

EXTENDED REPORT

TNF α polymorphisms and risk of psoriatic arthritis

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Background: Tumour necrosis factor α (TNF α) is a cytokine of critical importance in psoriatic arthritis. **Objectives:** (1) To examine the association between TNF α promoter gene polymorphisms and psoriatic arthritis in two well characterised Canadian populations with the disease; (2) to carry out a meta-analysis of all TNF α association studies in white psoriatic arthritis populations. **Methods:** DNA samples were genotyped for five TNF variants by time of flight mass spectrometry using the Sequenom platform. All five single nucleotide polymorphisms were in the 5' flanking region of TNF α gene at the following positions: –1031 (T \rightarrow C), –863 (C \rightarrow A), –857 (C \rightarrow T), –308 (G \rightarrow A), and –238 (G \rightarrow A). Primary analyses were based on logistic regression. Summary estimates of disease/genotype relations from several studies were derived from random effects meta-analyses. **Results:** 237 psoriatic arthritis subjects and 103 controls from Newfoundland and 203 psoriatic arthritis subjects and 101 controls from Toronto were studied. A combined analysis of data from both populations, showed a significant association between disease status and the –238(A) variant ($p=0.01$). The meta-analysis estimate for the –238(A) TNF α variant in eight psoriatic arthritis populations was also significant (odds ratio = 2.29 (95% confidence interval, 1.48 to 3.55)). **Conclusions:** Analysis of TNF α variants in psoriatic arthritis populations shows that the –238 (A) variant is a significant risk factor for this disease.

Psoriatic arthritis is a complex immunologically mediated disorder that results from interplay between multiple genetic and environmental factors.¹ Although the pathogenesis of psoriatic arthritis is still unclear, there is a substantial contribution of genetic factors to the aetiology of the disease.² The MHC region has long been considered to harbour the underlying psoriatic arthritis susceptibility gene or genes and it has been estimated that at least one third of the genetic contribution of psoriatic arthritis resides within this region.² The tumour necrosis factor α (TNF α) gene, which is located 250 kb centromeric from HLA-B, has been proposed as a high priority candidate gene in psoriatic arthritis.³ This premise is supported by studies noting significantly higher levels of serum, synovial fluid, and synovial membrane levels of TNF α in patients with psoriatic arthritis than in those with osteoarthritis or healthy controls.^{4–5} The importance of TNF α in psoriatic arthritis is further strengthened by the marked clinical response of TNF α blockade.⁶ Thus TNF α appears to be a cytokine of critical importance in this disease.

However, genetic studies of TNF α polymorphisms and psoriatic arthritis have produced conflicting results.^{7–14} Certain studies have noted a significant association of TNF α polymorphisms in psoriatic arthritis,^{7,8} while others have failed to detect any such association.^{9–12} The inconsistencies in these results may reflect the small effect size of TNF α , insufficient sample size of subjects and controls, differences in populations, the presence of linkage disequilibrium, or multiple testing. In view of the location and proposed biological effect of TNF α , we felt it was prudent to evaluate further the relation between TNF α promoter polymorphisms and psoriatic arthritis in two well characterised Canadian psoriatic arthritis populations—a founder population from Newfoundland and a heterogeneous population from Toronto, Ontario. This was followed by a meta-analysis of the TNF α association studies in psoriatic arthritis populations.

METHODS

Patients

This study was approved by the local ethics committees at Memorial University of Newfoundland and the University of

Toronto. Informed consent was obtained from all patients. Psoriatic arthritis was diagnosed as an inflammatory arthritis in patients with psoriasis, in the absence of other causes of inflammatory arthritis. All psoriatic arthritis probands were white. Information was collected systematically and included age at onset of psoriasis and psoriatic arthritis, and the disease pattern. The control subjects were of similar ethnicity to the cases. Controls for the Newfoundland population were volunteers from Newfoundland who participated in our study as a result of a local campaign seeking population based controls for genetic studies. The Toronto controls were ascertained from the local HLA laboratory DNA bank which includes healthy volunteers and organ donors.

Laboratory methods

Blood samples were collected from patient volunteers with psoriatic arthritis and healthy controls in EDTA anticoagulant. DNA was extracted from peripheral blood lymphocytes using the Wizard Genomic DNA purification kit from Promega (Madison, Wisconsin, USA). DNA samples were genotyped for five TNF variants by time of flight mass spectrometry using the Sequenom platform. All five single nucleotide polymorphisms (SNPs) were in the 5' flanking region of TNF α gene at the following positions: –1031 (T \rightarrow C), –863 (C \rightarrow A), –857 (C \rightarrow T), –308 (G \rightarrow A), and –238 (G \rightarrow A). Primer sequences were determined using Sequenom SpectroDESIGNER software v1.3.4 (table 1).

For each sample, 2.5 ng of genomic DNA were amplified under standard conditions using the forward and reverse primer pairs. After DNA amplification, all unincorporated nucleotides in the polymerase chain reaction (PCR) product were deactivated using shrimp alkaline phosphatase. A primer extension reaction was then carried out using the mass extend primer and the appropriate termination mix. The primer extension products were then cleaned and spotted onto a SpectroChip. The chip was scanned using a mass spectrometry workstation (Bruker), and the resulting spectra

Abbreviations: HWE, Hardy–Weinberg equilibrium; SNP, single nucleotide polymorphism; TNF α , tumour necrosis factor α

Table 1 Primer sequences for TNF α single nucleotide polymorphisms

SNP ID	rs No	Forward primer	Reverse primer	Mass extend primer
-1031	rs1799964	5'-ACG TTG GAT GGG GAA GCA AAG GAG AAG CTG-3'	5'-ACG TTG GAT GTA CAT GTG GCC ATA TCT CCC-3'	5'-GAC CCT GAC TTT TCC TTC-3'
-857	rs1799724	5'-ACG TTG GAT GCT ATG GAA GTC GAG TAT GGG-3'	5'-ACG TTG GAT GTA TTC CAT ACC TGG AGG TCC-3'	5'-CCT CTA CAT GGC CCT GTC TTC-3'
-238	rs361525	5'-ACG TTG GAT GAC ACA AAT CAG TCA GTG GCC-3'	5'-ACG TTG GAT GAT CAA GGA TAC CCC TCA CAC-3'	5'-AGA AGA CCC CCC TCG GAA TC-3'
-308	rs1800629	5'-ACG TTG GAT GGG TCC CCA AAA GAA ATG GAG-3'	5'-ACG TTG GAT GGA TTT GTG TGT AGG ACC CTG-3'	5'-GAG GCT GAA CCC CGT CC-3'
-863	rs1800630	5'-ACG TTG GAT GCT ATG GAA GTC GAG TAT GGG-3'	5'-ACG TTG GAT GTA TTC CAT ACC TGG AGG TCC-3'	5'-CGA GTA TGG GGA CCC CC-3'

TNF α , tumour necrosis factor α .

were analysed using the Sequenom SpectroTYPER-RT software.

With respect to the meta-analysis, the literature was searched up to and including October 2004. All articles pertaining to TNF α polymorphisms in psoriatic arthritis were searched in Medline and Embase. In addition, the reference lists of the articles identified were also searched. We then selected studies that examined white populations and provided enough data for the numbers of minor alleles and the total number of alleles to be determined. The data was extracted by PR and then cross checked by CB.

Statistical analysis

Logistic regression was used to study the relation between typing information and case/control status. The results are summarised in terms of odds ratios and significance tests. In addition an exploratory haplotype analysis based on EM imputation¹⁵ was conducted.

Pairwise linkage disequilibrium was assessed for all combinations of TNF α variants using χ^2 tests. Strong associations were noted between -1031 and the other variants. The most notable association was between -863 and -1031 ($p < 0.001$), which was present in separate populations, both Newfoundland ($p < 0.001$) and Toronto ($p < 0.001$). For this reason -1031 was dropped from the haplotype analysis, which was based on the -238, -308, -857, and -863 variants.

Meta-analyses were based on random effects analyses.

RESULTS

We examined 237 psoriatic arthritis patients and 103 controls from Newfoundland and 203 patients and 101 controls from Toronto. The mean (SD) age of the psoriatic arthritis group in Newfoundland was 50.1 (11.3) years, and in Toronto, 50.5 (13.2) years. Forty nine per cent of patients were female in the Newfoundland cohort and 41% were female in the Toronto cohort. With respect to the subtype of psoriatic arthritis, overall for both populations 61% had the poly-articular pattern, 27% the oligoarticular pattern, 5.2% the isolated spondyloarthritis, and 7% were the remaining patterns. All probands had psoriasis vulgaris.

For the genotypes in the controls, there was no evidence of a departure from Hardy-Weinberg equilibrium (HWE) in the Newfoundland control population (p values were 0.13, 0.31, 0.29, 0.43, and 0.15 for 238(A), 308(A), 857(T), 863(A), and 1031(C), respectively). For the Toronto control population the comparable p values were 0.16, 0.04, 0.08, 0.24, and 0.23. While there is some weak evidence of departure from HWE for the 308(A) and possibly the 857(T) polymorphisms, this evidence would not survive any form of adjustment for multiple testing.

The genotypes and allele frequencies for psoriatic arthritis subjects and controls for TNF α polymorphisms in the Newfoundland and Toronto population are presented in tables 2 and 3, respectively. For completeness these tables present significance levels based on Fisher's exact test for an association between allelic frequency and disease status in

Table 2 TNF α genotypes and minor allele frequencies of the Newfoundland population

	Genotype	NF PsA patients	Controls	OR	p Value
TNF -238	G/G	181 (79.4%)	93 (90.3%)	2.13	0.03
	G/A	45 (19.7%)	9 (8.7%)		
	A/A	2 (0.9%)	1 (1.0%)		
Allele F (A)		10.7%	5.3%		
TNF -308	G/G	146 (64.9%)	67 (65.1%)	0.97	0.91
	G/A	75 (33.3%)	33 (32.0%)		
	A/A	4 (1.8%)	3 (2.9%)		
Allele F (A)		18.4%	18.9%		
TNF -857	C/C	191 (86.8%)	88 (85.4%)	0.87	0.74
	T/C	28 (12.7%)	14 (13.6%)		
	T/T	1 (0.5%)	1 (1.0%)		
Allele F (T)		6.8%	7.8%		
TNF -863	C/C	167 (72.3%)	70 (68.0%)	0.82	0.36
	A/C	60 (26.0%)	30 (29.1%)		
	A/A	4 (1.7%)	3 (2.9%)		
Allele F (A)		14.7%	17.5%		
TNF -1031	T/T	128 (58.2%)	63 (61.2%)	1.09	0.69
	T/C	77 (35.0%)	33 (32.0%)		
	C/C	15 (6.8%)	7 (6.8%)		
Allele F (C)		24.3%	22.8%		

NF, Newfoundland; OR, odds ratio; PsA, psoriatic arthritis; TNF, tumour necrosis factor.

Table 3 TNF α genotype and minor allele frequencies of the Toronto population

	Genotype	Toronto PsA patients	Controls	OR	p Value
TNF -238	G/G	164 (82.4%)	90(89.1%)	1.53	0.26
	G/A	35 (17.6%)	10(9.9%)		
	A/A	0 (0%)	1 (1.0%)		
Allele F (A)		8.8%	5.9%		
TNF -308	G/G	144 (70.9%)	69 (68.3%)	0.80	0.31
	G/A	53 (26.1%)	25 (24.8%)		
	A/A	6 (3.0%)	7 (6.9%)		
Allele F (A)		16.0%	19.3%		
TNF -857	C/C	148 (74.4%)	86 (85.1%)	1.89	0.03
	T/C	43 (21.6%)	13 (12.9%)		
	T/T	8 (4.0%)	2 (2.0%)		
Allele F (T)		14.8%	8.4%		
TNF -863	C/C	155 (77.5%)	71 (68.0%)	0.69	0.13
	A/C	41 (20.5%)	26 (29.1%)		
	A/A	4 (2.0%)	4 (2.9%)		
Allele F (A)		12.3%	16.8%		
TNF -1031	T/T	126 (63%)	61 (61.6%)	0.92	0.67
	T/C	65 (32.5%)	32 (32.3%)		
	C/C	9 (4.5%)	6 (6.1%)		
Allele F (C)		20.8%	22.2%		

OR, odds ratio; PsA, psoriatic arthritis; TNF, tumour necrosis factor.

the separate populations, but formal comparison of these must be based on tests of heterogeneity reported subsequently.

A combined analysis of data from both populations, based on a stratified logistic regression of allelic frequencies, showed a significant association between disease status and the -238(A) variant ($p = 0.01$). There was no evidence of heterogeneity of the association between the populations ($p = 0.49$). The observed frequencies in the Newfoundland psoriatic arthritis population and controls for the -238(A) variant were 10.7% *v* 5.3% respectively, while in the Toronto population they were 8.8% *v* 5.9%.

For the -857(T) variant, there was no evidence of a relation with disease status based on the combined analysis ($p = 0.42$). However, there was marginal evidence of heterogeneity between the populations ($p = 0.07$). Observed allelic frequencies for the -857(T) variant in the Toronto population were 14.8% *v* 8.4% in cases and controls, respectively, whereas no comparable marked difference was found in the Newfoundland population, in which the frequencies were 6.8% *v* 7.8%.

For the -308(A), -863(A), and -1031(C) variants, there was no evidence of relation with disease status (p values of 0.48, 0.28, and 0.64, respectively) or heterogeneity of effects between populations (p values of 0.53, 0.61, and 0.57, respectively).

Results based on a more conservative genotype analysis¹⁶ not influenced by HWE assumptions¹⁷ were very similar.

We then conducted a haplotype analysis for SNPs -238, -308, -857, and -863, in the two populations. The most notable result concerns the frequencies of the 1222 haplotype (where (1) indicates the presence of a minor allele, and (2) the presence of a major one) in patients and controls from Newfoundland ($p = 0.04$). The analysis suggests a greater frequency of this haplotype in cases than in controls. In Toronto, no significance was attached to this haplotype ($p = 0.27$). In the Toronto population the haplotype that appeared to be associated with the disease expression was 2212 ($p = 0.03$). This relation was not evident in Newfoundland ($p = 0.6$). Adjustments for multiplicity are required for interpretation purposes, however. A simple Bonferroni adjustment would generate a significance levels of $0.04 \times 9 = 0.36$ and $0.03 \times 7 = 0.21$ (as we have nine possible haplotypes in Newfoundland and seven in Toronto). Thus we report these haplotype frequencies as hypothesis-generating for future studies. Nevertheless, these haplotype analyses do

support the univariate SNP analyses, as they indicate that the presence of minor alleles at -238 in Newfoundland and at -857 in Toronto may be of importance for disease expression.

Meta-analysis

Nine cohorts from eight studies (including our two Canadian cohorts) were identified in the meta-analysis.⁷⁻¹³ The leading author, year of publication, population, TNF α variants, and the number of minor and total alleles for each of the variants are listed in table 4.

The results of the meta-analyses are summarised in fig 1 for the TNF α variants -238 and -308, which have been most extensively studied. The figures related to the other variants are not presented as they involve only three populations. Only the -238 variant was noted to have a significant association (odds ratio (OR) = 2.29 (95% confidence interval (CI), 1.48 to 3.55)). If the Japanese study is excluded from the meta-analysis, the pooled estimates for all the TNF variants were: -238(A), OR = 2.37 (95% CI, 1.52 to 3.69); -308(A), OR = 0.92 (0.69 to 1.23); -857 (T), OR = 1.30 (0.61 to 2.79); -863(A), OR = 0.75 (0.55 to 1.04); and -1031(C), OR = 1.00 (0.75 to 1.33), the latter three being based only on the combined analysis of the Newfoundland and Toronto data. If, however, the Japanese study is included in the meta-analyses, this did not have a significant impact on the above results, leaving them practically unchanged (see fig 1 for -238(A) and -308(A)). Note that a test for heterogeneity in the -238 meta-analysis was associated with a marginal significance level of 0.05, probably associated with the higher odds ratios observed in the German studies.^{7,8} A more significant result was associated with the -308 analysis ($p = 0.01$) due to the German_2 study's outlying odds ratio.⁸ This serves as justification for the use of a mixed effects model which adjusts for heterogeneity.

DISCUSSION

Psoriatic arthritis has a strong heritability, as reflected by a relative risk of 55 among first degree relatives with the disease.¹⁸ The TNF α gene has long been considered a major susceptibility gene in immunologically mediated disease, including psoriatic arthritis, for the pathogenesis of which it is of critical importance.² The associations between the two most widely cited TNF α promoter polymorphisms (-238 and -308 variants) and psoriatic arthritis have been evaluated in several populations.⁷⁻¹² Before our study, a significant association for TNF α and psoriatic arthritis was noted only

Table 4 Summary of TNF α associations studies in psoriatic arthritis

Author (reference)	Year	Population		-238(A)	-308(A)	-857(T)	-863(A)	-1031(C)	488(A)
Rahman*	2005	NF	Cases	49/456 (10.7%)	83/450 (18.4%)	30/440 (6.8%)	68/462 (14.7%)	107/440 (24.3%)	
			Controls	11/206 (5.3%)	39/206 (18.9%)	16/206 (7.8%)	36/206 (17.5%)	47/206 (22.8%)	
Rahman*	2005	Toronto	Cases	35/398 (8.8%)	65/406 (16.0%)	59/398 (14.8%)	49/400 (12.2%)	83/400 (20.8%)	
			Controls	12/202 (5.9%)	39/202 (19.3%)	17/202 (8.4%)	34/202 (16.8%)	44/198 (22.2%)	
Balding ¹⁰	2003	Irish	Cases		70/298 (23.5%)				
			Controls		172/780 (22.1%)				
Hohler ⁷	2002	German_1	Cases	30/174 (17.2%)	9/174 (5.2%)				
			Controls	7/198 (3.5%)	34/198 (17.2%)				
Gonzalez ¹²	2002	Spanish	Cases	15/162 (9.3%)	25/162 (15.4%)				
			Controls	14/220 (6.4%)	24/220 (10.9%)				
Al-Heresh ⁹	2002	Irish	Cases	23/248 (9.3%)	52/248 (21.0%)				17/248 (6.9%)
			Controls	14/202 (6.9%)	33/202 (16.3%)				14/202 (6.9%)
Gonzalez ¹¹	2001	Jewish	Cases	7/104 (6.7%)	8/104 (7.7%)				
			Controls	3/146 (2.0%)	15/146 (10.3%)				
Hamamoto ¹³	2000	Japanese	Cases	0/40 (0%)	0/40 (0)	7/40 (17.5)	6/40 (15.0)	4/40 (10.0)	
			Controls	4/174 (2.3%)	5/174 (2.9%)	27/174 (15.5)	27/174 (15.5)	22/174 (12.6)	
Hohler ⁸	1997	German_2	Cases	20/124 (16.1%)	19/124 (15.3%)				
			Controls	7/198 (3.5%)	32/198 (16.1%)				

*Current study, NF, Newfoundland.

in German populations.^{7, 8} In this study, we examined five common variants with the TNF α promoter gene, including -238 and -308. We noted a significant association between -238 variant and psoriatic arthritis in the Newfoundland population. The magnitude of our risk (OR = 2) was not as high as reported in the German studies (OR = 5). This may reflect a difference in population diversity, although it is well recognised that early association studies tend to overestimate the magnitude of the association conferred by a genetic polymorphism.¹⁹

Our pooled analysis of all TNF α studies in psoriatic arthritis populations also noted a significant association between -238(A) and psoriatic arthritis. The -238(A) variant increased the odds of psoriatic arthritis by twofold in the populations studied. The meta-analysis failed to support the association with the -308 (A) variant, which was previously reported in one of the German studies.⁷ The pooled estimates for the other variants showed no significant association, although the estimates for -857, -863, and -1031 were based only on the combined analysis of the two Canadian populations and the small Japanese cohort.

The differing results noted in the Irish^{9, 10} and Spanish^{11, 12} populations may be the result of ethnic admixture causing population stratification, population specific gene-gene or gene-environment interactions, variable linkage disequilibrium between the polymorphisms, and statistical

fluctuations.^{20, 21} Another possible explanation is the weak genetic effect of the underlying polymorphisms. In a meta-analysis of 370 studies addressing 36 genetic associations for various outcomes, it was noted that when a sample size of less than 150 patients was used, there was a sevenfold higher rate of discrepancy between the first and subsequent studies, as compared with studies where the sample size was at least 150.¹⁹ Except for our studies in the Canadian cohorts, all other studies reported their finding using fewer than 150 probands. As a result these studies may be underpowered to assess the impact of TNF α polymorphisms in psoriatic arthritis reliably. Furthermore, larger studies may give different results from small studies and thus our inferences here should be interpreted with caution until large scale evidence is generated on these associations.²²

As the previous studies were modest in size, we conducted a meta-analysis to assist in estimating the population-wide genetic effect of the commonly cited TNF α polymorphisms. Our pooled analysis showed a significant association between -238(A) and psoriatic arthritis. However, we acknowledge that population stratification was not entirely avoided as family based controls were not used in these studies. Furthermore, publication bias may exist in the meta-analysis, as small negative association studies are often not published. As demonstrated in our study, because meta-analysis of association studies in complex diseases are helpful in estimating

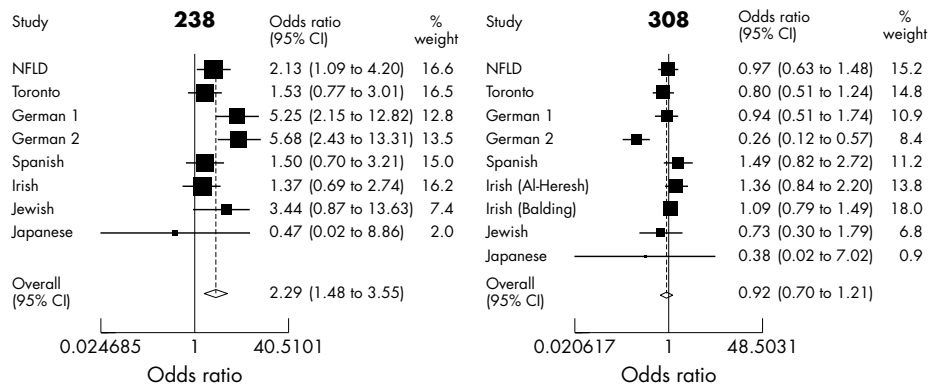


Figure 1 Meta-analysis of -238 and -308 variants of TNF α .

population-wide genetic effects, further efforts must be made to track all association data for a given polymorphism (positive or negative, small or large, published or not).

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