Genetics of Psoriasis in Iceland: Evidence for Linkage of Subphenotypes to Distinct Loci

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Psoriasis is a chronic inflammatory skin disease with overlapping subphenotypes. It has a strong complex genetic component, but has been problematic to identifying significant loci. We evaluated 1000 patients with chronic plaque psoriasis and documented several subphenotypes. Here we report results of genome-wide linkage scans for psoriasis genes in 238 Icelandic families with 874 patients. MHC linkage was confirmed with LOD score of 10.9. When the entire cohort was analyzed, two other loci with LOD scores of 2.5 and 1.5 were observed on 16q and 4q, respectively. Stratification into subphenotypes revealed additional loci with LOD scores exceeding or approaching significance. A LOD score of 5.7 appeared on 16q in PsA patients with analysis conditioned on parental inheritance. A LOD score of 3.6 on 4q was detected when disease occurred at or older than 17 y, our median cohort age. This locus was defined by a marker near one reportedly displaying significant linkage in a Chinese psoriasis population and near suggestive linkage in a Caucasian population. A LOD of 3.0 was observed on 10q when disease onset occurred in the scalp. Furthermore, clinical stratification either revealed or increased LOD scores when compared to unstratified analysis and some coincided with previous reports.

Key words: psoraisis/subphenotypes/linkage/stratification
J Invest Dermatol 124:1177–1185, 2005

Psoriasis [MIM177900] is a chronic inflammatory and hyperkeratotic skin disease that is believed to be mediated by T lymphocytes (Baker *et al*, 1984; Valdimarsson *et al*, 1986; Prinz, 1999). The etiology of psoriasis is unknown but it has a strong genetic component (Farber and Nall, 1974; Elder *et al*, 1994). Several distinct but overlapping subphenotypes of the disease have been identified, including chronic plaques that are the most common form, sebopsoriasis-type lesions, guttate eruptions, pustular lesions, and the rare but severe erythrodermic form. Although these different phenotypes may all converge on a common pathogenic pathway, they probably have somewhat different genetic backgrounds. Previous studies have shown possible linkage to many loci, including the major histocompatibility molecules (MHC) as well as loci on chromosomes 1q, 1p, 2p, 3q, 4q, 8q, 10q,16q, 17q, 18p, 19p, and 20p (Tomfohrde *et al*, 1994; Matthews *et al*, 1996; Nair *et al*, 1997; Trembath *et al*, 1997; Burden *et al*, 1998; Jenisch *et al*, 1998; Capon *et al*, 1999; Enlund *et al*, 1999a, b; Lee *et al*, 2000; Veal *et al*, 2001; Asumalahti *et al*, 2003). A recent study was conducted by an international consortium on the genetics of psoriasis that combined patient material from three groups studying the genetics of psoriasis. They found linkage and association of statistical significance only at the MHC (International Psoriasis Genetics Consortium, 2003).

Abbreviations: MHC, major histocompatibility molecules; LOD, logarithm of odds ratio; HLA, human leukocyte antigen; POPP, pediatric onset psoriatic patients; AOPP, adult onset psoriatic patients

Some groups that have detected significant loci in genomic regions other than the MHC have launched fine mapping projects, aimed at locating regions of association signifying proximity to a contributing gene (Capon *et al*, 2001; Hewett *et al*, 2002). At least two groups have located candidate genes outside the MHC: one, named SLC12A8, is homologous to a cotransporter family, was found in a Swedish population (Hewett *et al*, 2002) and an RUNX1 binding site variant also near a transporter gene (SLC9A31), associated with psoriasis (Helms *et al*, 2003) in a region previously described as containing an interesting immunoglobulin superfamily gene cluster in the middle of their area of linkage on 17q (Speckman *et al*, 2003). RUNX1 binding sites have previously been associated with auto-immune diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (Prokunina *et al*, 2002; Tokuhiro *et al*, 2003). But only the MHC locus has met accepted criteria for genome-wide significance and been consistently replicated in independent studies (Elder *et al*, 2001). Additionally, many studies have reported an association between psoriasis and alleles in the MHC, particularly human leukocyte antigen (HLA)-Cw0602 (Jenisch *et al*, 1998; Balendran *et al*, 1999; Oka *et al*, 1999; Nair *et al*, 2000). Estimates of the carrier frequency of this allele in Caucasian populations are around 15% whereas in psoriasis patients it ranges between 55% and 80%, leading to risk ratios between 4 and 15 (Tiilikainen *et al*, 1980; Mallon *et al*, 1999). Other genes within HLA class III/I have also been implicated in several studies (Ishihara *et al*, 1996; Jenisch *et al*, 1999; Tazi Ahnini *et al*, 1999; Asumalahti *et al*, 2000, 2002; Schmitt-Egenolf *et al*, 2001; Orru

et al, 2002), although these findings have not been confirmed by others (Enerback *et al*, 2000; Chia *et al*, 2001; O'Brien *et al*, 2001), and no group has been able to identify a single allele as tightly associated with psoriasis as HLA-Cw6. Clearly, HLA-Cw0602 allele, or an allele close to HLA-C, contributes strongly to predisposition to psoriasis. Nonetheless, the MHC association explains only a portion of the genetic contribution to psoriasis and the remaining genetic factors are largely unknown and may vary between populations.

Confirmation of non-MHC loci between populations is rare and, a confirmation linkage has never reached the criteria for independent genome-wide significance although several have reached the confirmation criteria of logarithm of odds ratio (LOD) 2 (Nair *et al*, 1997; Enlund *et al*, 1999; Karason *et al*, 2003). It seems that despite the almost universally observed association with HLA-Cw6, genetic studies of psoriasis have been difficult as have genetic studies of other complex diseases. We and others have failed to observe increases in the LOD scores of suggestive loci outside the MHC region by increasing cohort size. The reasons for this may include locus heterogeneity, epistasis, and dynamic mutations. Furthermore, twin studies indicate that age at onset and various other differences in the clinical features of psoriasis are determined by genetic factors (Farber and Nall, 1974; Brandrup *et al*, 1982), and it may be difficult to identify such subphenotypic components when patients' cohorts are analyzed as a single clinical entity. Stratification of patients using clinical phenotypes might help to localize predisposing genes, and we have already reported a significant linkage to the arthritic phenotype of psoriasis that was not detected when our psoriasis cohort was analyzed as a homogenous group (Karason *et al*, 2003). As we have carefully evaluated the medical history and a standardized set of clinical features for all patients in our cohort, it was decided to use other phenotypic features for further genetic analysis of patients. In this way, an increase in LOD score was observed at several loci that had previously shown a modest linkage to psoriasis, including one narrowly missing independent genome-wide significance.

Results

The broad psoriasis phenotype Using the genealogy database, 874 patients were clustered into 238 families with up to and including six meioses. Without clinical stratification of patients, the results showed a highly significant linkage to the MHC region on chromosome 6p21.3 with an LOD score of 10.9 at marker TNFA (Fig 1) Chromosome 16q showed suggestive linkage with an LOD score of 2.5 at around 84 cM where we have a genome-wide significant locus for psoriatic arthritis, and several groups have reported suggestive linkage (Nair *et al*, 1997; Karason *et al*, 2003), and a modest LOD score of 1.5 was observed on chromosome 4q (Fig 2) (marker DG4S106). A scan of female psoriasis patients yielded an LOD score of 2.6 on the q arm of chromosome 5 at D5S2090 (Fig 3), which maps within 17 Mb of the RUNX1 binding site associated with RA. No other suggestive linkage was observed in the unstratified cohort.

We also confirmed previously reported allelic association between HLA-Cw*0602 and psoriasis. Sixty-four percent of patients (643/997) were carriers of Cw6 compared with 15%, (79/505) of controls, giving an estimated risk ratio of 9.8 for Cw6 carriers *versus* non-carriers. Our data are consistent with the MHC risk allele being either HLA-Cw*0602 itself or a risk variant located very close to HLA-C (data not shown). Even though Cw6 carriers had a much higher risk of developing psoriasis than non-carriers, we estimated the penetrance of Cw6 at 10%, assuming that the population risk of psoriasis is 2.5%.

To further explore the contribution of Cw6-associated susceptibility, we divided patients into two groups based on Cw6 carrier status and repeated the linkage analysis for each group. When only patients who carry HLA-Cw6 were classified as affected, the LOD score in the MHC region predictably rose to 17 (Fig 3). Loci with LOD scores of suggestive linkage (greater than 2.2) were found on 5p and 7q. Conversely, we performed linkage analysis classifying only the Cw6-negative patients as affected. An LOD score approaching 2 was seen on 1q (Fig 4). In addition, Cw6-negative patients showed modest linkage on chromosome 17q (LOD score 1.5) at the location where Tomfohrde *et al* found the first non-MHC locus in 1994 and where the RUNX1 binding site is located (Helms *et al*, 2003) (Fig 5), perhaps suggesting that the associated variant segregates more frequently in families where Cw6 is not prevalent.

Subphenotype analysis The MHC locus and the excess of HLA-Cw6 are the only genetic findings that have consistently been reported in psoriasis patients. It is unlikely, however, that a gene in the MHC locus is involved in the pathogenesis in all psoriasis patients, because HLA-Cw6 is only present in approximately 60% of patients. Patients with chronic plaque psoriasis, however, show a marked clinical heterogeneity, which is likely genetically determined (Brandrup *et al*, 1982), but is only to some extent associated with the presence or absence of Cw6 (Gudjonsson *et al*, 2002). We therefore decided to analyze genotypes in relation to certain clinical subphenotypes of this disease.

Age at disease onset The age at onset ranged from 1–72 y in our cohort with a median of 17 y. Seventeen years was defined by Raychaudhuri and Gross (2000) as a cutoff point for defining pediatric onset psoriatic patients (POPP) and adult onset psoriatic patients (AOPP). Marked clinical differences have been reported between these early- and late-onset groups. Therefore, we decided to compare these two groups in our genetic study. About 75% of the POPP group carried Cw6 compared with 45% of the AOPP group. The two groups were clustered into families using our genealogy database at a maximum genetic distance of seven meioses. This left us with 449 patients in 170 families for the POPP group and 516 patients in 186 families for the AOPP group. The combined number of families in the AOPP and POPP groups (356) does not contradict the total number in the unstratified scan (238) because clustering is performed on each new phenotype and new and often smaller family structures are expected. When linkage analysis was performed on AOPP, an LOD score of 3.6 was observed

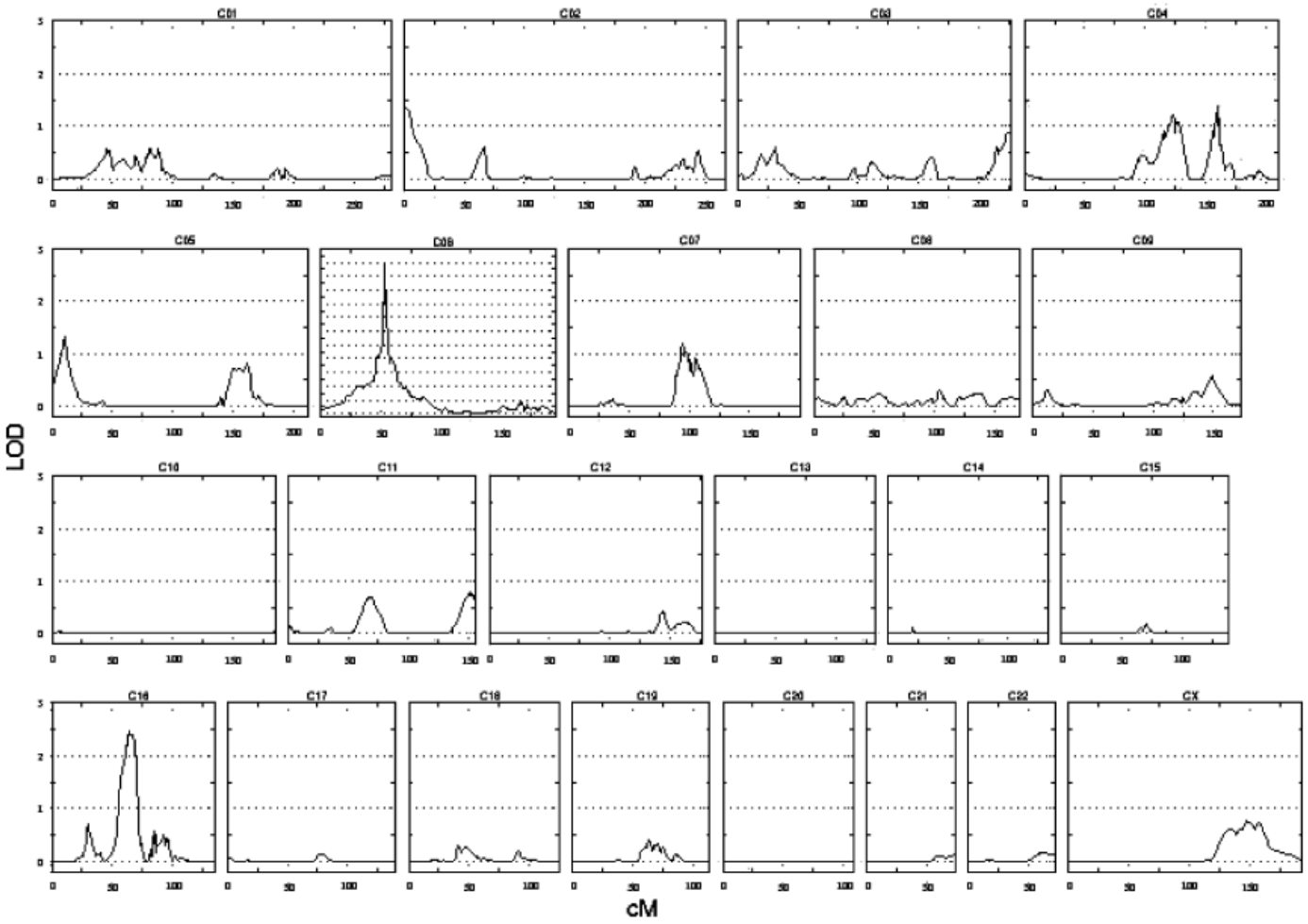

Figure 1
The linkage result of 874 psoriasis patients in 238 families up to and including six meioses, genotyped with a 1000 marker genome-wide microsatellite screening set showing a highly significant linkage to the major histocompatibility complex region on chromosome. 6p21.3 with a logarithm of odds ratio (LOD) score of 10.9.

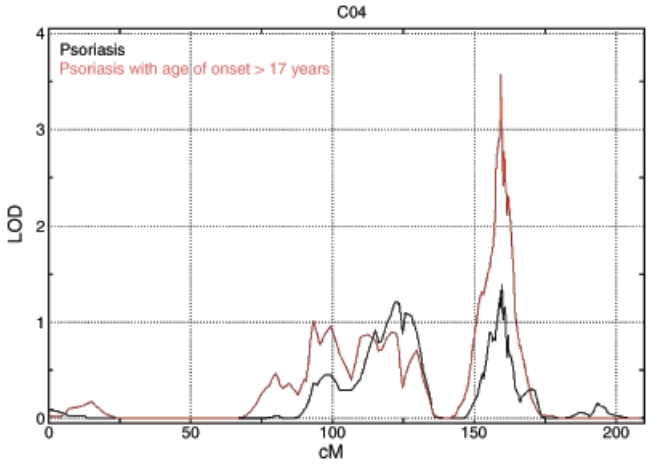

Figure 2
The linkage result at chromosome 4 for all patients (*in black*) and patients whose age at onset is greater than 16 y genotyped with a 1000 marker genome-wide microsatellite screening set revealing a logarithm of odds ratio (LOD) score of 3.6.

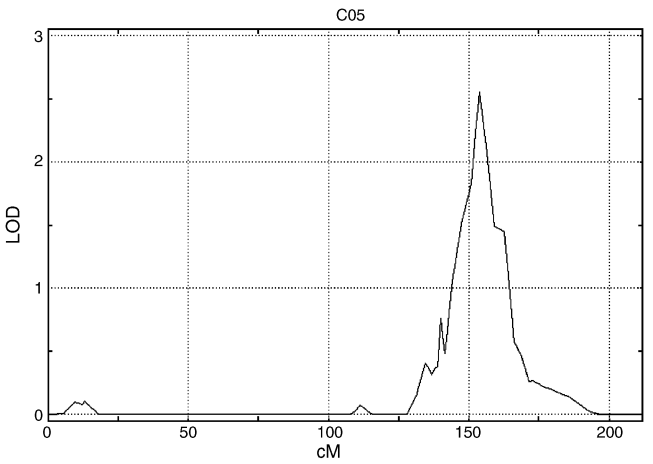

Figure 3
The linkage result at chromosome 5 for female psoriasis patients genotyped with a 1000 marker genome-wide microsatellite screening set genotyped with a 1000 marker genome-wide microsatellite screening set showing a logarithm of odds ratio (LOD) score of 2.6.

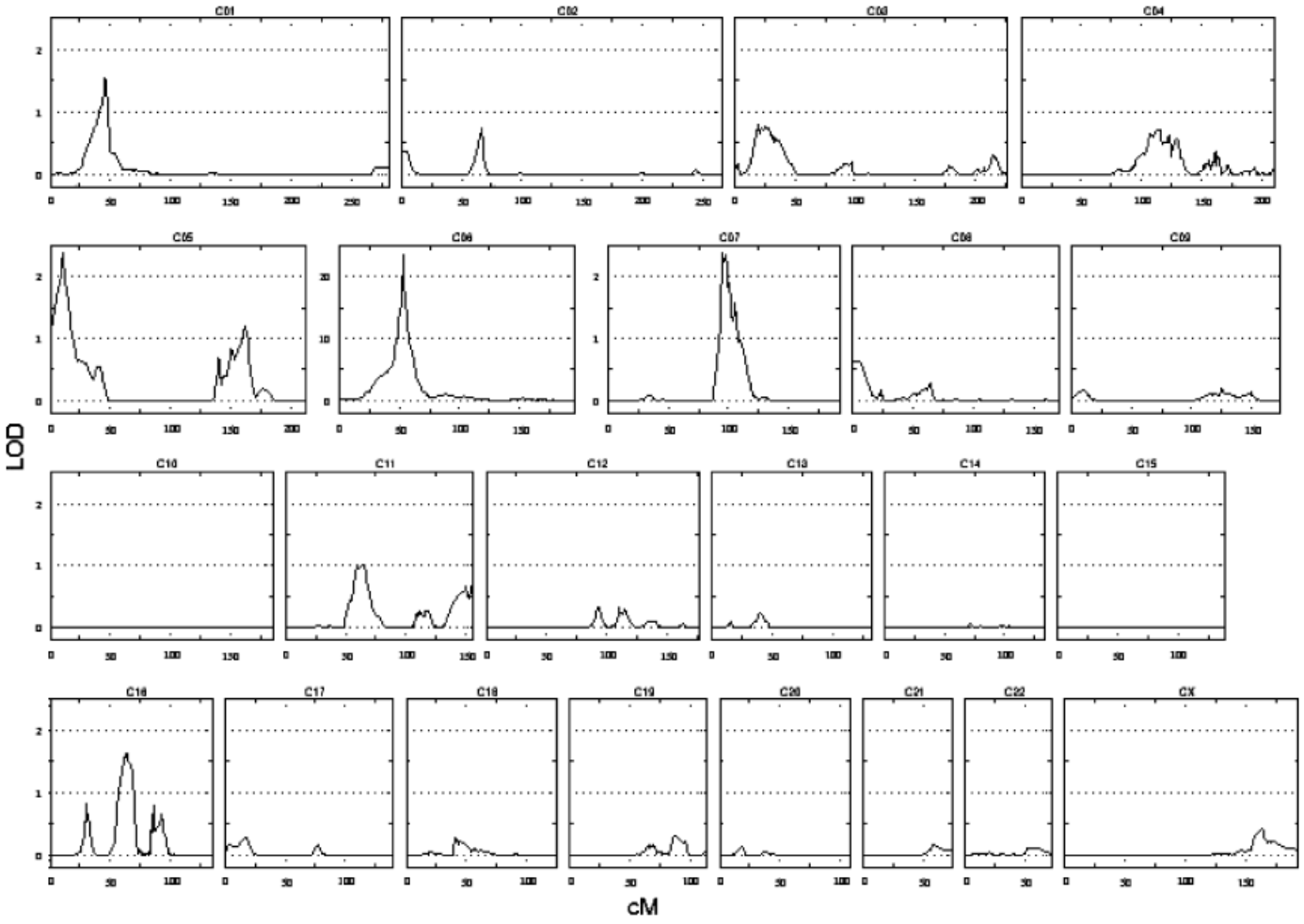

Figure 4
The linkage result of psoriasis patients who carry at least one Cw6 allele genotyped with a 1000 marker genome-wide microsatellite screening set showing suggestive linkage on chromosomes 5 and 7.

on chromosome 4q at DGS106 (Fig 2), almost meeting accepted criteria for genome-wide significance compared with a modest score of 1.5 in the cohort as a whole, near a region that has been linked to psoriasis families in the UK (Matthews *et al*, 1996). Linkage has recently been reported in Chinese Hans at D4S413 (Zhang *et al*, 2002), which maps within 5 Mb of our linkage peak on 4q. We observed another suggestive locus in the older onset group with an LOD score of 3.1 on chromosome 14p (marker D14S261). The AOPP group had an LOD score of 7.2 in the MHC despite the previously stated relative deficit of patients carrying Cw6 in patients with late disease onset compared with the early-onset group.

Linkage analysis of the POPP group gave an LOD score of 8.6 at the MHC. No other location approached genome-wide significance in this group, except that a suggestive LOD score of 2.5 is observed for maternal transmission on 6q at D6S1603 within 10 Mb of where Nair *et al* (1997) found evidence for linkage.

Nail involvement We also analyzed 310 patients who had one or more types of psoriatic nail lesions. They were clustered at six meioses into 119 families and a linkage scan revealed an LOD score of 6.0 in the MHC at marker TNFA. In addition, when maternal transmissions were analyzed, suggestive LOD scores of 2.6 were observed on 6q at D6S1614, the same location as POPP and on 9p at D9S235, and an LOD score of 2.7 on chromosome 11 at D11S4162.

Scalp onset Psoriasis of the scalp is a characteristic feature of sebo-psoriasis (van de Kerkhof and Franssen, 2001) and has been reported as the most common site affected by psoriasis as well as the most frequent site of disease onset (Farber and Nall, 1992; Gudjonsson *et al*, 2002). Of 1000 patients, 296 (30%) reported that psoriasis began on their scalp. Of these patients, 198 clustered into 79 families and an LOD score of 3.4 was observed, at the q-telomeric end of chromosome 10 (Fig 6). A similar score of 3.1 was found closeby in males with scalp affection at D10S1700. This position may coincide with a locus reported by Nair *et al* (1997).

Koebner's phenomenon Some psoriasis patients develop psoriatic lesions at sites of trauma and this is referred to as Koebner's phenomenon. In our cohort, the ratio of female patients to male patients with Koebner's is 58%–42%. Of 398 patients who had experienced this reaction, it was possible to cluster 259 into 98 families yielding an LOD

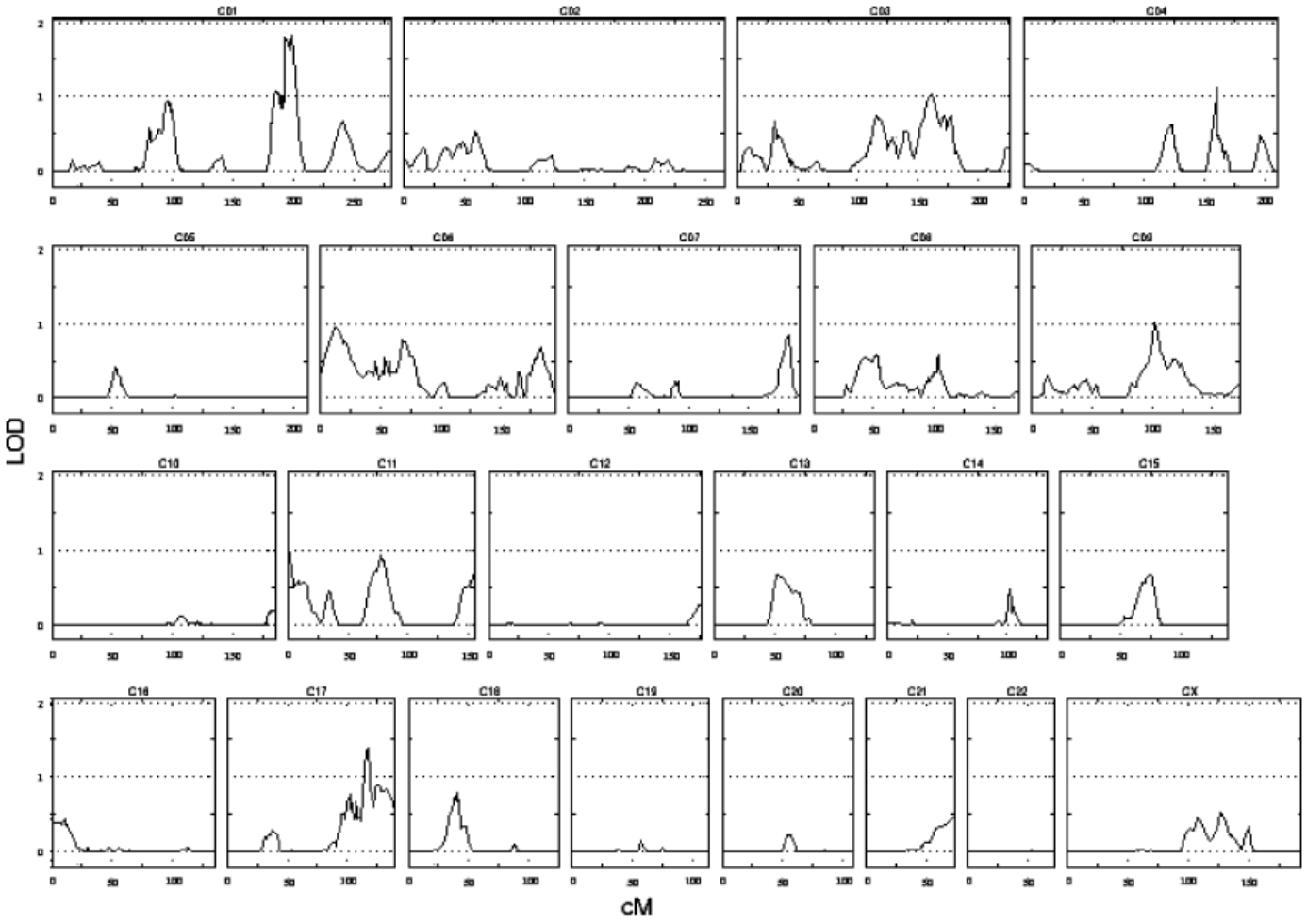

Figure 5
The linkage result of psoriasis patients who do not carry a Cw6 allele genotyped with a 1000 marker genome wide microsatellite screening set showing modest linkage on chromosomes 1 and 17.

score of 4.8 in the MHC. Additionally, when female Koebner's patients were designated as affected, a score exceeding 3.1 was observed on chromosome 14q at D14S1050 (Fig 6).

Psoriatic arthritis We have previously reported an LOD score of 4.19 on the q-arm of chromosome 16 for paternal transmission of psoriatic arthritis in 100 patients who clustered into 39 families (Karason *et al*, 2003). Addition of

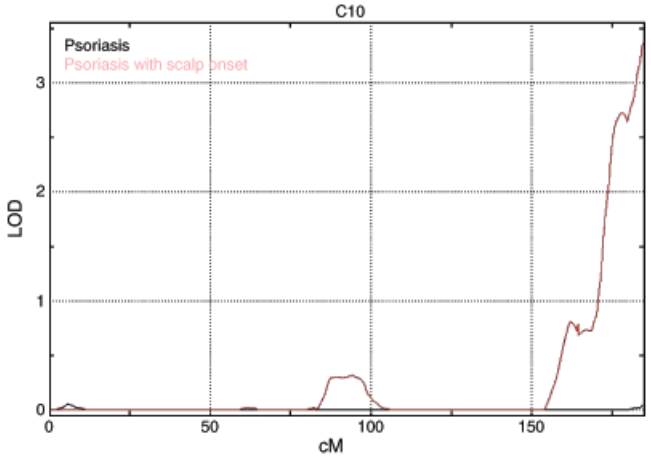

Figure 6
The linkage result on chromosome 10 of psoriasis patients genotyped with a 1000 marker genome-wide microsatellite screening set whose psoriasis onset was on the scalp in red and unstratified in black showing a logarithm of odds ratio (LOD) score of 3.4.

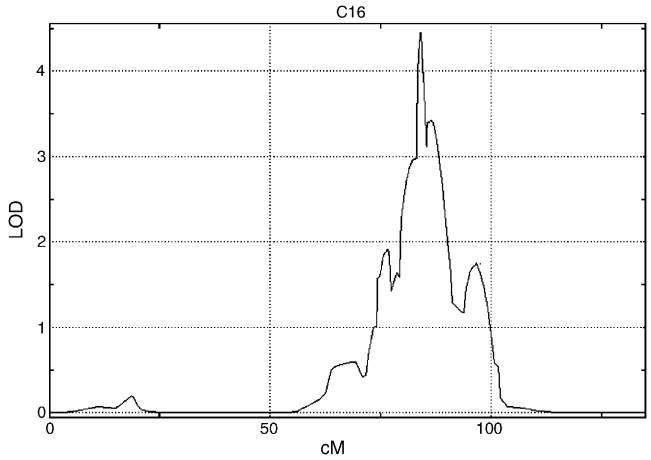

Figure 7
The linkage result on chromosome 16 of psoriatic arthritis patients when the analysis was conditioned on paternal transmission genotyped with a 1000 marker genome-wide microsatellite screening set with a score of 5.69.

Table I. The entire cohort was genotyped using this set of 36 microsattelite markers in the MHC

Marker	Primer forward	Primer reverse
C78-32886-2	GGTCAGGTGTAATGGAATTTGA	TTGCAGGTGATCTGCTTCTC
CA-RING3	TTTACAGATTCCCACCTCGG	TAGGGAGACTACCGATCCCC
D6S1621	AAAGATTTAGAGTAAATGCTGATGA	ACCACAGATGAGAATGCCTT
G-511525	GGTAAAATTCCTGACTGGCC	GACAGCTCTTCTTAACCTGC
GATA61E03	CTGTATTAGTCGGGGTTCTCC	GGTATTTTTTGCCACATGA
SA-99508	TGGAATCTCATCAAGGTCAGAA	TTGATACTTTCCTAATTCTCCTCC
TNFC	GCTTTCTCTGACTGCATCTTGTCC	TCATGGGGAGAACCTGCAGAGAA
CA-JAP-119	CCTTAGCCCCTGTCCTTCAC	AGGGAGGAGAGAAAAGTGGG
CA-MICB-1	GGCGTGCCATTTTGTATTTC	TGAGAAGCTATGGGGGAG
D6S265	ACGTTCGTACCCATTAACTT	ATCGAGGTAAACAGCAGAAA
D6S273	GCAACTTTTCTGTCAATCCA	ACCAAACTTCAAATTTTCGG
D6S306	TTTACTTCTGTTGCCTTAATG	TGAGAGTTTCAGTGAGCC
GATA4A03	CCTCCATAATTGTGTGAGCC	CCAATCTTCTAACCCAAGCA
NOTCH-47	TCCACGTTGTGATCATCCAT	GGGGCAGGTAAAAACATCCT
C2-AAAAT	ACCCAGCTACTTGGGAGGAT	CCTCGACGTGCAATGAGTA
CA-J-180	GAAGAAATCCTGCCTCAGAA	TGTTCCTGTAGAACCACTCTTCG
CA-J-269	AGGGCCCAGTAGTAAGCCAG	TGACTTCATATCCTGAAAGGG
D6S464	TGCTCCATTGCACTCC	CTGATCACCCTCGATATTTTAC
GCT4BO5	GGGTCTGACCACTGAGACAC	CAGTGAGAGCTCTGAGGGTC
C78-12480	CCAAGATCACCCTACCACAC	TCAAGGAACCTGGAGGGAGAA
C78-57190	TGTTCACACCATAAACAAATGG	GGTGAAAATCTACCTGTTGGC
D6S1558	GCTACTTGGGAGGCTGGAC	CTGGCAGGAGGGCTAG
D6S2443	CCATACCAAAGTAAAACCCAG	GAGGATGAAGGGAAATTAGAG
D6S258	GCAAATCAAGAATGTAATTCC	CTTCCAATCCATAAGCATGG
HLAF	AATTGCACTTGCCTCACG	ATGCTTTGGTTGTTGCCACC
D6S306	TTTACTTCTGTTGCCTTAATG	TGAGAGTTCAGTGAGCC
CA-DQBA	GGGAAGGATTCTAAATAGGGGA	CAGCATTCTGGAGGTGTGTG
D6S1683	CTGCACATGTATCCGAGAA	TTTNAAGTAGAGACAGGATTTCTTG
M6S176	GAAAGTCTTGAAGTCAGGTGTGGC	TGAGAGTTCAGTGAGCC
M6S178	TTGAACCAGGAGGTGGAGGTTG	CAAGCATTCTGGAGGTGTGTG
M6S162	CGCTATTGCATTCCAGCCTG	TCTAGTCATCCCTCCCTACTGCTG
M6S102	CCTAATCCAAAGGCATGGCTTC	GGTGACAAAGCGAGACACCATC
M6S105	GGGTGCCACAAGAATTGCAG	TCCAGCCTGTGATAGAGTGAGACC
M6S198	AGATCATGCCACTGCACTCCAG	CTCAAGCCTGGGTGATAGAGAAAG
M6S161	TTGAACACAACCATCTCTGCTCC	ATCAGCCTGCTTCTGGGATTCTCC
M6S224	AACTGTTCCTCTCTCTTAGAAGGCAGC	ACCTGGGCAATACAGCAAGACC

Many of them were developed in-house and carry names unfamiliar to the reader. Many of them have likely found their way into the literature and carry standardized names.
MHC, major histocompatibility molecules.

markers to this region in order to increase information content increased the LOD score to 5.69 when analysis was conditioned on paternal inheritance, providing further confirmation of the importance of this locus.

Discussion

In the course of analyzing subphenotypes in psoriasis, we have replicated linkage to a number of loci found by

other groups to be at least suggestive of linkage to psoriasis. In the past, an LOD score exceeding 2 in one cohort at a location where another cohort has had a genome-wide significant locus has been regarded as confirmation. Replication of the MHC locus has been almost universal (Capon *et al*, 2002), but secondary loci in various populations have been diverse, suggesting that HLA-C or some gene very close to it is a major susceptibility allele. When such observations are made in more than one population, it becomes more likely that the mapped gene reflects more than a population-specific trigger or modifying effect and justifies the expenditure of resources on fine mapping.

The presence of a suggestive locus with an LOD score of 2.5 at D16S205 at 84 cM from the p-telomere in addition to the increased LOD score of the paternally inherited locus in psoriatic arthritis patients increases our confidence that a gene contributing to psoriasis and psoriatic arthritis is located within that genomic region. Fine mapping efforts are already reducing the size of the interval.

In general, our findings are consistent with the possibility that a careful phenotypic classification may help to localize genes that contribute to complex genetic diseases. Thus, differences in phenotypic composition of study cohorts might, in addition to variations between different populations, explain, at least in part, divergent findings reported by individual study groups. It is interesting in this context that the locus on 4q that we observed in Icelandic psoriasis patients with adult onset has the same location as linkage found in Chinese psoriasis patients. Although LOD scores that we report here for various subphenotypes are not statistically significant even before accounting for multiple testing of phenotype classes, this approach provides a way to: (1) predict the relative contribution of a given locus to specific or general phenotypes of psoriasis, and (2) alter the follow-up collection strategy to focus limited resources to increase the number of patients whose subphenotypes map to particular loci. That is, guided by early linkage analysis of large cohort, the future strategy on a particular population could become focused to increase the likelihood of a statistically significant linkage and ultimate isolation of at least one psoriasis gene. Further analysis of psoriasis subphenotypes may therefore be an effective strategy for localizing and identifying genes that predispose to psoriasis and such an approach has also been successful in other complex diseases including fine mapping of autistic disorders (Shao *et al*, 2003).

In order to stratify patients according to phenotypic criteria, there are two major prerequisites. First, the patient population must be large enough so that dividing the population in half or thirds does not decrease the power below a threshold for mapping genes. Second, systematic collection of phenotypic traits used for stratification must be carried out on at least 90% of the cohort so that power does not suffer because of incompleteness of data and to decrease the possibility of bias. In our psoriasis study, we began with one of the largest cohorts on psoriasis ever collected and we strived for close to complete ascertainment of clinical information (our phenotype data set was 95%–100% complete). In addition, the ability to recreate large extended families using a computerized genealogy database (rather than maintaining the original pedigrees, many of which will fall out when only one patient remains within each pedigree) increases the number of families available for the study of each subphenotype, further increasing power for mapping psoriasis genes.

It is concluded that a careful characterization of subphenotyes may greatly help to analyze complex genetic diseases.

Materials and Methods

The National Bioethics Committee of Iceland and Data Protection Authority (DPA) of Iceland approved this study and informed consent was obtained from all participants. We used our comprehensive Icelandic genealogical database (Gulcher and Stefansson, 1998) to automatically derive families that included patients separated up to and including seven meioses (six meioses separate second-cousins). All personal identifiers associated with medical information and blood samples as well as the Icelandic genealogical database were reversibly encrypted by the DPA (Gulcher *et al*, 2000).

Patients and phenotypic documentation Altogether, over 3000 individuals were evaluated and 1000 patients with definite psoriasis identified. The majority of participants in this study had at least one first- or second-degree relative affected by psoriasis, and were recruited by the Icelandic Psoriasis Association (SPOEX). As previously described (Gudjonsson *et al*, 2002), patients were evaluated by either of the two physicians (J. E. G., H. V.). A detailed clinical history was obtained by a structured questionnaire, and a careful physical examination was also carried out and the localization, distribution, and the size of the lesions were recorded. The patients had to have at least one unequivocal psoriatic plaque at the time of examination to be included as affected. Information recorded for each patient included age, site, and mode of onset, disease severity, Koebner's phenomenon, nail lesions, arthritis, and the effects of a variety of environmental factors. Nail changes were only recorded for the fingers, because of a high frequency of fungal infections in toenails (Gudnadottir *et al*, 1999) that can mimic psoriatic nail lesions. Patients with seborrheic or pustular psoriasis or a history of guttate psoriasis were only included if they had typical chronic psoriatic plaques at the time of examination. We were able to connect a number of families using our computerized geneology database (Gulcher and Stefansson, 1998), and ended up with 238 extended pedigrees. Approximately 505 Icelandic controls were genotyped in order to ascertain control allelic frequency for all markers in the Icelandic population.

Genotyping and analysis of linkage Participants were genotyped using a 1000 marker fluorescently labelled microsatellite screening set with an average density of 3 cM, where genetic locations are based on the deCode map (Kong *et al*, 2002). Additional markers were genotyped for regions showing the strongest evidence for linkage, increasing the density up to 1 cM. Genotyping was performed under standard conditions (Gretarsdottir *et al*, 2002). HLA-B and HLA-C were typed using Dynal SSP (Dynal Biotech, Oslo, Norway) typing kits under standard protocol conditions.

All reported LOD scores were calculated with Allegro (Gudbjartsson *et al*, 2000). Allegro computes non-parametric, multipoint, affected only, allele-sharing LOD scores based on the S-pairs scoring function (Kruglyak *et al*, 1996), and an exponential allele-sharing model (Kong and Cox, 1997). It should be noted that the published deCode genetic map was constructed based on the Haldane map function, or a no-interference model, but distances were converted to Kosambi distances to make them directly comparable with the Marshfield map (Broman *et al*, 1998). But Allegro, like many other multipoint linkage programs, can only process a no-interference model. Hence, calculations here were based on

the originally estimated Haldane map. Positions of markers not in the deCode map were determined by interpolation based on physical distances.

Families were weighted halfway on the log scale between weighting families equally and weighting all pairs of affected equally. This scheme gives similar weights as those proposed by Weeks and Lange (1988) as an extension of the scheme Hodge (1984) designed for sibships, and we have used as the default (see for example Gretarsdottir *et al*, 2002). Exact p-values were calculated by comparing the observed LOD score with its complete data sampling distribution under the null hypothesis (Gudbjartsson *et al*, 2000), where linkage results are considered significant if the single test p-value is below 2×10^{-5} (Lander and Kruglyak, 1995).

We thank the patients and their families for their participation, which made this study possible. We also thank the Association of Psoriasis and Eczema Patients in Iceland for their help in recruiting patients.

DOI: 10.1111/j.0022-202X.2005.23703.x

Manuscript received January 22, 2004; revised August 17, 2004; accepted August 18, 2004

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