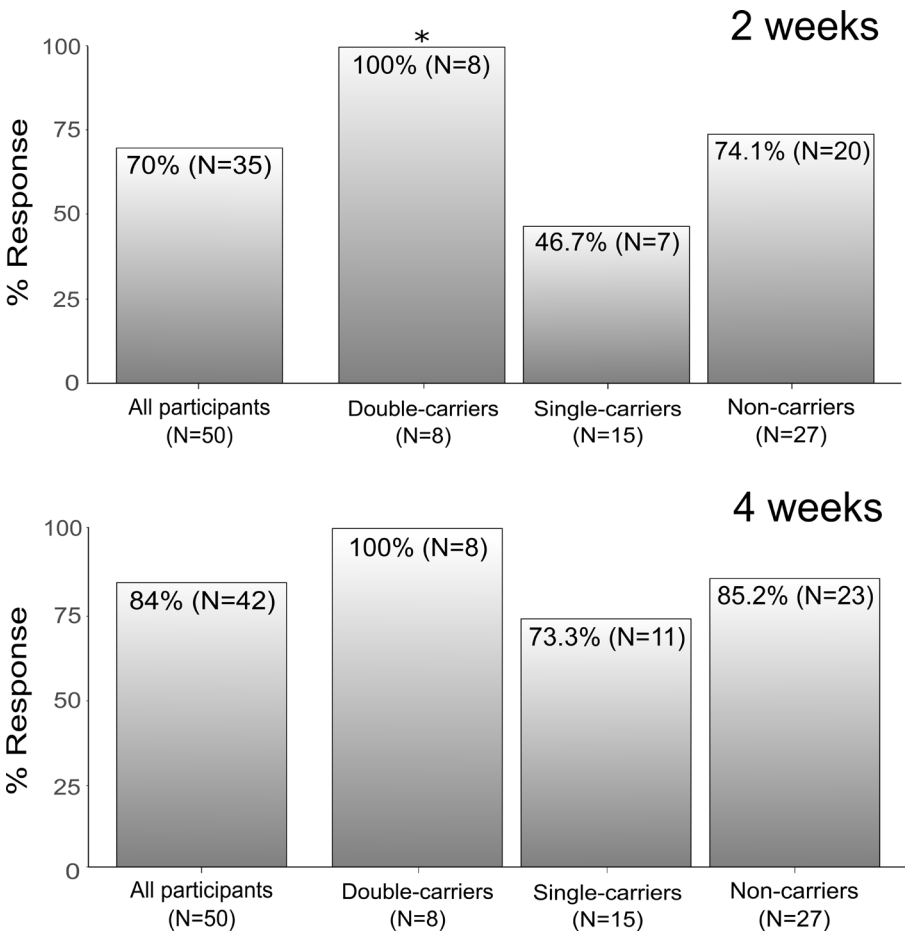

Figure 1 Response to SSRD in IBS-D patients, stratified according to *SI* hypomorphic genotype (double-carrier, single-carrier and non-carrier groups), at 2 weeks (top) and 4 weeks (bottom). *p=0.043 for double-carriers versus other groups (one-tailed Fisher's exact test). IBS-D, irritable bowel syndrome-diarrhoea; SI, sucrase-isomaltase; SSRD, sucrose and starch-restricted diet.

Abdullah Hoter,[3] Koldo Garcia-Etxebarria ,[4,5] Usune Etxeberria,[6,7] Lucía Gayoso,[6,7] Gabriele Mayr,[2] Clara Nilholm,[8] Rita J. Gustafsson,[9] Oliver Ozaydin,[10] Tenghao Zheng ,[10] Cristina Esteban-Blanco,[1] Isotta Bozzarelli,[1] Ferdinando Bonfiglio,[11,12] Sandra Rizk ,[13] Andre Franke,[2] Luis Bujanda,[4,5,14] Hassan Y. Naim ,[3] Bodil Ohlsson,[8] Mauro D'Amato [1,15,16]

[1]Gastrointestinal Genetics Lab, CIC bioGUNE - BRTA, Derio, Spain
[2]Institute of Clinical Molecular Biology, Kiel University and University Medical Center Schleswig-Holstein, Kiel, Germany
[3]Department of Biochemistry, University of Veterinary Medicine Hannover, Hannover, Germany
[4]Department of Gastrointestinal and Liver Diseases, Biodonostia HRI, San Sebastián, Spain
[5]Centro Investigación Biomédica Red Enfermedades Hepáticas y Digestivas (CIBERehd), Madrid, Spain
[6]BCC Innovation, Technology Center in Gastronomy, Basque Culinary Center, San Sebastián, Spain
[7]Basque Culinary Center, Faculty of Gastronomic Sciences, Mondragon Unibertsitatea, San Sebastián, Spain
[8]Department of Internal Medicine, Lund University, Skåne University Hospital Malmö, Malmö, Sweden
[9]Department of Gastroenterology and Nutrition, Lund University, Skåne University Hospital Malmö, Malmö, Sweden
[10]School of Biological Sciences, Monash University, Clayton, Victoria, Australia
[11]CEINGE Biotecnologie Avanzate s.c.ar.l, Naples, Italy
[12]Department of Chemical, Materials and Production Engineering, University of Naples Federico II, Naples, Italy
[13]School of Natural Sciences, Lebanese American University - Byblos Campus, Byblos, Lebanon
[14]Universidad del País Vasco (UPV/EHU), San Sebastián, Spain
[15]Ikerbasque, Basque Foundation for Science, Bilbao, Spain
[16]Department of Medicine and Surgery, LUM University, Casamassima, Italy

Correspondence to Professor Mauro D'Amato, Department of Medicine and Surgery, LUM University, Casamassima, Italy; damato@lum.it

Twitter Andreea Zamfir-Taranu @ZamfirTaranu and Mauro D'Amato @damato_mauro

Contributors MD'A, LB, HN and BO study design and supervision; B-SL, DH, AH, KG-E, UE, LG, GM, CN, RG, OO, TZ, CE-B, IB, FB, SR, AF, LB and BO data acquisition, patients characterisation; AZT, B-SL, KG-E and GM statistical and computational analyses; AZT, B-SL, DH, LB, HN, BO and MD'A data analysis and interpretation; MD'A obtained funding and technical support; AZT and MD'A drafted the manuscript, with input and critical revision from all other authors. All authors approved the final draft of the manuscript.

Funding Funded by MCIN/AEI/10.13039/501100011033 (PID2020-113625RB-I00).

Competing interests MD'A has received unrestricted research grants and consulting fees from QOL Medical LLC. HN has received unrestricted research grants from QOL Medical.

Patient consent for publication Not applicable.

Ethics approval The Swedish study protocol was approved by the Ethical Review Board of Lund University (2017/171, 2017/192), and registered at ClinicalTrials.gov (NCT03306381). The Spanish study protocol was approved by the Local Ethics Committee (Comité de Ética del Área Sanitaria de Gipuzkoa, code: BUJ-NUT-2019-01). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

OPEN ACCESS

B-SL and DMH contributed equally.

LB, HYN, BO and MD are joint senior authors.

To cite Zamfir-Taranu A, Löscher B-S, Husein DM, *et al*. *Gut* 2024;**73**:706–708.

Received 12 February 2023
Accepted 22 February 2023
Published Online First 6 March 2023

Gut 2024;**73**:706–708. doi:10.1136/gutjnl-2023-329695

ORCID iDs
Andreea Zamfir-Taranu http://orcid.org/0000-0001-7087-6735
Britt-Sabina Löscher http://orcid.org/0000-0001-9022-9017
Koldo Garcia-Etxebarria http://orcid.org/0000-0002-6107-9416
Tenghao Zheng http://orcid.org/0000-0003-1587-7481
Sandra Rizk http://orcid.org/0000-0002-4405-5703
Hassan Y. Naim http://orcid.org/0000-0003-4884-8425
Mauro D'Amato http://orcid.org/0000-0003-2743-5197

REFERENCES

1 Camilleri M, Boeckxstaens G. Irritable bowel syndrome: treatment based on pathophysiology and biomarkers. *Gut* 2023;72:590–9.
2 Gibson PR, Halmos EP. The FODMAP diet: more than just a symptomatic therapy? *Gut* 2022;71:1693–4.
3 Foley A, Halmos EP, Husein DM, *et al*. Adult sucrase-isomaltase deficiency masquerading as IBS. *Gut* 2022;71:1237–8.
4 Zheng T, Eswaran S, Photenhauer AL, *et al*. Reduced efficacy of low fodmaps diet in patients with IBS-D carrying sucrase-isomaltase (Si) hypomorphic variants. *Gut* 2020;69:397–8.
5 Nilholm C, Roth B, Ohlsson B. A dietary intervention with reduction of starch and sucrose leads to reduced gastrointestinal and extra-intestinal symptoms in IBS patients. *Nutrients* 2019;11:1–15.
6 Gayosoa L, Garcia-Etxebarria K, Arzalluse T, *et al*. The effect of starch- and sucrose-reduced diet accompanied by nutritional and culinary recommendations on the symptoms of irritable bowel syndrome patients with diarrhea [in press]. *Therap Adv Gastroenterol* 2023.
7 Drossman DA, Tack J. Rome foundation clinical diagnostic criteria for disorders of gut-brain interaction. *Gastroenterology* 2022;162:675–9.
8 Henström M, Diekmann L, Bonfiglio F, *et al*. Functional variants in the sucrase-isomaltase gene associate with increased risk of irritable bowel syndrome. *Gut* 2018;67:263–70.
9 Garcia-Etxebarria K, Zheng T, Bonfiglio F, *et al*. Increased prevalence of rare sucrase-isomaltase pathogenic variants in irritable bowel syndrome patients. *Clin Gastroenterol Hepatol* 2018;16:1673–6.
10 Zheng T, Camargo-Tavares L, Bonfiglio F, *et al*. Rare hypomorphic sucrase isomaltase variants in relation to irritable bowel syndrome risk in UK biobank. *Gastroenterology* 2021;161:1712–4.