Letters to the Editor

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Evidence for Interaction between Psoriasis-Susceptibility Loci on Chromosomes 6p21 and 1q21

To the Editor:

Psoriasis (PS [MIM 177900]) is a common inflammatory skin disorder affecting ~2% of the Caucasian population (Nevitt and Hutchinson 1996). The disease is characterized by the occurrence of red scaly patches and, in 5% of cases, is complicated by severe arthritis (Christophers and Sterry 1993). Despite the determining influence of several environmental factors, familial clustering of PS is well established, and empirical recurrence risk in first-degree relatives of isolated patients is in the range of 8%–23% (Hellgren 1967). Moreover, twin studies indicate that PS heritability is in the range of 70%–90% (Farber et al. 1974). An association between PS and the HLA Cw6 antigen has been repeatedly reported (reviewed by Elder et al. 1994), and a susceptibility locus has been identified, by parametric and nonparametric linkage (NPL) analysis (Nair et al. 1997; Trembath et al. 1997; Jenisch et al. 1998; Leder et al. 1998), on chromosome 6p21, within the HLA region. Further candidate loci have been assigned to chromosomes 2q, 4q, 8q, 16q, 17q, and 20p, although confirmation of linkage is so far available only for chromosomes 6p21 and 17q (Tomfohrde et al. 1994; Matthews et al. 1996; Nair et al. 1997; Enlund et al. 1999). Our group has recently identified an additional susceptibility locus in a sample of Italian three-generation psoriatic pedigrees, in which we demonstrated a significant linkage with chromosome 1q21 markers. In particular, NPL scores peaked within the region of the epidermal differentiation complex, between markers D1S1664 (NPL score 4.04) and D1S305 (NPL score 4.07) (Capon et al. 1999). These findings are in agreement with preliminary data obtained in an independent genome scan carried out on 23 U.S. extended pedigrees (Bhalerao and Bowcock 1998).

Since PS is considered a polygenic disorder (Elder et al. 1994), we tested the hypothesis that the 1q21 locus may interact with the one mapping within the HLA region. For this purpose, 15 three-generation families in which PS segregates with chromosome 1q21 markers (i.e., 15 pedigrees displaying positive LOD scores and posterior probabilities of linkage that were >0.6) were selected from our original sample, to investigate the relationship between 1q21 and 6p21 loci. We first tested these 15 families for association with Cw6, by typing one randomly selected trio from each 1q-linked pedigree. In a second phase, we extended HLA-C typing to all family members, and we investigated the correlation between NPL scores at HLA-C and D1S305 loci. Finally, we incorporated evidence of linkage to chromosome 1q21, in assessing linkage at the HLA-C locus.

Analysis 1: testing for association with Cw6.—The protocol described by Tatari et al. (1995) was used for HLA-C molecular typing of the 15 trios, including a randomly selected affected individual and his parents. Association with Cw6 was assessed by means of the transmission/disequilibrium test (TDT [Spielman et al. 1993]), which revealed the presence of the Cw6 antigen in 11 transmitted and 2 nontransmitted chromosomes. One parent was found to be homozygous for Cw6. The *P* value generated by the TDT test was .014, indicating an association with Cw6 in our sample of 1q-linked pedigrees.

Analysis 2: investigating the correlation between NPL scores.—In this phase, HLA-C typing was extended to all family members from the 15 1q-linked pedigrees. The corresponding NPL scores were assessed by use of GENEHUNTER+ 1.3 (Kong and Cox 1997), setting the "single on" and "skip large off" options. As expected, positive NPL scores resulted from the segregation of the HLA-Cw6 allele only (data not shown, available on request).

The correlation between NPL scores at HLA-C and D1S305 loci was investigated by means of SigmaStat 1.0 software (Jandel Scientific), to run Pearson's test. A correlation coefficient of .83 ($P = .0054$) was thus obtained.

Analysis 3: incorporation of evidence of linkage to chromosome 1q21 in assessment of linkage at the HLA-C locus.—This analysis was implemented by use of the ASM 1.0 program (Kong and Cox 1997) exponential model and by application of the proportional weighting scheme described by Cox et al. (1999). In brief, each family was assigned a weight corresponding to its NPL score for marker D1S305 on chromosome 1q21. A "weighted" LOD score was thus obtained, and the sig-

nificance of its increment with respect to the HLA-C baseline LOD (i.e., the LOD score calculated without consideration of linkage to 1q21) was assessed by means of a χ^2 test with 1 df (see Cox et al. 1999).

This analysis yielded a "weighted" LOD score of 4.66, whereas the baseline LOD was 2.89. The significance associated with the increased LOD corresponded to a χ^2 of 8.14 ($P = .0043$). This latter P value is comparable to the one generated by the correlation test.

The purpose of this study was to investigate the relationships between HLA-C and 1q21 loci, with respect to their contribution to PS susceptibility. At first, we demonstrated an association with Cw6 in our sample of 1q-linked pedigrees, by means of the TDT test (analysis 1).

The association between PS and HLA-Cw6 has been reproduced in numerous case-control studies performed in different populations (reviewed in Elder et al. 1994). However, it is noteworthy that Tomfohrde et al. (1994) failed to detect association with Cw6 in their sample of three-generation pedigrees that had linkage to chromosome 17q. Barnes et al. (1998) also reported a sample of 115 nuclear families stratified according to the presence of Cw6 among the affected individuals and were able to observe evidence for linkage on chromosome 1q only when analyzing the Cw6 negative sample. Therefore, our data provide the first evidence of association with Cw6 within a sample of families linked to a non-MHC locus. The discrepancy between our results and those reported by Barnes et al. (1998) might be due to the existence of two distinct susceptibility loci lying close to each other on chromosome 1q21, each interacting with different gene products. Since the 1q21 region contains >30 genes regulating epidermal growth and differentiation (Marenholz et al. 1996), this hypothesis is not altogether unlikely. On the other hand, the discrepancy between the two sets of results might be accounted for by differences in methods, population, and/or sample composition.

In the second phase of this study (analysis 2), the 15 1q-linked families were subjected to an analysis of the correlation between the NPL scores at HLA-C and D1S305 loci. In fact, the use of correlation between LOD scores has long been suggested as a means to assess interaction between unlinked regions (MacLean et al. 1993). This method has recently been extended to the analysis of complex disorders and NPL scores, by Cox et al. (1999). The correlation coefficient of .83 ($P = .0054$) that we report here was computed on a sample selected for an allele-sharing excess at 1q21 markers. NPL score and correlation analysis show that these families also tend to display an allele-sharing excess at the HLA-C locus. Thus, our data can be interpreted as preliminary evidence of an epistatic interaction between the 1q21 and 6p21 PS-susceptibility loci.

In the last phase of this study (analysis 3), assuming an interaction between 6p21 and 1q21 loci, we computed a "weighted" NPL score at the HLA-C locus. Thus, we could observe a significant increment of the "weighted" LOD score (4.66) with respect to the baseline LOD (2.89). This provided the first significant evidence for linkage, in the Italian population, with the HLA region. In fact, in a previous study, we had failed to detect any significant LOD score between marker D6S273 (mapping close to HLA-C) and PS (Capon et al. 1999); moreover, the Cw6 baseline LOD that we have reported in this study is on the threshold of statistical significance. Thus, only the assumption of interaction allowed us to replicate the linkage to the HLA region. This suggests that some of the difficulties in replication of results obtained in genome scans for PS susceptibility and, more generally, for complex disorders might be smoothed in the near future, by analyses allowing identification of potential interactions.

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