Correlation between interleukin 10 gene promoter region polymorphisms and clinical manifestations in Japanese patients with Sjögren's syndrome

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Sjögren's syndrome (SS) is an autoimmune disease characterised by lymphocytic infiltration and glandular tissue dysfunction of exocrine glands such as the salivary and lachrymal glands in genetically susceptible people. Several cytokines, including interleukin 10 (IL10), have been proposed to have a role in the pathogenesis of the disease. Although the major genes involved in susceptibility to SS are within the major histocompatibility complex (MHC) region, several putative non-MHC genetic loci (Ro52,[1] IL1,[2] IL6,[3] Fas/FasL,[4] mannose binding lectin,[5 6] TAP2,[7] and glutathione S-transferase M1 gene[8]) have been proposed as candidate genes. Recently, Hulkkonen *et al* reported that in Finnish patients the haplotypes formed on the basis of the IL10 gene alleles (at the -1082, -819, and -592 loci) were related to susceptibility to primary SS.[9] However, no correlation between extraglandular symptoms and IL10 haplotypes was found in that study. In this study we analysed promoter region polymorphisms of the IL10 gene in 47 Japanese patients with primary SS, and compared them with the values of several clinical and immunological variables.

The haplotype and genotype frequencies in Japanese subjects differed from those in white subjects. The GCC haplotype, which is predominant in white subjects, was less common in Japanese people. In contrast, the frequency of the ATA haplotype was significantly increased in Japanese subjects compared with white controls. The ACC haplotype carrier rate was significantly decreased in patients with SS compared with that in control subjects (34% *v* 51%, $p = 0.047$) (table 1). The frequency of the ACC haplotype was also decreased in patients with SS (18% *v* 29%). In contrast, the frequency of the ATA haplotype was increased in patients with SS compared with that in control subjects (73% *v* 65%). Further, we divided the patients with SS into a high s-IgG concentration group (≥15 g/l) and a normal s-IgG group (s-IgG<15 g/l) (table 1). The ATA/ATA genotype was significantly increased in the high s-IgG group (61% *v* 11%, $p = 0.012$). The ATA haplotype frequency was also significantly increased in the high s-IgG group (77% *v* 50%, $p = 0.033$). In contrast, the ACC haplotype was decreased in the high s-IgG group (13% *v* 33%).

Next, we compared the mean age at onset among genotypes of the IL10 gene in patients with SS (fig 1). The age at onset of patients with the ATA/ATA genotype was the lowest among the patients with SS (fig 1, upper). In contrast, that of patients with the ACC/ACC genotype was the highest among patients with SS. The age at onset of ACC haplotype non-carriers was significantly lower than that of ACC haplotype carriers ($p<0.001$). A younger age at onset of SS was likely to be positively related to the ATA haplotype and negatively to the ACC haplotype (fig 1, lower). The frequency of ACC haplotype was decreased in HTLV-I seropositive patients with SS compared with seronegative patients with SS, though the difference was not significant (data not shown). We failed to detect any association between IL10 gene polymorphisms and any of the following parameters:

Table 1 Individual IL10 genotypes, haplotype carrier rates, and haplotype frequencies in healthy controls and patients with Sjögren's syndrome (SS)

	Sjögren's syndrome (n = 47)	Healthy controls (n = 107)	χ^2, p value	Sjögren's syndrome		
				IgG≥15 g/l (n = 28)	IgG<15 g/l (n = 9)	χ^2, p value
Genotype No (%)						
ACC/ACC	1 (2)	6 (6)	0.313*	0 (0)	1 (11)	0.243*
ACC/ATA	14 (30)	45 (42)	0.149	6 (21)	4 (44)	0.959*
ATA/ATA	24 (51)	42 (39)	0.173	17 (61)	1 (11)	0.012*
ACC/GCC	1 (2)	4 (4)	0.516*	1 (2)	4 (44)	0.516*
ATA/GCC	7 (15)	10 (9)	0.312	3 (11)	3 (33)	0.757*
GCC/GCC	0 (0)	0 (0)		0 (0)	0 (0)	
Haplotype carrier rate, No (%)						
ACC carriers	16 (34)	55 (51)	0.047	7 (25)	5 (56)	0.100*
ATA carriers	45 (96)	97 (91)	0.230	26 (93)	8 (89)	0.578*
GCC carriers	8 (17)	14 (13)	0.520	4 (14)	3 (33)	0.955*
Haplotype frequency, No (%)						
ACC	17/94 (18)	61/214 (29)	0.053	7/56 (13)	6/18 (33)	0.988*
ATA	69/94 (73)	139/214 (65)	0.145	43/56 (77)	9/18 (50)	0.033
GCC	8/94 (9)	14/214 (7)	0.537	4/56 (7)	3/18 (17)	0.385*

*Value with Fisher's exact probability. Values underlined indicate $p<0.05$.

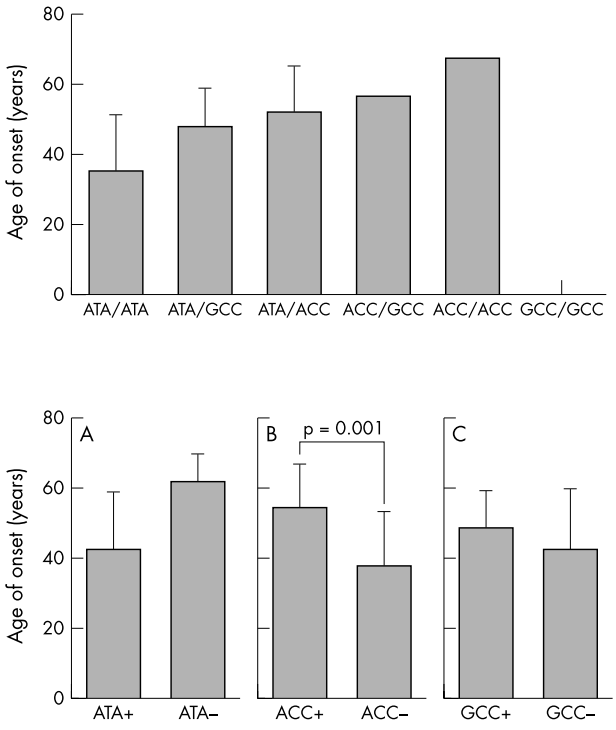

Figure 1 The effect of interleukin 10 (IL10) genotypes (upper part) on age at onset in Japanese patients with primary SS. (Lower part) Age at onset (mean and SD) is shown among the carriers and non-carriers of the IL10 ATA haplotype (panel A), ACC haplotype (panel B), and GCC haplotype (panel C), respectively.

sex, the presence of sicca symptoms, Schirmer test, salivary flow, or anti-Ro and anti-La antibodies (data not shown).

Our results suggested that the presence of the ATA haplotype and the absence of the ACC haplotype of the IL10 gene were associated with an increased sucseptibility to primary SS. Moreover, IL10 gene promoter region polymorphism affected the age at onset of SS, and supported evidence that variation in the age at onset of SS was genetically determined. We also clarified the association between IL10 gene polymorphisms and serum IgG levels. Brennan *et al* reported that a raised IgG level had a high specificity and high positive predictive value for SS.[10] IL10 gene polymorphism may become a useful predictor of SS.

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Cigarette smoking, TB, and TNF inhibitors

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Accompanying the tremendous excitement about the introduction of TNF inhibitors into the clinic has been caution about potential adverse events that may be associated with the use of these potent immunomodulators. Increased susceptibility to certain infections, particularly *Mycobacterium tuberculosis* (TB), has been a particular concern.[1] Data from animal studies suggest that TNF has a central role in host defence against TB, in part related to effective granuloma formation.[2] For infliximab, 277 cases of TB had been reported world wide through August 2002 among more than 365 000 patients treated. Interestingly, although about 75% of infliximab use has been in the United States, more than two thirds of the reported TB cases were from outside the USA, mainly from the European Union. Part of the reason for this discrepancy may relate to a higher incidence of latent TB infection in the EU. However, we suggest that cigarette smoking may also be a relevant factor. In 2000, just over 23% of adults in the USA were current cigarette smokers, compared with about 30% of European adults (http://www.cdc.gov/tobacco; http://www.cisid.who.dk/tobacco—accessed