Food Intolerance: Associations with the rs12212067 Polymorphism of FOXO3 in Crohn’s Disease Patients in New Zealand

Gareth Marlow\textsuperscript{a, c}, Dug Yeo Han\textsuperscript{a, c}, Christopher M. Triggs\textsuperscript{b}, Lynnette R. Ferguson\textsuperscript{a, c}

\textsuperscript{a}Discipline of Nutrition, Faculty of Medical and Health Sciences, and \textsuperscript{b}Department of Statistics, The University of Auckland, and \textsuperscript{c}Nutrigenomics, Auckland, New Zealand

**Key Words**
FOXO3 · Crohn’s disease · Diet · Tolerance · Intolerance

**Abstract**

**Background:** Diet is known to play a major role in Crohn’s disease (CD). It has also been reported that the minor G allele from the rs12212067 polymorphism (T>G) in FOXO3 is associated with milder CD. The aim of this study was to investigate the association between the rs12212067 polymorphism and food intolerances for a total of 253 foods.

**Methods:** Tolerances and intolerances were recorded on a self-reported dietary questionnaire. Each food was scored on a 5-point ordinal scale: beneficial effects as ‘+ +’ or ‘+’, adverse effects as ‘– –’ or ‘–’, and ‘makes no difference’ as ‘=’. Dietary and genotype data were available for a total of 283 CD patients.

**Results:** We identified 17 foods with beneficial effects in our study which were significantly associated with the G allele of the FOXO3 rs12212067 polymorphism. Of these, sweet potatoes had the highest reported frequency of beneficial responses. We also identified 4 foods with detrimental effects in more than 25% of our study population. These were mustard, wasabi, and raw and cooked tomatoes, which again were significantly associated with the G allele in FOXO3.

**Conclusions:** There was strong evidence that adverse effects of mustard, wasabi, and raw and cooked tomatoes were significantly associated with the G allele of FOXO3 and that these foods should be avoided by people carrying this allele.

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Lynnette R. Ferguson
The University of Auckland
Private Bag 92019
Auckland 1142 (New Zealand)
E-Mail l.ferguson@auckland.ac.nz
Introduction

Crohn's disease (CD) is one of the two common forms of inflammatory bowel disease (IBD), the other being ulcerative colitis (UC). They are considered to be caused by aberrant intestinal immune responses in genetically susceptible individuals [1–3]. In New Zealand, CD affects 16 per 100,000 and UC 7 per 100,000 adults, and the incidence is increasing. Symptoms include pain, diarrhoea, bleeding and weight loss, which can result in a severe reduction in quality of life [4]. Genome-wide association studies to date have highlighted 163 IBD susceptibility loci [5] – 30 with CD, 23 with UC and 110 with both [5–8]. Apart from genetic predisposition there are also environmental factors in the development of IBD. IBD is more prevalent in industrialised/Westernised countries, which is believed to be a result of diet and lifestyle [6, 9, 10]. If diet is a trigger for disease progression and symptom development, this suggests that diet could be used to relieve symptoms or prevent the disease from developing in the first place.

It is well known that certain diets or dietary patterns can lead to the emergence of symptoms of CD or exacerbate an existing condition [11, 12]. It is also well known that enteral nutrition is one of the most effective treatments for inducing remission in paediatric cases [13]. CD patients learn which foods to avoid, some from personal experience, others from what they have been told by fellow sufferers or at support groups. However, unlike some other diseases where diet is a cause, no single diet is beneficial to all CD patients, and substantially more research is needed to determine an optimal diet for a specific individual. Unfortunately, it is not currently feasible to determine a diet for each individual, but we may be able to make recommendations based on a person’s genotype to avoid additional problems. CD patients tend to avoid foods to which they are intolerant. Our previous study showed which foods CD patients avoid or prefer [14]. That one particular food might be beneficial for one person but detrimental for another could be a result of the person’s genotype.

One identified gene is FOXO3 (forkhead box O3), a member of the O subclass of the transcription factor forkhead family of proteins, which are characterised by a distinctive forkhead DNA-binding domain. A single nucleotide polymorphism, rs12212067, was identified in FOXO3 that associates with CD prognosis [5].

FOXO proteins are highly conserved and essential in several cellular processes including regulating cell cycle gene expression [15, 16], DNA damage repair [17], energy metabolism [18], oxidative stress resistance [19–21] and apoptosis [22, 23], although many of these roles are redundant between family members [24]. FOXO3 has been reported to have a role in suppressing inflammatory cytokine production [25, 26].

Lee et al. [27] reported that the minor G allele of rs12212067 is associated with less severe symptoms and a less severe course in CD and rheumatoid arthritis, due to the down-regulation of pro-inflammatory cytokines including TNF and the up-regulation of IL-10, an anti-inflammatory cytokine [28, 29]. We were interested to consider if this single nucleotide polymorphism also related to dietary intolerances in people with CD. The overall results of examining food intolerances in CD patients have previously been published [14]. The aim of this study was to investigate specific food tolerance/intolerances associated with the rs12212067 polymorphism in FOXO3.

Subjects and Methods

Study Population

Participants were recruited from the North Island in New Zealand. The participants were recruited through gastroenterology clinics, or they responded to media publicity as volunteers of the study Genes and Diet in Inflammatory Bowel Disease. The participants’ gastroenterologists were approached, and clinical
Table 1. List of dietary items included in the questionnaire

<table>
<thead>
<tr>
<th>Food group</th>
<th>Food items</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cakes and biscuits</td>
<td>Cake, chocolate biscuits, corn crackers, wheat crackers, croissants, doughnuts, muesli bars, muffins/ sweet buns, pancakes, pita/flat bread, plain biscuits, rice crackers, scones</td>
</tr>
<tr>
<td>Breads and cereals</td>
<td>Barley, corn bread, rice bread, rye bread, sourdough bread, white bread, wholegrain bread, wholemeal bread, sugar-coated children’s cereals, cornflakes, couscous, gluten-free products, egg noodles, flour noodles, rice noodles, cornmeal polenta, porridge oats, quinoa, arborio risotto rice, brown or unpolished rice, rice bubbles/Coco Pops, white rice, wild rice, tacos, tortillas, Weet-Bix/shredded wheat All-Bran, wheat flakes</td>
</tr>
<tr>
<td>Dairy</td>
<td>Cheese, cream, custard, eggs, goat milk, ice cream, low-fat milk, sheep milk, soya milk, standard milk, yoghurt</td>
</tr>
<tr>
<td>Drinks</td>
<td>Beer, champagne, Coca Cola, diet Coca Cola, flavoured water, ginger ale, ginger beer, lemonade/ Sprite, Red Bull, red wine, sports drink, V energy drink, white wine</td>
</tr>
<tr>
<td>Fish</td>
<td>Crab, crayfish, dried fish, fresh white fish, fried fish, mussels, oily fish, oysters, paua, prawns/ shrimps, salmon, scallops, smoked white fish, tinned salmon, tinned sardines/anchoovies, tinned tuna, tuna, white fish cakes, white fish fingers</td>
</tr>
<tr>
<td>Fruit</td>
<td>Apples, apricots, bananas, blackberries, blueberries, cherries, coconuts, dried apricots, dried cranberries, dried figs, dried peaches, feijoas, figs, grapefruit, kiwifruit, mandarins, mangoes, melons, nectarines, oranges, pawpaw/papaya, peaches, pears, pineapples, plums, prunes, raisins, raspberries, strawberries, sultanas, tamarillos</td>
</tr>
<tr>
<td>Herbs and spices</td>
<td>Aniseed, basil, chives, cinnamon, coriander, cumin, dill, fennel, five-spice powder, ginger, lemongrass, mixed spice, nutmeg, oregano, paprika, parsley, rocket, rosemary, saffron, sage, sesame, thyme, turmeric</td>
</tr>
<tr>
<td>Mixed dishes</td>
<td>Chinese, Indian dahl, Indian fish curry, Indian meat curry, Indian vegetable curry, meat and vegetables, meat stew, cheese pasta, cream pasta, meat pasta, vegetable pasta, Thai fish curry, Thai meat curry, Thai vegetable curry</td>
</tr>
<tr>
<td>Meat</td>
<td>Bacon, roast beef, beef sausages, beefsteak, boiled corned beef, fried chicken, grilled chicken, chicken sausages, ham, ham chicken luncheon, liver, mince, roast chicken, roast lamb, roast pork, salami, sausages, tinned corned beef</td>
</tr>
<tr>
<td>Nuts</td>
<td>Almonds, brazil nuts, cashews, hazelnuts, linseed, peanuts, pecans, pine nuts, pistachios, poppy seeds, sunflower seeds, walnuts</td>
</tr>
<tr>
<td>Snacks</td>
<td>Apple chips, chocolate candy, chewing gum, chocolate, corn snacks, other sweets, popcorn, potato crisps</td>
</tr>
<tr>
<td>Spreads and sauces</td>
<td>Butter, chili sauce, chutney, gravy, honey, horseradish, hummus, jam, margarine, Marmite/ Vegemite, mayonnaise, mustard, Nutella, olive oil spreads, peanut butter, soya sauce, teriyaki, tomato sauce, vinegar dressings, wasabi</td>
</tr>
<tr>
<td>Vegetables</td>
<td>Asparagus, avocado, baked beans, beetroot, broccoli, cabbage, capsicum, carrots, cassava, cauliflower, celery, chickpeas, Chinese greens, corn, cucumber, dried beans, eggplant, garlic, green bananas, green beans, Jerusalem artichokes, kumara, leeks, lentils, mushrooms, onions, parsnip, peas, potato chips, potatoes baked in skin, boiled potatoes, fried potatoes, roasted potatoes, puha, pumpkin, salad greens, silverbeet spinach, taro, cooked tomatoes, raw tomatoes, tomato puree, tomato sauce, watercress, yams</td>
</tr>
</tbody>
</table>
records scrutinised, to confirm the diagnosis using established criteria. In this study, we have limited our participants to those who self-reported European ancestry and had both dietary assessment and genotype data for the rs12212067 polymorphism of the FOXO3 gene available. The rs12212067 polymorphism was genotyped using Immunochip, an Illumina iSelect HD custom genotyping array [30]. The study was conducted under ethical protocol MEC/04/12/011, authorised through the New Zealand Multi-Region Human Ethics Committee. All participants gave written informed consent.

**Dietary Assessment**

The dietary assessment has previously been described in detail [14]. Briefly, a total of 253 food items in 13 groups (table 1) were included in the questionnaire. Each food item was scored on a 5-point ordinal scale (−−, −, =, + and ++) where the most negative (−−) reflects the highest intolerance (adverse effect) and ‘++’ the most positive tolerance (beneficial effect). For statistical analysis, each individual food was classified as a binary outcome: adverse response (percentage of participants reporting ‘−−’ or ‘−’) and beneficial response (percentage reporting ‘+’ or ‘++’). Data recorded as ‘makes no difference’ (‘=’) were not used in this analysis. Where there were queries raised regarding a participant’s response, the participant was contacted and the answer checked by a registered nurse, dietitian or nutritionist.

**Statistical Analysis**

The dietary questionnaire data were analysed as percentages of participants reporting that response on a logit scale to stabilise variance of proportions. The two-dimensional plots show the spread between beneficial proportions for foods having the same adverse proportions. The rs12212067 polymorphism was coded as 0, 1 or 2 based on the number of the G allele and used as an additive model [31]. A generalised linear model within the binomial family was fitted for the gene-diet association. There was no indication of a deviation from Hardy-Weinberg equilibrium. The analyses were implemented using R [http://www.R-project.org] and SAS (v9.3; SAS Institute, Cary, N.C., USA).

**Results**

The rs12212067 polymorphism was genotyped on a total of 347 New Zealand Caucasian patients with CD, of whom 285 (82.1%) completed a dietary questionnaire on 253 items in 13 food groups. Gherkin was excluded from the analysis as there were no data for the minor G allele. Table 2 shows the percentages of responses reporting adverse and beneficial effects. In addition, for each food, table 2 shows whether the frequency of the minor G allele differs from its overall incidence in the study group for either the patients reporting an adverse or a beneficial effect for that food, together with the OR for differential incidence and its 95% CI. Thus, for example, although more patients (70%) gave adverse responses to beefsteak than reported beneficial responses (5%), within the group experiencing beneficial responses the G allele was over-represented (OR 1.2–7.2). Most foods were reported as ‘makes no difference’, and few were reported as beneficial to CD patients. Foods from 7 groups (breads and cereals, dairy, drinks, fish, fruit, nuts and snacks) were not significantly beneficial or detrimental to CD patients in association with the G allele of the rs12212067 polymorphism.

Seventeen foods from 6 groups appeared to have a significant beneficial effect on CD patients in association with the G allele of the rs12212067 polymorphism (table 2). The top 5 of the most significantly beneficial foods were sweet potatoes (more commonly called kumara in New Zealand; 17.5%), Jerusalem artichokes (7.1%), green beans (5.8%), beefsteak (5.1%) and peas (3.9%).

Five foods from 3 groups appeared to have a significant adverse effect on CD patients in association with the G allele of the rs12212067 polymorphism (table 2). These 5 detrimental foods were wasabi (38.9%), raw tomatoes (34.9%), mustard (28.5%), cooked tomatoes (25.2%) and ginger (16.7%).
Table 2. Percentage of responders reporting beneficial or adverse effects for the tested foods

<table>
<thead>
<tr>
<th>Food group</th>
<th>Food item</th>
<th>Adverse effects</th>
<th>Beneficial effects</th>
<th>No differences, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>OR (95% CI)</td>
<td>p</td>
<td>n (%)</td>
</tr>
<tr>
<td>Biscuits</td>
<td>croissants</td>
<td>76 (31.54)</td>
<td>0.099 (0.542–1.831)</td>
<td>0.990 (3.124)</td>
</tr>
<tr>
<td>Herbs and spices</td>
<td>ginger</td>
<td>41 (16.67)</td>
<td>1.983 (1.015–3.872)</td>
<td>0.045 (26.105)</td>
</tr>
<tr>
<td></td>
<td>turmeric</td>
<td>30 (15.38)</td>
<td>1.073 (0.463–2.487)</td>
<td>0.870 (5.256)</td>
</tr>
<tr>
<td>Meat</td>
<td>beefsteak</td>
<td>70 (25.27)</td>
<td>0.894 (0.480–1.666)</td>
<td>0.724 (14.50)</td>
</tr>
<tr>
<td></td>
<td>fried chicken</td>
<td>102 (40.00)</td>
<td>1.076 (0.424–3.134)</td>
<td>0.310 (4.15)</td>
</tr>
<tr>
<td></td>
<td>ham chicken luncheon</td>
<td>57 (24.05)</td>
<td>1.079 (0.538–2.165)</td>
<td>0.830 (8.33)</td>
</tr>
<tr>
<td>Mixed dishes</td>
<td>Indian dahl</td>
<td>87 (59.18)</td>
<td>1.224 (0.578–2.592)</td>
<td>0.598 (3.20)</td>
</tr>
<tr>
<td></td>
<td>Indian fish curry</td>
<td>101 (66.45)</td>
<td>0.917 (0.426–1.975)</td>
<td>0.826 (2.132)</td>
</tr>
<tr>
<td></td>
<td>Indian meat curry</td>
<td>161 (67.36)</td>
<td>0.939 (0.496–1.777)</td>
<td>0.846 (2.08)</td>
</tr>
<tr>
<td></td>
<td>Indian vegetable curry</td>
<td>156 (66.38)</td>
<td>1.186 (0.612–2.297)</td>
<td>0.614 (2.885)</td>
</tr>
<tr>
<td></td>
<td>Thai fish curry</td>
<td>103 (62.80)</td>
<td>1.042 (0.496–2.185)</td>
<td>0.914 (4.244)</td>
</tr>
<tr>
<td></td>
<td>Thai vegetable curry</td>
<td>127 (59.07)</td>
<td>1.779 (0.884–3.581)</td>
<td>0.107 (4.186)</td>
</tr>
<tr>
<td>Spreads and sauces</td>
<td>mustard</td>
<td>63 (28.51)</td>
<td>2.711 (1.430–5.138)</td>
<td>0.002 (4.181)</td>
</tr>
<tr>
<td></td>
<td>wasabi</td>
<td>58 (38.93)</td>
<td>2.595 (1.227–5.485)</td>
<td>0.013 (3.20)</td>
</tr>
<tr>
<td></td>
<td>chutney</td>
<td>61 (25.00)</td>
<td>1.214 (0.644–2.288)</td>
<td>0.550 (2.82)</td>
</tr>
<tr>
<td></td>
<td>margarine</td>
<td>25 (9.62)</td>
<td>0.875 (0.337–2.275)</td>
<td>0.785 (3.15)</td>
</tr>
<tr>
<td>Vegetables</td>
<td>cooked tomatoes</td>
<td>65 (25.19)</td>
<td>2.206 (1.258–3.869)</td>
<td>0.006 (13.50)</td>
</tr>
<tr>
<td></td>
<td>raw tomatoes</td>
<td>94 (34.94)</td>
<td>2.019 (1.182–3.449)</td>
<td>0.010 (12.46)</td>
</tr>
<tr>
<td></td>
<td>green beans</td>
<td>49 (19.07)</td>
<td>1.161 (0.606–2.226)</td>
<td>0.652 (5.294)</td>
</tr>
<tr>
<td></td>
<td>Jerusalem artichokes</td>
<td>15 (21.43)</td>
<td>1.203 (0.327–4.421)</td>
<td>0.781 (5.714)</td>
</tr>
<tr>
<td></td>
<td>kumara</td>
<td>12 (4.67)</td>
<td>1.686 (0.551–5.155)</td>
<td>0.360 (45.1751)</td>
</tr>
<tr>
<td></td>
<td>peas</td>
<td>94 (33.69)</td>
<td>1.349 (0.790–2.303)</td>
<td>0.272 (11.39)</td>
</tr>
</tbody>
</table>

Foods where beneficial or adverse effects are significantly associated with the G allele of the rs12212067 polymorphism are shown in bold.

To highlight the differential responses to a specific food, all significant data sets are represented in two-dimensional summary figures (fig. 1–6). In these figures, if a food is in the top left-hand quadrant, more participants reported beneficial effects. Conversely, if a food is in the bottom right-hand quadrant, more participants reported adverse effects. Foods significantly associated with the G allele are named on the figures.

The two-dimensional summary for biscuits is shown in figure 1. Rice crackers (No. 12) are often seen as beneficial, with fewer adverse effects reported than for any other biscuit. However, this beneficial effect is not associated with the FOXO3 polymorphism. The converse is true for doughnuts (No. 6), but this detrimental effect is not associated with the FOXO3 polymorphism either. Croissants (No. 5) were reported to be detrimental by 30% of the study population, but they were beneficial for 1.2%, which was significantly associated with the G allele of the FOXO3 polymorphism.

The two-dimensional summary for herbs and spices is shown in figure 2. Although ginger (No. 10) has the highest reported beneficial effect, more people reported adverse effects, and this was significantly associated with the FOXO3 polymorphism.

The two-dimensional summary for meats is shown in figure 3. Grilled and roast chicken (No. 7 and 13, respectively) had the highest reported beneficial and lowest reported adverse effects, but it was fried chicken that was significantly associated with the FOXO3 G allele and beneficial effects, despite being reported as detrimental by 40% of the population. Beefsteak (No. 4) and ham chicken luncheon (No. 10) were also reported to have significantly beneficial effects.

The two-dimensional summary for mixed dishes is shown in figure 4. All the curries (No. 2–5, 12 and 14), with the exception of Thai meat curry, were reported to be significantly asso-
Fig. 1. Proportions of participants reporting a beneficial or an adverse response on a logit scale for foods in the cakes and biscuits category. Foods reported to be significantly associated with the G allele are highlighted with the name shown in Table 2. 1 – Cake; 2 – chocolate biscuits; 3 – corn crackers; 4 – wheat crackers; croissants (5); 6 – doughnuts; 7 – muesli bars; 8 – muffins/sweet buns; 9 – pancakes; 10 – pita/flat bread; 11 – plain biscuits; 12 – rice crackers; 13 – scones.

Fig. 2. Proportions of participants reporting a beneficial or an adverse response on a logit scale for foods in the herbs and spices category. Foods reported to be significantly associated with the G allele are highlighted with the name shown in Table 2. 1 – Aniseed; 2 – basil; 3 – chives; 4 – cinnamon; 5 – coriander; 6 – cumin; 7 – dill; 8 – fennel; 9 – five-spice powder; ginger (10); 11 – lemongrass; 12 – mixed spice; 13 – mustard; 14 – nutmeg; 15 – oregano; 16 – paprika; 17 – parsley; 18 – rocket; 19 – rosemary; 20 – saffron; 21 – sage; 22 – sesame; 23 – thyme; 24 – turmeric.

Fig. 3. Proportions of participants reporting a beneficial or an adverse response on a logit scale for foods in the meat category. Foods reported to be significantly associated with the G allele are highlighted with the name shown in Table 2. 1 – Bacon; 2 – roast beef; 3 – beef sausages; 4 – beefsteak; 5 – boiled corned beef; fried chicken (6); 7 – grilled chicken; 8 – chicken sausages; 9 – ham; ham chicken luncheon (10); 11 – liver; 12 – mince; 13 – roast chicken; 14 – roast lamb; 15 – roast pork; 16 – salami; 17 – sausages; 18 – tinned corned beef.
associated with the G allele and beneficial effects; however, the majority of respondents (>60%) reported adverse effects.

The two-dimensional summary for spreads and sauces is shown in figure 5. Wasabi (No. 19) and mustard (No. 11) were identified as being significantly associated with the G allele and detrimental effects, while the opposite was true for margarine (No. 8) and chutney (No. 2). Honey (No. 4) had the highest reported beneficial effect, but this effect was not associated with the G allele.

The two-dimensional summary for vegetables is shown in figure 6. Pumpkin (No. 35), kumara (No. 22) and boiled potatoes (No. 31) have the highest reported beneficial effects, but kumara is the only one of the three which is significantly associated with the G allele. Cooked and raw tomatoes (No. 39 and 40, respectively) were both reported with adverse effects significantly associated with the G allele.
Discussion

Although very few participants reported being able to modify what they eat to completely relieve symptoms, most reported that making specific changes to their diet could help control the frequency and severity of flare-ups. When we examined food tolerances in relation to the G allele of FOXO3, we found some significant results for a small number of foods. Based on our results, it is difficult to recommend a food that will be beneficial to sufferers of CD with the G allele of rs12212067 in FOXO3. The best recommendation would be kumara, for which 17.5% reported beneficial effects from eating and only <5% reported suffering adverse effects, with the majority reporting no change in symptoms. It is easier to make recommendations of which foods to avoid for those with the G allele of rs12212067, with mustard, wasabi, and cooked and raw tomatoes all having reported adverse effects in >25% of our study population and beneficial effects in <5% of the population. Ginger also shows this pattern, although this effect occurred in <25% of the population. We would recommend that CD patients with the G allele should avoid eating mustard, wasabi and tomatoes, and that they could try kumara, as it may be beneficial and has only a small chance of being detrimental.

The list of foods showing adverse effects in this particular group is of some interest, since all quite commonly appear in lists of foods having anti-inflammatory components that might be expected to be generally beneficial. Ginger contains two such components, [6]-gingerol and [6]-shogaol [32]. Of these, the best characterised is [6]-gingerol, which has been found to inhibit inflammation by down-regulating activity of the nuclear transcription factor NF-κB.
It also induces apoptosis and autophagy in cancer cells [34], inhibits angiogenesis [35] and induces apoptosis [36], meaning that it may be able to help eliminate an early-stage cancer cell. However, ginger is quite pungent, and individuals carrying the FOXO3 genetic variant may be especially sensitive to strong odours and flavours. This characteristic could also extend to two others on this list of adverse foods, mustard and wasabi. These food plants are members of the Brassicaceae family, which contain some quite distinctive phytochemicals, especially glucosinolates, which are not found in other plant families [37]. This assumes that the mustard under consideration is Indian mustard, *Brassica juncea*, the most commonly used type of mustard in commercial pastes. Some other components of wasabi are also of interest [38]. The two other adverse foods in this group are both different preparations of tomato, again usually considered beneficial because of the high antioxidant component, including ascorbic acid [39] and lycopene [40].

The list of foods that become especially beneficial to those individuals carrying the variant FOXO3 allele is also of interest, and some may be harder to explain than others. Turmeric is a traditional Indian spice which contains the important ingredient curcumin. Strimpakos and Sharma [41] have reviewed the vast literature from various studies, showing the multiple anti-inflammatory actions of curcumin, which may be especially relevant in the context of carrying the FOXO3 variant allele. This may also be reflected in the fact that the 6 different mixed dishes appearing beneficial would all have a high probability of containing curcumin as a major ingredient. It may also be a component of some chutneys. The appearance of 3 different meats in these lists may initially appear surprising, given that many lines of nutritional advice recommend a low dietary component of meats, especially red meats [42]. However, the high protein content and good nutrient spectrum may be beneficial to those individuals with IBD who may have a problem with keeping food down. The final item which may be appropriate to comment on is Jerusalem artichokes, which do not even appear in some food frequency questionnaires. These contain inulin, a type of polysaccharide that acts as a prebiotic, enhancing the growth of bifidobacteria in the colon [43]. FOXO3 variants may be especially reliant on such a pathway [44].

One of the strengths of this study is the use of a dietary questionnaire which included a 5-point scale to assess people’s responses to specific food items; the inclusion of the scale allowed us to incorporate more food items than a standard questionnaire and to get a truer representation of people’s dietary patterns than using a food frequency questionnaire. However, one of the main limitations of this study concerns participant numbers, since only 285 individuals completed the dietary questionnaire, and not every question was answered by them.

We would like to conduct a replication study in a larger population to confirm the reproducibility of our findings. We would then like to follow that up with a controlled intervention in two characterised populations, one with the G allele and the other with the wild type, to confirm the effect of the G allele. The minor G allele of FOXO3 has been shown to down-regulate pro-inflammatory cytokines including TNF and to up-regulate the anti-inflammatory cytokine IL-10, which accounts for the less severe symptoms of CD [27]. This reduced inflammatory response may account for the positive association of FOXO3 with tolerance to some foods, but it does not explain why it is associated with an adverse response to other foods.

CD is inherently more complex than just a single gene-diet interaction. The latest genome-wide association study identified 163 genes [5] that could account for the variation observed between participants and a specific food. In order to determine conclusively the effect of a specific food on a particular patient, we would need to examine the genotype of all of the 163 identified genes of that person and determine the effect of the food and that particular genotype combination.
Conclusions

These findings are important, since we have shown that people carrying the FOXO3 variant may have a greater risk of adverse symptoms if they consume ginger, mustard, wasabi, and raw or cooked tomatoes. Symptomatic CD sufferers may already know this and avoid these foods accordingly; however, these data support using genotype information in order to help tailor personal dietary advice.

Acknowledgements

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Disclosure Statement

The authors declare no conflict of interest.

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