Polymorphisms within interleukin 15 are associated with juvenile idiopathic arthritis

Sirs,

Interleukin (IL-) 15 is a pivotal cytokine in the regulation of chronic inflammatory and autoimmune diseases (1). It acts together with IL-18 in the induction and maintenance of chronic inflammation during experimental and clinical rheumatoid synovitis in mice (2). The role of IL-15 in human rheumatoid arthritis has extensively been investigated: Serum levels of IL-15 are elevated in adult patients with rheumatoid arthritis, especially in patients with long term disease (3). In children, IL-15 levels in synovial fluid have been shown to be about 20-fold higher than in serum from either juvenile idiopathic arthritis (JIA) or healthy children (4).

The genetics of arthritis is very complex and several candidate genes have been described. Besides, linkage and association studies have shown that chronic inflammatory diseases share some genetic factors.

Previously we had ruled out a major effect of polymorphisms within IL-18 on the genetics of JIA and asthma (5). However, we identified 5 polymorphisms in IL-15 and showed that haplotypes out of these polymorphisms were strongly associated with asthma (6). We were now interested whether IL-15 shows association with JIA. Thus we genotyped the same polymorphisms in a pediatric JIA population (n = 107) fulfilling the classification published by the International League of Associations for Rheumatology (7). In addition, all patients included in the study tested positive for antinuclear antibodies (ANA) in the serum, i.e. titer > 1:80. 270 randomly chosen adults served as controls.

Genotyping was performed as described previously (6). Association analysis was performed by the Armitage's trend test; calculation of Hardy Weinberg Equilibrium (HWE) made use of Finetti. In addition, we performed haplotype analyses with FAMHAP (8). The experimental procedures were approved by the local Ethical Committee.

The allelic frequency, p-values for HWE and association are given in Table I. All but one polymorphism were in HWE in both populations. The deviation in HWE seen with A10504G is most likely due to the low frequency of this polymorphism. The polymorphism C13687A was weakly associated with JIA (p = 0.033). Haplotype analyses revealed all polymorphisms in tight linkage disequilibrium. The haplotype distribution differed significantly between controls and children with JIA by p = 0.019. As we have previously typed the same polymorphisms in a pediatric asthmatic population we also calculated whether a difference in haplotype structure exists between children with asthma and JIA. Interestingly we found no difference (p = 0.23).

Table I. Listed are the polymorphisms under investigation, the allelic frequencies of the wildtype alleles and HWE as calculated by Finetti. In addition, the p-values for association with JIA calculated by the Armitage's trend test are given.

Polymorphism	JIA		Controls		p
	Frequency (%)	HWE (p)	Frequency (%)	HWE (p)	
C267T	0.69	0.629	0.71	0.705	0.688
G367A	0.52	0.289	0.53	0.384	0.722
A10504G	0.89	1.000	0.86	0.020	0.312
C13687A	0.93	0.413	0.88	0.148	0.033
A14035T	0.52	0.857	0.57	0.566	0.491

This is the first study to describe association of IL-15 with JIA. The association seen with single polymorphisms was only weak and it must be stated that this p-value has not been adjusted for multiple testing. However, as all polymorphisms were in very close linkage disequilibrium the classical Bonferroni correction would be far to conservative. Furthermore we found a significant difference in haplotype distribution.

As JIA is regarded as a typical TH1 disease, whereas asthma represent a TH2 disorder we would have expected to find an opposite haplotype distribution in between children with asthma and JIA. However, no difference was seen between these two diseases. Thus it seems that the same IL-15 polymorphisms promote both disorders.

This is in accordance to studies showing that IL-15 cannot definitely be classified as a TH1 or TH2 cytokine: IL-15 increases the production of the classical TH1 cytokine IFN-γ (9) and at the same time, supports TH2 diseases by enhancing IL-5 production (10). The here presented results might just underline the wide variety of immunological functions of IL-15.

In conclusion, we describe association of IL-15 with JIA. Though the results need confirmation in additional populations this could be a first hint of an involvement of IL-15 in the genetics of JIA.

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