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TNFSF15 is an Ethnic Specific IBD Gene

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Abstract

Background—Inflammatory bowel disease (IBD) is a clinically, and likely genetically, heterogeneous group of disorders. A recent report suggests that genetic variations in the *TNFSF15* gene contribute to the susceptibility of IBD in both Japanese and caucasian populations.

Aims—To confirm the association between *TNFSF15* high and low risk haplotypes and IBD in a caucasian population.

Methods—Five SNPs that comprise the two common haplotypes were genotyped in 599 caucasian patients with Crohn’s disease (CD), 382 caucasian patients with Ulcerative Colitis (UC) and 230 ethnically-matched healthy controls, including both Jews and non-Jews.

Results—The previously reported ‘risk’ haplotype was not associated with CD or UC (88.2% in CD cases vs. 88.3% in controls, $p=0.96$; 88.1% in UC cases vs. 88.3% in controls, $p=0.78$). We did however observe an increased frequency of the “protective” haplotype in Non-Jewish controls for both CD and UC (38.8% CD cases vs. 50% controls, $p=0.01$; 37.3% UC cases vs. 50% controls, $p=0.01$) with no such effect observed in the Jewish samples. There was an interactive effect between ethnicity and the protective haplotype in CD ($p=0.04$).

Conclusions—We observed a protective haplotype, consisting of the minor alleles for all five markers, to have a higher frequency in the non-Jewish controls than in CD and UC. Of further interest, the haplotype frequency was in the opposite direction, in our Jewish case-control panels (both CD and UC), leading us to conclude (1) *TNFSF15* is indeed an IBD susceptibility gene, and (2) the disease susceptibility is ethnic specific.

Keywords

Inflammatory bowel disease; Crohn’s disease; Ulcerative Colitis; genotype; genetics

Introduction

Inflammatory bowel disease (IBD) is a group of complex idiopathic disorders, resulting from gene-environment interactions. The major forms of IBD are Crohn’s disease (CD) and ulcerative colitis (UC). A major distinction between CD and UC is the distribution of the inflammation. Inflammation in CD can affect any portion of the gastrointestinal tract, affecting most commonly the terminal ileum of the small intestine. It is discontinuous, asymmetric and can involve all layers of the bowel wall, with aggressive disease including intestinal

perforations, strictures, and fistulas to adjacent tissues. UC is confined to the colon and is continuous, symmetric, and affects only the innermost layers of the bowel wall. In North America, the incidence rates for UC range from 2.2 to 14.3 cases per 100,000 persons-years and for CD it ranges 3.1 to 14.6 cases per 100,000 persons¹. The prevalence of UC ranges from 37 to 246 cases/100,000 people and 26 to 199/100,000 persons for CD.

Factors such as ethnicity and the presence of affected first-degree relatives have been repeatedly shown to be significant in the frequency of disease expression. Relatives of persons with either CD or UC have an increased risk to develop either form of IBD². The relative risk to first-degree relatives of a proband with IBD is 4–10 fold³. There have been several familial aggregation studies that indicate UC and CD are genetically complex traits that involve incomplete penetrance due to genetically multigenic and/or heterogeneous defects⁴. Linkage studies, identifying seven different IBD linkage regions, paved the path to potential candidate genes^{5–14}. Several candidate gene studies have since emerged, revealing association to IBD or one of its clinical subphenotypes, including *MDR1*^{15, 16}, *IBD5* (inclusive of *OCTN*)^{14, 18}, *DLG5*^{17, 18}, *ICAM-1*¹⁹ and the most notable association, predisposing in ~30% of CD patients, the *NOD2/CARD15* association in the IBD1 region^{5, 6}. These findings confirmed the role genetics has in IBD pathogenesis and stimulated interest in identifying further susceptibility genes. Our group has recently focused efforts on the candidate gene *TNFSF15* (also known as *TLIA*) reported by Yamazaki and colleagues in 2005. Yamazaki²⁰ found a core haplotype of *TNFSF15* showing association with increased risk for CD in a Japanese case control and in a caucasian family study population. They also identified a common haplotype that was found to be associated with a lowered risk of disease susceptibility in both their family-based and in case-control samples.

TNFSF15 was first cloned in 2002 at Human Genome Sciences²¹. It is thought to be involved in the inflammatory process of both rheumatoid arthritis and atherosclerosis²². However, *TNFSF15* seems to exert its effects most profoundly in the gut^{23–27}. *In vitro* studies have shown that *TNFSF15* is produced by human umbilical vein endothelial cells (HUVEC), as well as by T-cells, monocytes/macrophages, and dendritic cells^{23, 25, 28–30}. *TNFSF15* enhances the induction of interferon-gamma (IFN- γ) expression in human T cells, and natural killer cells when combined with IL-12/18^{23–25}. *TNFSF15* is a very potent enhancer of IFN- γ production in that as little as 100pg/ml is capable of inducing a 5–10 fold increase in IFN- γ levels from IL-12/IL-18 activated human T-cells²⁴. In a mouse model of *Listeria monocytogenes*, Hsu *et al* demonstrated a central role for this molecule in providing protection against dissemination of this pathogen³⁰. Thus, *TNFSF15* is central for optimizing Th1 responses for protection of mucosal pathogens, yet can be critical for generation of enhanced Th1 responses in abnormal mucosal inflammation such as seen with Crohn's disease. Therefore, defining genetic variations in the *TNFSF15* gene that could alter expression and/or function of this molecule may allow a better understanding of the role of this molecule in gut homeostasis and abnormal inflammation.

Our group sought to replicate the CD-*TNFSF15* association that Yamazaki *et al* 2005 observed in our own caucasian case control cohort. Given the importance of ethnicity in genetics, especially that of IBD, we analyzed our data overall and within each ethnic group, Jewish and non-Jewish.

Materials and Methods

Patients

We ascertained 1211 caucasian subjects seen at Cedars-Sinai Medical Center. The cohort consisted of 599 CD patients, 382 ulcerative colitis patients and 230 controls. Part of this cohort has been studied previously^{31–33}. The Institutional Review Board at Cedars-Sinai Medical

Center approved the study protocol, and informed consent was obtained from all study subjects. The diagnosis of Crohn's disease, ulcerative colitis and clinical sub-phenotypes were based on standard criteria including clinical, endoscopic, radiographic, and histopathological criteria 31, 32, 34–36. Patients with indeterminate colitis were excluded. All of the controls were geographically and ethnically selected to be maximally similar to our patients, while having no family history of IBD or autoimmune disorders. Also, we evaluated our cohort on ethnicity, Jewish or non-Jewish. We defined Jewish as those individuals with at least one of four grandparents of Jewish origin 37, 38 and more specifically, our Jewish population is primarily of Ashkenazi descent.

Genotyping

DNA was extracted from the peripheral whole blood collected using PureGene DNA isolation kit (Gentra Systems; Minneapolis, MN.) Five single nucleotide polymorphisms (SNP) previously found to be associated with CD in a Japanese cohort (rs3810936, rs6478108, rs6478109, rs7848647, rs7869487) were tested 20. These SNPs were used to construct 2 common haplotypes previously seen in both a Japanese and a caucasian population, as shown in Figure 1 20. Probes and primers were designed for the TaqMan MGB allelic discrimination method (Applied Biosystems, Foster City, CA.) The fluorescent amplifications were measured using the ABI Prism 7000 Sequence Detection System.

Statistical Analysis

None of the markers exhibited significant deviation from the Hardy-Weinberg equilibrium in our sample set ($p=0.05$ level). Genotype distributions of individual markers were compared between cases and controls. Individual haplotypes were estimated by using Bayesian statistical method as implemented in the PHASE software (v2.0) 39, 40. For each haplotype, a dominant model was assumed, i.e., carriers of the particular haplotype versus non-carriers were compared. Chi-square (χ^2) tests were used to test associations between the haplotypes and disease status and disease phenotype characteristics. A one-tailed p -value of less than 0.05 under the χ^2 distribution was considered statistically significant. All analyses were done in total sample first, and then separated in Jewish and non-Jewish population. Multiple logistic regression was used to test the interactive effect between ethnicity and haplotype in the total sample. Statistical analysis was conducted by SAS software (SAS Institute; Cary, NC.).

Considering the modest sample size in our Jewish control population, we also did a power calculation in the analysis. Two types of power analyses were conducted. First, we calculated the power for testing association between *TNFSF15* and disease under the current sample size in the Jewish population by using the odds ratio reported for the caucasian population. Second, we computed the power for detecting interaction between ethnicity and *TNFSF15* under different estimates of joint gene-ethnicity effect, using the reported odds ratio for estimate of marginal gene effect and ethnicity effect. The alternative hypothesis was 1-sided and type I error rate was 0.05. The program QUANTO was used for the power calculation.

Results

The five genotyped SNPs formed three common haplotypes in our population (A, B and C), and all were observed in the prior work by Yamazaki 20. The haplotypes carrier frequencies are shown in Tables 1–3. We were unable to confirm the association Yamazaki found between Haplotype A, the risk haplotype, and their Japanese case control population. In our IBD population the Haplotype A carrier frequency was 88.5% in cases vs. 88.3% in controls, in CD it was 88.2% in cases vs. 88.3% in controls and in UC it was 89.1% in cases and 88.3% in controls, with p -values 0.93, 0.96, and 0.78 respectively. Also, when stratified by Jewish ethnicity, Haplotype A was not found to be associated with CD, UC or IBD.

Overall, Haplotype A had a carrier frequency in controls of 88.3%, Haplotype B 44.4%, and Haplotype C 7.0%. However, the overall result masked distinct ethnic differences. In non-Jews, the haplotype carrier frequencies in controls were 88.1%, 50.0% and 6.3% respectively, while in Jews they were 88.9%, 25.9% and 9.3%. When the results are separated by ethnicity into non-Jewish and Jewish subgroups, Haplotype B carriers, consisting of the rare allele for each marker, were found to be protective against CD, but specifically only in non-Jews (38.8% in CD *vs* 50.0% in controls, OR: 0.64 CI: 0.44–0.92, $p=0.01$.) These results were similar to the caucasian population of the Yamazaki et al. In contrast, Haplotype B frequencies had an opposite trend in our Jewish population, with 32.3% in the CD cases versus 25.9% in controls; this difference was not significant ($p=0.36$). The ethnic distinction was further verified through logistic regression, in which an interactive effect between ethnicity and Haplotype B in CD was detected ($p=0.04$).

The same haplotype analysis was performed on the UC cohort. The combined UC cohort (including both Jewish and non-Jewish panels) did show an association between Haplotype B and UC as shown in Table 2 ($p=0.005$, OR: 0.62 CI: 0.44–0.86.) However, the association was clarified when results were separated by ethnicity, with the non-Jewish population having a significant association with Haplotype B (37.3% *vs* 50.0%, OR: 0.59 CI: 0.40–0.88, $p=0.01$.) In the Jewish UC cohort, there was no difference in Haplotype B carrier frequency (26.0% in cases and 25.9% in controls).

The CD cohort was further stratified by clinical phenotypes: uc-like, fibrostenotic, internal perforating, perianal penetrating and small bowel surgery to investigate anymore detailed associations. No association was found between clinical phenotypes and TNFSF15 haplotypes in the non-Jewish population (data not shown). However, in the Jewish population, patients undergoing small bowel surgery appeared to have a higher frequency of Haplotype B ($p=0.005$, OR 2.2 CI 1.3, 3.8) and lower frequency of Haplotype A ($p=0.009$, OR 0.33, 95%CI: 0.14, 0.76) than those without small bowel surgery. Since previous research studies have shown age and gender effects in IBD susceptibility genes, namely *DLG5*^{41, 42}, we analyzed for these variables with the TNFSF15 haplotypes. We found the distribution of the major haplotype is similar in early-onset *vs*. late-onset CD/UC and male *vs*. female (Supplementary materials, Tables 1–4.) Finally, since a similar effect was seen in both CD and UC, we combined both disease groups and the result was that the protective effect achieved even greater statistical significance (Table 3.)

Discussion

We sought to replicate the conclusions drawn from Yamazaki's caucasian panel results, identifying both a high and low-risk haplotype association with CD. While we were unable to confirm association with the high-risk Haplotype A, we did see similar results Yamazaki found in their caucasian case control group. Neither group showed association between Haplotype A and CD, UC or IBD in this population. The protective Haplotype B was observed in both Yamazaki's and our caucasian panels. Our results demonstrated an association between the low-risk Haplotype (B) and CD, UC and IBD in the non-Jewish caucasian population. We identified a distinct ethnic relationship, in that the result was confined to non-Jews. This confirms and clarifies the Yamazaki et al 2005²⁰ finding that Haplotype B is protective against IBD in a caucasian population, but it is specifically in a non-Jewish caucasian population. The frequency trend of Haplotype B was in fact in the opposite direction in our Jewish CD and UC panels compared with the direction seen in our non-Jewish panels and Yamazaki's caucasian cohorts. One possible explanation for this difference in frequency between our overall study cohort and Yamazaki's is that latter study consisted mainly of patients from non-Jewish descent. This protective haplotype association with both UC and with CD and IBD (CD+UC)

in our non-Jewish cohort, demonstrates that this gene is not CD or UC specific, but is in fact an IBD gene.

When analyzing *TNFSF15* haplotype association with the various CD phenotypes, we observed an association between Haplotype B and small bowel surgery in Jewish patients only ($p=0.006$, OR 2.2 (CI 1.25, 3.75).) This further supports our hypothesis that there are ethnic differences in the susceptibility, powered by the gene.

One limitation of our study is that the sample size for the Jewish controls is relatively modest. We agree that the sample size may not be large enough for identifying the association in Jewish case-control if we assume the same gene effect as non-Jews (power: 0.55–0.72). However, since we observed an opposite trend of effect of Haplotype B in Jews compared with non-Jews, this finding justified us performing an interaction test. Table 4 shows the power to detect interaction under the different estimates for joint gene-ethnicity effect in our current sample size, assuming the odds ratios for marginal gene effect and marginal Jewish ethnicity effect are 0.7 (from the reference) and 2.5, respectively. From the table, we can see that when the odds ratio for the joint effect is greater than 2.0, there will be appropriate power to identify the interaction (>0.7). The results of our study support the interactive effect between ethnicity and *TNFSF15* gene in CD, which indicated that the effects of gene may depend on the ethnic group. To confirm the finding, the results should be repeated in other samples.

Only some of the genes providing genetic susceptibility genes for IBD have been identified. Some of the genes that have been implicated in IBD susceptibility, such as *NOD2/CARD15*, *IBD5*, *interleukin 1 receptor antagonist*, *HLA class II* and herein *TNFSF15*, demonstrate different gene frequencies in different ethnic groups^{43–47}. Thus, lack of an association in one ethnic group cannot be used to exclude a relationship with disease status in other ethnic groups. In fact, it emphasizes the importance of defining haplotype frequencies and gene marker associations for different ethnic groups.

It is worthwhile to make distinctions between populations' ethnicities, as it is well recognized that there is a 2–4 fold increased frequency of Crohn's disease in Jews as compared with non-Jewish groups in the same geographic area^{48, 49}. Genes predisposing Jewish people to CD may be different than those in a non-Jewish caucasian population due to the population's unique evolutionary history⁴⁹. Various studies have focused their efforts on understanding the apparent frequency discrepancy of IBD in Jews vs. non-Jews dating back to the 1960s^{50–52} and most recently a study of potential risk factors for IBD in a Canadian population found that being Jewish was significantly associated with CD and UC (OR=4.32, 95% CI 1.10–16.9 and OR=7.46, 95% CI, 2.33–23.89 respectively)⁵³. This finding helps illustrate that it would be expected that there will be some difference in genetic predisposition amongst Jewish and non-Jewish populations.

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Figure 1.
Main haplotype structure of TNFSF15 gene

TNFSF15 haplotype carrier associations with CD

Table 1

Haplotype	Cases(n=599)	Overall Haplotype Carrier Controls(n=230)	Frequency P	OR (95% CI)	Cases(n=345)	Non-Jew Haplotype Carrier Controls(n=176)	Frequency P	OR (95% CI)	Cases(n=254)	Jew Haplotype Carrier Controls(n=54)	Frequency P	OR (95% CI)
A	88.2%	88.3%	0.96	0.99(0.62, 1.59)	87.8%	88.1%	0.94	0.98(0.56, 1.71)	88.6%	88.9%	0.95	0.97(0.38, 2.46)
B	36.1%	44.4%	0.03	0.71 (0.53, 0.96)	38.8%	50.0%	0.01	0.64 (0.44, 0.92)	32.3%	25.9%	0.36	1.4 (0.7, 2.6)
C	5.5%	7.0%	0.43	0.78 (0.42, 1.45)	5.2%	6.3%	0.63	0.83 (0.38, 1.79)	5.9%	9.3%	0.36	0.62 (0.2, 2.27)

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Table 2

TNFSF15 haplotype carrier associations with UC

Haplotype	Cases(n=382)	Overall Haplotype Carrier Controls(n=230)	P	OR(95% CI)	Cases(n=236)	Non-Jew Haplotype Carrier Controls n=176)(	P	OR(95% CI)	Cases(n=146)	Jew Haplotype Carrier Controls(n=54)	P	OR (95% CI)
A	89.1%	88.3%	0.78	1.1 (0.64, 1.8)	89.8%	88.1%	0.57	1.2(0.642,22)	87.7%	88.9%	0.81	0.89 (0.33, 2.37)
B	33.0%	44.4%	0.005	0.62 (0.44, 0.86)	37.3%	50.0%	0.01	0.59 (0.4,0.88)	26.0%	25.9%	0.99	1 (0.49, 2.05)
C	4.2%	7.0%	0.14	0.58 (0.29, 1.19)	3.4%	6.3%	0.18	0.53 (0.21, 1.34)	5.5%	9.3%	0.34	0.57 (0.16, 2.32)

Table 3

TNFSF15 haplotype carrier associations with IBD (CD+UC)

Haplotype	Cases (n=981)	Overall Haplotype Carrier Controls (n=230)	Frequency P	OR (95% CI)	Cases (n=581)	Non-Jews Haplotype Carrier Controls (n=176)	Frequency P	OR (95% CI)	Cases (n=400)	Jews Haplotype Carrier Controls (n=54)	Frequency P	OR (95% CI)
A	88.5%	88.3%	0.93	1.02 (0.65, 1.6)	88.6%	88.1%	0.83	1.1 (0.63, 1.78)	88.3%	88.9%	0.81	0.94(0.38, 2.31)
B	34.9%	44.4%	0.007	0.67(0.5, 0.9)	38.2%	50.0%	0.005	0.62 (0.44, 0.87)	30.0%	25.9%	0.54	1.22 (0.64, 2.33)
C	5.0%	7.0%	0.23	0.7(0.39, 1.26)	4.5%	6.3%	0.34	0.7(0.34, 1.45)	5.8%	9.3%	0.36	0.6(0.21, 2.11)

Table 4
Power for detecting interaction between different joint gene-ethnicity effects

OR (gene-Jewish ethnicity)	Power (1-beta)*
1.9	0.61
2	0.67
2.1	0.72
2.2	0.76
2.3	0.8
2.4	0.83
2.5	0.86

* assuming type I error=0.05 (one-sided)