

Original articles

Identification of a novel psoriasis susceptibility locus at 1p and evidence of epistasis between *PSORS1* and candidate loci

C D Veal, R L Clough, R C Barber, S Mason, D Tillman, B Ferry, A B Jones, M Ameen, N Balendran, S H Powis, A D Burden, J N W N Barker, R C Trembath

Division of Medical Genetics, Departments of Medicine and Genetics, University of Leicester, Adrian Building, Leicester LE1 7RH, UK

C D Veal
R L Clough
R C Barber
S Mason
R C Trembath

Department of Dermatology, University of Glasgow, Glasgow, UK
D Tillman
B Ferry
A D Burden

St John's Institute of Dermatology, King's College London, UK
A B Jones
M Ameen
N Balendran
J N W N Barker

Centre for Nephrology, Royal Free and University College Medical School, University College London, UK
N Balendran
S N Powis

Correspondence to:
Dr Trembath,
rtrembat@hgmpr.mrc.ac.uk

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Abstract

The pathogenesis of all forms of psoriasis remains obscure. Segregation analysis and twin studies together with ethnic differences in disease frequency all point to an underlying genetic susceptibility to psoriasis, which is both complex and likely to reflect the action of a number of genes. We performed a genome wide analysis using a total of 271 polymorphic autosomal markers on 284 sib relative pairs identified within 158 independent families. We detected evidence for linkage at 6p21 (*PSORS1*) with a non-parametric linkage score (NPL)=4.7, $p=2 \times 10^{-6}$ and at chromosome 1p (NPL=3.6, $p=1.9 \times 10^{-4}$) in all families studied. Significant excess ($p=0.004$) paternal allele sharing was detected for markers spanning the *PSORS1* locus. A further three regions reached NPL scores of 2 or greater, including a region at chromosome 7 (NPL 2.1), for which linkage for a number of autoimmune disorders has been reported. Partitioning of the data set according to allele sharing at 6p21 (*PSORS1*) favoured linkage to chromosomes 2p (NPL 2.09) and 14q (NPL 2.0), both regions implicated in previous independent genome scans, and suggests evidence for epistasis between *PSORS1* and genes at other genomic locations. This study has provided linkage evidence in favour of a novel susceptibility locus for psoriasis and provides evidence of the complex mechanisms underlying the genetic predisposition to this common skin disease.

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Psoriasis is a chronic disfiguring skin disorder characterised by the triad of keratinocyte hyperproliferation, inflammatory infiltration, and vascular dilatation and proliferation.¹ Chronic plaque psoriasis (vulgaris) is the most common (>90%), while other clinical forms include guttate, erythrodermic, and palmoplantar psoriasis.² In 5-10% of psoriatics, a frequently debilitating arthritis may coexist.³

The estimated prevalence of psoriasis in the USA and northern Europe is 2%, yet is 10-fold lower among Japanese, west Africans, and mongaloids.² The peak incidence occurs between the ages of 20 and 40 years, affecting males and females equally. While the aetiology of psoriasis remains unknown, current evidence indicates a central role for T lymphocytes in disease pathogenesis.¹ Familial clustering,^{4,5} together with the higher rates of concordance in monozygotic compared to dizygotic twins,⁶ suggests an important role for genetic susceptibility in the development of disease.

Predisposition to psoriasis is considered to be a complex genetic trait, with inheritance not following any simple Mendelian model.⁷ To date, seven independent genome wide scans have been performed to identify susceptibility genes for psoriasis, using both parametric and non-parametric approaches. It is now clear that a major locus for psoriasis susceptibility is located at chromosome 6p21.3 (*PSORS1*) with lod scores in excess of 3 being replicated by at least five reported studies, including our own.⁸⁻¹² Significant evidence for linkage (lod score >3) has been identified for loci on chromosomes 17q (*PSORS2*),¹³ 4q (*PSORS3*),¹⁴ 1q (*PSORS4*),¹⁵ and 3q (*PSORS5*).¹⁶ Loci suggestive of linkage (lod score >1, <3) include those on chromosomes 2q, 8q, 16q, 19p, and 20p,^{8,9,13-17} but independent replication of these studies has proved difficult.

Because of the likelihood that multiple genes, acting either in an additive or multiplicative manner, may contribute to disease susceptibility, we have now undertaken a large sib pair family approach to map additional loci through a genome wide analysis. We report evidence for a novel locus at chromosome 1p, significant parental effect for genetic susceptibility at 6p21, and epistasis between a locus within the MHC and loci on chromosomes 2 and 14.

Materials and methods

FAMILIES

White families containing at least one informative affected relative pair were recruited primarily through two separate academic

dermatology clinics in Glasgow and London, as well as additional dermatology centres. A standardised proforma, common to all sites, was used recording all essential clinical and family data including medical history, age of onset, and examination. Affected status was accepted only on the basis of active disease at the time of examination by a trained experienced clinician at each study site. Standard diagnostic criteria were used.² Where affected status could not be assigned, subjects were retained in the genetic study as unknown phenotype. All subjects provided informed consent for this molecular genetic study, which was approved by local ethics committees.

SAMPLES AND GENOTYPING

Genomic DNA was extracted from 10 ml of peripheral blood using standard conditions.⁸ Genotyping was performed using a modification of the marker set described by Reed *et al*¹⁸ and consisted of 271 markers and average heterozygosity of 79%. PCR was performed on MJ Research DNA Engines (10 µl reactions; 40 ng DNA, 1.5-2.5 mmol/l MgCl₂, 0.2 mmol/l dNTPs (Pharmacia), 0.2 µmol/l primer, 0.2 units of *Taq* polymerase (Advanced Biotechnologies) in a 1 × KCl PCR buffer).

Products were pooled and electrophoresed through 6% polyacrylamide gels (FMC) on an ABI 377 or 373 DNA sequencer. Semi-automated fragment sizing was performed using GENESCAN 2.1 software (PE-ABI) followed by marker peak detection using GENOTYPYER 2.0 software (PE-ABI). Each genotype was reviewed manually to confirm the accuracy of allele designation. The Genetic Analysis System 2.0 (Alan Young, Oxford University, 1993-1995) was used to code allele sizes into whole numbers, to confirm Mendelian inheritance and to generate appropriate files for downstream analysis.

DATA ANALYSIS

Non-parametric analysis was assessed using the sib pair program of ANALYZE by J Terwilliger,^{8,19} while non-parametric multipoint analysis was performed with Genehunter 2.0²⁰ using the "all" statistic. Marker map positions were obtained from sex averaged maps available at the Genetics Location Database (<http://cedar.genetics.soton.ac.uk/pub/>) and the Marshfield clinic (<http://www.marshmed.org/genetics/>).

For analysis of epistasis and parental effect, the dataset was partitioned according to sharing of particular loci within families. For this the output for each family from Genehunter 2.0 was used.²¹ Those families with a *NPL* score >0.8 for a particular region were designated NPLPOS (66 families, 136 ASPs) and those families with a *NPL* score <-0.8 were designated NPLNEG (22 families, 22 ASPs). Remaining families were not included in the further analyses. This method of partitioning was performed for loci located on 6p21 and 1p. NPLPOS families for chromosome 6p21 and chromosome 1p were assessed using the SIBDES program of the Genetic

Table 1 Details of study cohort

Affected relationships	No	Total ASP
2 sibs	33	133
3 sibs	29	87
4 sibs	9	54
5 sibs	1	10
Cumulative ASPs	284	284
Total independent families	158	
Total No of subjects	767	
Total No of affected subjects	472	

For 95% of nuclear families, one or both parents were available. Additional unaffected sibs or data from other relative pairs were used to reconstruct unknown parental genotypes.

Analysis System 2.0 which also includes a 1:0 distribution for each parental sex, allowing the comparison of sharing for alleles derived for each parent.

Results

We performed a genome wide screen using 284 ASPs (222 independent sibships²²) identified within 158 nuclear families (table 1). Of the 472 affected subjects (258 female, 214 male) the mean age of onset was 15.8 (2-70) for females and 19.2 (1-60) for males. We used a panel of 271 markers distributed across the 22 autosomes with an average intermarker distance of 13 cM. Fig 1 shows the non-parametric linkage (NPL) score obtained using the Genehunter 2.0 program, plotted for each chromosome, for all families and also for chromosome 6p21 NPL positive (NPLPOS) and NPL negative (NPLNEG) families.

NOVEL LOCUS FOR PSORIASIS SUSCEPTIBILITY AT 1P

Highly suggestive evidence for linkage was observed on chromosome 1p, with a peak between markers D1S197 and D1S200 (NPL=3.6, $p=1.9 \times 10^{-4}$). This observation approximates to the 5% genome wide significance level for a 10 cM scan.²³

A total of 16 regions generated nominal evidence for linkage (NPL >1.0), and these were distributed across 14 chromosomes. Of these, five regions reached or exceeded NPL scores of 2, including chromosome 7 (NPL=2.1, $p=0.0167$), a region showing clustering of autoimmune diseases,²⁴ between D7S519 and D7S669, chromosome 18 (NPL=1.97, $p=0.025$), between D18S59 and D18S1150, and chromosome 19 (NP=2.4, $p=0.008$), between D19S901 and D19S221.

These regions and others previously reported as putative susceptibility loci for psoriasis were also investigated using a two point test for allele sharing within the ANALYZE package (table 2). Probability values=0.05 were observed at D3S1314 ($p=0.05$), D6S300 ($p=0.03$), D7S519 and D7S669 ($p<0.03$), D18S59 and D18S1150 ($p=0.04$).

EVIDENCE FOR PARENTAL EFFECT AT 6p21

Genome wide, the most significant evidence for linkage was observed at chromosome 6p21, spanning the region containing the human MHC. Genehunter generated the strongest evidence for linkage for the markers D6S273 and D6S291 (NPL=4.7, $p=2 \times 10^{-6}$) (fig 1).

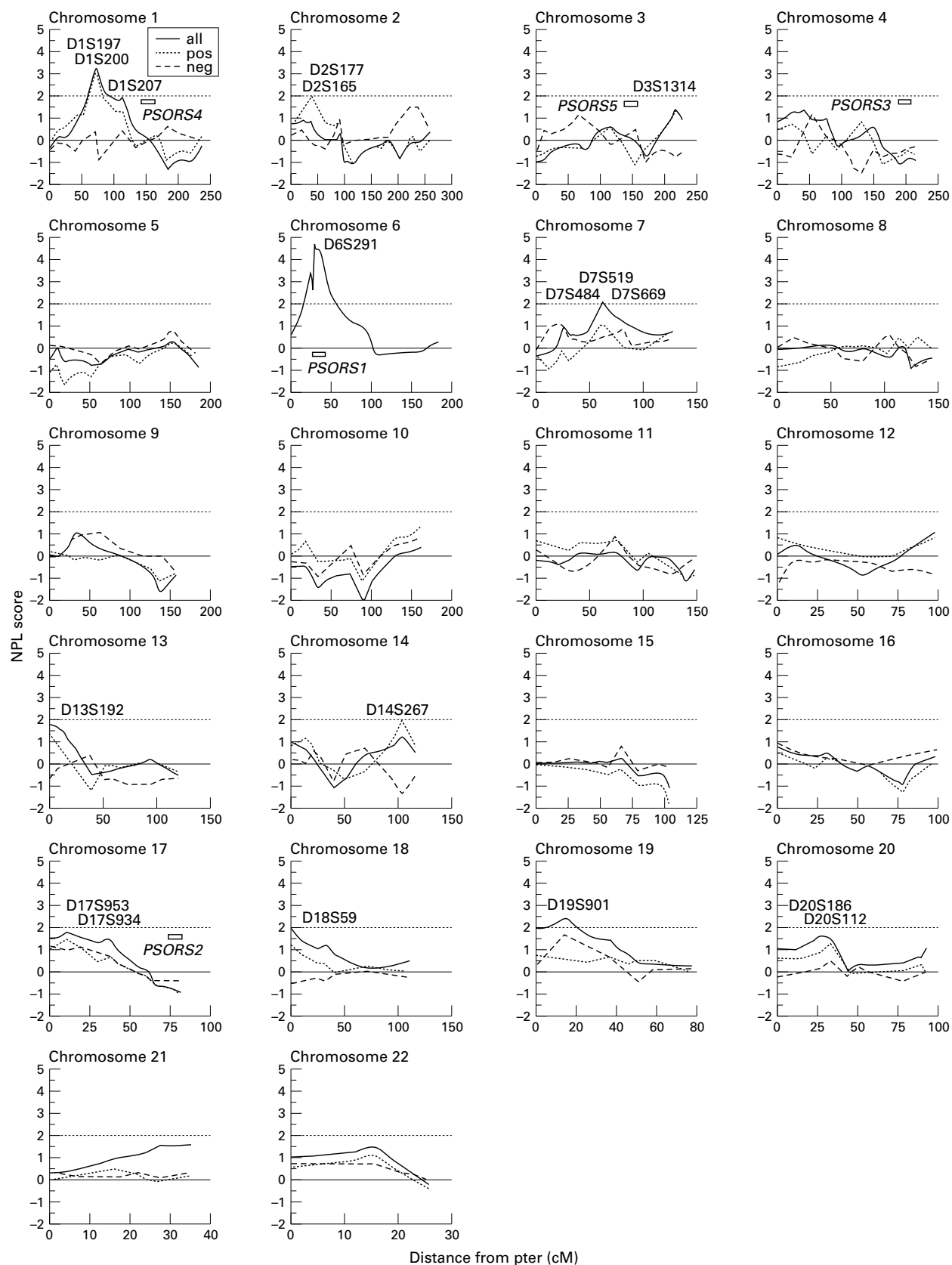


Figure 1 Non-parametric multipoint linkage analysis in 284 psoriasis affected sib pairs performed using Genehunter. This includes all families (solid line), families which obtain positive NPL scores for the MHC region of chromosome 6 (dotted line), and families which obtain a negative NPL score (dashed line). Markers are shown for regions of interest and previously identified regions submitted to OMIM are marked. Map positions obtained from the sex averaged maps compiled by J Weber (<http://www.marshmed.org/genetics>). A full marker list is available from the corresponding author.

Table 2 Summary of potential psoriasis susceptibility loci : non MHC loci

Chromosome	Designation	Marker	Interval*	% sharing†	p value†	Ref
1		D1S197	1p32.2-p31.1	55.77	0.04	
1		D1S200		54.75	0.02	
1	PSORS4	D1S305	1q12-q24.1	50.33	0.5	15,17
1		D1S484		49.52	0.5	
2		D2S134	2p14	48.81	0.5	8,17
2		D2S177		50.5	0.5	
3	PSORS5	D3S1303	3q21	48.3	0.5	16
3		D3S1314	3q29	53.91	0.05	
4	PSORS3	D4S403	4p15.33	52.8	0.179	
4		D4S1565	4q28.3-q32.1	53.93	0.07	9
4		D4S415		44.43	0.5	14
6		D6S300	6q16.3	54.55	0.03	
7		D7S629	7p15.3-q11.21	53.23	0.06	
7		D7S519		54.72	0.03	
7		D7S669		56.32	0.02	
8		D8S284	8q24.3	46.93	0.5	8
9		D11S910	11q25	42.24	0.5	8
12		D12S99	12p13.31	49.73	0.5	8
14		D14S50	14q12	53.74	0.153	8
14		D14s267	14q32	53.07	0.08	17
16		D16S415	16q13	56.29	0.17	9
16		D16S422	16q24.3	49.11	0.5	8
17	PSORS2	D17S789	17q22-q25.3	47.87	0.5	9,11,13,14
17		D17S784		46.56	0.5	
18		D18S59	18p11.32-p11.22	54.97	0.029	
18		D18S1150		55.88	0.04	
19		D19S901	19p13.3	55.07	0.07	
19		D19S391		56.06	0.2	
20		D20S186	20p12.1-q12	53.03	0.02	8,9
20		D20S112		54.14	0.043	

*Chromosome location determined from maps available at <http://cedar.genetics.soton.ac.uk>

†SIBPAIR (2.1) within ANALYZE by J Terwilliger.⁸

Table 3 Markers within or flanking the MHC on 6p21 (PSORS1)

Marker	Lod score*	SIBPAIR*	% sharing*
D6S470	0.087	0.26	50
D6260	0.817	0.026	58
D6S276	2.92	0.00012	59
tn62	4.51	0.0000026	61
D6S273	4.33	0.000004	61
D6S291	6.33	0.00000034	65
D6S300	1.32	0.0069	56

*SIBPAIR (2.1) within ANALYZE by J Terwilliger.⁸

Comparable results were observed using a two point sib pair analysis ($p=3.4 \times 10^{-8}$) (table 3).

We next examined those families designated NPLPOS for the region at 6p21, for sharing of alleles IBD between affected sib pairs according to parental origin. A highly significant difference for allele sharing was detected for the markers D6S276, tn62, D6S273, D6S291, and D6S300, with up to 92% of allele sharing between ASPs being paternally derived (p value of 0.004 for alleles at D6S273 in a test for heterogeneity using a 2×2 contingency table chi square test) (table 4). For comparison we also analysed those families found to be NPLPOS for the next most

significant region for linkage, namely that between markers D1S197 and D1S200 at chromosome 1p. No significant parental effect was observed for any of the markers from chromosome 1p (fig 2).

EVIDENCE OF EPISTASIS BETWEEN PSORS1 AND OTHER LOCI

In the light of evidence for multiple loci contributing to psoriasis susceptibility within our cohort, we sought to reduce the heterogeneity of the data set by partitioning based on sharing of alleles at 6p21, the region showing the greatest evidence for linkage. Families providing either positive or negative NPL scores were reanalysed using Genehunter. NPLPOS families provided NPL scores above 2 for regions on chromosome 2p (NPL=2.09, $p=0.019$) and chromosome 14q (NPL=2.0, $p=0.026$), both within regions previously reported in genome wide scans.^{8,17} In contrast, NPLNEG families made no contribution to the 1p and 19p linkage scores.

Discussion

The pathogenesis of psoriasis is complex, with both genetic and environmental factors contributing to the development of the disease. This and previous genome scans have identified a major psoriasis susceptibility locus within the MHC (PSORS1) on chromosome 6p21, which is estimated to contribute up to 50% of the familial clustering underlying psoriasis.⁸⁻¹² Hence, non-MHC loci must exist but individually these are likely to have a small genetic effect, the detection and replication of which is likely to require both the use of large datasets and more dense genetic marker panels. In this study, we have used a much larger number of affected relative pairs, with an optimised polymorphic STS marker set.

Table 4 Sharing between affected sib for paternally and maternally derived alleles on chromosome 6p

Marker	Paternally derived allele			Maternally derived allele		
	No of sibs	Shared %	p value	No of sibs	Shared %	p value
D6S470	60	73	0.0002	52	54	0.34
D6S276	31	87	0.000017	40	68	0.019
tn62	52	92	6.5×10^{-11}	48	73	0.001
D6S273	39	92	1.8×10^{-8}	38	66	0.036
D6S291	55	87	6.5×10^{-9}	47	72	0.0015
D6S300	46	76	0.00027	46	65	0.027
D6S268	29	62	0.13	31	55	0.36

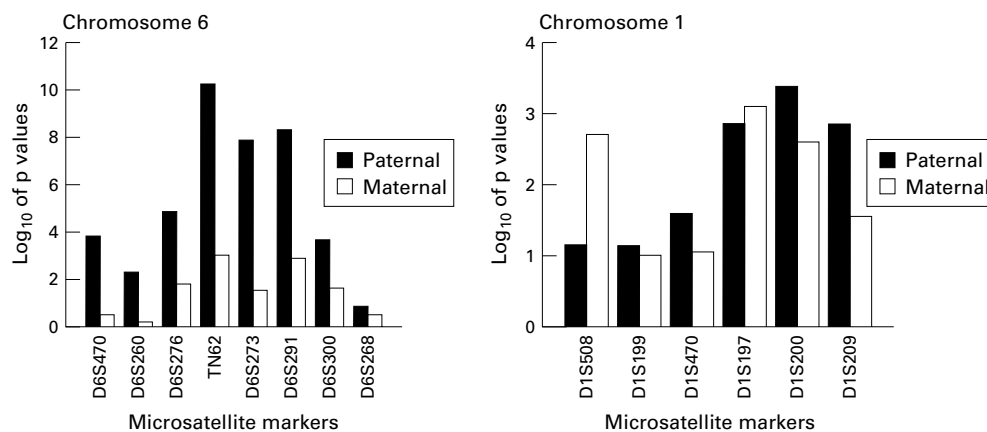


Figure 2 *P* values plotted from GAS 2.0 for markers from the two linkage regions at chromosomes 6p21 and 1p. Black boxes represent *p* values for sharing of the paternally derived alleles and white boxes the maternally derived alleles. (Left) Parental origin for NPLPOS families for the 6p21 linkage region (*PSORS1*). (Right) Parental origin for NPLPOS families for 1p linkage region.

Our genome scan provides both confirmation of the MHC susceptibility locus (*PSORS1*) and evidence for a locus on the short arm of chromosome 1.

Three consecutive markers, D1S197, D1S200, and D1S207 at chromosome 1p contributed to a significant NPL score of 3.6, which reaches published criteria for genome wide significance in the search for loci contributing to complex disease susceptibility.²³ Of interest, in our initial genome scan, using an independent cohort of psoriasis kindreds, marker D1S197 generated a single point sib pair analysis value $p=0.018$.⁸ Neither study detected evidence for linkage disequilibrium using the transmission disequilibrium test for the markers described. This may reflect a spacing of markers too broad to detect LD with a disease gene or the absence of any such association. A number of immune related genes have been mapped to 1p. Intriguingly, the region includes the gene encoding EPS15, a highly specific intracellular substrate for the EGF receptor which itself is known to be overexpressed in psoriatic epidermis.²⁵ The presence of positional biological candidate genes combined with the replication of findings from a previous genome analysis suggest this region is now worthy of more detailed investigation.

We also provide further confirmation for the major role of a gene or genes located within the MHC at chromosome 6p21 to psoriasis susceptibility. Using an ancestral haplotype strategy, the minimum interval for the *PSORS1* locus has been mapped to a 300 kb genomic fragment between the class 1 *HLA C* gene and the *S* gene,^{26, 27} which encodes the late epidermal differentiation protein, corneodesmosin.^{28–30} The genomic sequence of this region has recently been published and a number of novel genes identified, each of which represents a positional candidate for *PSORS1*.³¹ This region is currently the focus of intense investigation using a combination of genetic and functional studies. Of the other regions of putative interest identified in this study, intriguingly markers on chromosome

19p13.3 (D19S901) lie within a region paralogous to the MHC, a region assumed to have arisen as an early duplication event.³² Identification of the *PSORS1* gene variants will enable further assessment of this finding and in particular a search for sequence homology between the two regions.

The pivotal role of *PSORS1* justifies more detailed exploration of its potential interactions with other susceptibility loci in the aetiology of psoriasis. We partitioned families displaying evidence of linkage for markers (table 4) on chromosome 6p21 as this region has been replicated in several independent genome wide scans and has been refined to a limited genomic region. This approach has the potential to separate heterogeneous contributions to psoriasis. For two independent chromosomal regions, 2p and 14q, suggestive evidence for linkage (NPL score ≥ 2.0) was detected in the NPLPOS group, indicating a potential epistatic effect. However, these data must be interpreted cautiously, both because of the multiple statistical tests applied (stratification) and the relatively small sample size from which the results are derived.¹ However, it is of interest that both of these regions have previously been implicated as putative susceptibility loci.^{8, 17} Further study of larger cohorts (in excess of 1000 sib pairs) will be required to enable detailed genetic analysis of these regions with a smaller contribution to the familial clustering in psoriasis.

We next examined the contribution of *PSORS1* according to parental sex. Previous segregation analysis data showed a significantly higher penetrance of psoriasis if the father was either affected or a presumed gene carrier.⁷ Distortion of sharing of paternally derived alleles at markers on chromosome 6p has been suggested previously by Burden *et al*.³³ and is now shown in a larger data set. Possible mechanisms that may account for these observations include genetic imprinting of a susceptibility allele, and similar findings have been proposed for type 1 diabetes mellitus susceptibility locus *IDDM2*.^{34, 35} Whatever the mechanism, the strength of this finding would

suggest that parental effects should be considered in regard of the fine mapping and characterisation of the genetic variant(s) contributing to *PSORS1*.

Despite the use of a larger data set, which readily detected linkage to *PSORS1*, we did not find support for linkage for a number of previously identified psoriasis susceptibility loci (table 2). Replication of findings from independent genome wide scans has rarely been achieved to date. It has been suggested that confirmation of linkage will require yet larger study cohorts than those used in the initial scan. Furthermore, the marker set used in this study was not developed to enable optimal replication of previously reported loci. Finally, the possibility of both false positive and negative findings, particularly in association with multiple statistical testing, has been widely discussed.³⁶

We can conclude that the molecular genetic basis of susceptibility to psoriasis is complex, with heterogeneity, multiple genes, and possible epistatic interactions all contributing. The susceptibility locus *PSORS1* appears to represent the major locus in this disorder and fine scale mapping of this region is now feasible. This study points to the utility of the reduction of heterogeneity in pooled data sets that will be achieved through future analysis, based upon the presence or absence of the genomic variants that contribute to *PSORS1*. The elucidation of the molecular mechanisms underlying such genetic interactions must await the identification and functional analysis of the relevant genes.

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