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Genetic polymorphisms in fatty acid metabolism modify the association between dietary n3:n6 intake and risk of ulcerative colitis: A prospective cohort study

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Abstract

Introduction—High intake of dietary n-3 polyunsaturated fatty acids (PUFA) is associated with a decreased risk of ulcerative colitis (UC) and Crohn's disease (CD). However, results have been heterogeneous suggesting that genetic variations in PUFA metabolism may modify this risk.

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Methods—We conducted a case-control study nested within two prospective cohorts, the Nurses' Health Study (NHS) and NHS II. Among women providing blood (n=62,437) or buccal cells (n=59,543) for genotyping, we confirmed new diagnoses of CD or UC. Dietary intake was assessed 4 years prior to diagnosis. Confirmed cases were matched 1:2 to controls. Subjects were genotyped for SNPs at *CYP4F3*, *FADS1*, and *FADS2* loci. Conditional logistic regression models examined the interaction between genotype, n3:n6 PUFA intake and risk of CD and UC.

Results—Our study included 101 CD and 139 UC patients matched to 495 controls. On multivariable analysis, high intake of n3:n6 PUFA (above median) demonstrated a trend towards reduced risk of UC (Odds ratio (OR) 0.71, 95% confidence interval (CI) 0.47 – 1.09, p=0.11). High n3:n6 PUFA intake was associated with a reduced risk of UC in individuals with the GG/AG genotype at a SNP in CYP4F3 (OR 0.57, 95% CI 0.32 – 0.99) but not those with the AA genotype (OR 0.95, 95% CI 0.47 – 1.93) (p-interaction = 0.049). No gene-diet interactions were noted for CD.

Conclusion—The association between dietary n3:n6 PUFA intake and risk of UC may be modified variants at *CYP4F3*. Further gene-environment studies of the association between diet and IBD risk are warranted.

Keywords

Crohn's disease; ulcerative colitis; PUFA; genetics; dietary fat

Introduction

Inflammatory bowel diseases (IBD; Crohn's disease (CD), ulcerative colitis (UC)) have emerged as global diseases, affecting over 1.6 million individuals in the United States, 2.5 million in Europe, and several thousands more worldwide[1-3]. Despite significant breakthroughs defining the role of genetics, immunologic abnormalities, and gut microbial composition in the pathogenesis of these complex and disabling diseases, much remains unknown about the predisposition to develop CD or UC[4-7]. Dietary patterns and constituents have long been proposed to be an important factor contributing to the development of CD and UC[8-11]. The relatively rapid emergence of these diseases in regions of the world where they were previously uncommon[1] and an increased risk of IBD in immigrants from low-incidence countries migrating to Europe and North America[12] has brought attention to changes in diet that occur with ‘westernization’ including a reduction in dietary fiber and increase in animal proteins and fat consumption, particularly saturated fats and n-6 polyunsaturated fatty acids (PUFA).

Strong experimental evidence and mechanistic plausibility support a contrasting role for n-6 and n-3 PUFA in intestinal inflammation[13-18]. Arachidonic acid (AA), an n-6 PUFA is a precursor to generation of pro-inflammatory eicosanoids such as leukotriene B4 (LTB4), this conversion occurring through a series of enzymatic steps[16, 18]. On the other hand, n-3 polyunsaturated fatty acids like docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) have anti-inflammatory effects through generation of resolvins, protectins, and other endogenous factors that down regulate inflammation[16, 18]. Genome-wide association studies (GWAS) have identified that genetic variation can influence plasma and tissue n-3 and n-6

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PUFA concentrations and their biological pathways[19-21]. Consequently, such genetic variation may also alter the association between dietary n-3 and n-6 PUFA and risk of CD and UC, explaining some of the heterogeneity in clinical effects noted. The single prior study to examine this hypothesis focused exclusively on pediatric CD and relied on recall to retrospectively assess pre-illness diet, which is susceptible to bias and inaccuracy[22].

In a previous analysis of two large prospective cohorts, we found that greater intake of long-chain n-3 PUFA and ratio of n-3/n-6 PUFA intake was associated with a reduced risk of ulcerative colitis. In this study, we examined the interaction between genetic variations in enzymes involved in PUFA metabolism, dietary intake of n-3 and n-6 PUFA, and risk of CD and UC.

Methods

Study Cohort

The participants in our study were women who were enrolled in the Nurses' Health Study (NHS) or Nurses' Health Study II (NHS II). Details of these cohorts have been described previously[13, 23-27]. In brief, the NHS enrolled 121,700 female registered nurses who were between the ages of 30 and 55 years in 1976 while the NHS II included 116,430 female nurses between the ages of 25 and 42 years in 1989. Women in both cohorts were followed through biennial questionnaires detailing new medical diagnoses and environmental exposures including diet. The rate of completion of the biennial questionnaires consistently exceeds 95%. In each of the biennial questionnaires, women self-reported a diagnosis of CD and UC. Each diagnosis was followed by a supplemental questionnaire that ascertained further details regarding the disease and requested permission to review medical records. Chart review was performed independently by two board-certified gastroenterologists blinded to exposure to confirm the diagnosis of CD or UC. Disagreements were infrequent and resolved through consensus. A final diagnosis of CD was established based on the presence of typical symptoms for at least 4 weeks duration accompanied by supporting endoscopic, radiologic, and histologic features suggesting small bowel involvement, skip lesions, transmural inflammation or granulomas[2, 28]. A final diagnosis of UC similarly required at least 4 weeks of symptoms and typical contiguous inflammation beginning from the rectum extending proximally[3].

Selection of Cases and Controls

In each of these cohorts (1989-90 for NHS I and 1996-99 for NHS II), a subset of women provided blood samples stored on ice packs through overnight courier. This included 32,826 women in NHS and 29,611 women in NHS II. Upon receipt, the blood samples were processed immediately and buffy coat extracted for genotyping and stored in a continuously monitored liquid nitrogen freezer. In 2001-04, an additional 29,684 women in NHS and 29,859 women in NHS II who had not previously provided blood provided buccal cells using a swish-and-spit method. DNA was extracted from the cheek cells and stored for genotyping as noted above.

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This nested case-control study included women with a confirmed diagnosis of CD and UC who provided either blood or cheek cells for genotyping. For each case, 2 controls matched for age, menopausal status, month of blood sample collection, and use of menopausal hormone therapy were selected from the cohort. Premenopausal blood samples were matched for the day of luteal phase.

Assessment of Dietary Fat

Details about the assessment of dietary intake in these cohorts have been published previously[13, 24, 29-32]. Briefly, in 1980, women in NHS were administered a 61-item semi-quantitative food frequency questionnaire that was expanded to a 121-item questionnaire in 1984 and 136-item questionnaire in 1986 that was repeated every 4 years. Initial dietary assessment was performed in 1991 in NHS II using a 131-item questionnaire and similarly repeated every 4 years. Total intake of dietary fat, saturated fatty acids (SFA), n-3 PUFA, n-6 PUFA, and ratio of n-3/n-6 PUFA was calculated based on U.S. Department of Agriculture food composition data incorporating fats used in cooking and baking. Intake of specific fatty acids including EPA, DHA, linoleic acid, and arachidonic acid were also calculated. Prior studies have demonstrated the assessment of fat intake to be valid and reproducible, correlating well with 1-week dietary records, red blood cell measurements, and composition from subcutaneous fat aspirates[29, 33-36]. Dietary intake was energy-adjusted. To minimize potential for bias, we used prospectively assessed diet four years prior to diagnosis of CD or UC.

Covariates

Information was obtained on other covariates demonstrated previously to be associated with CD or UC in these cohorts including smoking[37], oral contraceptive use[25], menopausal hormone therapy use[38], regular use of non-steroidal anti-inflammatory drugs defined as use 2 or more times per week[39], and dietary intake of fiber[24] and vitamin D[23]. Body mass index was calculated using self-reported height and weight and expressed as kilograms per square meter (kg/m^2)[40].

Genotyping

We selected eight single nucleotide polymorphisms (SNPs), four in *CYP4F3*, and two each in *fatty acid desaturase (FADS) 1* and *FADS2* for genotyping based on previous studies on their possible role in modifying the association between n-3/n-6 PUFA intake and risk of pediatric CD[22, 41]. Extraction of genomic DNA was performed using conventional methods and direct genotyping was performed by the 5′ nuclease assay (TaqMan®) and the ABI PRISM 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA). Primers and probes were designed using the Primer Express® Oligo Design software v2.0 (ABI PRISM). Genotyping was performed by personnel blinded to exposure and outcome. A randomly selected 10% sample was genotyped in duplicate and demonstrated 100% concordance. All SNPs were in Hardy-Weinberg equilibrium ($p > 0.25$).

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Statistical Analysis

Continuous variables were summarized using means and standard deviations while categorical variables were expressed as proportions and compared using the chi-square test. Each dietary constituent including total n-3 and n-6 PUFA intake and ratio of n-3/n-6 PUFA were dichotomized based on intake above or below the median for the cohort. Conditional multivariable logistic regression was performed to identify the independent association between total n-3 and n-6 PUFA intake and ratio of n-3/n-6 PUFA and risk of CD and UC separately, adjusting for other covariates that had a univariate p-value < 0.10 or had previously been shown to modify risk of CD or UC. The p-value for interaction between dietary n-3, n-6 or n-3/n-6 PUFA intake and genotype was performed by introducing a cross-product term with genotype. If we identified a statistically significant interaction between a particular genotype and ratio of n-3/n-6 PUFA intake and CD or UC or if the association was statistically significant in individuals with specific genotypes alone, we performed further analyses for each individual n-3 or n-6 fatty acid. A two-sided p-value < 0.05 indicated independent statistical significance. Institutional review board approval for the study was obtained from Partners Healthcare.

Results

Study Population

Our final study population comprised of 101 and 139 incident cases of CD and UC respectively, matched to 495 healthy controls. Table 1 compares the characteristics of the three groups. There was no difference in the mean age between the three groups though women with CD tended to be slightly older than the other groups (p=0.07). There was no difference in the distribution of body mass index and physical activity between the three groups. Regular use of NSAIDs was infrequent and similar between those with CD, UC, and healthy controls. The daily mean caloric intake [CD (1733 kCal/day), UC (1750 kCal/day) and healthy controls (1756 kCal/day)] as well as total consumption of carbohydrates, protein, and fat were similar in those with CD, UC, or healthy controls. With respect to individual fatty acids, the three groups were similar in their total intake of n-6 PUFA and n-3 PUFA, with similar ratio of n-3/n-6 PUFA. None of the 8 SNPs genotyped were independently associated with CD or UC (Supplemental Table 1).

Ulcerative colitis

In the nested case-control study population, neither total intake of n-3 PUFA (Odds ratio (OR) 0.92, 95% confidence interval (CI) 0.62 – 1.37) nor n-6 PUFA (OR 1.19, 95% CI 0.80 – 1.76) was associated with risk of UC while a higher ratio of n-3/n-6 PUFA intake demonstrated a non-statistically significant trend (OR 0.71, 95% CI 0.47 – 1.08, p=0.11) upon adjustment for other covariates. The magnitude of the association was consistent with our prior prospective analysis of this cohort[13]. However, the association of the ratio of n-3/n-6 PUFA appeared to differ according to genetic variation at the CYP4F3 locus. Among women with a GG genotype at rs4646904 at the *CYP4F3* locus (84 cases, 282 controls), a significant reduction in risk of UC was observed when the intake was greater than the median for the cohort when compared to intake less than the median (adjusted OR 0.57, 95% CI 0.32 – 0.99) (Table 2). However, among individuals with the AA or AG

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genotype, there was no association between n-3/n-6 PUFA intake and risk of UC (OR 0.95, 95% CI 0.47 – 1.93) (p-interaction=0.049). At rs1290617 at the *CYP4F3* locus, a reduction in risk of UC was only noted in those with a GT or TT genotype (OR 0.47, 95% CI 0.26 – 0.84) but not in those with the GG genotype (1.03, 95% CI 0.49 – 2.17). However, a formal test for heterogeneity at this SNP was not statistically significant (p-interaction=0.32). Similarly, at rs379497, a reduced risk of UC was noted only in those with the GG genotype (OR 0.56, 95% CI 0.33 – 0.96) but not in those with GA/AA genotypes (OR 0.75, 95% CI 0.31 – 1.81). No statistically significant interactions were noted with any of the other SNPs.

Table 3 presents the results of the interaction across levels of intake of n-3 PUFA, n-6 PUFA, DHA, EPA, and long-chain n-3 PUFA spectively. Non-statistically significant trends were noted with a reduction in risk of UC with high intake of total n-3 PUFA (p-interaction=0.20) and EPA (p-interaction=0.20) among those with GG genotype of rs4646904 at *CYP4F3* but not among those with AG/AA genotypes. At the rs1290617 SNP, a higher intake of total n-3 PUFA was associated with lower risk of CD in individuals with GT/GT genotype (OR 0.48, 95% CI 0.27 – 0.85) but not in those with the GG genotype (OR 1.51, 95% CI 0.76 – 3.00) (p-interaction=0.02).

Crohn's disease

Total n-3/n-6 PUFA ratio was not associated with risk of CD in our nested case-control cohort (OR 0.82, 95% CI 0.44 – 1.55) (Table 4). Stratifying by genotypes at *CYP4F3, FADS1,* and *FADS2* loci also did not yield any significant associations.

Discussion

While diet has long been purported to modify risk of CD and UC, studies of the association between constituents of diet and IBD have yielded inconsistent results[9-11]. One possible explanation for this heterogeneity is genetic variation in enzymes responsible for activation or inactivation of biologically active metabolites arising from such dietary factors. Using data from two large prospective cohorts, we identify that two variants in the *CYP4F3* locus involved in PUFA metabolism may modify the association between n-3 and n-6 PUFA intake and risk of UC.

A role of dietary fatty acids in the pathogenesis of IBD is supported by mechanistic plausibility from their roles as precursors for many pro- and anti-inflammatory mediators as well as epidemiologic trends suggesting an increase in incidence of IBD that parallels rising consumption of n-6 PUFA along with reduced n-3 PUFA intake[1, 16, 18]. Several observational studies have examined the association between dietary fatty acid intake and risk of IBD[9, 13-15, 22, 42-45]. In a prior analysis of the prospective cohorts we demonstrated that a diet rich in long-chain n-3 PUFA and intake of n-3/n-6 PUFA was inversely associated with a risk of UC but not CD[13]. While a pediatirc case-control study by Amre *et al.* [42] and an analysis of the European Prospective Investigation in Cancer (EPIC) cohort suggested an inverse relationship between n-3 PUFA intake and CD[42], other studies, similar to our findings, did not identify an association between n-3 PUFA intake and CD[9, 46]. As well, randomized controlled trials of n-3 PUFA supplementation in established CD failed to demonstrate a benefit over placebo in maintaining remission[47]. Studies in UC have been

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more consistent with analysis of both the European[14, 15, 44, 45] and Nurses' Health Study cohorts[13] demonstrating an inverse association between intake of n-3 PUFA, EPA, and DHA and risk of UC while greater intake of n-6 PUFAs like linoleic acid or arachidonic acid and a higher n-6/n-3 PUFA ratio was associated with an increased risk of UC.

One reason for the heterogeneous results from the different studies is that effect of dietary PUFA may be modified by genetic polymorphisms in enzymes involved in their metabolism. The main finding of our study was that the beneficial effect of a higher n-3/n-6 PUFA or total n-3 PUFA intake in the diet appeared to be modified by two SNPs at the *CYP4F3* locus (rs4646904 and rs1290617). Dietary n-3 PUFA exerts an anti-inflammatory effect through generation of resolvins and lipoxins which down-regulate inflammation through both receptor mediated mechanisms and post-translational modification[16, 18, 48-50]. In contrast, the pro-inflammatory effects of n-6 PUFA are mediated by their role, particularly arachidonic acid, as precursors to several pro-inflammatory mediators including leukotrienes and prostagladins[16, 18]. In particular, leukotriene B4 (LTB4) has strong pro-inflammatory effects and is present in higher concentration in tissues at the site of inflammation accompanied by an increase in expression of enzymes responsible for its biosynthesis[16, 50-53]. CYP4F3 is an enzyme belonging to the cytochrome P450 superfamily, encoded by a gene *CYP4F3* on chromosome 19[22, 41, 54]. This forms the precursor for two enzyme subfamilies, CYP4F3A and CYP4F3B which localize to leukocytes and the liver respectively. The primary function of this enzyme is to inactivate and degrade LTB4, thereby dampening the pro-inflammatory cascade. Variants in this enzyme that interfere with its function may result in persistence of proinflammatory eicosanoids at tissue sites, thereby propagating intestinal inflammation[22, 41]. Only one prior study examined the effect of variation in PUFA metabolism, dietary PUFA intake, and risk of CD[22]. In an elegant study of 182 children with newly diagnosed CD, a diet high in n-3/n-6 PUFA was associated with a reduced risk of CD in the presence of specific variants in *CYP4F3* and *FADS2*. However, this study relied on pre-illness diet assessed retrospectively in newly diagnosed children which is susceptible to bias introduced by modification of eating habits prior to formal diagnosis. However, together our findings provide support for a gene-environment interaction between dietary PUFA, variants involving PUFA metabolism, and risk of IBD. There is need for further study in individuals with established disease to examine if there is a clinical benefit to n-3 PUFA supplementation (and an increase in n-3/n-6 PUFA ratio) based on underlying genotype.

We readily acknowledge several limitations to our study. First, the cohort consisted exclusively of women, most of who were of Caucasian ethnicity. However, few studies have suggested that gender modifies the effect of genes or environment including diet on risk of IBD and the incidence of IBD in our cohorts is comparable to that reported from other population-based cohorts[26]. Second, while being the largest prospective study to evaluate gene-environment interactions in IBD, the numbers of patients with each genotype were small. Furthermore, we could not examine associations with disease phenotype, extent, or severity owing to limited numbers of patients with each characteristic of interest. Finally, while we studied polymorphisms influencing 3 enzymes that may influence the biologic effect of PUFA, other variants such as *ALOX5* and *CYP4F2* merit examination in future studies. In addition, polymorphisms at genes not involved in PUFA metabolism may modify

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its effect. For example, in prior studies, genetic variants in tumor necrosis factor α or PPAR α were noted to modify the effect of n-3 PUFA intake on inflammatory response[55, 56].

In conclusion, we report a novel gene-environment interaction between variants in *CYP4F3*, ratio of dietary n-3/n-6 PUFA and risk of UC. We did not identify an association between dietary n-3 or n-6 PUFA and CD. There is need for additional studies examining the impact of other polymorphisms in modifying diet-IBD associations as well as studies in patients with established disease to identify if individuals with specific genotypes may experience clinical benefit from PUFA supplementation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of included patients

Characteristic	Controls (n=495)	Ulcerative colitis (n=139)	p-value	Crohn's disease(n=101)	p-value
Mean age	49 (12)	48 (11)	0.39	51 (12)	0.07
Smoking			0.77		0.38
Never	59	56		59	
Former	34	37		30	
Current	7	7		11	
Body mass index			0.90		0.93
< 20 kg/m^2	11	11		12	
20 – 24.9 kg/m^2	41	43		38	
25 – 29.9 kg/m^2	28	28		30	
> 30 kg/m^2	21	18		21	
Oral contraceptive use			0.59		>0.99
Never	21	19		21	
Ever	79	81		79	
NSAID use			0.05		0.58
< 2 / week	78	70		75	
> 2 / week	22	30		25	
Appendectomy			0.15		0.05
No	80	86		71	
Yes	20	14		29	
Physical activity (mets-hr/wk)	19 (17)	19 (20)	0.98	18.9 (19.8)	0.84
Dietary intake					
Total calories (cal/d)	1750 (535. 5)	1756 (540.8)	0.90	1733 (538.6)	0.78
Carbohydrate (g/d)	219.4 (32.8)	223.0 (31.4)	0.24	214.7 (34.0)	0.20
Protein (g/d)	81.2 (13.4)	81.5 (12.6)	0.85	80.5 (12.2)	0.60
Fat (g/d)	60.7 (10.1)	61.0 (9.9)	0.77	59.9 (9.0)	0.46
Vitamin D (IU/d)	412.3 (265.3)	425.1 (272.5)	0.62	450 (296)	0.20

Characteristic	Controls (n=495)	Ulcerative colitis (n=139)	p-value	Crohn's disease(n=101)	p-value
Fiber (g/d)	18.5 (4.9)	19.0 (5.0)	0.26	18.2 (4.9)	0.64
Fatty acids (g/d)					
Total n3	1.21 (0.35)	1.22 (0.32)	0.79	1.24 (0.30)	0.51
Total n6	9.88 (2.63)	9.86 (2.21)	0.95	9.94 (2.22)	0.83
n3:n6 ratio	0.12 (0.02)	0.13 (0.02)	0.79	0.13 (0.03)	0.58
DHA	0.13 (0.09)	0.13 (0.11)	0.58	0.13 (0.08)	0.95
EPA	0.06 (0.05)	0.06 (0.07)	0.41	0.06 (0.04)	0.95
Long-chain n3	0.21 (0.15)	0.22 (0.19)	0.51	0.21 (0.13)	0.97

Cal/d – calories per day; g/d – grams per day; IU – International Unit;

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Table 2

Risk of ulcerative colitis by ratio of n-3/n-6 fatty acid intake, stratified by genotype

Polymorphism	Wild-type		Variant		P(interaction)
	Cases/ Control	Odds ratio (95% CI)	Cases/ Control	Odds ratio (95% CI)	
CYP4F3					
rs4646904 (GG/AG,AA)	84 / 282	0.57 (0.32 – 0.99)	55 / 212	0.95 (0.47 – 1.93)	0.049
rs1290617 (GG/GT-TT)	48 / 192	1.03 (0.49 – 2.17)	79 / 270	0.47 (0.26 – 0.84)	0.32
rs3794987 (GG/GA-AA)	91 / 334	0.56 (0.33 – 0.96)	36 / 128	0.75 (0.31 – 1.81)	0.55
rs2683037 (TT/AT-AA)	84 / 318	0.67 (0.39 – 1.15)	43 / 144	0.57 (0.24 – 1.33)	0.65
FADS1					
rs174561 (TT/CT-CC)	79 / 292	0.64 (0.36 – 1.11)	48 / 170	0.56 (0.26 – 1.21)	0.81
rs174556 (TT/CT-TT)	36 / 151	0.46 (0.19 – 1.07)	91 / 311	0.69 (0.40 – 1.18)	0.66
FADS2					
rs3834458 (TT/-T --)	70 / 270	0.70 (0.38 – 1.29)	57 / 192	0.48 (0.23 – 0.96)	0.56
rs174575 (CC/CG-GG)	46 / 197	0.74 (0.34 – 1.59)	81 / 265	0.61 (0.35 – 1.07)	0.30

All odds ratio are for intake > median vs. intake < median

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Table 3

Risk of ulcerative colitis by individual fatty acid intake, for CYP4F3 polymorphism

Fatty acid	Wild type	Variant	P(interaction)
Total n3 intake	0.78 (0.46 – 1.32)	1.09 (0.56 – 2.15)	0.20
Total n6 intake	1.19 (0.71 – 1.99)	1.21 (0.61 – 2.37)	0.54
DHA	0.80 (0.48 – 1.35)	0.85 (0.43 – 1.66)	0.50
EPA	0.74 (0.44 – 1.26)	1.10 (0.56 – 2.19)	0.20
Long-chain n3	0.80 (0.48 – 1.35)	0.87 (0.44 – 1.73)	0.44

All odds ratio are for intake > median vs. intake < median

Table 4

Risk of Crohn's disease by ratio of n-3/n-6 fatty acid intake stratified by genotype

Polymorphism	Wild-type		Variant		P(interaction)
	Cases/ Control	Odds ratio (95% CI)	Cases/ Control	Odds ratio (95% CI)	
CYP4F3					
rs4646904 (GG/AG,AA)	66 / 282	0.92 (0.50 – 1.70)	35 /212	1.73 (0.77 – 3.88)	0.48
rs1290617 (GG/GT-TT)	43 / 192	1.43 (0.67 – 3.03)	74 / 270	0.99 (0.51 – 1.91)	0.94
rs3794987 (GG/GA-AA)	70 / 334	1.03 (0.58 – 1.83)	27 /128	1.77 (0.66 – 4.76)	0.81
rs2683037 (TT/AT-AA)	70 / 318	1.20 (0.68 – 2.11)	27 / 144	0.96 (0.35 – 2.63)	0.85
FADS1					
rs174561 (TT/CT-CC)	60 / 292	1.02 (0.55 – 1.89)	37 / 170	1.21 (0.54 – 2.68)	0.71
rs174556 (TT/CT-TT)	31 / 151	1.58 (0.63 – 3.96)	66 / 311	1.00 (0.56 – 1.80)	0.21
FADS2					
rs3834458 (TT/-T --)	61 / 270	1.28 (0.69 – 2.36)	36 / 192	0.93 (0.41 – 2.13)	0.88
rs174575 (CC/CG-GG)	38 / 197	1.83 (0.82 – 4.10)	59 / 265	0.82 (0.44 – 1.55)	0.07

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