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A Susceptibility Gene for Psoriatic Arthritis Maps to Chromosome 16q: Evidence for Imprinting

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Several genetic loci have been reported for psoriasis, but none has been specifically linked to psoriatic arthritis (PsA), a condition that affects >10% of patients with psoriasis. A genetic component for PsA is suggested by segregation within families and high concordance among identical twins. We performed a linkage scan to map genes contributing to PsA. We identified 178 patients with PsA out of 906 patients who were included in our genetic study of psoriasis. Using a comprehensive genealogy database, we were able to connect 100 of these into 39 families. We genotyped the patients using a framework marker set of 1,000 microsatellite markers, with an average density of 3 cM, and performed multipoint, affected-only, allele-sharing linkage analysis using the Allegro program. On the basis of the initial results, we genotyped more markers for the most prominent loci. A linkage with a LOD score of 2.17 was observed on chromosome 16q. The linkage analysis, conditioned on paternal transmission to affected individuals, gave a LOD score of 4.19, whereas a LOD score of only 1.03 was observed when conditioned for maternal transmission. A suggestive locus on chromosome 16q has previously been implicated in psoriasis. Our data indicate that a gene at this locus may be involved in paternal transmission of PsA.

Introduction

Psoriasis (MIM 177900) is a common inflammatory skin disease that may have an autoimmune basis and be predominantly mediated by T lymphocytes (Baker et al. 1984; Valdimarsson et al. 1995; Prinz 1999). Several overlapping clinical types of the disease have been identified, but the chronic plaque form (psoriasis vulgaris) is most common and is characterized by well-demarcated, indurated, erythematous, and scaly lesions, or plaques, most frequently located on knees, elbows, or scalp. The lesions are infiltrated by inflammatory cells, but a marked increase in proliferation and turnover of keratinocytes distinguish psoriasis from other inflammatory skin diseases. The disease has a strong but complex genetic basis, with a concordance rate of 50%–70% among MZ twins (Farber et al. 1974; Eastmond 1994; Costello and FitzGerald 2001). Several genetic loci have been suggested, but only a major histocompatability (MHC) locus on chromosome 6 has been independently reported by at least two groups as significant genome-wide (Elder et al. 2001). Psoriasis has a strong association with the Cw6 allele of the HLA-C gene in the MHC (Tiilikainen et al. 1980). Accordingly, strong linkage to the MHC region on chromosome 6p has been observed in most populations studied (Trembath et al. 1997; Jenisch et al. 1998; Samuelsson et al. 1999) and has been localized to the vicinity of HLA-C by linkage disequilibrium mapping (Balendran et al. 1999; Oka et al. 1999; Nair et al. 2000). Psoriatic arthritis (PsA) has been recognized since the late 19th century (Moll and Wright 1973*a*; Fearon and Veale 2001; Patel et al. 2001). It affects >10% of patients with psoriasis (Gladman et al. 2001), and, in most cases, there is an association between the severity of the arthritis and the skin involvement (Winchester 1995).

Several types of characteristic nail lesions are observed in 35%–40% of patients with psoriasis, including pitting, onycholysis, subungual hyperkeratosis, and dystrophy, and it has been reported that PsA is more common in patients with nail changes (Rahman et al. 2000). Several different types of PsA have been identified, and, in contrast to rheumatoid arthritis, most patients with PsA are negative for rheumatoid factor (Moll and Wright 1973*a*). Although a clear genetic component has been reported in PsA, with a concordance rate range of 30%–70% among MZ twins (Moll and

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Wright 1973*b*; Winchester 1995), there is, to our knowledge, no report of a genetic locus for the arthritic manifestations of psoriasis. We have recently found that PsA is somewhat more common in patients with HLA-Cw6 negative than those with Cw6 positive (Gudjonsson et al. 2002). We find that psoriatic nail lesions are also observed more often in patients with PsA. Several association studies dealing with the genetics of PsA that focused on the MHC (Bruce and Silman 2001; Gladman et al. 2001; Gonzalez et al. 2001, 2002; Al-Heresh et al. 2002) found greater excess of one allele or another over the Cw6 allele associated with skin psoriasis. The association to the MHC is present in PsA, although it is less pronounced than in the skin manifestations (Eastmond 1994; Gonzalez et al. 2002). The only other study to attempt linkage analysis on families with PsA was performed in a Scottish population, typing 11 microsatellite markers at three psoriasis loci described elsewhere (Burden et al. 1998). Although a significant LOD score was obtained for psoriasis, no evidence of linkage was detected for PsA. A recent epidemiological study has indicated that there are more patients suffering from PsA who have affected fathers than have affected mothers (Rahman et al. 1999). In the course of performing linkage analysis on families with psoriasis, we observed a locus on chromosome 16q, with linkage to PsA, that exhibited an even higher LOD score when the study was restricted to pairs of affected relatives in whom the last transmission came from the father.

Subjects and Methods

This study was approved by the National Bioethics Committee of Iceland and the Data Protection Committee of Iceland. Informed consent was obtained from all individuals whose DNA was used in our analysis. We used our comprehensive Icelandic genealogical database (Gulcher and Stefansson 1998) to automatically create 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 were reversibly encrypted by the Data Protection Committee of Iceland (Gulcher et al. 2000). The Icelandic genealogical database was also encrypted by the Data Protection Committee of Iceland (Gulcher et al. 2000).

Of 906 patients with chronic plaque psoriasis whom we have evaluated clinically, 178 patients had been diagnosed with and treated for PsA by rheumatologists. The diagnostic criteria were inflammatory arthritis, seronegativity for rheumatoid factor, and unequivocal psoriatic skin lesions at the time of diagnosis of PsA. We genotyped these patients using a 1,000-marker fluorescent labeled microsatellite screening set with an average density of 3 cM in the genome, where genetic locations are based on the Decode map (Kong et al. 2002). Additional markers were genotyped for the regions showing the strongest evidence for linkage, increasing the density up to ~1 cM. Genotyping was performed with our standard conditions (Gretarsdottir et al. 2002).

All reported LOD scores were calculated with Allegro (Gudbjartsson et al. 2000). The program computes nonparametric, multipoint, affected-only, and allele-sharing LOD scores on the basis of the S-pairs scoring function (Kruglyak et al. 1996) and an exponential allele-sharing model (Kong and Cox 1997). We note that the published Decode genetic map was originally constructed on the basis of the Haldane map function, or a no-interference model, but the distances were converted to Kosambi distances in the publication to make them directly comparable with the Marshfield map (Broman et al. 1998). However, Allegro, like many other multipoint linkage programs, can only process a no-interference model. Hence, our calculations here were based on the originally estimated Haldane map, but the results are presented with the locations converted to the published Kosambi map to ease referencing. Positions of markers not in the Decode map were set by interpolation on the basis of physical distances. Families were weighted halfway on the log scale between weighting families equally and weighting all pairs of affected relatives equally. This scheme gives weights similar to those proposed by Weeks and Lange (1988) as an extension of the scheme Hodge (1984) designed for sibships, and we have been using it as the default (see, e.g., 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 a linkage result is considered significant if the single test P value is $< 2 \times 10^{-5}$ (Lander and Kruglyak 1995). We have extended our linkage analysis program, Allegro, to include an imprinting-based scoring function. The extension allows us to assign weights to allele sharing specific to parental origins. For example, to investigate paternal imprinting, the scoring functions considers only the sharing of alleles transmitted to two affected relatives through their fathers. When these imprinting-based scoring functions were used, sex-specific genetic maps (Kong et al. 2002) were used in the calculations.

Results

The prevalence of PsA was ~20% in our study group (178 out of 906 patients). Using our genealogy database and patients related to up to and including seven meioses, we were able to connect 100 of these patients, 41

males (41%), and 59 females (59%), into 39 families for linkage analysis. Of these 100 patients, 45 and 50, respectively, were informative for linkage when pairs of affected individuals related only through their fathers and pairs related only through their mothers were used. After the addition of extra markers, the strongest evidence for linkage was observed on chromosome 16, with a LOD score of 2.17 at the marker D16S3038, which is located 75.62 cM from the p telomere of chromosome 16 (fig. 1). D16S3110, a marker we have mapped to within 1 Mb of D16S3038, has been reported elsewhere as marking a suggestive locus for psoriasis (Nair et al. 2000), and both of these markers are within 20 Mb of the *NOD2* gene (MIM 605956), mapped to around 60.4 cM on the Decode map, thought to confer risk for inflammatory bowel disease (Hugot et al. 2001; Ogura et al. 2001). Linkage analysis using only paternal transmissions to affected individuals gave a maximum LOD score of 4.19 at marker D16S267; that is, at 81.25 cM from the p telomere of chromosome 16 or within 6 cM of our highest linkage marker for the entire cohort (fig. 2). The exact P value for this result was 5.31×10^{-6}, which was still significant after adjustment for multiple testing because of the three linkage scans performed. The markers demarcating the 1-LOD drop are D16S3393 (82.7 cM from the p telomere) and D16S3089 (79.5 cM from the p telomere). All markers used in this analysis are available on request. When considering maternal transmissions only, the maximum LOD score was 1.03 at marker D16S3089 (fig. 2), which we genetically mapped to 4 cM telomeric of D16S3038, as mentioned above. We note in our ongoing study of psoriasis, as opposed to PsA, that there is currently no evidence for linkage to this location (data not shown).

Discussion

Genetic imprinting in human disease, a phenomenon involving a preferential paternal or maternal inheritance of a susceptibility allele to affected individuals, has been suggested in several complex genetic diseases (Lee et al. 2000; Cichon et al. 2001; Naumova et al. 2001; Strauch et al. 2001; Alcolado et al. 2002; DeLisi et al. 2002; Lindsay et al. 2002; Vandenbroeck et al. 2002) and is well established in some rarer diseases, such as the Prader-Willi and Angelman syndromes (Christian et al. 1998; Mann and Bartolomei 1999). Parental imprinting has also been suggested for several complex genetic diseases from an epidemiological standpoint (Lichter et al. 1995; Kato et al. 1996; Eapen et al. 1997; Haghighi et al. 1999; Rahman et al. 1999; Meigs et al. 2000). There is also suggestive evidence from linkage analysis, reported elsewhere, of common diseases and phenotypes where LOD scores increase or decrease when the analysis is conditioned on parental transmission. These include noninsulin-dependent diabetes mellitus, atopic dermatitis, bipolar disease, insulin-dependent diabetes mellitus (IDDM), schizophrenia, Crohn disease, and birth weight (Akolkar et al. 1997; Lee et al. 2000; Meigs et al. 2000; Cichon et al. 2001; Lindsay et al. 2001, 2002). However, in almost all of these and other linkage scans, conditioning on parental transmission, the interpretation of the existence of imprinted disease genes, must be tempered by the fact that almost none of the loci met the criteria for statistical significance, even without correction for the testing of multiple models. Of particular interest here is one linkage scan on psoriasis that showed an increased paternal transmission at the MHC susceptibility region (Burden et al. 1998), although we have not observed this phenomenon for any of the loci that we find contributing to the skin manifestations of psoriasis in Iceland.

Our findings support at the molecular genetic level the recent epidemiological observation that paternal imprinting might play a role in PsA (Rahman et al. 1999). Reanalysis of an IDDM genome scan performed in the United Kingdom (Mein et al. 1998) showed a paternal inheritance factor at D16S3098, which maps to within 20 Mb of our locus on 16q, with a LOD score of 1.81 for male meioses and a LOD score of 0.33 for female meioses at the same locus (Paterson et al. 1999). These results are interesting, although they are far from reaching statistical significance. The LOD score of 4.19 we observe at this location, however, exceeds the accepted criteria for genomewide significance and provides the first indication of a location for a non-MHC gene predisposing to PsA.

The position of the locus we report here is also interesting considering that a locus on chromosome 16q has been implicated in psoriasis elsewhere (Nair et al. 1997) and in Crohn disease. The Crohn disease susceptibility factor consists of an insertion mutation and several missense mutations in the *NOD2* gene (which we map to 21 cM from our highest linkage marker) that have been identified in a subset of patients (Hugot et al. 2001; Ogura et al. 2001). This insertion causes a truncation of the NOD2 product that may lead to abnormal NF-κB responses to certain bacterial products (Lesage et al. 2002).

It has also been reported in an epidemiological study that the inheritance of Crohn disease may be influenced by parental imprinting (Akolkar et al. 1997). Patients with Crohn disease have approximately sevenfold increased risk of developing psoriasis, and they are at risk for a seronegative polyarthritis themselves (Lee et al. 1990; Nair et al. 1997), but the insertion mutation in the *NOD2* gene observed in Crohn disease has not been found in psoriasis (Nair et al. 2001). It is possible that other variants of the *NOD2* gene may be involved in

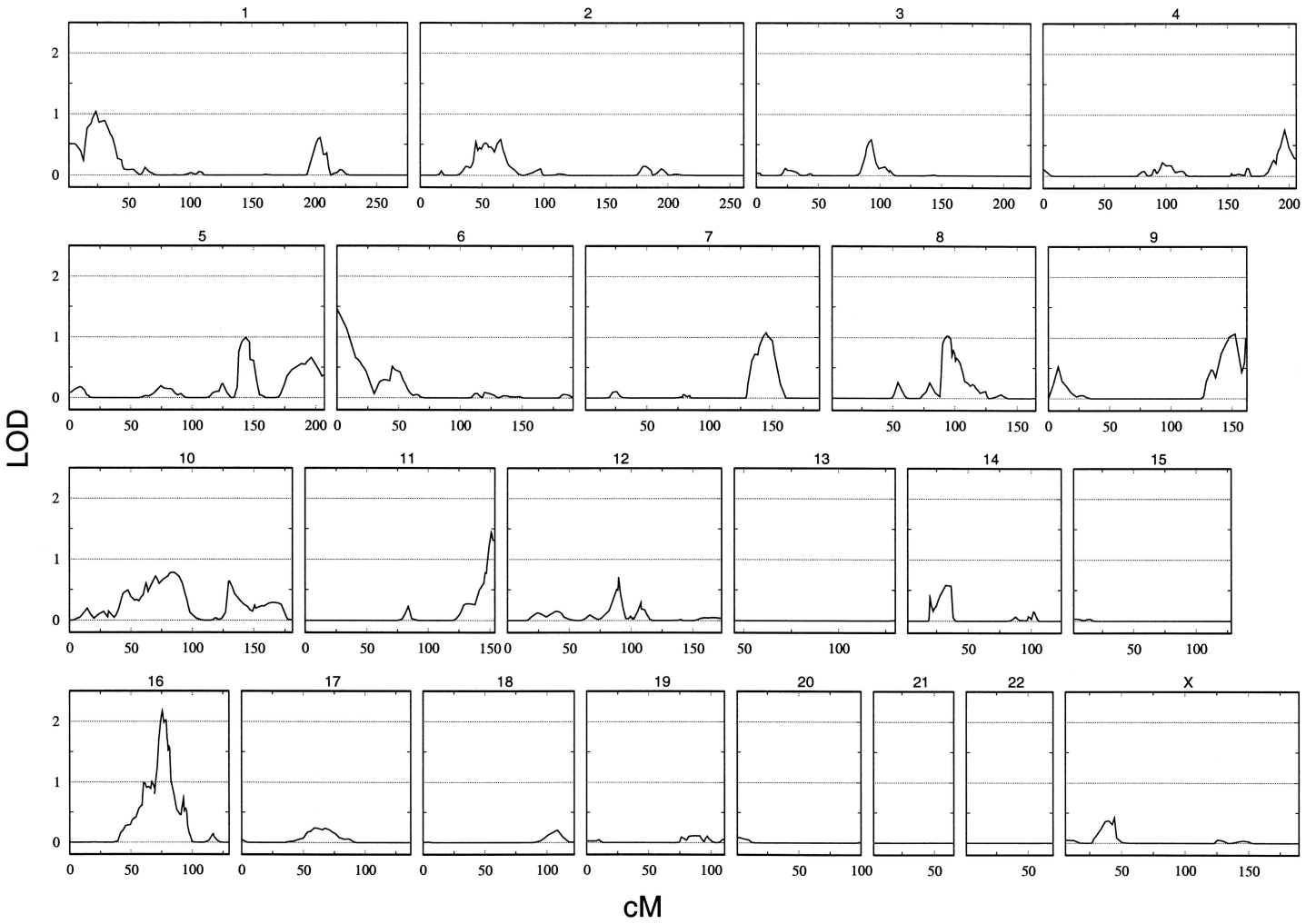

Figure 1 Genome scan of 39 families with PsA with 1,000-microsatellite framework marker set, in addition to the fine mapping markers in all locations of interest. The multipoint LOD score is shown on the vertical axis; the distance from the p-terminal end of the chromosome (in cM) is shown on the horizontal axis.

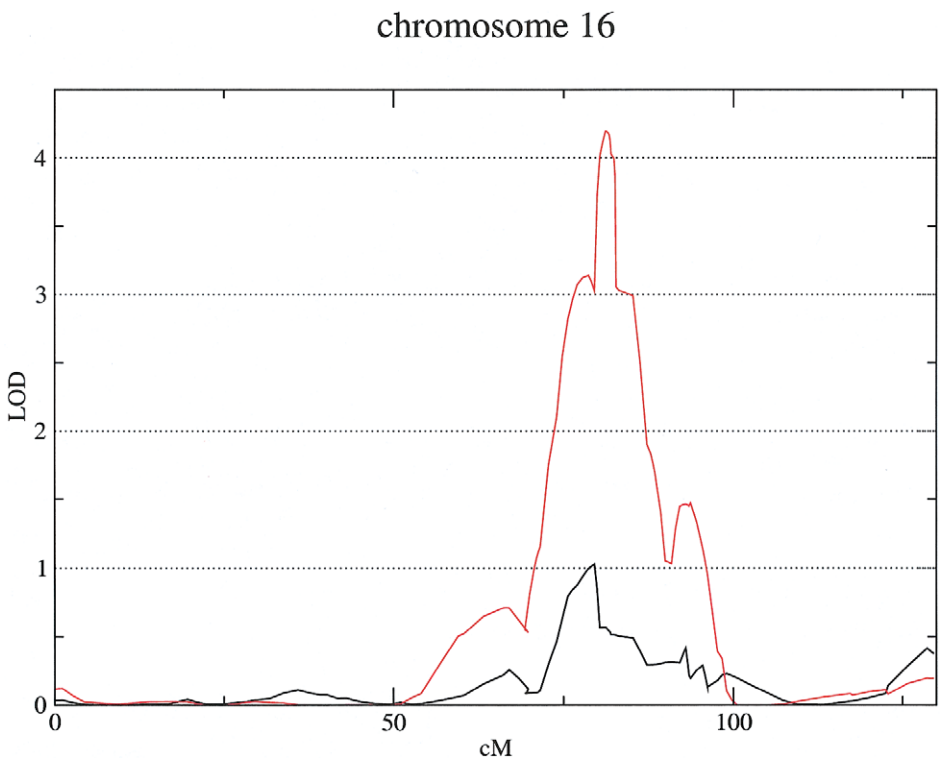

Figure 2 Linkage result of 39 families on chromosome 16 with additional markers and considering paternal transmissions only (*black line*) and maternal transmissions only (*red line*). The multipoint LOD score is shown on the vertical axis; the distance from the p-terminal end of the chromosome (in cM) is shown on the horizontal axis.

psoriasis or a gene that is closely linked to *NOD2*. Our PsA cohort has not been screened for the known mutations in the *NOD2* gene.

The peak we observe on chromosome 16 overlaps with a peak we have observed in families with osteoarthritis (OA) (data not shown). It is also, therefore, possible that what we are observing is a gene that causes susceptibility to joint afflictions. On the one hand, it may lead to OA when other susceptibility factors (trauma or other genetic factors) are present, and on the other hand, it may lead to PsA when factors predisposing to psoriasis are present. Our study shows the importance of the ability to link large numbers of patients together as we have done using our genealogy database. Additionally, looking at parental effects on the inheritance of phenotypes may add a new dimension to previous or future linkage scans, as we have found in this case.

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Electronic-Database Information

Accession numbers and URLs for data presented herein are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for psoriasis [MIM 177900] and NOD2 [MIM 605956])

Center for Medical Genetics, Marshfield Medical Research Foundation, http://research.marshfieldclinic.org/genetics/

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