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ORIGINAL INVESTIGATION

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A genome-wide search for genes predisposing to familial psoriasis by using a stratification approach

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Abstract We have performed a genome scan, using markers spaced by 10 cM, in the search for psoriasis-susceptibility loci. The family material of 134 affected sibling pairs was ascertained on the basis of a population genetic study in which 65% of the probands had two healthy parents. Genotyping results were analyzed for non-random excessive allele-sharing between sib pairs by using GENEHUNTER ver 1.1. A stratification approach was applied to increase the homogeneity of the material by means of an operational definition of joint complaints among affected individuals. Significant linkage to the human leukocyte antigen region on chromosome 6p in a cohort including 42 families without joint complaints (non-parametric linkage score of 2.83, P=0.002) strongly supported the validity of this operational definition as it replicated results from an earlier linkage report with similar stratification criteria. New candidate regions on chromosomes 3 and 15 were identified. The highest non-parametric linkage values in this study, 2.96 (P=0.0017) and 2.89 (P=0.0020), were reached on chromosome 15 in a subgroup with joint complaints and on chromosome 3 in a subgroup without joint complaints. In addition, confirmation of previously reported loci was established on chromosomes 4q, 6p, and 17q. This study indicates that distinct disease loci might be involved in psoriasis etiology for various phenotypes.

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Introduction

Psoriasis is a skin disease affecting 2%–3% of the Caucasian population. The disease is manifested by an inflammatory reaction resulting in red scaly skin lesions. An early event in the pathogenesis is an increased infiltration of activated T-cells into the skin. A triggering factor preceding the onset of the disease is sometimes found. Such a factor may be a streptococcal throat infection, skin trauma, or even psychological stress. The onset of psoriasis varies from birth to old age. About 50% of those who develop the disease have an onset before the age of 25 years (Swanbeck et al. 1995). Henseler and Christophers (1985) distinguish between two variants of psoriasis: a familial form with an early age of onset and a sporadic form with a later age of onset.

The familial occurrence of psoriasis has been known for a long time. This has been thoroughly investigated in the small but homogeneous population on the Faeroe Islands by Lomholt (1963). The concordance rate among twins clearly indicates a strong hereditary factor (Farber et al. 1974; Brandrup 1982). We have shown that the occurrence of psoriasis among first degree relatives in 11,366 families is compatible with an autosomal recessive inheritance of psoriasis, taking into account a high gene frequency (Swanbeck et al. 1995).

The first factor recognized as being involved in psoriasis etiology was the human leukocyte antigen (HLA) complex located on chromosome 6p (Russel et al. 1972). In case-control studies, associations with certain HLA antigens were seen, most strongly to HLA-Cw6 and HLA-B57 (Tiililkainen et al. 1980;Gottlieb and Krueger 1990). HLA-Cw6 seems to influence the age of onset of the disease, with a concordance rate of 80% for having the Cw6 allele and developing psoriasis before 20 years of age (Enerbäck et al. 1997).

Attempts have been made to localize genes involved in psoriasis by linkage studies in family sets of different sizes and configurations. The first reported candidate regions, besides the established chromosome 6p association

(Genome Database [GDB] locus: *PSORS1*; MIM 177900), were on chromosomal regions 17q (GDB locus: *PSORS2*; MIM 602723) and 4q (GBD locus: *PSORS3*; MIM 601454; Tomfordhe et al. 1994; Matthews et al. 1996). These localizations were identified in a small number of multi-generation families. Later, three genome scans of both nuclear and multiplex families were conducted (Nair et al. 1997; Trembath et al. 1997; Capon et al. 1999). Novel psoriasis-susceptibility loci on chromosomes 1q (Capon et al. 1999), 2p, 8q, (Trembath et al. 1997), 16q (Nair et al. 1997), and 20p (Nair et al. 1997; Trembath et al. 1997) were suggested. The original candidate regions on chromosomes 4q, 6p, and 17q have, in addition to the genome scans, been evaluated in limited studies by our group and by others. Several studies have been unable to confirm the suggested region on chromosome 4q (Trembath et al. 1997; Burden et al. 1998; Enlund et al. 1999a), whereas the loci on chromosomes 6p (HLA region) and 17q have been confirmed (Nair et al. 1997; Trembath et al. 1997; Burden et al. 1998; Enlund et al. 1999a; Leder et al. 1998).

Psoriasis arthritis is an inflammatory joint disease known to be associated with psoriasis. In the majority of cases, the onset of psoriasis precedes the onset of psoriasis arthritis. In both conditions, symptoms can show periodical behavior. Various studies have reported that the prevalence of psoriasis arthritis among individuals affected with psoriasis is 10%–36% (Zanolli and Wikle 1992; Barisic-Drusko et al. 1994; Salvarani et al. 1995). In a report by Burden et al. (1998), linkage to the HLA region on chromosome 6p was investigated in a psoriasis family set stratified according to presence of psoriasis arthritis among affected individuals. Only the subgroup without signs of psoriasis arthritis showed linkage to the HLA region.

We have performed a genome-wide scan on a Swedish psoriasis family set with 134 sib pairs by using 390 microsatellite markers with an average spacing of 10 cM. Non-parametric linkage (NPL) analysis has been carried out on the total family material. In addition, we have stratified the material based on the presence of joint complaints among affected individuals and performed NPL analysis on the two stratification groups independently. The purpose of the study is two-fold: (1) to identify candidate regions for the location of psoriasis-susceptibility genes and (2) to evaluate previously reported candidate regions in family material of a different composition from earlier studies.

Materials and methods

Ascertainment of families

In order to perform a population genetic study on a Swedish psoriatic data set, 22,000 questionnaires were sent to members of the Swedish Psoriasis Association. Data were collected from 11,366 probands. This work is described elsewhere (Swanbeck et al. 1995, 1997). Families suitable for linkage studies were selected and contacted for the collection of blood samples. Criteria for including families were: (1) both parents must be unaffected and available for genotyping, and (2) at least two siblings must be affected. Criterion 1 was used to increase the power to detect loci with a recessive mode of inheritance, in which case, allele-sharing from an affected parent would be random. At the time of blood sample collection, all family members, except for three individuals, were examined by an experienced dermatologist (A.I.) to ensure correct diagnosis. Only subjects with confirmed psoriasis vulgaris were included in the study, but no classification was made based on the severity of the disease. The median age among the probands was 41 years (lower quartile: 35; upper quartile: 47). Informed consent was obtained from all subjects.

In an earlier study (Enlund et al. 1999a), we used a family set of 104 nuclear families ascertained as previously described. The set of 86 families used in this genome scan were included in that larger material. For 31 families, information concerning the place of birth of the probands' grandparents was collected and, for the remaining families, of the probands' parents. The vast majority were of Swedish heritage for many generations. Configurations for 86 families included in this study were as follows: 68 families with two affected children, 14 families with three affected children, and 4 families with four affected children. Taken together, the family set consisted of a total number of 366 individuals and 134 affected sib pairs, counting all possible combinations. Pedigrees are available on request.

Stratification based on "psoriasis arthritis"

At the time of examination by a dermatologist, all individuals were also asked about other medical problems, including joint complaints. If they were or had previously been suffering from significant aches or pain localized to one or several joints, the dermatologist classified these individuals as having joint complaints but did not try to make a specific diagnosis. In a few persons denying aches or pain from joints, joint deformation from joint inflammation could still be observed. These persons were also classified by the dermatologist as having joint complaints. Muscle pain and diffuse aching from the neck and shoulder region were not classified as joint complaints. Based on this definition, 29% (57 out of 194 affected) of the psoriatic individuals in this family set were classified as having joint complaints. This subgroup of affected individuals is referred to as stratification group A (group A). The remaining group of 136 affected without joint complaints is referred to as stratification group B (group B).

Markers and genotyping

All DNA samples were extracted from blood samples by using standard chloroform/phenol extraction protocols (Ausubel 1995). Polymerase chain reactions (PCRs) for genotyping were performed on a Perkin-Elmer/ABI 877 PCR-robot with fluorescent-labeled primers. PCR conditions were as suggested by the manufacturer, i.e., 0.4 U *Taq*, 100 ng DNA, 200 μM dNTPs, and 2 pmol primers in a total volume of 5 μl. A total of 390 markers from the CHLC/Weber Screening Set ver 6 A was used with an average heterozygosity of 76%. Two markers not included in the above set were used, viz., D3S1551 and D17S802. Each marker was used in an individual PCR, and up to 16 reactions were pooled before gel electrophoresis on a 4% acrylamide gel run for 2 h at 2400 V. Electrophoresis was performed on a Perkin-Elmer/ABI 377 Sequencer. Genotypes for each individual were determined by Perkin-Elmer/ABI Genescan and Genotyper version 1.1 software. All genotyping was checked manually.

Statistical analysis

Genotyping data were analyzed for excessive allele-sharing between affected sib pairs by using the GENEHUNTER ver 1.1 software (Kruglyak et al. 1996), generating an NPL score. GENEHUNTER ver 1.3 (Kruglyak and Lander 1998) was used for chro-

Table 1 NPL and *P* values for the total family set and for families with and without joint complaints

Marker	Distance from p-telomere (cM)	Total family material (86 families)	Families with joint complaints (44 families, stratification group A)	Families without joint complaints (42 families, stratification group B)
D1S179	256	0.73 (0.23)	1.98 (0.025)	–1.02 (0.84)
D2S1360	27	1.67 (0.048)	1.09 (0.14)	1.28 (0.10)
D2S1326	156	1.67 (0.048)	1.20 (0.12)	1.12 (0.13)
D2S1363	244	1.81 (0.036)	1.41 (0.080)	1.13 (0.13)
D3S1768	59	1.56 (0.059)	–0.44 (0.67)	2.89 (0.002)
D3S2409	71	1.13 (0.13)	–1.06 (0.85)	2.89 (0.002)
D3S2465	112	1.69 (0.046)	2.11 (0.019)	0.48 (0.32)
D3S1551	143	1.62 (0.052)	2.64 (0.004)	–0.51 (0.69)
D4S2361	88	1.65 (0.050)	2.45 (0.008)	–0.17 (0.57)
D4S2623	110	1.14 (0.13)	1.76 (0.039)	–0.18 (0.57)
D4S2431 (at *PSORS3*)	175	1.74 (0.042)	0.95 (0.17)	1.51 (0.064)
D5S816	152	2.22 (0.014)	2.45 (0.008)	0.64 (0.26)
D5S1456	194	1.67 (0.048)	1.10 (0.13)	1.26 (0.11)
D6S1281 (at *PSORS1*)	39	1.92 (0.030)	–0.06 (0.52)	2.83 (0.002)
D6S1019	49	2.07 (0.020)	0.41 (0.34)	2.58 (0.005)
D6S1053	77	1.86 (0.032)	1.37 (0.090)	1.26 (0.10)
6 cM dist D9S925	18	2.03 (0.021)	0.80 (0.21)	2.11 (0.018)
4 cM prox D9S930	112	1.67 (0.048)	1.10 (0.14)	1.16 (0.13)
D12S1294	72	1.04 (0.15)	–0.68 (0.75)	2.27 (0.010)
8 cM dist D121045	165	1.82 (0.033)	1.11 (0.14)	1.50 (0.068)
D14S749	102	1.53 (0.060)	2.11 (0.018)	–0.05 (0.50)
D15S817	0	2.33 (0.010)	2.96 (0.0017)	0.28 (0.39)
D17S921	43	0.63 (0.26)	–0.60 (0.73)	1.54 (0.061)
D17S784 (at *PSORS2*)	133	0.98 (0.16)	2.41 (0.009)	–1.10 (0.87)
D18S843	34	1.67 (0.048)	0.90 (0.18)	1.49 (0.069)
D20S604	27	0.62 (0.28)	1.95 (0.027)	–1.18 (0.88)
GATA31E08 (chr. X)	155	1.04 (0.15)	–0.66 (0.74)	2.16 (0.016)

mosome X. Although the sample of affected sib pairs is purposely biased because of no affected parents, the NPL score is still an unbiased test statistic (it still has an asymptotically normal distribution, and the false positive rate is not increased). Genetic maps for each chromosome were applied as given in the Weber Screening Set version 6.0 A. Markers not included in the Weber Screening Set were positioned by means of available integrated genetic maps.

Results

Total material

The most significant NPL value detected in the unstratified material was 2.33 (*P*=0.01) for marker D15S817. Marker D5S816 gave an NPL value of 2.22 (*P*=0.014). All NPL values equal or greater than 1.65 (*P*=0.05) are listed in Table 1. For a graphic view see Figure 1.

Stratified material

In an attempt to reduce the heterogeneous situation likely to be present in psoriasis, we decided to stratify our family set with regard to the presence of joint complaints among affected individuals (as defined above). Of the affected individuals distributed in 44 families, 30% belonged to the subgroup with joint complaints (group A), whereas in 42 families, none of the affected individual had any indications of joint complaints. NPL analyses as previously described were performed on both stratification groups. NPL values equal to or greater than 2.27 (*P*=0.01) were obtained for five markers in group A, i.e., D3S1551, D4S2361, D5S816, D15S817, and D17S784, and for five markers in group B, i.e., D3S1768, D3S2409, D6S1281, D6S1019, and D12S1294. Of all ten markers, only marker D15S817 gave a *P* value of 0.01 in the unstratified material. For a graphic view see Figure 2.

Discussion

We have previously presented population genetic data from extensive Swedish psoriasis material. It is striking that, on analyzing these data from a population genetic viewpoint, psoriasis behaved as a monogenic, autosoma-

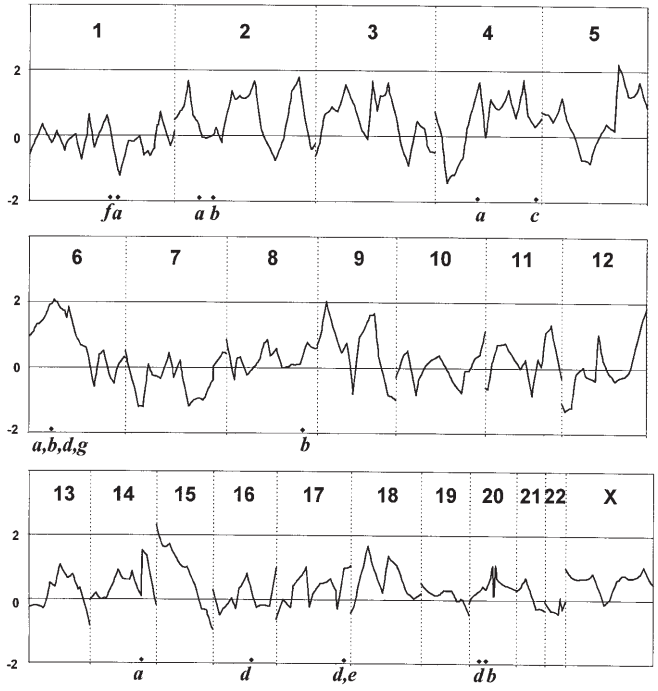

Fig. 1 NPL results from the genome scan on Swedish psoriasis family material. *Top panel* Data for chromosomes 1–5, *middle panel* those for chromosomes 6–12, *lower panel* those for chromosomes 13–22 and X. Loci implicated by other groups are indicated (*solid diamond*): ***a*** Bhalerao and Bowcock (1998), ***b*** Trembath et al. (1997), ***c*** Matthews et al. (1996), ***d*** Nair et al. (1997), ***e*** Tomfordhe et al. (1994), ***f*** Capon et al. (1999), ***g*** Leder et al. (1998)

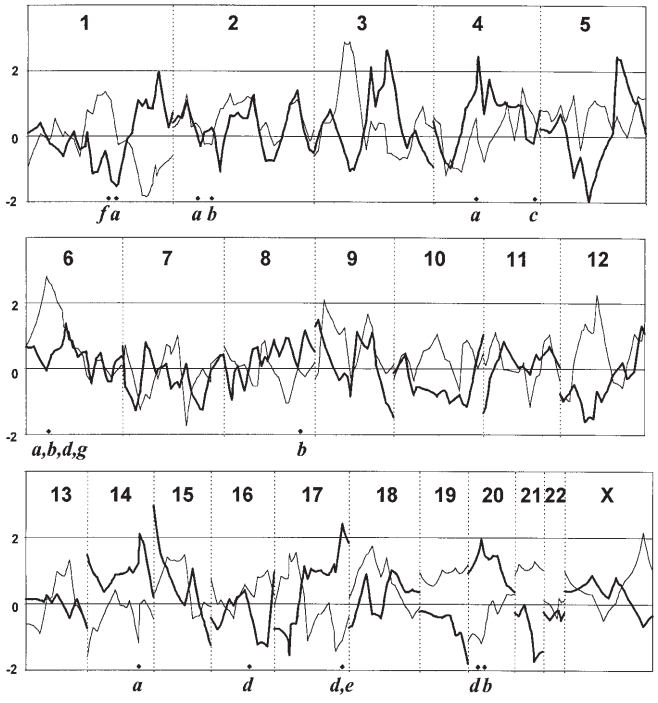

Fig. 2 NPL results from the genome scan on Swedish psoriasis family material stratified for the presence of joint complaints. The results for the families with joint complaints are presented as a *thick line*; the results for the families without joint complaints are presented as a *thin line*. Loci implicated by other groups are indicated as in Fig. 1

lly recessive disease, with a high gene frequency (Swanbeck et al. 1995, 1997). However, on looking at the linkage data presented here by us and previously by others, psoriasis strongly looks like a multigenic or complex disease. One explanation for these seemingly contradictory findings is a heterogeneity of the type "multiple single gene disorders with similar phenotype", which is the type of heterogeneity on which the calculation of lod scores under heterogeneity, e.g., hLOD, is based (Ott 1991). Other possible explanations cannot, however, at this stage be ruled out. In this respect, it should be stressed that our earlier population genetic data are based on a very large number of psoriasis patients, i.e., more than 11,000 inquiries, whereas all genome scans performed are inevitably based on a selection of a limited number of families.

The first candidate region for a psoriasis-susceptibility gene identified by linkage analysis was reported by Tomfohrde et al. (1994). Linkage to chromosome 17q was established in a limited number of extended pedigrees of Caucasian origin by means of two-point linkage analysis with a dominant mode of inheritance. This localization has been evaluated in family sets of different composition and size. Some studies confirm the localization (Nair et al. 1997; Enlund et al. 1999a), whereas other studies find no support for a psoriasis-susceptibility locus on chromosome 17q (Matthews et al. 1995; Trembath et al. 1997; Capon et al. 1999). Following this first psoriasis linkage study, several groups have conducted genome scans and more limited studies for the identification of psoriasis-susceptibility genes in family material of larger sizes and different ethnic origins. To date, candidate regions have been reported on chromosome 1 (Bhalerao and Bowcock 1998; Capon et al. 1999), chromosome 2 (Trembath et al. 1997; Bhalerao and Bowcock 1998), chromosome 4 (Matthews et al. 1996; Bhalerao and Bowcock 1998), chromosome 6 (Nair et al. 1997; Trembath et al. 1997; Bhalerao and Bowcock 1998; Enlund et al. 1999a; Leder et al. 1998), chromosome 8 (Trembath et al. 1997), chromosome 14 (Bhalerao and Bowcock 1998), chromosome 16 (Nair et al. 1997), chromosome 17 (Tomfordhe et al. 1994; Nair et al. 1997), and chromosome 20 (Nair et al. 1997; Trembath et al. 1997). Candidate regions replicated in independent family sets lie on chromosomes 1q, 6p (HLA region), 17q, and 20p. The involvement of a gene within or close to the HLA-C locus has been confirmed by family-based association studies (Nair et al. 1997; Jenisch et al. 1998), and a paternal effect on the inheritance of this locus has been suggested (Burden et al. 1998). Factors that might explain the discrepancies between various studies include the presence of phenocopies, reduced penetrance, misdiagnosis, and lack of a correct genetic model that explains the observed family aggregation of the trait.

We have previously shown that the results from a population genetic study on a large set of Swedish psoriasis family material are compatible with an autosomal recessive mode of inheritance (Swanbeck et al. 1995). On this basis, we have selected families with two or more affected children and unaffected parents. For the statistical analy-

ses, we have used non-parametric methods, as mentioned above, and a large number of nuclear families for the genome scan. All families are from Sweden and are ethnically homogeneous. Thus, this family set is genetically distinct from family sets used in earlier reported genome scans.

Validity of a stratification approach

The results presented here provide indications that different disease loci are involved in subsets of individuals affected with psoriasis, in this case with and without joint complaints. If linkage studies could be performed on family sets of a sufficient size ascertained on the basis of differences in phenotypic appearance, the present situation with a number of proposed candidate regions replicated in some family material but not all could be explained. Individual psoriasis loci might have various degrees of importance in different ethnic groups, because of dissimilarities in allele frequencies, therefore making it necessary to use a population of similar ethnic background for confirmation. One can imagine a similar situation for psoriatic individuals with various phenotypes. In order to detect "phenotype-specific" disease genes, linkage analysis needs to be applied to a distinct sub-group of psoriatics showing a particular phenotype.

The most common non-cutaneous symptom in psoriasis is arthritis. Most individuals affected with both diseases have an onset of psoriasis preceding the onset of psoriasis arthritis. It is reasonable to assume the existence of some common mechanism in the pathogenesis for the two conditions. In this study, we have used the presence of joint complaints as a basis for stratification in order to "enrich" our data with families exhibiting this specific phenotype, thereby detecting linkage that otherwise might be non-significant because of the inclusion of families without the specific phenotype. Although our operational definition of "joint complaints" is not necessarily synonymous with the diagnosis of psoriasis arthritis, we think that individuals with joint complaints, as defined above, have an increased risk of being affected with psoriasis arthritis.

The rationale behind the stratification approach is supported by the results from chromosome 6p. No significant linkage to the HLA region on chromosome 6p has been established when linkage analysis is performed on the subgroup including psoriatics with joint complaints only. In contrast, significant linkage is obtained when the analysis is carried out on the cohort of families in which no psoriatic individual has joint complaints. Indeed, combining the two groups doubles the number of families but reduces the NPL value from 2.83 (P=0.002) to 1.92 (P=0.03) (without adjusting for type 1 errors). The results confirm findings of linkage to the HLA region in a family set stratified by using similar criteria (Burden et al. 1998). Again, no significant linkage was obtained in a group including families in which affected individuals were considered to have psoriasis arthritis. Interestingly, one large family used in the first study reporting linkage to chromosome 17q did not show linkage to the HLA region on chromosome 6p (Tomfordhe et al. 1994). Several individuals in this family were affected with psoriasis arthritis (Bhalerao and Bowcock 1998).

Confirmation of previous findings

HLA region on chromosome 6p (PSORS1)

Results from this genome scan have confirmed the existence of a gene involved in psoriasis in the HLA region on chromosome 6p. For marker D6S1281, we have obtained an NPL value of 1.92 (P=0.03) for the total material and 2.83 (P=0.002) in group B. Marker D6S1019 gives similar results: an NPL value of 2.07 (P=0.02) in the total material and 2.58 (P=0.005) in group B. Linkage analysis of group A has shown no indications of linkage to the HLA region (NPL=–0.06, P=0.52 for marker D6S1281) or to marker D6S1019 (NPL=0.41, P=0.34). This is in agreement with an earlier report (Burden et al. 1998), indicating that there is no linkage to HLA in a subset of 46 families with psoriasis arthritis and a two-point LOD score of 3.64 for marker D6S291 in a subgroup of 57 families without psoriasis arthritis. This strongly suggests that different genetic factors give rise to the psoriatic phenotype in affected individuals with and without inflammatory joint disease. The lack of linkage to chromosome 6p in group A indicates a disease mechanism with a smaller contribution from genes within the HLA region.

Chromosome 4q

For marker D4S2361, we obtained an NPL value of 1.65 (P=0.05) in the total material and 2.45 (P=0.008) in group A. This marker is located at approximately the same position as D4S400, where Bhalerao and Bowcock (1998) have reported a P-value of 0.004. Our result supports the location of a psoriasis-susceptibility gene in this region.

Matthews et al. (1996) have reported the localization of a psoriasis gene region on the q-terminal part of chromosome 4 (GDB locus: *PSORS3*) with an NPL value of 4.22 (P=0.0026) for marker D4S1535 identified in families from Northern England and Ireland. In an earlier study of the same family set as that used here with the addition of 18 families, we tried to replicate this finding. No significant values were reported in that study (Enlund et al. 1999a). Different markers have been employed in this genome scan compared with the more limited study, but similar results have been achieved. The highest NPL value, 1.74 (P=0.042), was reached in the unstratified family material for marker D4S2431, located within the reported candidate region.

Chromosome 17q

On chromosome 17q, we achieved an NPL score of 2.41 (P=0.009) for marker D17S784. Again, we detected a dif-

ference between the two subgroups. The finding for D17S784 was only present in group A. This candidate region (GDB locus: *PSORS2*) was reported by Tomfordhe et al. (1994) in material of Caucasian origin. We and others have previously confirmed this localization. Our most significant finding has been made in a subgroup of psoriatic individuals with joint complaints; this might further add to our understanding of the action of this candidate locus.

Novel candidate regions

In addition to candidate regions implicated by other studies, we have identified novel candidate regions for psoriasis-susceptibility genes on chromosomes 3, 5, 12, and 15 with NPL values equal to or greater than 2.27 (P=0.01). The two findings on chromosome 3, on markers D3S1768 and D3S1551 respectively, were detected when the analysis was made on the stratified material. Marker D3S1768 maps to a potential "autoimmune loci" cluster on chromosome 3p (Becker et al. 1994). The chromosomal region around D3S1551 has been further analyzed in an extended family set by linkage and association studies. Results from these studies confirm the localization of a psoriasis-susceptibility locus on chromosome 3q21 (Enlund et al. 1999b). On chromosome 5, marker D5S816 gives an NPL value close to 2.27 (P=0.01) in the unstratified material (NPL=2.22, P=0.014) and increases above an NPL value of 2.27 in group A (NPL=2.45, P=0.008). Marker D15S817 is located at the p-terminal region of the acrocentric chromosome 15. In a recent study of ours, 477 individuals from different families and affected with psoriasis were cytogenetically analyzed for the presence of chromosomal aberrations (Enerbäck et al. 1998). Three constitutional aberrations in the form of 15cen+ and two sporadic aberrations in the form of 15p+ were detected, thus giving further support for the involvement of this region in psoriasis etiology.

In a genome scan with an average spacing of 10 cM between markers, one can expect to find P-values of 0.01 or less in 7–8 regions just by chance (Lander and Kruglyak 1995). In this stratified genome scan, we have obtained P-values of 0.01 or lower in a total of nine chromosomal regions. In addition to chromosome 6p, two more regions give P-values of 0.002, on chromosomes 3 and 15. A P-value of 0.0015 can be expected by chance approximately once in three genome scans of a similar composition to this one. Although P-values obtained for novel regions in this study do not reach the recommended level required for establishing suggestive linkage (Lander and Kruglyak 1995), it is important to report and follow up all positive regions so that failure to identify a novel candidate region can be avoided (Curtis 1996). Nominal P-values confirming earlier candidate regions include loci on chromosomal regions 4q, 6p, and 17q (Lander and Kruglyak 1995).

In several chromosomal regions with NPL values equal to or gtreater than 2.27 (P=0.01), the highest NPL values have been obtained after stratification. The negative aspect of the decreased number of sib pairs in the subgroups seems to be outweighed by the positive effect of having a more homogeneous family set. It is of course important that all localizations are evaluated with extended family materials of the right phenotype, i.e., with and without joint complaints, and with a denser set of markers, before any report of psoriasis-susceptibility genes in these regions can be made.

It is interesting to note that the two newly identified regions with P-values of 0.002 or less were found in the subgroup without joint complaints for chromosomes 3 and in the subgroup with joint complaints for chromosome 15. If potential disease alleles at these new candidate regions only participate in psoriasis etiology in specific subgroups, the increased risk that they confer might be too small to show even suggestive linkage in heterogeneous psoriasis family material.

In conclusion, we have identified new candidate regions for psoriasis-susceptibility genes on chromosomes 3, 5, and 15 in a family set of a unique composition compared with earlier published studies. In addition, we have shown that stratification can help to identify loci acting in distinct disease mechanisms.

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Electronic database information

URLs for data in this article are as follows:

- GENEHUNTER software, http://www.genome.wi.mit.edu/ftp/distribution/software/genehunter
- Genome Database (GDB), http://www.gdb.org (for loci denotation and marker information)
- Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nml.nih.gov (for PSORS1, PSORS2 and PSORS3)
- Perkin Elmer/Applied Biosystem, http://www.perkin.elmer (for information on the Genescan and Genotyper version 1.1 software)
- Research Genetics, http://www.resgen.com (for information on CHLC/Weber Screening Set ver 6 A)

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