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Report

The International Psoriasis Genetics Study: Assessing Linkage to 14 Candidate Susceptibility Loci in a Cohort of 942 Affected Sib Pairs

The International Psoriasis Genetics Consortium*

In an effort to confirm previously reported linkages to psoriasis, we analyzed 942 affected sibling pairs (ASPs) from 710 pedigrees for 53 polymorphic microsatellites spanning 14 psoriasis candidate regions at an intermarker spacing of ~5 cM. Maximum LOD score (MLS) analysis of ASPs yielded allele sharing of 60% for markers within the major histocompatibility complex (MHC) ($P = 2 \times 10^{-14}$), which yielded a gene-specific λ_s of 1.6. Across the remainder of the genome, the strongest evidence of allele sharing was obtained on chromosomes 16q (D16S3032; MLS = 1.3; $P = .007$) and 10q22–q23 (D10S2327; MLS = 1.1; $P = .012$). None of the remaining loci exceeded MLS = 0.9, the value expected to occur by chance once in this study. In agreement with previous studies, strong linkage disequilibrium was also observed between psoriasis and the MHC (pedigree disequilibrium test $P = 3.9 \times 10^{-8}$ for D6S1014). Two psoriasis-associated MHC haplotypes were identified with the haplotype-based transmission/disequilibrium test. Analysis of only those families carrying either of these haplotypes significantly increased the chromosome 16q LOD score from 1.3 to 2.4 ($P = .045$). These results underscore the importance of the MHC in psoriasis and provide a rationale for more-detailed examination of candidate regions on chromosomes 16q and 10q.

Psoriasis (MIM 177900) is an inflammatory, hyperproliferative disorder of the skin, the pathogenesis of which remains poorly understood (Barker 1998; Elder 1998). Psoriasis is common, affecting >2% of adults in most populations, yet current therapeutic strategies remain suboptimal (Camp 1998). Susceptibility to the development of psoriasis has a significant genetic component, with the λ_s, a measure of the risk ratio of disease in siblings of affected subjects, reported to be in the range 4–6 (Bhalerao and Bowcock 1998; Elder et al. 2001). Psoriasis appears to be a disorder of complex etiology that requires the interaction of unknown environmental triggers and genetic susceptibility (Elder et al. 2001; Capon et al. 2002). Resolution of the molecular genetic contributions to the pathogenesis of psoriasis will provide a logical framework against which future advances in treatment and/or prevention are likely to evolve. In recent years, a number of genomewide linkage scans have been performed, by use of family material ascertained from dispersed geographical locations. In no fewer than five studies, significant evidence of linkage has been reported for *PSORS1* (psoriasis susceptibility 1) a region located on the short arm of chromosome 6 and specifically within the major histocompatibility complex (MHC) (Nair et al. 1997; Trembath et al. 1997; Samuelsson et al. 1999; Lee et al. 2000; Veal et al. 2001; Zhang et al. 2002). Further linkage disequilibrium–mapping studies, including the use of non-MHC gene polymorphic markers, when taken together, localize *PSORS1* to a genomic segment ~150 kb in length. This region includes the class 1 MHC gene HLA-C and the gene that encodes corneodesmosin, a component of the keratinocyte desmosome (Balendran et al. 1999; Oka et al. 1999; Nair et al. 2000). Intensive genetic studies to identify risk haplotypes from this region are now under way (Nair et al. 2000; Veal et al. 2002). However, initial assessment of allele sharing between affected sibling pairs suggests that the *PSORS1* locus may account for no more than 50% of the sibling relative risk (Trembath et al. 1997), which supports the view that, in addition

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Table 1

The Consortium Data Set: Sample Composition

Cohort	No. of Pedigrees	No. of ASPs	Origin
London/Leicester/Glasgow	228	349	United Kingdom
Ann Arbor/Kiel	244	361	United States, Germany
Dallas/St. Louis	238	232	United States
Total	710	942	

to potential environmental triggers for disease onset, susceptibility is dependent on the role of other genetic loci. To date, at least seven regions outside of the MHC *(PSORS2–8)* have been proposed to harbor psoriasis susceptibility loci, on the basis of genomewide linkage scans (Tomfohrde et al. 1994; Matthews et al. 1996; Nair et al. 1997; Capon et al. 1999; Samuelsson et al. 1999; Lee et al. 2000; Veal et al. 2001). Support for a putative susceptibility locus is greatly enhanced by replication (at a statistically significant level) in independent data sets. Indeed, this process is perceived as a critical strategy to aid distinction from false-positive linkages, in the data sets generated by marker-dense genomewide analyses (Lander and Kruglyak 1995). An alternative strategy is to analyze very large samples (Risch 2000). This strategy is aimed at overcoming the low power inherent in diseases characterized by low-penetrance, high-prevalence susceptibility loci. All such studies require careful attention to population selection so as to minimize the effects of ethnic and clinical heterogeneity.

To better understand the genetics of psoriasis, we have established a consortium of investigators to investigate 14 previously reported potential psoriasis-susceptibility loci in a cohort of 710 families with psoriasis. Although the subjects have been ascertained across broad geographical regions, the vast majority of patients and relatives are of European descent.

Subjects.—The International Psoriasis Genetics Consortium patient cohort consists of independently ascertained pedigrees, providing a total of 942 affected sib pairs (ASPs). Details are presented in table 1 and table 2. All families were recruited by experienced consortium members (based in Dallas/St. Louis; Ann Arbor/Kiel, Germany; and London/Leicester/Glasgow), by use of criteria as described in detail elsewhere (Tomfohrde et al. 1994; Nair et al. 1997; Trembath et al. 1997). The Ann Arbor/Kiel data set included 221 ASPs typed in a genome scan performed by Nair and colleagues (1997), together with a further 140 ASPs recruited for this study. The London/Leicester cohort included family material described by Veal and colleagues (2001), with no duplication of the data set used by the same group in an initial genome scan (Trembath et al. 1997). The Dallas/St. Louis sample comprised 238 pedigrees and specifically did not include the multiply affected families used in the scan that localized PSORS2 on 17q (Tomfohrde et al. 1994). The three groups used comparable diagnostic criteria and excluded case subjects where palmo-plantar pustulosis or seborrheic dermatitis occurred in the absence of other clinical signs of psoriasis (Camp 1998).

Table 2

The Consortium Data Set: Pedigree Structures

		No. of Affected Subjects						
Family Type	No. of Families	1	2	3	4	5	6	≥7
Nuclear	566	38	320	176	31	2	1	0
Extended	144	0	14	43	29	26	12	18
Total	710	38	334	219	60	28	13	18

Each group obtained approval for these studies from its own institutional review board or ethics committee (U.K.). All subjects participating in this study provided informed consent.

Genotyping.—The candidate regions were defined as (i) any locus identified by genome scans published at the outset of the study and (ii) loci that had displayed suggestive evidence of linkage in at least one genome scan, including unpublished surveys by Consortium members. All 14 regions that met these criteria are reported in table 3. A total of 53 polymorphic microsatellites spanning the candidate loci at an average of 5-cM intervals (table 3) were selected from the Marshfield (Broman et al. 1998) and Généthon (Dib et al. 1996) marker sets. Genotyping was performed by the London/Leicester and Dallas/St. Louis groups by use of fluorescent dyes (Trembath et al. 1997), with electrophoresis and signal recording performed on ABI 377 automated sequencers (Applied Biosystems). The Ann Arbor/Kiel group performed genotyping using ^{32}P labeling of a single primer, as described elsewhere (Nair et al. 1997). CEPH individual 1347-02 was genotyped by all three groups as a standard for comparison. Completeness of genotyping varied from group to group and from marker to marker, with a range of 66%–95% in the pooled sample. Mendelian inconsistencies in pedigree data were identified and eliminated by the PedCheck software (O'Connell and Weeks 1998).

Statistical analyses.—Allele sharing in affected siblings was assessed by use of Risch's maximum LOD score (MLS) method (Risch 1990), as implemented in a modification of GENEHUNTER 2.1 (Kruglyak et al. 1996; Markianos et al. 2001). This method employs a 1-df

Table 3

Psoriasis Susceptibility Regions Typed in Consortium Data Set

Region and Marker	Distance from pter (cM)	MLS	MAS	References
1q21 (PSORS4):				Bhalerao and Bowcock 1998; Capon et al. 1999
D1S1679	235.8	.6	.52	
APOA2	243.865	.3	.51	
D1S1677	245.44	.6	.52	
2p:				Trembath et al. 1997; Bhalerao and Bowcock 1998
D2S1342	89.375	0	.5	
D2S136	90.735	0	.5	
D2S134[a]	105.87	0	.5	
D2S1772	106.965	0	.5	
4q13:				Bhalerao and Bowcock 1998
D4S427	178.775	.3	.52	
D4S2394	182.01	.4	.52	
4q21:				Samuelsson et al. 1999
D4S1548	214.455	.4	.52	
D4S1629	221.34	.5	.52	
D4S1554	262.02	.2	.51	
4qter (PSORS3):				Matthews et al. 1996
D4S1535	266.995	.2	.51	
D4S171	274.875	.3	.51	
6p21 (PSORS1):				Nair et al. 1997; Trembath et al. 1997; Samuelsson et al. 1999
TNFB	83.51	12.1	.59	
D6S273	84.125	12.6	.59	
D6S1014	84.635	12.6	.59	
D6S291	84.93	11.1	.59	
6q:				Nair et al. 1997
D6S270	184.57	.7	.53	
GATA184A08	198.07	.4	.52	
8q24:				Trembath et al. 1997
D8S1128	191.015	0	.5	
D8S1801	195.185	0	.51	
D8S284	197.495	.1	.51	
D8S558	200.56	.2	.51	
10q22:				Nair et al. 1997
D10S1136	126.955	.9	.53	
D10S569	133.365	1.1	.53	
D10S2327	137.315	1.1	.53	
11p13:				Nair et al. 1997
D11S935	81.55	.4	.52	
D11S1330	84.915	.4	.52	
D11S1360	87.51	.3	.52	
D11S903	90.995	.2	.51	
14q31:				Bhalerao and Bowcock 1998
D14S617	123.68	0	.5	
D14S81	128.225	.3	.51	
D14S1142	130.735	.1	.51	
D14S1434	134.46	0	.5	
16q:				Nair et al. 1997
D16S3396	91.84	.6	.52	
D16S770	92.3	.6	.52	
D16S415	96.635	.6	.52	
D16S3034	99.625	.6	.52	
D16S771	100.38	.5	.52	
D16S3032	102.62	1.3	.53	
17q25 (PSORS2):				Tomfohrde et al. 1994; Nair et al. 1997; Enlund et al. 1999
D17S2059	112.475	.2	.52	
D17S1301	122.795	.7	.53	
D17S674	141.935	.3	.52	
D17S784	161.535	0	.5	
D17S668[a]	179.825	0	.5	
D17S928	179.825	0	.5	
20p:				Nair et al. 1997; Trembath et al. 1997
D20S879	49.915	.1	.51	
D20S851	52.12	.1	.51	
D20S160	53.985	0	.5	
D20S894	57.015	0	.51	
D20S186	57.825	0	.5	
D20S604	59.92	0	.5	

[a] Markers D2S134 and D17S688 were not typed for the Ann Arbor/Kiel group.

Table 4

Evidence of Association with Psoriasis in Regions of Linkage Replication

Region	Haplotype[a]	Alleles	T:NT[b]	P[c]
6p21.3	TNFB-D6S273-D6S1014	103-136-136	164:50	$< 1 \times 10^{-6}$
6p21.3	TNFB-D6S273-D6S1014	113-130-148	88:41	3.5×10^{-5}
16q12-q13	D16S770-D16S415-D16S3034	131-208-272	37:10	8.2×10^{-5}

[a] Most-significant GENEHUNTER2 multipoint TDT haplotypes.

[b] Transmitted:nontransmitted.

[c] Nominal P values. After performance of empirical permutation testing to address multiple-allele combinations (by use of GENEHUNTER) and after multiplication by 3 to correct for the number of regions tested with MLS values <1.0 (6p, 10q, and 16q), the corrected P values are all <.05.

multiplicative MLS test, in which $p2$ = MAS × MAS, $p1 = 2 \times \text{MAS}(1 - \text{MAS})$, and $p0 = (1 - \text{MAS})(1 - \text{MAS})$, where "MAS" denotes mean allele sharing. To assess statistical significance of MLS values, 1,000 simulations of the Consortium cohort were performed by creating data sets matching the marker-map positions and allele frequencies, as well as the family structure, the genotyped individuals, and the missing data percentage of the total sample. Simulations were performed by use of the GENSIM software (available at Dr. Daly's Web page; see "Electronic-Database Information" section).

Association between marker haplotypes and psoriasis was assessed by the multilocus transmission/disequilibrium test (TDT) implementation of GENEHUNTER 2.1. Association between single markers and psoriasis was assessed by means of the pedigree-disequilibrium test (PDT) (Martin et al. 2000, 2001). The published version of the PDT uses all informative triads and discordant sibships in a pedigree. We extended the PDT to also use all informative dyads (one typed parent and affected child) if no informative triads are present. P values were determined for a global test of all alleles at each marker, by use of the PDT-average statistic. All dyads that could lead to bias in the disequilibrium statistic (Curtis and Sham 1995) were eliminated.

Possible interactions between *PSORS1* and the various non-MHC loci were assessed by analyzing a subset of 250 families in which at least one affected individual had an obligate or maximum-likelihood three-marker microsatellite haplotype matching one of the overtransmitted MHC chromosomes identified by the haplotype-based TDT. For this analysis, MHC haplotypes were scored as matching when two alleles matched and the third was ambiguous or missing.

Empirical simulations.—The analysis of 1,000 random replicas of the 710 families' genotypes demonstrated that an MLS of 2.0 could be expected to occur by chance, anywhere in the 14 analyzed regions, in ⩽5% of experiments. An MLS >2.0 can therefore be adopted as a criterion for declaring significant linkage in the context of this study. Our simulations also indicated that an MLS of 0.9 would be expected to occur by chance once per experiment and, as such, may be considered as a value suggestive of linkage in the context of this study (Lander and Kruglyak 1995).

Linkage analysis results.—A summary of linkage results is shown in table 3. Analysis of allele sharing at chromosome 6p21 confirmed the presence of a major susceptibility locus within the MHC, as documented by an MLS of 12.6 (marker D6S273; $P = 2 \times 10^{-14}$). Affected sibling pairs displayed allele sharing of 60%, which corresponds to a gene-specific λ_s of 1.6 for the MHC locus.

The strongest evidence of linkage to non-MHC loci was obtained on chromosomes 10q (MLS = 1.1 for D10S2327; $P = .012$) and 16q (MLS = 1.3 for D16S3032; $P = .007$) (table 3). The evidence of linkage at the remaining non-MHC loci failed to reach the MLS = 0.9 criterion expected to occur by chance once per study (table 3).

Association analysis results.—Haplotype association analyses were performed at the regions of linkage replication. Consistent with prior association studies (reviewed by Capon et al. 2002), strong linkage disequilibrium was observed between psoriasis and alleles within the MHC. Multipoint TDT analysis indicated preferential transmission of two MHC haplotypes (table 4). Comparison with data published elsewhere (Nair et al. 2000) revealed that one of these haplotypes carried HLA-Cw6 and HLA-B57, and the other carried HLA-Cw6 and HLA-B13 (data not shown). A putative susceptibility haplotype could also be defined on chromosome 16q (table 4), whereas no evidence of association could be observed for chromosome 10q markers.

Single-marker linkage disequilibrium testing was also performed at the regions of linkage replication by use of the PDT. Again, strong linkage disequilibrium was observed between psoriasis and MHC markers. The most highly significant P value was obtained within the MHC ($P = 1.3 \times 10^{-8}$ for marker D6S1014). The two other MHC markers also yielded P values <.01 (3.4 ×

10^{-3} and 3.2×10^{-3} for TNFB and D6S273, respectively). Chromosomes 10 and 16 did not yield any single-marker PDT *P* values <.3.

Interactions of MHC and non-MHC loci.—To define putative interactions between the MHC and other susceptibility loci, we analyzed a subset of 250 families in which at least one affected individual carried either of the MHC-risk haplotypes. In this set of families, evidence of linkage to chromosome 16 increased from MLS = 1.3 to MLS = 2.4, despite a marked reduction in sample size from 710 to 250 families. An increase in MLS from 1.3 to 2.4 in this chromosomal region would occur <5% of the time by chance, as evaluated by repeated resampling of the observed data (224/5,000 runs). No other region yielded MLS > 1.5 in this subgroup.

The International Psoriasis Genetics Consortium Cohort represents, to our knowledge, the largest available collection of families with psoriasis to date. The Consortium was established to allow the analysis of pooled data sets, by use of common statistical tools and an agreed-on marker panel, with spacing sufficiently dense to potentially extract a greater proportion of the inheritance information. Detailed assessment of cohorts of this size is likely to prove essential in efforts to refine the likely target genome locations for positional cloning of susceptibility genes. In this study, we chose to assess in some detail those regions of the human genome for which evidence of linkage to a psoriasis-susceptibility locus had already been observed at the outset of the study. Our results provided unequivocal evidence of linkage and allelic association for the susceptibility region on chromosome 6p21 (PSORS1) (Nair et al. 1997; Trembath et al. 1997). We identified two MHC haplotypes composed of alleles at loci TNFB-D6S273-D6S1014, which extend over 0.6 Mb, to be preferentially transmitted to subjects affected by psoriasis. We and others have recently performed linkage disequilibrium studies, using high-resolution microsatellite and SNP marker maps, and highlighted a 150-kb interval of conserved association (Balendran et al. 1999; Oka et al. 1999; Nair et al. 2000; Veal et al. 2002). These investigations have revealed a single likely ancestral risk haplotype, which is present on both of the overtransmitted chromosomes identified in this study (R. P. Nair, P. E. Stuart, S. Jenisch, J. T. Elder, C. D. Veal, F. Capon, J. N. W. N. Barker, and R. Trembath, unpublished data). The detection of two TNFB-D6S273-D6S1014 haplotypes that have HLA-Cw6 in common but differing in their HLA-B alleles is most likely explained by an ancestral recombination event between HLA-B and HLA-C. Further efforts to resolve the psoriasis-susceptibility allele(s) at PSORS1 by use of the large cohort reported here, together with ethnically diverse patient populations, are now under way.

Despite the exceptionally strong linkage signal generated at the 6p21 region, allele sharing between sib pairs was no greater than 60%, which suggests that the MHC locus-specific λ_s accounts for <50% of the familial clustering observed in psoriasis. The number and magnitude of effect for additional susceptibility loci for psoriasis, and the extent to which they may account for etiological heterogeneity, is currently unknown. In the present study, no other locus achieved a genomewide significance level <.05, equivalent to an allele-sharing LOD score >3.63 in a genomewide linkage scan (Lander and Kruglyak 1995). Since this study was designed to survey a number of regions of the genome for which prior evidence of linkage had been generated, we were anxious to avoid loss of potentially important observations through assessment against criteria put forward to aid the interpretation of primary genomewide linkage scans. We therefore developed specific significance thresholds by performing empirical simulations of the entire data set. Against these estimates of significance, we observed two regions on chromosomes 16q and 10q that provide evidence suggestive of linkage in the context of this study. However, it should be noted that partial overlap exists between the families originally studied by the Ann Arbor/Kiel group (Nair et al. 1997) and those analyzed here (see "Subjects" section). Elimination of these families reduced the MLS values for all non-MHC loci to below the criterion value of MLS = 0.9 (data not shown). By comparison, markers in the MHC region continued to yield MLS values as high as 12.3, even after exclusion of the overlapping Ann Arbor families (data not shown). Clearly, caution is required in assessing linkage to the non-MHC regions on 10q and 16q. An even larger data set will be required to discriminate with confidence between susceptibility loci with a minor effect and false-negative linkage results.

Notwithstanding these concerns, the involvement of a chromosomal locus at 16q in psoriasis susceptibility was supported by the results of MHC interaction analysis, which revealed an increase in MLS from 1.3 to 2.4, despite a reduction in sample size from 710 to 250 families. This change in MLS would be expected to occur in this chromosomal region <5% of the time by chance. Moreover, we identified a 2.5-cM haplotype, D16S770-D16S415-D16S3034, which is significantly overtransmitted to affected offspring with psoriasis ($P = 8.2 \times 10^{-5}$). Some additional evidence of independent replication of linkage to this region has recently emerged through the study of psoriatic subjects whose disease is complicated by the occurrence of a seronegative arthritis (Karason et al. 2003). Furthermore, a number of genomewide scans in a range of disorders that are characterized by an abnormal inflammatory response to environmental triggers have reported linkage to 16q (Becker et al. 1998). This region includes *CARD15*, a susceptibility gene underlying the inflammatory bowel

disorder, Crohn disease (Hugot et al. 2001; Ogura et al. 2001). Mutation analysis and lack of association between CARD15 alleles and psoriasis (Nair et al. 2001; Borgiani et al. 2002; Young et al., in press) together with its localization, which is at least 8 cM proximal to the marker D16S3034, would appear to eliminate *CARD15* as a likely psoriasis candidate gene in this region. Taken together, these findings strengthen the argument for further investigation of the 16q region in conferring susceptibility to psoriasis, since the mechanism is likely to be distinct from that contributing to Crohn disease. Given the relatively modest effect of this locus, the Consortium data set is among the very few which are likely to provide the power required for a reliable refinement study.

In conclusion, this large collaborative study is likely to facilitate further research efforts to determine and characterize susceptibility loci for the common skin disorder, psoriasis. These data provide unequivocal evidence of a major role for a gene or genes within the class 1 region of the MHC. Other loci are likely to confer lower risk to disease causation and, hence, will pose a considerable challenge for future detection and characterization.

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Electronic-Database Information

URLs for data presented herein are as follows:

Daly Lab at the Whitehead Institute, http://www-genome.wi.mit.edu/personal/mjdaly/ (for characterization of patterns of mammalian genetic variation)

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for psoriasis susceptibility)

References

Balendran N, Clough RL, Arguello JR, Barber R, Veal C, Jones AB, Rosbotham JL, Little AM, Madrigal A, Barker JN, Powis SH, Trembath RC (1999) Characterization of the major susceptibility region for psoriasis at chromosome 6p21.3. J Invest Dermatol 113:322–328

Barker JN (1998) Pathogenesis of psoriasis. J Dermatol 25: 778–781

Becker KG, Simon RM, Bailey-Wilson JE, Freidlin B, Biddison WE, McFarland HF, Trent JM (1998) Clustering of non-major histocompatibility complex susceptibility candidate loci in human autoimmune diseases. Proc Natl Acad Sci USA 95: 9979–9984

Bhalerao J, Bowcock AM (1998) The genetics of psoriasis: a complex disorder of the skin and immune system. Hum Mol Genet 7:1537–1545

Borgiani P, Vallo L, D'Apice MR, Giardina E, Pucci S, Capon F, Nistic S, Chimenti S, Pallone F, Novelli G (2002) Exclusion of CARD15/NOD2 as a candidate susceptibility gene to psoriasis in the Italian population. Eur J Dermatol 12:540–542

Broman KW, Murray JC, Sheffield VC, White RL, Weber JL (1998) Comprehensive human genetic maps: individual and sex-specific variation in recombination. Am J Hum Genet 63:861–869

Camp RDR (1998) Psoriasis. In: Champion RH, Burton JL, Burns DA, Breathnach SM (eds) Textbook of dermatology. Vol 2. Blackwell, London, pp 1589–1650

Capon F, Munro M, Barker J, Trembath R (2002) Searching for the major histocompatibility complex psoriasis susceptibility gene. J Invest Dermatol 118:745–751

Capon F, Novelli G, Semprini S, Clementi M, Nudo M, Vultaggio P, Mazzanti C, Gobello T, Botta A, Fabrizi G, Dallapiccola B (1999) Searching for psoriasis susceptibility genes in Italy: genome scan and evidence for a new locus on chromosome 1. J Invest Dermatol 112:32–35

Curtis D, Sham PC (1995) A note on the application of the

transmission disequilibrium test when a parent is missing. Am J Hum Genet 56:811–812

Dib C, Faure S, Fizames C, Samson D, Drouot N, Vignal A, Millasseau P, Marc S, Hazan J, Seboun E, Lathrop M, Gyapay G, Morissette J, Weissenbach J (1996) A comprehensive genetic map of the human genome based on 5,264 microsatellites. Nature 380:152–154

Elder JT, Nair RP, Henseler T, Jenisch S, Stuart P, Chia N, Christophers E, Voorhees JJ (2001) The genetics of psoriasis 2001: the odyssey continues. Arch Dermatol 137:1447–1454

Elder JT (1998) Psoriasis. In: JL Jameson (ed) Principles of molecular medicine. Humana, Totowa, NJ, pp 793–800

Enlund F, Samuelsson L, Enerback C, Inerot A, Wahlstrom J, Yhr M, Torinsson A, Riley J, Swanbeck G, Martinsson T (1999) Psoriasis susceptibility locus in chromosome region 3q21 identified in patients from southwest Sweden. Eur J Hum Genet 7:783–790

Hugot JP, Chamaillard M, Zouali H, Lesage S, Cezard JP, Belaiche J, Almer S, Tysk C, O'Morain CA, Gassull M, Binder V, Finkel Y, Cortot A, Modigliani R, Laurent-Puig P, Gower-Rousseau C, Macry J, Colombel JF, Sahbatou M, Thomas G (2001) Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. Nature 411: 599–603

Karason A, Gudjonsson JE, Upmanyu R, Antonsdottir AA, Hauksson VB, Runasdottir EH, Jonsson HH, Gudbjartsson DF, Frigge ML, Kong A, Stefansson K, Valdimarsson H, Gulcher JR (2003) A susceptibility gene for psoriatic arthritis maps to chromosome 16q: evidence for imprinting. Am J Hum Genet 72:125–131

Kruglyak L, Daly MJ, Reeve-Daly MP, Lander ES (1996) Parametric and nonparametric linkage analysis: a unified multipoint approach. Am J Hum Genet 58:1347–1363

Lander E, Kruglyak L (1995) Genetic dissection of complex traits: guidelines for interpreting and reporting linkage results. Nat Genet 11:241–247

Lee Y-A, Rüschendorf F, Windemuth C, Schmitt-Egenolf M, Stadelmann A, Nürnberg G, Ständer M, Wienker TF, Reis A, Traupe H (2000) Genomewide scan in German families reveals evidence for a novel psoriasis-susceptibility locus on chromosome 19p13. Am J Hum Genet 67:1020–1024

Markianos K, Daly MJ, Kruglyak L (2001) Efficient multipoint linkage analysis through reduction of inheritance space. Am J Hum Genet 68:963–977

Martin ER, Bass MP, Kaplan NL (2001) Correcting for a potential bias in the pedigree disequilibrium test. Am J Hum Genet 68:1065–1067

Martin ER, Monks SA, Warren LL, Kaplan NL (2000) A test for linkage and association in general pedigrees: the pedigree disequilibrium test. Am J Hum Genet 67:146–154

Matthews D, Fry L, Powles A, Weber J, McCarthy M, Fisher E, Davies K, Williamson R (1996) Evidence that a locus for familial psoriasis maps to chromosome 4q. Nat Genet 14: 231–233

Nair RP, Henseler T, Jenisch S, Stuart P, Bichakjian CK, Lenk W, Westphal E, Guo SW, Christophers E, Voorhees JJ, Elder JT (1997) Evidence for two psoriasis susceptibility loci (HLA and 17q) and two novel candidate regions (16q and 20p) by genome-wide scan. Hum Mol Genet 6:1349–1356

Nair RP, Stuart P, Henseler T, Jenisch S, Chia NVC, Westphal E, Schork NJ, Kim J, Lim HW, Christophers E, Voorhees JJ, Elder JT (2000) Localization of psoriasis-susceptibility locus PSORS1 to a 60-kb interval telomeric to HLA-C. Am J Hum Genet 66:1833–1844

Nair RP, Stuart P, Ogura Y, Inohara N, Chia NV, Young L, Henseler T, Jenisch S, Christophers E, Voorhees JJ, Nunez G, Elder JT (2001) Lack of association between NOD2 3020InsC frameshift mutation and psoriasis. J Invest Dermatol 117:1671–1672

O'Connell JR, Weeks DE (1998) PedCheck: a program for identification of genotype incompatibilities in linkage analysis. Am J Hum Genet 63:259–266

Ogura Y, Bonen DK, Inohara N, Nicolae DL, Chen FF, Ramos R, Britton H, Moran T, Karaliuskas R, Duerr RH, Achkar JP, Brant SR, Bayless TM, Kirschner BS, Hanauer SB, Nunez G, Cho JH (2001) A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. Nature 411:603–606

Oka A, Tamiya G, Tomizawa M, Ota M, Katsuyama Y, Makino S, Shiina T, Yoshitome M, Iizuka M, Sasao Y, Iwashita K, Kawakubo Y, Sugai J, Ozawa A, Ohkido M, Kimura M, Bahram S, Inoko H (1999) Association analysis using refined microsatellite markers localizes a susceptibility locus for psoriasis vulgaris within a 111 kb segment telomeric to the HLA-C gene. Hum Mol Genet 8:2165–2170

Risch N (1990) Linkage strategies for genetically complex traits. I. Multilocus models. Am J Hum Genet 46:222–228

Risch NJ (2000) Searching for genetic determinants in the new millennium. Nature 405:847–856

Samuelsson L, Enlund F, Torinsson A, Yhr M, Inerot A, Enerback C, Wahlstrom J, Swanbeck G, Martinsson T (1999) A genome-wide search for genes predisposing to familial psoriasis by using a stratification approach. Hum Genet 105: 523–529

Tomfohrde J, Silverman A, Barnes R, Fernandez-Vina MA, Young M, Lory D, Morris L, Wuepper KD, Stastny P, Menter A, Bowcock AM (1994) Gene for familial psoriasis susceptibility mapped to the distal end of human chromosome 17q. Science 264:1141–1145

Trembath RC, Clough RL, Rosbotham JL, Jones AB, Camp RD, Frodsham A, Browne J, Barber R, Terwilliger J, Lathrop GM, Barker JN (1997) Identification of a major susceptibility locus on chromosome 6p and evidence for further disease loci revealed by a two stage genome-wide search in psoriasis. Hum Mol Genet 6:813–820

Veal CD, Capon F, Allen MH, Heath EK, Evans JC, Jones A, Patel S, Burden D, Tillman D, Barker JNWN, Trembath RC (2002) Family-based analysis using a dense single-nucleotide polymorphism–based map defines genetic variation at *PSORS1,* the major psoriasis-susceptibility locus. Am J Hum Genet 71:554–564

Veal CD, Clough RL, Barber RC, Mason S, Tillman D, Ferry B, Jones AB, Ameen M, Balendran N, Powis SH, Burden AD, Barker JN, Trembath RC (2001) Identification of a novel psoriasis susceptibility locus at 1p and evidence of epistasis between PSORS1 and candidate loci. J Med Genet 38:7–13

Young C, Allen MH, Cuthbert A, Ameen M, Veal C, Leman J, Burden AD, Kirby B, Griffiths CEM, Trembath RC, Mathew CG, Barker JNWN (2003) A Crohn's disease-associated insertion polymorphism (3020insC) in the NOD2 gene is not associated with psoriasis vulgaris, palmo-plantar

pustular psoriasis or guttate psoriasis. Exper Dermatol 12: 506–509

Zhang XJ, He PP, Wang ZX, Zhang J, Li YB, Wang HY, Wei SC, Chen SY, Xu SJ, Jin L, Yang S, Huang W (2002) Evidence for a major psoriasis susceptibility locus at 6p21(PSORS1) and a novel candidate region at 4q31 by genome-wide scan in Chinese Hans. J Invest Dermatol 119: 1361–1366