

Sucrase-isomaltase hypomorphic variant Val15Phe affects the response to a sucrose challenge test in patients with IBS

A growing body of literature, including recent studies published in *Gut*,^{1,2} links hypomorphic (defective) variants in the sucrase-isomaltase gene (*SI*; coding for a brush border disaccharidase) not only to rare recessive forms of sucrose intolerance but also to increased risk of irritable bowel syndrome (IBS), its severity and the efficacy of carbohydrate-reducing diets.^{3–7} This provides rationale for personalizing therapeutic (dietary) approaches across a clinical continuum of genetic SI deficiencies (GSID) ranging from severe monogenic forms to complex (milder) IBS manifestations.⁸ While most hypomorphic *SI* alleles are rare, the Val15Phe variant (rs9290264) is common (allele frequency=0.30 in Europeans), shows 35% reduced activity and confers increased IBS risk.^{5,7} Moreover, Val15Phe appears to exert pharmacogenetic effects by modulating the hypoglycaemic efficacy of acarbose, an SI inhibitor used in the treatment of type 2 diabetes.⁹ Hence, the Val15Phe variant may influence the outcome of diagnostic tests relying on carbohydrate digestion (breath/sucrose challenge tests) and/or affect post-ingestive symptoms and metabolic responses. In the current pilot survey, we aimed to investigate whether Val15Phe contributes to modulating bowel symptoms and/or serum glucose concentrations following a sucrose challenge test (SCT, see online supplemental methods) in patients with IBS.

We enrolled 33 genotyped IBS patients (table 1) whose bowel symptoms and blood glucose levels were recorded at baseline and multiple timepoints up to 2 hours post-SCT (online supplemental methods). Age-adjusted and sex-adjusted

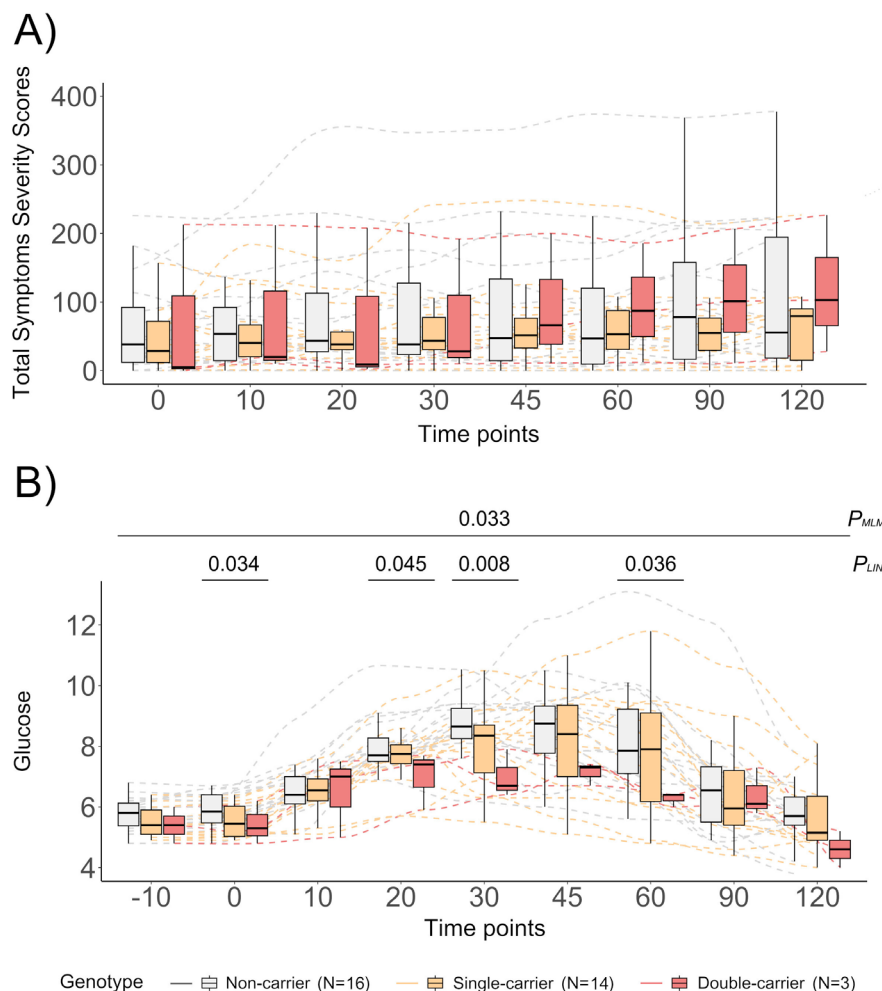


Figure 1 Val15Phe genotype in relation to total symptoms severity scores and blood glucose levels post sucrose challenge test (SCT). Total severity symptom scores recorded on a visual analogue scale (VAS) data (A) and blood glucose levels (B) at baseline and post-SCT in 33 IBS patients stratified by Val15Phe genotype. Significant p values from age-adjusted and sex-adjusted mixed linear model (P_{MLM}) and linear regression (P_{LIN}) are reported in the figure.

linear regression and mixed linear models were applied to test Val15Phe genotype associations under an additive genetic model (a dosage-dependent framework based on the presence of 0, 1 or 2 copies of the defective *SI* allele), at individual and

multiple timepoints, respectively (online supplemental methods).

Different Val15Phe genotype groups did not differ for demographics, clinical manifestations and baseline bowel symptoms, which exhibited considerable interindividual

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

	All	Val15Phe double-carriers*	Val15Phe single-carriers*	Val15Phe non-carriers*
Patients: N	33	3	14	16
Females: N (%)	24 (72.7)	3 (100.0)	9 (64.3)	12 (75.0)
Age: mean±SD	51.6±11.1	49.9±6.0	52.2±12.1	51.7±11.3
Baseline Symptoms Severity Scores				
Total symptoms severity: mean±SD	57.2±64.6	72.6±121.6	46.3±46.3	63.8±69.7
Flatulence severity: mean±SD	8.7±12.5	13.6±23.7	6.4±8.1	9.8±13.9
Diarrhea severity: mean±SD	11.6±16.1	21.0±36.3	9.1±12.8	12.1±14.4
Abdominal pain severity: mean±SD	11.0±15.8	12.3±21.4	8.4±12.6	12.9±18.0
Nausea severity: mean±SD	7.2±12.8	3.6±6.3	5.0±7.0	9.9±16.8
Bloating severity: mean±SD	18.6±20.3	22.0±33.9	17.4±19.3	19.1±19.9

*No significant difference detected for any of the variables (Kruskal-Wallis and/or Fisher's exact test as appropriate).

variability (table 1). Although not reaching statistical significance (possibly due to the small sample size or the short 2-hour observation period, which may have been insufficient to capture colonic fermentation-related manifestations), a trend for increased symptom burden was observed relative to Val15Phe copy numbers, with double-carriers generally experiencing highest symptom burden starting 30–45 min post-SCT (figure 1A and online supplemental figure 1). Of note, significant findings were observed for blood glucose concentrations, whose expected increase post-SCT exhibited a different, less pronounced pattern in double and single Val15Phe carriers compared with non-carriers, possibly due to reduced SI-mediated breakdown of sucrose into glucose and fructose in these individuals (figure 1B).

These findings may have clinical implications. Key to identifying and treating IBS-GSID individuals is the characterization of SI (dys)function that is genetically determined and not secondary to other causes. Current gold-standard diagnostic approaches mostly rely on highly invasive methods (disaccharidase assays from duodenal biopsies) that have technical limitations and lack specificity in that they are agnostic to genetic information. Indeed, only 29% of sucrose deficiency identified via duodenal biopsy was associated with SI mutations in a recent survey.¹⁰ If confirmed in larger datasets, our results suggest SCT coupled to SI genotyping and blood glucose measurement may be an alternative approach to screen individuals for SI dysfunction prior to invasive investigation. This may be relevant not only to distinguish GSID from secondary SI deficiencies, but also to identify individuals more likely to develop IBS and/or to respond to carbohydrate-reduced diets.

Finally, the observation of an association between Val15Phe and blood glucose levels post-SCT parallels similar results obtained in relation to the hypoglycaemic effect of acarbose,⁹ whose specific inhibition of SI-mediated sucrose breakdown has been shown to be significantly lower in Val15Phe carriers. Hence, future studies are warranted to test whether Val15Phe and/or other SI variants might be relevant not only to IBS but also to modulating postprandial hyperglycaemia, with potential repercussions on metabolic health and diabetes.

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