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

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.

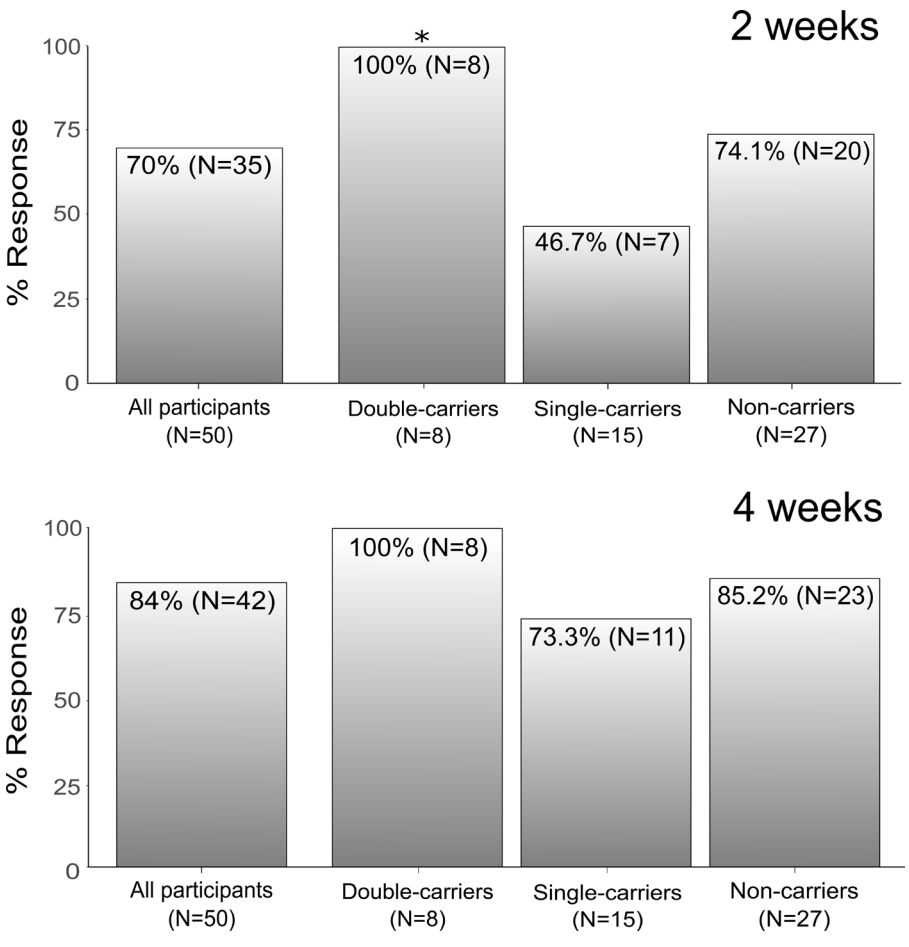

Figure 1 Response to SSRD in IBS-D patients, stratified according to *SI* hypomorphic genotype (double-carrier, single-carrier and non-carrier groups), at 2 weeks (top) and 4 weeks (bottom). *p=0.043 for double-carriers versus other groups (one-tailed Fisher's exact test). IBS-D, irritable bowel syndrome-diarrhoea;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

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. 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.

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