Polymorphisms in the sodium-dependent ascorbate transporter gene SLC23A1 are associated with susceptibility to Crohn disease\textsuperscript{1-3}

Mandana Amir Shaghaghi, Charles N Bernstein, Alejandra Serrano León, Hani El-Gabalawy, and Peter Eck

ABSTRACT

Background: Crohn disease (CD) and ulcerative colitis (UC) are 2 common inflammatory bowel diseases (IBDs) associated with intestinal inflammation and tissue damage. Oxidative stress is suggested to play a major role in the initiation and progression of IBD. Vitamin C (ascorbate, ascorbic acid) supplementation has reduced oxidative stress in persons with IBD. The role of ascorbate transporters in IBD remains to be determined. SLC23A1 is a major ascorbate transporter in the intestinal tract, and some of its genetic variants have been associated with severely decreased ascorbate transport and lower systemic concentrations.

Objective: This study aimed to determine whether common genetic variants in the vitamin C transporter SLC23A1 are associated with the risk of IBD.

Design: Genomic DNA samples from patients with CD (n = 162) and UC (n = 149) from the Manitoba IBD Cohort Study and ethnically matched controls (n = 142) were genotyped for 3 SLC23A1 polymorphisms (rs6596473, rs33972313, and rs10063949) by using TaqMan assays.

Results: Variation at rs10063949 (G allele for heterozygote and homozygote) was associated with increased susceptibility to CD (OR: 2.54; 95% CI: 1.38, 4.66; OR: 4.72; 95% CI: 2.53, 8.81; P < 0.0001; respectively). A strong linkage disequilibrium (LD) was observed across the SLC23A1 region (variation rs6596473 with rs10063949) for CD and UC (D\textsuperscript{+} = 0.94 and 0.96, respectively). The risk alleles confirmed a haplotype (CGG) that is carried more in CD patients (65.3%, P < 0.0001) than in controls (43.5%).

Conclusions: A genetic variant (rs10063949-G) in the SLC23A1 ascorbate transporter locus was identified and is associated with an increased risk of CD in a white Canadian IBD cohort. The presented evidence that SLC23A1 variants can modulate the risk of CD has implications for understanding ascorbate transport in CD patients and provides a novel opportunity toward individualized nutritional therapy for patients carrying the disease-associated genotype.


INTRODUCTION

Inflammatory bowel disease (IBD)\textsuperscript{4} includes Crohn disease (CD) and ulcerative colitis (UC), and results from the interface of environmental factors with an aberrant immune response in genetically susceptible individuals. IBD is accompanied by excessive production of reactive oxygen species, which play an important role in the pathogenesis of the disease through oxidative tissue damage (1). The antioxidant defense system of the intestinal mucosa is impaired in IBD patients, which results in increased oxidative injury and eventually delayed recovery of the inflamed mucosa (2, 3). Intestinal biopsies from IBD patients have shown deficiencies and imbalances in the levels of different antioxidants, including vitamin C (ascorbate) in inflamed mucosa compared with normal mucosa (2, 4).

Ascorbate is the primary essential water-soluble antioxidant from the diet, which acts as a direct scavenger of reactive oxygen species and contributes to prevention of oxidative damage. Ascorbate is also a redox cofactor for enzymes required for the synthesis of collagen, carnitine, and neurotransmitters (5–7). The antioxidant property of ascorbate is thought to prevent chronic diseases involving inflammatory events, including atherosclerosis (8–10), cancer (11), and type 2 diabetes (12, 13). In IBD patients, a loss of 35% to 73% total and reduced ascorbate has been observed in inflamed mucosa, which contributes to the overall loss of its antioxidant capacity (4). Plasma deficiencies of ascorbate have also been observed in IBD patients (14–16) and has been attributed to extensive depletion of ascorbate as an antioxidant or to inadequate dietary uptake (17). Whether reduction in ascorbate concentrations in inflammatory tissue in IBD is more cause or effect is unknown.

The sodium-dependent ascorbate transporter 1 (SLC23A1) is the major ascorbate transporter in the intestinal epithelium (18, 19) and is also found in cells involved in the immune defense (20, 21). Cellular ascorbic acid uptake is enhanced when SLC23A1 is present (19, 22, 23). Global elimination of slc23a1 in the mouse results in a dramatic decrease of ascorbic acid concentrations in cells and organs expressing slc23a1 in the wild type (19). A nonsynonymous genetic variation has been shown to reduce the transporters capacity by \textasciitilde 90% in vitro (19). We hypothesized that variation in the human SLC23A1 gene down regulates transporter activity and reduces intracellular antioxidant capaci-

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\textsuperscript{4}Abbreviations used: CD, Crohn disease; IBD, inflammatory bowel disease; SLC23A1, sodium-dependent ascorbate transporter 1; SNP, single nucleotide polymorphism; UC, ulcerative colitis.

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ity, resulting in impeding the enterocyte barrier function or modulating the capability of some intestinal immune cells to respond to oxidative stress. Therefore, the objective of this study was to examine whether genetic variation in the \textit{SLC23A1} gene could modulate the susceptibility to IBD and/or the severity of its complications.

\section*{SUBJECTS AND METHODS}

\subsection*{Study design and population}

The study design was previously described (24). Briefly, clinical data were collected from case records of participants in the Manitoba IBD Cohort Study, initiated in 2002. At enrollment in the Cohort Study, participants were \textup{$\geq$}18 y of age (18–80 y) with a diagnosis made within the previous 7 y (median: 4.3 y). Controls included healthy individuals with no chronic immune diseases or first-degree relatives with chronic immune diseases. A total of 311 persons with IBD (CD, \textup{$n$} = 162; UC \textup{$n$} = 149) and 142 healthy controls were studied. All of the study population (cases and controls) was white. The diagnosis and extent of IBD was determined based on surgical, endoscopic, radiologic, and histologic data. Phenotype was assigned according to the Montreal Classification (25). Every subject signed an informed consent form, and this study was approved by the Biomedical Research Ethics Board at University of Manitoba.

\subsection*{Single nucleotide polymorphism selection and genotyping methods}

Extensive sequencing analysis of the pattern of common genetic variation of \textit{SLC23A1} gene was previously performed defining haplotype tagging single nucleotide polymorphisms (SNPs) for the gene (26). Subsequently, a haplotype-based approach was implemented, and 3 SNPs in the \textit{SLC23A1} gene were identified (rs6596473C>G, rs33972313 A>G, and rs10063949 G>A). Variants were selected because they are located in the 5′, middle, and 3′ region of \textit{SLC23A1} and based on potential functional affect (eg, rs33972313 is nonsynonymous and has been shown to influence plasma ascorbic acid concentrations).

Genomic DNA was isolated from peripheral white blood cells as previously described (27). Genotyping was performed for all subjects for 3 SNPs in \textit{SLC23A1} by using TaqMan Real-Time polymerase chain reaction assays (Applied Biosystems), the assay condition for each optimized assay are shown in Table 1. Approximately 8% blinded quality control samples (36 individuals) were assayed 4 times, which showed 100% concordance.

\subsection*{RESULTS}

One hundred sixty-two patients with CD, 149 patients with UC, and 142 ethnically matched healthy controls (\textup{$n$} = 142) were genotyped for 3 \textit{SLC23A1} polymorphisms. Baseline characteristics of the study population are shown in Table 2. Genotype frequencies are summarized in Table 3 (CD) and Table 4 (UC). Genotype frequencies for all of the polymorphisms were in Hardy-Weinberg equilibrium within the CD and UC groups.

Of the 3 variants in \textit{SLC23A1} examined, the rs10063949-G allele is associated with increased CD risk (Table 3). Carriage of one (heterozygote) or 2 (homoygote) copies of the minor rs10063949 allele (G) was associated with an increased risk of CD (OR: 2.54; 95% CI: 1.38, 4.66; OR: 4.72; 95% CI: 2.53, 8.81, \textit{P} < 0.001; respectively). None of the SNPs were associated with UC risk.

A strong linkage was observed across the \textit{SLC23A1} gene (\textit{D}' = 0.94 between rs6596473 and rs10063949) in persons with CD (Figure 1A) and the haplotype CGG, which is carried in persons with CD (OR: 2.40; 95% CI: 1.54, 3.88, \textit{P} < 0.0001) (Table 3).

Table 1: Primers used to examine the 3 SNPs in the \textit{SLC23A1} gene involved in this study

\begin{tabular}{|c|c|c|c|c|c|}
\hline
\textbf{dbSNP} & \textbf{CGF assay ID} & \textbf{Position} & \textbf{Alleles} & \textbf{TaqMan primers} & \textbf{TaqMan probes} \\
\hline
rs6596473 & A-007155 & 138738475bp & C/G & F: CATTTGAGGTGCCCATTGAC & FAM: CCTATGGGCTGACAGACA \\
& & & & R: TGCCCGTTCAGGGTCTGAG & VIC: CCTATGGGCTGACAGACA \\
rs33972313 & 001–1224 & 138743401bp & A/G & F: AGACCTCCAGTGGCTCTCAGT & FAM: TCATGACCGCTGAGCGG \\
& & & & R: GCACACGTGCTTCAAGGTT & VIC: CATGACCGCTGAGCGG \\
rs10063949 & A-006670 & 138747425bp & G/A & F: TTTGACCCAACAGCCATGCAGATA & FAM: TCTGCAAACTTGG \\
& & & & R: GGCAGTCTGAGACCAACCT & VIC: TCTGCAAACTTGG \\
\hline
\end{tabular}

1 Adapted from reference 28. CGF, core genotyping facility; F, forward primer; R, reverse primer; SNP, single nucleotide polymorphism.
**DISCUSSION**

Here, for the first time, we identified a variation in the sodium-dependent ascorbic acid transporter gene \( SLC23A1 \) that is associated with CD, but not with UC. This finding confirms our hypothesis that a disturbance in the antioxidant balance could contribute to the development and severity of IBD. The rs10063949-G allele in the \( SLC23A1 \) gene is associated with an increased CD risk. Of persons with CD, two-thirds carried the G allele, corresponding to a CD risk that is elevated by 2.5 times compared with the rs10063949-A carriers. The rs10063949-GG genotype was significantly overtransmitted in the CD patients (47.5%) compared with the controls (25.4%). An allele dosage effect resembling haploinsufficiency was evident. Compared with rs10063949-AA homozygotes the 10063949-AG heterozygotes had a 2.5-fold elevated risk of CD, and the 10063949-GG homozygotes had a 4.7-fold elevated CD risk. No relation was observed between genetic variants in \( SLC23A1 \) and UC.

The SNP rs10063949 is located within the promoter region of the \( SLC23A1 \) gene, which is a collection of regulatory elements, such as hepatocyte nuclear factor 1 (HNF1), which is required for tissue specific transcription (29). Assuming that SNP rs10063949 contributes to intestinal inflammation, it would most likely act through differential regulation of \( SLC23A1 \) expression, which consequently would result in reduced cellular accumulation of ascorbate. In the current study, finding a genetic alteration in the \( SLC23A1 \) transporter gene in CD suggests that the observation of low ascorbate concentrations in inflamed mucosa in the study by Head and Jurenka (2) may be as much a cause of inflammation as effect.

The implication of the association between SNP rs10063949 and CD but not UC is undetermined. We suggest 3 possible cell-type specific mechanisms that could by themselves, or in combination with one another, cause the differential association. If one or all of them gets validated in future biological and clinical studies, SNP rs10063949 could be used as a predictive biomarker for CD. Furthermore, it should be determined whether it could also serve as a diagnostic biomarker for dietary intervention with ascorbate. First, cell-type specific transcription factors regulating \( SLC23A1 \) expression in immune regulatory cells involved in the development of CD, but not UC, might be affected by SNP rs10063949. \( SLC23A1 \) is expressed in lymphocytes; however, the specific expression during hematopoiesis, and therefore in the different types of lymphocytes and leukocytes in general, is not defined. Future genomic and functional studies should determine \( SLC23A1 \) expression patterns in all lymphocyte types (including natural killer cells), to define if indeed ascorbate accumulates differently in carriers of the SNP 10063949 genotypes. The concentrations of ascorbate will determine the antioxidative capacity (11) and as a consequence would contribute to the differential regulation of gene expression influencing CD but not UC risk.

A second possible mechanism addresses a potential dysregulation of macrophage function through reduction in ascorbate uptake of macrophages in epithelioid granulomas. A granuloma is a collection of macrophages and other inflammatory cells. Epithelioid granulomas are among the most specific microscopic features of CD, distinguishing it from UC (30). Intracellular ascorbic acid has a regulatory role in the granulocyte macrophage–colony-stimulating signaling response (31), which is

### TABLE 2

General characteristics of the study subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Crohn disease ( (n = 162) )</th>
<th>Ulcerative colitis ( (n = 149) )</th>
<th>Controls ( (n = 142) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>97 (59.9)</td>
<td>87 (58.4)</td>
<td>80 (56.3)</td>
</tr>
<tr>
<td>Male</td>
<td>65 (40.1)</td>
<td>62 (41.6)</td>
<td>62 (43.7)</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1 (&lt;17 y)</td>
<td>17 (10.5)</td>
<td>12 (8.1)</td>
<td>—</td>
</tr>
<tr>
<td>A2 (17–40 y)</td>
<td>101 (62.3)</td>
<td>78 (52.3)</td>
<td>—</td>
</tr>
<tr>
<td>A3 (&gt;40 y)</td>
<td>44 (27.2)</td>
<td>59 (39.6)</td>
<td>—</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L1 (ileal)</td>
<td>69 (42.6)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>L2 (colon)</td>
<td>37 (22.8)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>L3 (ileocolonic)</td>
<td>51 (31.5)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>L4 (isolated upper disease)</td>
<td>5 (3.1)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>E1 (denotes proctitis)</td>
<td>—</td>
<td>11 (7.4)</td>
<td>—</td>
</tr>
<tr>
<td>E2 (left-sided)</td>
<td>—</td>
<td>68 (45.6)</td>
<td>—</td>
</tr>
<tr>
<td>E3 (extensive colitis)</td>
<td>—</td>
<td>70 (47.0)</td>
<td>—</td>
</tr>
<tr>
<td>Behavior</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B1 (inflammatory)</td>
<td>69 (42.6)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>B2 (stricturing)</td>
<td>54 (33.3)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>B3 (penetrating/fistulizing)</td>
<td>39 (24.1)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

\( 1 \) Values are \( n (%) \). No significance difference was found between the baseline characteristics of the study populations.

rs10063949 (Figure 1B), and a major haplotype (frequency \( \geq 5\% \)) was inferred for UC patients (CAG: 41%). No association was found between \( SLC23A1 \) genotype and haplotype with UC risk (Table 4). No correlation was found between the presence of any genotype and specific phenotypes for CD and UC (data not shown).

### TABLE 3

Genotype, allele, and haplotype frequencies of \( SLC23A1 \) gene variants in Crohn disease patients and control subjects

<table>
<thead>
<tr>
<th></th>
<th>Crohn disease ( (n = 162) )</th>
<th>Controls ( (n = 142) )</th>
<th>OR (95% CI)(^2)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n (%) )</td>
<td>( n (%) )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs6596473</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td>77 (47.5)</td>
<td>67 (47.2)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>CG</td>
<td>65 (40.1)</td>
<td>64 (45.1)</td>
<td>0.88 (0.55, 1.42)</td>
<td>0.61</td>
</tr>
<tr>
<td>CC</td>
<td>20 (12.3)</td>
<td>11 (7.7)</td>
<td>1.58 (0.71, 3.54)</td>
<td>0.26</td>
</tr>
<tr>
<td>C carrier</td>
<td>rs33972313</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td>156 (96.3)</td>
<td>138 (97.2)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>GA</td>
<td>6 (3.7)</td>
<td>4 (2.8)</td>
<td>1.33 (0.37, 4.08)</td>
<td>0.67</td>
</tr>
<tr>
<td>AA</td>
<td>0</td>
<td>0</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>A carrier</td>
<td>rs10063949</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>24 (14.8)</td>
<td>53 (37.3)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>GA</td>
<td>61 (37.7)</td>
<td>53 (37.3)</td>
<td>2.54 (1.38, 4.66)</td>
<td>0.001</td>
</tr>
<tr>
<td>GG</td>
<td>77 (47.5)</td>
<td>36 (25.4)</td>
<td>4.72 (2.53, 8.81)</td>
<td>0.001</td>
</tr>
<tr>
<td>G carrier</td>
<td>216 (66.7)</td>
<td>125 (44)</td>
<td>2.54 (1.83, 3.53)</td>
<td>0.001</td>
</tr>
<tr>
<td>Haplotype(^3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGG</td>
<td>106 (65.3)</td>
<td>62 (43.5)</td>
<td>2.44 (1.54, 3.88)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

\( 1 \) Per-allele effects were derived from binary logistic regression. ND, not determined.

\( 2 \) ORs were adjusted for age and sex.

\( 3 \) The haplotypes were formed by the single nucleotide polymorphisms rs6596473, rs33972313, and rs10063949.
Haplotype rs10063949 is highly expressed in intestinal epithelial enterocytes, 
SLC23A1 oxidative stress can impede this barrier function (32, 33).

immunogenic bacteria within the intestinal lumen, and elevated 
intestinal epithelium constitutes a physical barrier that contains 
determine the severity of CD.

Genotype, allele, and haplotype frequencies of 
TABLE 4

<table>
<thead>
<tr>
<th></th>
<th>Ulcerative colitis</th>
<th>Controls</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 149)</td>
<td>(n = 142)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs6596473</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td>66 (44.3)</td>
<td>67 (47.2)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>CG</td>
<td>68 (45.6)</td>
<td>65 (45.8)</td>
<td>1.05 (0.65, 1.69)</td>
<td>0.85</td>
</tr>
<tr>
<td>CC</td>
<td>15 (10.1)</td>
<td>11 (7.7)</td>
<td>1.36 (0.58, 3.19)</td>
<td>0.47</td>
</tr>
<tr>
<td>C carrier</td>
<td>98 (32.9)</td>
<td>87 (30.6)</td>
<td>1.11 (0.78, 1.57)</td>
<td>0.56</td>
</tr>
<tr>
<td>rs33972313</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td>142 (95.3)</td>
<td>138 (97.2)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>GA</td>
<td>7 (4.7)</td>
<td>4 (2.8)</td>
<td>1.70 (0.49, 5.94)</td>
<td>0.40</td>
</tr>
<tr>
<td>AA</td>
<td>0</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>A carrier</td>
<td>7 (2.3)</td>
<td>5 (1.8)</td>
<td>1.34 (0.42, 4.27)</td>
<td>0.62</td>
</tr>
<tr>
<td>rs10063949</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>58 (38.9)</td>
<td>53 (37.3)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>GA</td>
<td>52 (34.9)</td>
<td>53 (37.3)</td>
<td>0.90 (0.53, 1.53)</td>
<td>0.69</td>
</tr>
<tr>
<td>GG</td>
<td>39 (26.2)</td>
<td>36 (25.4)</td>
<td>0.99 (0.55, 1.78)</td>
<td>0.97</td>
</tr>
<tr>
<td>G carrier</td>
<td>131 (43.9)</td>
<td>125 (44)</td>
<td>1.01 (0.72, 1.38)</td>
<td>0.98</td>
</tr>
<tr>
<td>Haplotype†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAG</td>
<td>63 (42.6)</td>
<td>60 (42.5)</td>
<td>1.00 (0.63, 1.59)</td>
<td>0.93</td>
</tr>
</tbody>
</table>

†Per-allele effects were derived from binary logistic regression. ND, not determined.
‡ORs were adjusted for age and sex.
§The haplotypes were formed by the single nucleotide polymorphisms rs6596473, rs33972313, and rs10063949.

involved in proinflammatory processes, and therefore could determine the severity of CD.

A third possible explanation is related to the fact that the 
intestinal epithelium constitutes a physical barrier that contains 
immunogenic bacteria within the intestinal lumen, and elevated 
oxidative stress can impede this barrier function (32, 33).

SLC23A1 is highly expressed in intestinal epithelial enterocytes, 
where its downregulation may lead to decreased intracellular 
ascorbic acid concentrations to compromise the physical barrier 
function against immunogenic bacteria and/or the ability to 
withstand prolonged intrinsic macrophage challenges. This by itself may not explain the causality of a genetic variation asso-
ciated with CD but not with UC; however, it could enhance the 
severity of any immune dysregulations specific for CD. This 
might be even more potentiated by the fact that oxidative stress in 
epithelial cells and macrophages leads to the activation of the 
nuclear factor-κ-B, an activator of prooxidative genes such as 
lipoxygenase, cyclooxygenase-2, and inducible-nitric oxide syn-
phase, which leads to further elevated oxidative stress and re-
duced function of the intestinal barrier (34, 35).

Previously, the 3 SNPs examined in this study were shown to be 
associated with circulating plasma ascorbic acid; however, the 
results are inconsistent (5, 36, 37). The inconsistency and/or 
heterogeneity among the results from different studies may be 
largely accounted for by the sensitivity of analyses for measuring 
plasma ascorbate, different assay protocols, and many confound-
incing factors that often make the interpretation of observational 
data difficult (36). Therefore, there is a need for additional 
udies to confirm a possible relation between SLC23A1 genetic 
variations and circulating plasma ascorbic acid. In the current 
udy, because of sampling collection methods, we were not able to 
include measurements of plasma ascorbic acid as a biomarker 
for ascorbate status. Although a limitation of this study, we 
speculate that the association of the genetic variation to CD may 
not influence plasma ascorbic acid concentrations, which are 
determined through renal reabsorption rather than intestinal 
absorption (24).

Compared with current genome-wide association studies, our 
Manitoban population-based case-control cohort could be consid-
ered suboptimal in terms of sample size (38). However, a previous study of the Manitoba IBD Cohort (39) found signif-
ificant associations for some of the previously described IBD-
associated SNPs identified by genome-wide association studies in 
other large population-based cohorts. Therefore, these results 
from a well phenotyped cohort of moderate size are noteworthy, 
but nonetheless should be reproduced in other cohorts.

If, as we hypothesize, intracellular ascorbate concentrations of 
specific intestinal cell types will decrease by the action of SNPs in 
SLC23A1, a supplementation with dehydroascorbate would be 
worthy of study as the therapy of choice to compensate for this 
shortfall. Dehydroascorbate, the oxidized form of vitamin C, 
does not exist under physiologic conditions (40, 41). However, if 
supplemented externally, dehydroascorbate enters the cell 
through facilitated glucose transporter of the GLUT family, not 
SLC23A1 (23), and intracellular dehydroascorbate is immedi-
ately reduced to ascorbate—the active form of vitamin C (40– 
42). Because dehydroascorbate is a minor component of some 
dietary supplements, the proposed gene-specific personalized 
nutritional therapy would boost intracellular vitamin C con-
centrations and be considered safe. Confirmation of our findings 
in independent association studies is warranted before the im-
plementation of any nutritional intervention.

We gratefully acknowledge the participants in the Manitoba IBD Cohort 
Study.

The authors’ responsibilities were as follows—MAS: was the principal 
manuscript author and was responsible for laboratory analysis, data 
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script; HE:G: was responsible for sample collection in healthy controls and 
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gator): was responsible for the conception and design of the project and 
for seeking financial support and contributed to the preparation of the
REFERENCES

