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Fine Mapping of the Psoriasis Susceptibility Gene PSORS1: A Reassessment of Risk Associated with a Putative Risk Haplotype Lacking HLA-Cw6

Cluster 17 Collaboration[1]

Human leukocyte antigen (HLA)-Cw6 has long been associated with psoriasis, and PSORS1 (psoriasis susceptibility 1), a major gene for psoriasis susceptibility, has been mapped to its vicinity. A previous analysis identified multiple risk haplotypes carrying HLA-Cw6 and one haplotype (cluster 17, HLA-Cw8-B65) that appeared to carry risk for psoriasis but did not carry HLA-Cw6. This haplotype was very similar to other risk haplotypes for at least 60 kb telomeric to HLA-C, suggesting identity by descent with the remaining risk chromosomes. The association, however, between psoriasis and this haplotype as assessed by the transmission/disequilibrium test (TDT) was of borderline significance (p-value 0.048). In order to better assess the risk associated with cluster 17, a multicenter collaboration typed additional subjects for a single marker (M6S161) for which one allele (249 bp) was found only on cluster 17. The new sample included 1275 pedigrees as well as 300 cases and 913 controls. Transmission of this allele to affected individuals was examined using the TDT and the pedigree disequilibrium test (PDT), and case–control samples were analyzed by a trend test across genotype categories. By all methods, the newly acquired genotypes failed to confirm the association originally reported, despite adequate power. In contrast, the 248 bp allele, which is found on all HLA-Cw6-positive risk haplotypes as well as several non-risk haplotypes, shows significant excess transmission for all cohorts. Taken together, these results indicate that cluster 17 does not carry a psoriasis-susceptibility allele, and expand the PSORS1 risk interval to approximately 300 kb.

Key words: cluster analysis/linkage disequilibrium/major histocompatibility complex/psoriasis
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Abbreviations: DSP, discordant sib pairs; GRR, genotype relative risk; GRR1, GRR for risk allele heterozygote; GRR2, GRR for risk allele homozygote; HLA, human leukocyte antigen; MHC, major histocompatibility complex; PDT, pedigree disequilibrium test; PSORS1, psoriasis susceptibility 1; TDT, transmission/disequilibrium test

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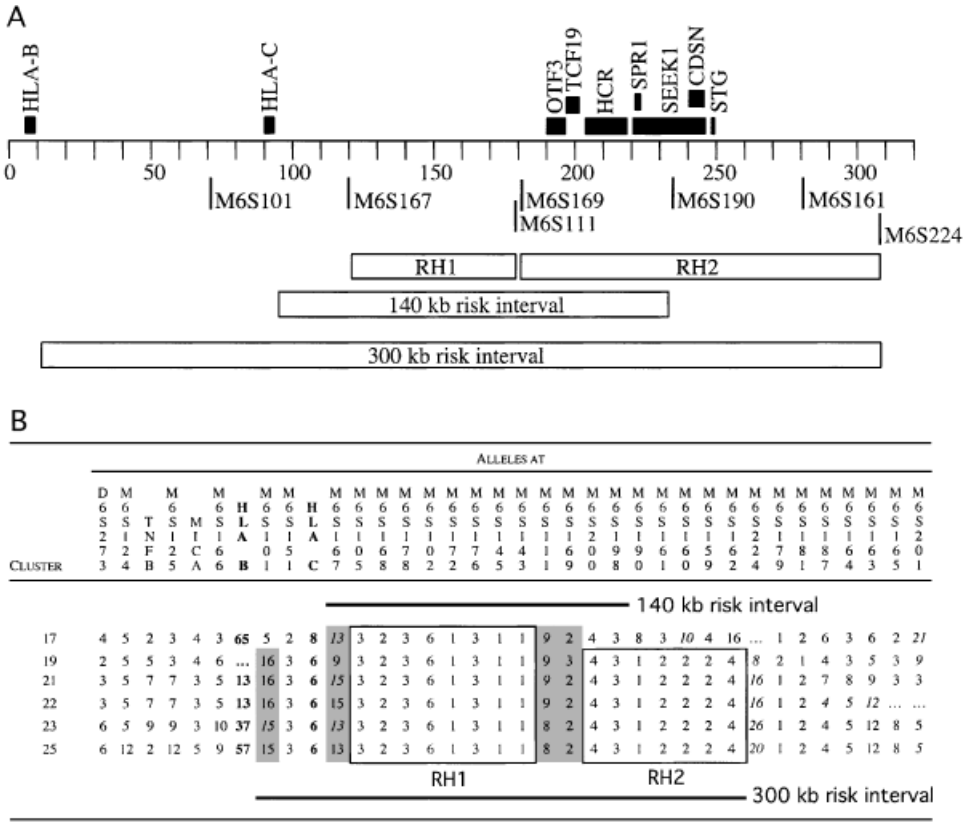

Figure 1
Delineation of the psoriasis susceptibility 1 (PSORS1) risk interval. In both panels, the risk interval is depicted as originally defined (RH1 and RH2), after initial expansion (140 kb risk interval), and after incorporating new cluster 17 results (300 kb risk interval). (*A*) Spatial map of risk intervals. Key microsatellites are shown below the distance axis, and known genes are shown above. All intervals are extended to the first reliable non-conserved flanking marker or gene. (*B*) Microsatellite alleles within risk intervals. All 34 markers of the six risk haplotype clusters of Nair *et al* (2000) are displayed, in centromeric to telomeric order from left to right. Alleles at HLA-B and HLA-C are indicated in boldface type. Ellipses (. . .) indicate that no allele occurred in >50% of the founder haplotypes comprising the cluster. Italicized and non-italicized numbers indicate that the allele shown occurred in 50%–80% and >80%, respectively, of the founder haplotypes comprising the cluster. Alleles are shaded when they differ among risk haplotypes for a marker but are not indicative of a significant difference in the underlying sequence of the region. The conserved alleles of RH1 and RH2 are depicted by boxes. The two risk intervals, depicted by bold lines, show the minimum region of conserved or shaded marker alleles shared in common by all risk haplotypes when including or excluding cluster 17 as a risk haplotype.

Psoriasis is a complex genetic disease whose etiology likely involves multiple genetic and environmental factors. The only putative psoriasis locus that has attained a genome-wide significant lod score in multiple genome-wide linkage scans is PSORS1 (psoriasis susceptibility 1), which lies in the major histocompatibility complex (MHC) on human chromosome 6p21.3 (Trembath *et al*, 1997; Jenisch *et al*, 1998; Veal *et al*, 2001; Zhang *et al*, 2002). Association of psoriasis with several human leukocyte antigens (HLA-C, -B, -DR, -DQ) has also been demonstrated by many groups (reviewed in Elder *et al*, 1994) and confirmed by analysis of polymorphic markers within the MHC (reviewed in Capon *et al*, 2002). PSORS1 has been estimated to account for approximately 35% of the genetic liability to psoriasis (Trembath *et al*, 1997). Thus, identification of the PSORS1 gene (or genes) is currently the highest priority for psoriasis genetics research.

Previous work by some of us attempted to localize PSORS1 to a smaller interval within the MHC (Nair *et al*, 2000). Sixty-two microsatellite markers spanning the entire 4 Mb of the MHC were typed in 339 families, and maximum likelihood haplotypes were constructed. Family-based association testing of single markers and short (2–5-marker) haplotypes narrowed the candidate region to a 1.2 Mb segment in the central MHC. An additional 139 families were typed for 34 markers in this 1.2 Mb segment. Haplotypes comprising 34 markers were then constructed for the combined set of 478 families and the 2156 haplotypes in founders were clustered by an agglomerative hierarchical method. Requiring 80% identity of haplotypes, 66 haplotype clusters, each represented in at least five founders, were identified. These clusters were then used to classify non-founder haplotypes in the combined pedigree set, and tested for association with the transmission/disequilibrium test (TDT). Twenty-six of the haplotype clusters exhibited at least ten independent transmissions plus non-transmissions from heterozygous parents to affected children. Of these 26, six (clusters 17, 19, 21–23, and 25) appeared to impart an increased risk for psoriasis, when risk is defined as $\geqslant$60% transmission to affected children. All six of these putative risk clusters share an 8-marker, 59.4 kb segment of homology, which was designated RH1. In addition, all clusters except cluster 17 share a 7-marker 126.6 kb segment of homology that lies just telomeric of RH1, which was designated RH2 (Fig 1). Although microsatellite alleles differ among risk haplotypes in the regions immediately flanking both sides of RH1, later sequencing work revealed that the risk haplotypes are nearly identical in the those areas.[2] This observation is compatible with the known higher mutation rate of microsatellite alleles (Ellegren, 2000), and redefined the candidate region to include a 140 kb segment lying between HLA-C and microsatellite M6S190 in the Class I region of the MHC (Fig 1), with the evidence for both boundaries deriving from cluster 17.

The sample size for cluster 17 was limited because of the relatively low frequency of this chromosome. Thus, despite a transmitted: non-transmitted ratio of 21:10, the TDT p-value was marginal ($p = 0.048$ using normal approximation

[2]Nair R, Stuart P, Voorhees J, Weichenthal M, Jenisch S, Christophers E, Elder JT: Manuscript, in preparation.

of binomial and $p = 0.071$ using exact two-sided binomial). Also, all risk clusters except 17 carry the HLA-Cw6 allele, which many groups have shown to be strongly associated with psoriasis, whereas cluster 17 carries the uncommon HLA-Cw8 allele, which no other group has implicated in psoriasis. Therefore, in order to increase sample size, a collaboration was initiated involving eight additional European groups to the original Ann Arbor/Kiel group. This collaboration took advantage of our observation that the 249 bp allele at microsatellite M6S161 was highly specific for cluster 17 and closely related haplotypes mapping directly adjacent to cluster 17 in the clustering dendrogram (Nair *et al*, 2000). Although this observation is based solely on the original Ann Arbor/Kiel cohort used to define these clusters (Nair *et al*, 2000), that cohort was made up largely of Caucasian Americans whose ancestors come from many different European countries, making it highly likely that the 249 bp allele is also specific for cluster 17 in the other cohorts in this study. The results of this effort indicate that cluster 17 is unlikely to be a risk haplotype, which expands the critical interval for PSORS1 from a 140 kb segment encompassing four known genes to a 300 kb segment containing eight known genes, including HLA-Cw6 and CDSN (Fig 1).

Results

Allele frequencies The frequency of the 249 bp allele at M6S161 varied considerably among family cohorts (Table Ia, complete allele frequency distributions for all cohorts and confidence intervals for the allele frequencies determined for the family cohorts are accessible at URL http://www.psoriasis.umich.edu/cluster17/.) Even though we have not randomly sampled the populations of these countries, the observed lack of association of the 249 bp allele with psoriasis (see below) indicates that the observed frequencies are probably a reasonable estimate of the actual frequencies in the general population. It has been shown by others that the Cw8-B65 haplotype of cluster 17 is found more frequently along the Mediterranean than other parts of Europe (Imanishi *et al*, 1992). This finding is borne out by our data, where frequencies less than 1.4% are seen in Sweden, Finland, Iceland, Germany, and England, and frequencies greater than 2.1% are seen in Italy, France, and the United States (the Ann Arbor/Kiel sample is largely from the United States, which is home to many individuals of Mediterranean origin).

The two case–control samples are summarized in Table I. Note that the frequency of allele 249 in the Ann Arbor and

Table I. Summary statistics for pedigrees and case–control samples used in collaborative study of risk for psoriasis of cluster 17 haplotype (M6S161 allele 249–HLA-Cw8–HLA-B65)

Cohort	Country	# pedigrees	# dyad pedigrees	# triad pedigrees	# triad and dyad pedigrees	# DSP pedigrees[a]	# LD pedigrees[b]	# founder chromosomes	Frequency M6S161 allele 249
(*a*) Pedigree samples									
AA/Kiel (old)	USA/Germany	509	102	376	478	111	484	2204	0.0209
AA/Kiel (new)	USA/Germany	190	26	118	144	22	151	692	0.0260
Reykjavik	Iceland	296	104	96	200	119	249	1163	0.0138
Gothenburg	Sweden	196	31	154	185	0	185	736	0.0109
Stockholm	Sweden	63	14	34	48	30	51	222	0.0045
Helsinki	Finland	90	3	78	81	0	81	357	0.0057
Leicester	United Kingdom	134	55	56	111	35	118	531	0.0132
Muenster	Germany	210	38	164	202	18	204	791	0.0101
Evry	France	46	4	41	45	42	45	520	0.0250
Rome	Italy	50	0	50	50	0	50	200	0.0250
New pedigrees		1275	275	791	1066	266	1134	5212	0.0150
All pedigrees		1784	377	1167	1544	377	1618	7416	0.0167

Cohort	Country	# cases	# controls	# total	Frequency M6S161 allele 249
(*b*) Case–control samples					
Ann Arbor	USA	104	153	257	0.0214
Reykjavik	Iceland	196	760	956	0.0120
Total		300	913	1213	0.0140

[a]Discordant sib pair (one affected and one unaffected sibling).
[b]Linkage disequilibrium (i.e., pedigree has at least one triad, dyad, or DSP).

Reykjavik case–control samples is very similar to its frequency among founders in the pedigree samples for these same two countries (1.2% *vs* 1.4% for Reykjavik; 2.1% *vs* 2.1 and 2.6% for Ann Arbor).

Power analysis Power to detect association of cluster 17 and psoriasis depends in part upon the genotype relative risk (GRR) for developing psoriasis when carrying one or two copies of the cluster 17 haplotype. If cluster 17 is truly associated with psoriasis, then recombinant haplotype analysis of the original Ann Arbor/Kiel cohort (Nair *et al*, 2000) strongly suggests that the cluster 17 haplotype and all Cw6 haplotypes carry the same PSORS1 risk allele within a segment of DNA that is inherited identical by descent from a common ancestor. Accordingly, an estimate of the GRR of a putative cluster 17 PSORS1 risk allele can be provided by estimating the GRR of Cw6 in our sample. We base the GRR estimate on Cw6 haplotypes only rather than on cluster 17 by itself or in combination with Cw6, because multiple studies have provided incontrovertible evidence that Cw6 haplotypes carry a PSORS1 risk allele, whereas the evidence for cluster 17 carrying PSORS1 is limited to one result of marginal significance.

Estimates of GRR for Cw6 in the original Ann Arbor/Kiel cohort (Nair *et al*, 2000) are 10.4 for homozygotes and 5.2 for heterozygotes, indicating that the relationship of psoriasis and PSORS1 approximately follows an additive mode of inheritance. These risks, however, are expressed relative to the risk of non-Cw6 carriers, whereas the power calculations for cluster 17 assume risk is expressed to non-cluster 17 carriers, many of which will carry at least one Cw6 haplotype. Including Cw6 carriers among the "non-risk" genotype category nearly doubles the penetrance of "non-risk" genotypes and thus halves the expected GRR for the putative cluster 17 PSORS1 allele. Accordingly, a reasonable estimate of GRR for cluster 17 as a PSORS1 risk haplotype would be ~ 5 for GRR2 and ~ 3 for GRR1.

These GRR values were used to perform power calculations as described in Subjects and Methods. The new cohort has 791 pedigrees with at least one triad, and the frequency of cluster 17 is assumed to be 0.015, the observed frequency of M6S161 allele 249 in the new pedigrees. For an additive model with a GRR2 of 5 (GRR1 = 3), which is reflective of the actual data, and a type I error rate of 0.05, power of the two-sided TDT is 99.8%. Importantly, 80% power is still achieved even if the relative risk of cluster 17 is much lower than that seen for Cw6 haplotypes. Thus, 80% power is achieved for GRR2 = 3.03 under an additive model (GRR1 = 2.01). Moreover, the true power of our pedigree disequilibrium test (PDT) analysis of full pedigrees is no doubt substantially higher than our estimates, which consider only TDT analysis of independent triads. Results are broadly similar for dominant and multiplicative models; however, power is much lower for recessive models (6% for a type I error rate of 0.05, GRR2 = 5, GRR1 = 1). Complete power curves are available at URL http://www.psoriasis.umich.edu/cluster17/.

Our original pedigrees showed marginal evidence for association (TDT p value=0.089), and our power calculations predict that we should see stronger evidence for association (i.e., a smaller p-value) with a probability of $>99.9\%$ if allele 249 was associated with psoriasis at a GRR2 of 5, assuming an additive or dominant mode of gene action. Under a multiplicative model, this probability is still $>95\%$.

Power was also determined for TDT analysis of the new and old samples combined. For the pooled pedigree sample, there are 1167 independent triads, and the observed frequency of M6S161 allele 249 is 0.0167. Power of the two-sided TDT to detect association of psoriasis and cluster 17 for a GRR2 of 5 and type I error rate of 0.05 is essentially 100% under the additive or dominant models, 99% under a multiplicative model, and 6% under a recessive model. 80% power is achieved if GRR2 = 2.52 (GRR1 = 1.76) under the additive model. As expected, the power of the pooled sample to detect association is substantially greater than the new sample alone. Thus, both the new and combined samples appear adequately powered, and we would expect to replicate our original association if M6S161 allele 249 were truly associated with an increased risk of psoriasis.

Family-based analyses Results of the TDT analysis are shown in Table II. The original cohort described by Nair *et al* (2000) suggests association of psoriasis with allele 249: a 65.7% transmission ratio, and p-values of 0.089 (exact) and 0.063 (asymptotic) (Table IIa). The number of transmission events is higher here (23:12) than in the original publication (21:10) because the 249 allele occurs on a few haplotypes that were directly adjacent to but not actually within cluster 17 in the clustering dendrogram. Inclusion of these haplotypes is justified because they are completely homologous to the cluster 17 consensus for those markers that lie within or near the PSORS1 candidate region. The new pedigrees, however, show no evidence for association of cluster 17 with psoriasis (T:NT = 21:21, p = 1.0). Combining the new pedigrees with the original cohort also yields no significant association (43:32, p = 0.25).

Results of the PDT analysis for allele 249 are given in Table III. The original cohort shows some evidence for association of cluster 17 with psoriasis, as expected. When analysis is restricted to triads and dyads, the asymptotic p-value gives somewhat stronger evidence for marker-trait association than was determined by the TDT (0.041 *vs* 0.063), even though the percent transmission is considerably lower (60.9% *vs* 65.7%). Analysis of discordant sib pairs (DSP) in the original cohort also shows evidence for association ($\overline{D} = 0.247$, see Subjects and Methods for definition of $\overline{D}$). When triads, dyads, and DSP are combined, the original cohort shows considerably more significant association of cluster 17 and psoriasis by the PDT ($\overline{D} = 0.219$, p = 0.027) than by the TDT. PDT analysis of the new pedigrees, however, shows no evidence for association of cluster 17 and psoriasis, whether the analysis uses triads and dyads ($\overline{D} = 0.025$, %T = 51.3, p = 0.80), DSP ($\overline{D} = 0.018$, p = 0.98), or both ($\overline{D} = 0.019$, p = 0.69). The combined cohorts also show no significant association of psoriasis and allele 249. PDT analysis of triads, dyads, and DSP, however, yields a result that approaches p = 0.05 ($\overline{D} = 0.108$, p = 0.083). Although the original cohort comprises only 29.9% of the 1618 pedigrees amenable to PDT analysis, it makes up 42.4% of the 92 pedigrees in the total

Table II. Results of biallelic TDT test (median of 999 runs)

Cohort	T:NT	% T	Exact p-value[a]	Asymptotic p-value[b]
(*a*) M6S161 allele 249 (cluster 17)				
AA/Kiel (old)	23:12	65.7	0.089	0.063
AA/Kiel (new)	5:3	62.5	0.73	0.48
Reykjavik	2:2	50.0	—	—
Gothenburg	5:2	71.4	—	—
Stockholm	0:1	0.0	—	—
Helsinki	1:1	50.0	—	—
Leicester	1:2	33.3	—	—
Muenster	5:3	62.5	—	—
Evry	1:1	50.0	—	—
Rome	0:5	0.0	—	—
New pedigrees	21:21	50.0	1.00	1.00
All pedigrees	43:32	57.3	0.25	0.20
(*b*) M6S161 allele 248				
AA/Kiel (old)	197:151	56.6	0.016	0.014
AA/Kiel (new)	62:52	54.4	0.40	0.35
Reykjavik	56:29	65.9	0.0045	0.0034
Gothenburg	76:51	59.8	0.033	0.027
Stockholm	24:12	66.7	0.065	0.046
Helsinki	45:34	57.0	0.26	0.22
Leicester	34:17	66.7	0.024	0.017
Muenster	85:62	57.8	0.069	0.058
Evry	21:17	55.3	0.63	0.52
Rome	30:21	58.8	0.26	0.21
New pedigrees	431:294	59.5	4.1×10^{-7}	3.6×10^{-7}
All pedigrees	630:447	58.5	2.7×10^{-8}	2.5×10^{-8}

[a]p-value is exact two-sided binomial and is computed only when there are at least ten informative pedigrees in the cohort; all p-values are nominal (uncorrected for multiple testing).
[b]p-value uses the normal approximation to a binomial distribution and is given here for comparison with the normal approximation p-values of the PDT analysis of Tables III and IV.
TDT, transmission/disequilibrium test; PDT, pedigree disequilibrium test.

cohort that are actually informative for allele 249 on account of the higher frequency of the 249 bp allele in the original cohort *versus* the new pedigrees (2.1% *vs* 1.5%).

In contrast to the negative results obtained for allele 249, TDT analysis of the 248 bp allele at M6S161, a common allele that is found on all HLA-Cw6-positive risk haplotypes as well as several non-risk haplotypes, shows an excess transmission for all cohorts, ranging from 54.4% to 66.7% (Table IIb). The association is moderately significant for the original Ann Arbor/Kiel cohort (197:151, $p = 0.016$) and highly significant for the new pedigrees combined (431:294, $p = 4.1 \times 10^{-7}$) and for the total sample (630:447, $p = 2.7 \times 10^{-8}$). The association of allele 248 with psoriasis reflects the fact that this allele is carried on all HLA-Cw6-positive haplotypes. The association of psoriasis with allele 248 (58.5% transmission, Table IIb) is lower than that seen for HLA-Cw6-positive haplotypes (73.6% transmission (Nair *et al*, 2000)) because allele 248, by far the most frequent allele of M6S161, is also found on many common non-risk haplotypes.

Results for PDT analysis of allele 248 are shown in Table IV. As was observed using the TDT (Table IIb), highly significant evidence of association of psoriasis and allele 248 is seen for the original, new, and combined cohorts. PDT analysis of triads and dyads gives more striking evidence for association than TDT analysis ($p = 0.0070$ *vs* 0.014 for the original cohort, 4.5×10^{-8} *vs* 3.6×10^{-7} for the new cohort, and 1.4×10^{-9} *vs* 2.5×10^{-8} for the total cohort), although the percent transmission values are very similar (57.1% *vs* 56.6% for original, 59.4% *vs* 59.5% for new, and 58.6% *vs* 58.5% for total cohort). Inclusion of DSP yields even greater significant evidence for association of psoriasis and the 248 bp allele. Although the p-values for DSP analysis of allele 248 are less impressive than for triads

Table III. Results of PDT analysis for cluster 17 (M6S161 allele 249)

	Triads and dyads only				DSP only			Triads, dyads, and DSP		
Cohort	# informative pedigrees[a]	$\overline{D}$[b]	% T	p-value[c]	# informative pedigrees	$\overline{D}$	p-value	# informative pedigrees	$\overline{D}$	p-value
AA/Kiel (old)	39	0.218	60.9	0.041	8	0.247	—	39	0.219	0.027
AA/Kiel (new)	10	0.200	60.0	0.32	3	—	—	12	0.200	0.093
Reykjavik	4	−0.250	37.5	—	3	−0.667	—	5	−0.188	—
Gothenburg	7	0.429	71.4	—	0	—	—	7	0.429	—
Stockholm	1	−0.333	33.3	—	1	−0.667	—	1	−0.500	—
Helsinki	2	0.000	50.0	—	0	—	—	2	0.000	—
Leicester	3	0.000	50.0	—	2	0.500	—	5	0.125	—
Muenster	8	0.250	62.5	—	0	—	—	8	0.250	—
Evry	8	0.067	53.4	—	5	0.239	—	8	−0.062	—
Rome	5	−1.000	0.0	—	0	—	—	5	−1.000	—
New pedigrees	48	0.025	51.3	0.80	14	0.018	0.98	53	0.019	0.69
All pedigrees	87	0.111	55.5	0.13	22	0.113	0.29	92	0.108	0.083

[a]Number of informative pedigrees. A pedigree contains an informative triad if there is at least one affected typed child whose parents are typed and at least one of these parents is heterozygous for M6S161 allele 249. Pedigrees have an informative dyad if the sole typed parent is heterozygous for the 249 allele and the child has a heterozygous M6S161 genotype different from that of the parent. A pedigree contains an informative DSP if it has a sibship with at least one affected and one unaffected sibling with different M6S161 genotypes and at least one of these genotypes has one or more 249 alleles (the parents do not need to be typed). See Martin *et al* (2000) for more details.
[b]Mean standardized D, a scaled measure of linkage disequilibrium for the allele being tested, averaged over all pedigrees that are informative for the allele. $\overline{D}$ has a range of [−1,1] and is equal to 0 in the absence of linkage disequilibrium (see Subjects and Methods for details).
[c]p-value is for the "PDT-avg" test statistic of Martin *et al* (2001). It is based on the χ^2 distribution and is computed only when there are at least ten informative pedigrees in the cohort. All p-values are nominal (uncorrected for multiple testing).
PDT, pedigree disequilibrium test; DSP, discordant sib pair.

Table IV. Results of PDT analysis for M6S161 allele 248

	Triads and dyads only				DSP only			Triads, dyads, and DSP		
Cohort	# informative pedigrees[a]	$\overline{D}$[b]	% T	p-value[c]	# informative pedigrees	$\overline{D}$	p-value	# informative pedigrees	$\overline{D}$	p-value
AA/Kiel (old)	293	0.141	57.1	0.0070	67	0.202	0.016	310	0.132	0.0041
AA/Kiel (new)	91	0.077	53.9	0.35	13	−0.083	0.48	98	0.082	0.30
Reykjavik	74	0.340	67.0	0.0024	52	0.307	0.016	109	0.284	0.0016
Gothenburg	102	0.216	60.8	0.021	0	—	—	102	0.216	0.021
Stockholm	28	0.280	64.0	0.016	16	0.393	0.047	33	0.292	0.0059
Helsinki	54	0.093	54.7	0.16	0	—	—	54	0.093	0.16
Leicester	46	0.270	63.5	0.013	24	−0.260	0.31	61	0.135	0.017
Muenster	113	0.161	58.1	0.051	8	0.650	—	119	0.188	0.029
Evry	35	0.183	59.2	0.13	34	0.120	0.13	39	0.127	0.28
Rome	39	0.128	56.4	0.21	0	—	—	39	0.128	0.21
New pedrigrees	582	0.187	59.4	4.5×10^{-8}	147	0.133	0.0011	654	0.173	1.0×10^{-8}
All pedrigrees	875	0.172	58.6	1.4×10^{-9}	214	0.158	4.8×10^{-5}	964	0.159	1.9×10^{-10}

[a]Number of informative pedigrees. As in Table III, except calculations refer to allele 248 instead of allele 249.
[b]Mean standardized D. See Table III and Subjects and Methods for details.
[c]p-Value is for the "PDT-avg" test statistic. See Table III for details. All p-values are nominal (uncorrected for multiple testing).
PDT, pedigree disequilibrium test; DSP, discordant sib pair.

and dyads because of the smaller numbers of informative pedigrees, the levels of disequilibrium for triads and dyads *versus* DSP are comparable ($\overline{D} = 0.202$ *vs* 0.141 for the original cohort, 0.133 *vs* 0.187 for the new cohort, and 0.158 *vs* 0.172 for the total cohort). Hence, concerns that PDT analysis of DSP would be adversely affected by the relatively low penetrance of PSORS1 (i.e., that unaffected siblings of psoriatics may often be carriers for PSORS1 haplotypes) are apparently unwarranted.

Case–control analysis Table Va gives results for the case–control analysis of allele 249 (cluster 17). Applying the trend test to the three genotype categories found no significant evidence for association of disease and allele 249 within the Ann Arbor cohort (odds ratio (OR) = 0.31, p = 0.12) or the Reykjavik cohort (OR = 1.38, p = 0.45). For these data, the "allele" and "serological" tests (Sasieni, 1997) would have given exactly the same p-values as the "genotype" test because there are no homozygotes for the 249 allele. Although the OR differ for the two cohorts, there is no significant evidence for heterogeneity in the association of genotype and disease across cohorts (p = 0.093). The Mantel extension of the linear trend test found no significant association of allele 249 and psoriasis across both cohorts (p = 0.64). Thus the case–control analysis confirms the results of the family-based tests.

Table Vb lists results for case–control analysis of allele 248, which is found on all Cw6-positive haplotypes as well as many common non-risk haplotypes. The Ann Arbor cohort shows significant evidence for association of allele 248 with psoriasis (p = 0.015), whereas the Reykjavik cohort fails to reach the threshold for significance (p = 0.090). Linear association appears to be homogeneous across cohorts (p = 0.31), so it is appropriate to test for conditional independence. As expected, the Mantel extension of the trend test across both cohorts provides more power than the individual cohort tests, finding strong evidence for association of allele 248 genotype and psoriasis (p = 0.0053). Thus, once again, analysis of case–control data confirms the results of the pedigree analysis.

Note that the OR for homozygotes is greater than that for heterozygotes in both cohorts (2.74 *vs* 2.05 in Ann Arbor cohort; 1.93 *vs* 1.75 in Reykjavik cohort), and that the difference in risk of carrying two *versus* one copy of the 248 bp allele most closely resembles an additive model. Similar results have been reported recently by some of us (Gudjonsson *et al*, 2003).

Discussion

A critical task in the identification of the PSORS1 gene is to identify the shortest genetic interval that contains it. This task is challenged by the substantial linkage disequilibrium that characterizes the human MHC (Walsh *et al*, 2003). This

Table V. Results of case–control analysis

	Ann Arbor			Reykjavik		
	Psoriatics	**Controls**	**Total**	**Psoriatics**	**Controls**	**Total**
(*a*) M6S161 allele 249[a]						
249/249	0	0	0	0	0	0
249/other	2	9	11	6	17	23
Other/other	102	144	246	190	743	933
Total	104	153	257	196	760	956
Odds ratio (249/other)	0.31			1.38		
Cochran–Armitage test for linear trend	$\chi^2 = 2.37$, p = 0.12			$\chi^2 = 0.45$, p = 0.50		
	Ann Arbor			**Reykjavik**		
	Psoriatics	**Controls**	**Total**	**Psoriatics**	**Controls**	**Total**
(*b*) M6S161 allele 248[b]						
248/248	53	60	113	102	361	463
248/other	41	62	103	83	324	407
Other/other	10	31	41	11	75	86
Total	104	153	257	196	760	956
Odds ratio (248/248)	2.74			1.93		
Odds ratio (248/other)	2.05			1.75		
Cochran–Armitage test for linear trend	$\chi^2 = 5.96$, p = 0.015			$\chi^2 = 2.88$, p = 0.090		

[a]Likelihood ratio test of homogeneous linear association: $G^2 = 2.82$ (p = 0.093). Mantel linear trend test of conditional independence: $\chi^2 = 0.22$ (p = 0.64).
[b]Likelihood ratio test of homogeneous linear association: $G^2 = 1.05$ (p = 0.31). Mantel linear trend test of conditional independence: $\chi^2 = 7.78$ (p = 0.0053).

collaboration was undertaken because cluster 17 (HLA-Cw8-B65) was suggested as associated in a previous study, albeit with a marginally significant p-value of 0.046 (Nair *et al*, 2000). This cluster displayed great similarity to other risk-associated haplotypes in the proximal MHC Class I region, yet it lacked HLA-Cw6 (Nair *et al*, 2000). When combined with subsequent sequence information (see Introduction), it became evident that the length of the risk interval depended critically on a more definitive assessment of the risk associated with cluster 17. As shown in Fig 1, if cluster 17 is not a genuine risk haplotype, the candidate region for PSORS1 expands from a 140 kb region encompassing four genes to a 300 kb region encompassing eight genes.

Comparison of haplotype clusters revealed that the 249 bp allele at M6S161 was specific for cluster 17. Indeed, marker M6S161 and the flanking genes OTF3, TCF19, HCR, SPR1, SEEK1, CDSN, and STG reside within one of the seven strongest regions of linkage disequilibrium in the MHC (Walsh *et al*, 2003). This finding greatly facilitated collaboration, because it was possible for each participating center to type only a single marker as a surrogate for cluster 17. Although different typing methodologies were used by different groups, the provision of DNA from a single reference individual (a 248 bp/249 bp heterozygote at M6S161) allowed for accurate calibration of allele sizes.

The replication set formed by this collaboration provided no evidence for association between psoriasis and cluster 17 in the TDT (Table IIa), the PDT (Table III), or in the trend test for case–control genotypes (Table V). Even when combined with the original cohort that yielded a marginally significant result (Nair *et al*, 2000), the data also fail to identify a significant association between cluster 17 and psoriasis by either the TDT or the PDT (Tables IIa). These data are in accord with (but not fully independent of) a study of over 1000 Icelandic patients with psoriasis, which failed to identify an association between psoriasis and HLA-Cw8 (Gudjonsson *et al*, 2003).

We have given careful consideration to the power of our sample to detect a significant association if one truly existed. Our power calculations demonstrate excellent power to detect association, under all reasonable genetic models, for realistic values of GRR. Although our data set lacked power under a recessive model, GRR values derived from our own data and association studies performed on over 1000 Icelandic psoriatics (Gudjonsson *et al*, 2003) strongly suggest that PSORS1 does not act in a recessive fashion. Our power calculations are conservative, in that they include only a subset of the individuals and genetic relationships actually used by our association tests.

Taken together, the findings presented here demonstrate that cluster 17 is highly unlikely to encode a PSORS1 risk allele. Although this result extends the length of the risk haplotype from 140 to 300 kb (Fig 1), it also provides a much larger number of candidate genes on that haplotype (eight) than did the previous interval (four). Of these, HLA-Cw6, the "WWCC" allele at HCR, and "allele 5" at CDSN remain particularly plausible, whereas the evidence in favor of the remaining genes is less robust (Asumalahti *et al*, 2002; Capon *et al*, 2002). The paucity of recombination between these alleles has made it extremely difficult to identify enough informative recombinant individuals to distinguish the risk associated with each of them. Although transracial mapping of a Gujarati Indian population has suggested a co-equal role for HLA-Cw6 and CDSN, but not for HCR (Capon *et al*, 2003), other studies of Japanese, Thai, Chinese, and Spanish psoriatics have failed to confirm the importance of CDSN allele 5 independently of HLA-Cw6 (Gonzalez *et al*, 2000; Hui *et al*, 2002; Chang *et al*, 2003; Romphruk *et al*, 2003). Two additional studies of HCR have suggested that the WWCC allele at HCR is unlikely to play a genetically causal role in psoriasis, even though it is highly associated with the disease (Chia *et al*, 2001; O'Brien *et al*, 2001). HCR, however, was recently functionally assayed in transgenic mouse models, and the risk allele WWCC was suggested to induce allele-specific effects on the expression of some genes relevant for psoriasis, even though the animals remained healthy (Elomaa *et al*, 2004). Clearly, additional very large studies involving multiple ethnic/racial groups will be required to distinguish between these three attractive candidate genes. This study demonstrates that such collaborations are feasible and can be productive. An ongoing study involving ourselves and others will analyze thousands of psoriatics, family members, and controls, making use of the emerging resources of the HapMap project (2003) in an effort to address this important problem. The use of markers carrying alleles that are specific for particular haplotype blocks, or, as in this analysis, for particular combinations of haplotype blocks, will undoubtedly lead to substantial savings of effort, time, and cost.

Subjects and Methods

Subjects In addition to the samples supplied by each group of European collaborators, the Ann Arbor/Kiel group has continued to collect clinical material (families, single affected individuals with parents, and cases and controls) since the time of our original publication (Nair *et al*, 2000). As shown in Table Ia, these sources combined to provide an additional 1275 pedigrees for association testing. The number of pedigrees is shown for each cohort, along with the subset of this number that contains at least one triad (affected child with two typed parents), at least one dyad (affected child with one typed parent) but no triads, or at least one DSP. By any measure, the new sample contains more than twice the number of pedigrees in the original cohort of Nair *et al* (2000). Combined, the two samples yield a total of 1544 pedigrees for TDT analysis and 1618 pedigrees for PDT analysis.

The Ann Arbor and Reykjavik groups were also able to provide case–control samples (Table Ib). Together, these two samples provide 300 cases and 913 controls, allowing a second independent test for association of cluster 17 and psoriasis.

Enrollment of subjects and genotyping was carried out under protocols approved by the medical ethical committees of each participating institution. Written, informed consent was obtained from all subjects. This study was conducted according to the Declaration of Helsinki Principles at all participating institutions.

Marker typing All members of the pedigree and case–control samples were typed for microsatellite marker M6S161, which is one of the markers used to create the 34-marker haplotypes described by Nair *et al* (2000). This marker carries an allele of size 249 bp that is highly specific to the cluster 17 haplotype. All of the other risk clusters (19, 21–23, 25) carry the 248 bp allele at M6S161, which is the most common allele at this marker and is also found on many non-risk haplotypes. The M6S161 amplimer produces several different one-nucleotide variations in allele size,

because it includes two different length polymorphisms—a TC dinucleotide repeat and a 1 bp C/-indel (see foonote 2). Each group performed its own genotyping, utilizing ^{32}P-labeled or fluorescent oligonucleotide primers by standard methods (Nair *et al*, 1995; Veal *et al*, 2001). DNA from a reference individual known to be heterozygous for the M6S161 248 and 249 bp alleles was genotyped in parallel by all groups, allowing calibration of results and comparison of allele sizes across centers. Each genotyping center employed its own established procedures to minimize genotyping errors. Whenever possible, genotyping accuracy was further assessed by checking for Mendelian inheritance errors.

Family-based association analysis The pedigrees were analyzed for M6S161 alleles 248 and 249 by two different family-based association tests—the TDT (Spielman *et al*, 1993) and the PDT (Martin *et al*, 2000; Martin *et al*, 2001). We utilized the "PDT-avg" test described by Martin *et al* (2001), which gives equal weighting to all families, rather than the "PDT-sum" test, which gives greater weight to larger pedigrees. Both the TDT and PDT were extended to include dyads when triads were not available.

The value $\overline{D}$ is a scaled measure of linkage disequilibrium between the allele being tested by the PDT and the disease phenotype. It is an alternative to reporting the percentage of transmitted alleles in the TDT. $\overline{D}$ has a range of [−1, 1] and is equal to 0 in the absence of linkage disequilibrium. The original description of the PDT (Martin *et al*, 2000) provided no standardized measure of the level of linkage disequilibrium measured by the PDT statistic. Martin *et al* do define a random variable D, where D_i summarizes the amount of linkage disequilibrium for all possible triads and DSP for the *i*th pedigree in a sample of N-independent pedigrees. The range of permissible values of D, however, depends upon the structure of the pedigree and upon the parental genotypes in the triads, dyads, and DSP (we have extended the analysis to dyads, as mentioned above). In order to standardize the D_i for each pedigree, we divided it by the maximum possible D value (conditional on known parental genotypes) for that pedigree. This restricts the range of D to the [−1,1] interval. Mean standardized D values were then computed over all analyzed pedigrees.

Many of the pedigrees in the sample are large nuclear families or extended families that contain more than one triad and/or dyad. Because the TDT is a valid test of association only when the triads and dyads analyzed are genetically independent, analysis was restricted to a single triad or dyad randomly selected from each pedigree. Since results vary depending upon the particular random selection, the analysis was repeated 999 times with different random number seeds, and the median result reported. To avoid bias, we restricted the analysis of dyads to instances where the parent has a heterozygous genotype different from that of the affected child (Curtis and Sham, 1995). Although TDT and PDT were both run as biallelic tests, determination of alleles transmitted and non-transmitted from heterozygous parents was based on the full allele diversity of the marker. This permits use of at least some of the dyads, which would never qualify for unbiased analysis if the marker alleles were first downcoded to a biallelic system (Curtis and Sham, 1995).

The biallelic PDT-avg test statistic is asymptotically distributed as a χ^2 with one degree of freedom. Unlike the biallelic TDT test statistic, it is not possible to compute an exact binomial p-value for the PDT. Hence, for comparison purposes, asymptotic p-values will be used whenever TDT and PDT results are compared.

Cohorts were analyzed individually and in combination (original cohort, new cohorts combined, and all cohorts combined). We considered it permissible to directly analyze the combined data with family-based tests, because the validity of such tests is not affected by population stratification or admixture for the locus being tested (Spielman *et al*, 1993; Martin *et al*, 2000).

Case–control association analysis As recommended by Sasieni (1997), we have analyzed our case–control data as genotypes, in conjunction with the Cochran–Armitage test for linear trend. The assumptions of the linear trend test fit the data most optimally under a multiplicative model, but the trend test is appropriate as long as the risk for individuals with two copies of the disease-associated allele is not intermediate between those who carry one or zero copies. This is certainly the case for PSORS1, which seems to follow an additive model (see below). Unlike family-based association tests such as the TDT and PDT, case–control methods are sensitive to population stratification, so we did not directly combine data for the Ann Arbor and Reykjavik cohorts. Mantel's extension of the Mantel–Haenszel test to allow for ordinal variables (Mantel, 1963) was used to test for the conditional independence of psoriasis and M6S161 genotype while controlling for cohort. Genotype categories were assigned scores for the number of test alleles (0, 1, 2), which is the implicit scoring system of the Cochran–Armitage trend test. The Mantel test works best when linear association is similar across strata (cohorts); for this reason, a likelihood ratio test for homogeneous linear association was constructed by comparing the logistic regression models that include and exclude an interaction term between genotype and cohort.

Power analysis Our sample consists of a variety of family structures, for which analytical power calculations are unavailable. To simplify the power analysis, we determined the power of the TDT to detect association when considering only genetically independent triads of the new and pooled cohorts, using the first approximation method of Knapp (1999). This provides a conservative estimate of the actual power of our pedigree sample, since it discards all dyads (used by the TDT and PDT), additional triads in the family (used by the PDT), and DSP (used by the PDT). This method also allowed us to compute power for a reasonable range of alternative hypotheses, basing the alternatives on what we know about the likely GRR of PSORS1, the observed frequencies of the 249 bp allele in our cohorts, and reasonable genetic models (i.e., recessive, dominant, multiplicative, and additive).

We estimated the penetrance, or the probability of disease for carriers of a particular genotype, using estimates of genotype frequencies from our previous study of PSOR1 (Nair *et al*, 2000), and from 189 US organ transplant donor candidates and 124 German blood donors (Jenisch *et al*, 1998), each weighted by the relative contribution of each country to our cohort. We assumed a population prevalence of 2% for psoriasis. We then used these penetrance estimates to define GRR, the penetrance of a designated risk genotype divided by the penetrance for a genotype that carries zero copies of the allele of interest, which is the key parameter for the formulas of Knapp (1999).

Note added in proof: While this manuscript was under review, a study of Sardinian psoriasis by Orru *et al* (Am J Hum Genet 76:164–171) also found no evidence for association between psoriasis and Cluster 17 (designated haplotype H in their study).

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