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7. A 100-μl guanosine affinity column (Fig. 1) contained 15 mM guanosine 5′-*O*-(2-thiodiphosphate) (GDP-βS) linked through sulfur to Affi-Gel 102 agarose (Bio-Rad) derivatized with bromoacetyl *N*-hydroxysuccinimide (*26*). The eluant contained 375 mM NaCl, 5 mM $MgCl_2$, 1 mM EDTA, and 40 mM tris-HCl (pH 7.8) at 4°C. The initial RNA pool consisted of 72-nucleotide oligomer transcripts containing 25 central randomized positions, encoded within flanking PCR primer sequences containing a T7 promoter. Approximately 20 μg of this RNA in water (~5×10^{14} molecules, transcribed from 5×10^{13} molecules) was heated at 65°C for 5 min, the salt concentration was adjusted, and the RNA cooled to 4°C over 10 min. Then 25 μl of RNA solution was loaded. After washing out weakly bound RNAs, we eluted bound RNA with 20 mM GMP in column buffer. Cycle 5 is shown (Fig. 1); the initial cycle was less stringent to minimize possible loss of poorly represented transcripts. Pooled RNA was purified on glass beads (BIO 101) and complementary DNA (cDNA) was synthesized, amplified by PCR, and transcribed into RNA for the next round of selection as described (*3*). After cycle 3, RNA was depleted of column-binding sequences by passage through acetylated agarose, and only the first 70 to 80% of RNA was applied to the subsequent guanosine column. Arginine affinity chromatography was similar, but utilized 19.7 mM arginyl-cysteine dipeptide linked through the sulfydryl to a thiopropyl Sepharose 6B (Pharmacia) matrix (*5*).
8. After five selection-amplification cycles, GMP-eluted RNA was refractionated on the guanosine column and washed successively with 20 mM CMP and AMP before GMP elution. The GMP-eluted pool was reverse transcribed, amplified, and cloned in pUC19 as for the joint RNA. Late cycles of enrichment in both selections showed minor low-affinity species eluting from the guanosine column (Fig. 1), which were not removed with subsequent purification. These are an alternative RNA conformation; when the low-affinity peak was pooled, de- and renatured, and again run through the column, it again yielded both high- and low-affinity peaks. In addition, increased Mg^{2+} (to 20 mM) plus 0.5 mM spermidine converted most low-affinity molecules from pure transcripts to a high-affinity form. However, this buffer did not alter elution of the initial random pool. For all subsequent work on the guanosine column, spermidine and the higher concentration of Mg^{2+} were used. However, they decreased affinity for the arginine column and were not used for arginine selections.
9. Analogs were initially screened for elution of RNA from the guanosine column. All were checked at 2 mM except for 8-mercaptoguanosine which was checked at a concentration of 1.1 mM (dictated by solubility). The K_d's were determined by competitive affinity chromatography (*5, 10*). We estimate that K_d's greater than 20 mM would not have been detected. All nucleotide ultraviolet spectra matched literature data.
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12. RNA was modified with DMS under native conditions (4°C for 2 hours in 100 mM NaCl, 5 mM $MgCl_2$, 1 mM EDTA, and 50 mM Hepes, pH 7.7) in the presence of 5 mM arginine, 200 mM lysine, or no amino acid. RNA was also modified with DMS under denaturing conditions (90°C for 1 min in 1 mM EDTA and 50 mM Hepes, pH 7.7), then refolded as above. For chromatographic selection among modified RNAs, an arginine column was used as in the initial selection. The column was washed with three successive 300-μl volumes of buffer, then eluted with 25 mM L-arginine. Modified RNAs were precipitated and reverse transcribed with a three- to sixfold molar excess of ^{32}P-kinased primer (*29*).
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Gene for Familial Psoriasis Susceptibility Mapped to the Distal End of Human Chromosome 17q

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A gene involved in psoriasis susceptibility was localized to the distal region of human chromosome 17q as a result of a genome-wide linkage analysis with polymorphic microsatellites and eight multiply affected psoriasis kindreds. In the family which showed the strongest evidence for linkage, the recombination fraction between a psoriasis susceptibility locus and *D17S784* was 0.04 with a maximum two-point lod score of 5.33. There was also evidence for genetic heterogeneity and although none of the linked families showed any association with *HLA-Cw6*, two unlinked families showed weak levels of association. This study demonstrates that in some families, psoriasis susceptibility is due to variation at a single major genetic locus other than the human lymphocyte antigen locus.

Psoriasis is a chronic inflammatory dermatosis that affects ~2% of the population. It is characterized by hyperproliferation of epidermal cells and inflammation resulting from infiltration of activated T helper cells and mononuclear cells and release of pro-inflammatory cytokines (*1, 2*). It may also be associated with arthritis and can be present as a severely inflammatory dermatosis in patients with acquired immunodeficiency syndrome (AIDS) (*3*). An understanding of the pathogenesis of psoriasis remains an important challenge in dermatologic research.

Associations between psoriasis and certain human lymphocyte antigen (HLA) alleles have been described, supporting the hypothesis that psoriasis is a T cell–mediated, autoimmune disorder (*4*). The presence of the *HLA-Cw6* allele may predispose to psoriasis because there is a strong association between age of onset, family history, and the presence of *HLA-Cw6, B-13* and *B-w57* (*5*), and the relative risk of *HLA-Cw6* carriers developing psoriasis is 20 (*6*). An "association" between a disease and HLA indicates that certain HLA alleles are more frequent in patients than in controls. Loci are "linked" when they do not assort independently at meiosis.

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It has been found that monozygotic twins have significantly higher concordance rates of disease than dizygotic twins (*7*) and that psoriasis aggregates in some families (*8*), suggesting that the disease can be inherited as an autosomal dominant trait with penetrance values of 10 to 50%. About 30% of psoriasis patients have a first-degree relative with the disease (*2*, *9*).

Additional predisposing loci unlinked to HLA are beginning to be identified for some diseases previously described as HLA-associated. One example is insulin-dependent diabetes mellitus where there is evidence that the insulin gene on chromosome 11p can confer susceptibility (*10*). Evidence for predisposing loci other than HLA in autoimmune diseases encouraged us to embark on a genome-wide study for markers linked to psoriasis susceptibility.

Some of the problems associated with mapping common genetic diseases have been described (*11*). When only a small proportion of cases are due to bona fide inherited susceptibility, some apparently familial cases may be present only because the disease is so common. Other factors that may confound a linkage analysis are incomplete penetrance of the trait in susceptible individuals and variations in phenotypic expression of the trait [which may depend on age, gender, modifier genes, and environmental trigger factors such as antecedent streptococcal infection (*12*)]. The existence of more than one major gene accounting for psoriasis (genetic heterogeneity) is likely, again decreasing the ability to detect linkage by pooling lod scores (the logarithm of the likelihood ratio for linkage) from different kindreds.

We began a genome-wide search for DNA markers cosegregating with a psoriasis susceptibility locus in eight multiply affected families with a total of 65 cases of psoriasis (Fig. 1). All 151 participating relatives were Caucasian and sampled from 15 states of the United States. Presence or absence of psoriasis was determined from thorough medical history and clinical evaluation. All patients had plaque psoriasis. Informed consent was obtained from all family members available for venipuncture. Lymphoblastoid cell lines were established by Epstein-Barr virus transformation of peripheral blood lymphocytes, and genomic DNA was isolated from these cells or from whole blood by phenol-chloroform extraction as described (*13*).

A set of polymorphic microsatellites spanning the genome (*14–16*) and at an approximate resolution of 10 cM were selected with MultiMap (*17*). Polymorphic microsatellites were genotyped as described (*14*).

Because no adequate models exist for the inheritance of psoriasis, three different approaches were used to identify a DNA marker cosegregating with psoriasis susceptibility. The lod score approach was first used and 14 different analyses were performed in which the mode of inheritance and the penetrance were varied. The second approach was an "affected-only" analysis of the first approach that was used to determine if nonaffected individuals could obscure potential linkage. This approach was independent of penetrance, and all individuals who were not coded as affected were recoded as unknown. The LINKAGE software package (*18*) was used for these analyses. The third approach was the affected-pedigree-member (APM) method that does not depend on the mode of inheritance of the disease and was used because the results of the first two approaches are sensitive to inaccuracies in the assumed genetic model. The APM method does not necessarily trace the segregation of alleles with a disease in families, but tests for excess sharing of alleles at the marker locus among related affected individuals (*19*). This allows one to evaluate allelic identity-by-state among affected individuals. The programs from the APM GENETICS PROGRAMS package (*19*, *20*) were used for this. For all analyses, marker allele frequencies were estimated from Centre d'Etude du Polymorphisme Humaine (CEPH) families.

After genotyping 69 polymorphic microsatellites, we obtained evidence of linkage with *D17S784* [*AFM044xg3* (*16*)] when psoriasis susceptibility was treated as a dominant trait. Pairwise lod score data for the first approach for *D17S784* and for additional linked loci (*D17S785*, *D17S802*, and *D17S928*) (*16*, *21*) are presented by family and are shown in Table 1. For family PS1, a maximum two-point lod score of 5.33 at 4% recombination with *D17S784* was obtained with the first model (at 99% penetrance), and a maximum two-point lod score of 3.33 at 4% recombination with *D17S784* was obtained with the "affecteds-only" model. When the inverse square root weighting function was used, the multilocus APM analysis indicated that there was a highly significant excess of haplotypes that were shared among affected members of the PS1 family (empirical P value < 0.0001). All three approaches supported linkage to markers at the distal region of 17q.

No segregation analysis has been performed for psoriasis susceptibility; consequently, there was no estimated penetrance value to use for the calculations, and we initially had to calculate lod scores over a variety of penetrance values. Considering just the large linked family (PS1) in which evidence for linkage was strongest, there were 21 individuals with the susceptibility haplotype and 20 of these were affected,

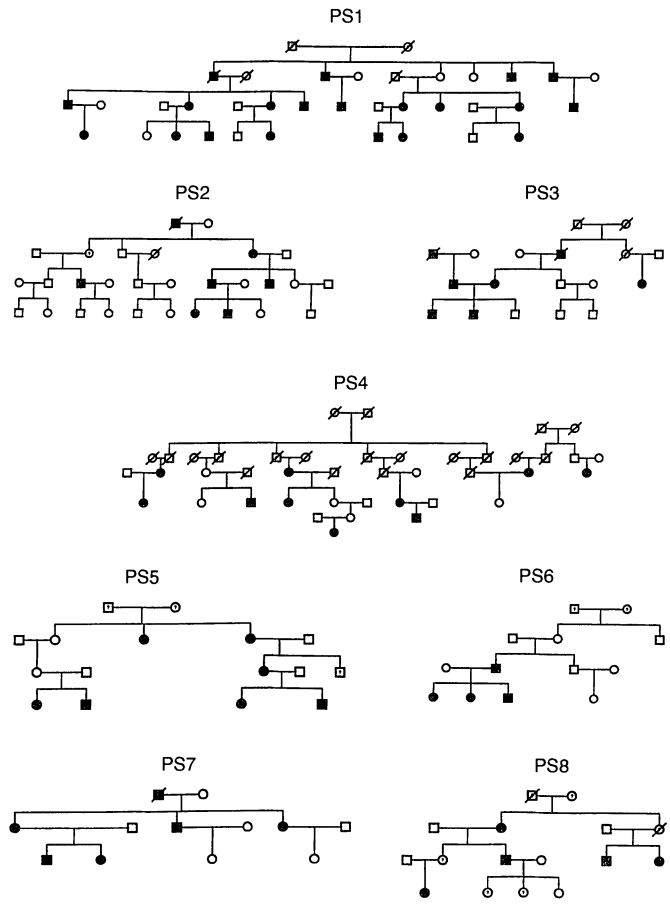

Fig. 1. Psoriasis families participating in this study. Circles, females; squares, males; solid symbols, individuals with psoriasis. Deceased individuals are represented by diagonal lines through symbols. The average age of onset of psoriasis in these families is shown in parenthesis: PS1 (18), PS2 (6), PS3 (17), PS4 (29), PS5 (23), PS6 (unknown), PS7 (21), and PS8 (21). Three families had affected members who had developed the disease in infancy (PS1: 4 of the 17 members for whom the ages of onset were known; PS2: 3 of the 6 affected members; PS5: 1 of the 11 affected members for whom the ages of onset were known).

giving a penetrance estimate of ~95%. However, four unaffected members in this family were not sampled for genotyping. If one or more of these unaffected individuals did harbor the susceptibility haplotype, the penetrance estimate would be less. In this family, varying the penetrance from 60 to 99% or varying the frequency of the disease allele did not affect the results significantly. Considering all eight families, the maximum two-point lod score was obtained when a penetrance of 80% was used (Z_{max} = 6.04, $\hat{\theta}$ = 0.10). However, there was no significant difference in the conclusions when penetrance values of 60% (Z_{max} = 5.96, $\hat{\theta}$ = 0.08) or 99% (Z_{max} = 5.70, $\hat{\theta}$ = 0.15) were used. The "affecteds-only" analyses gave similar results, though the lod scores were smaller (for the eight families combined Z_{max} = 4.04, $\hat{\theta}$ = 0.10).

To refine the location of the psoriasis susceptibility locus, we constructed a genetic map of polymorphic microsatellites from this region (*22*) and used it as a baseline map for multipoint linkage analysis of family PS1. The order and sex-average recombination fractions between the marker loci are as follows: centromere—*D17S785*–0.04–*D17S802*–0.10–*D17S784*–0.11–*D17S928*—telomere. Because of computational limitations, multilocus linkage analyses were performed after recoding the data to reduce the number of marker alleles. We obtained a peak multipoint lod score of 6.42 between *D17S784* and *D17S928* (6.6% distal to *D17S784* and 5.1% proximal to *D17S928*), suggesting that this psoriasis susceptibility gene lies within this interval. However, the next most likely region, distal to *D17S928*, was only 16:1 times less likely. The odds against placement proximal to *D17S802* were greater than 1000:1. Location scores obtained under the assumption of different recombination fractions in males and females lead to the same conclusion regarding the location of the disease locus. The data obtained with the "affecteds-only" model were in close agreement, giving a peak lod score of 4.41 for tight linkage to *D17S928* (no recombination). Chromosome 17q haplotypes for family PS1 are shown in Fig. 2. Multipoint linkage analysis with families PS6, PS7, and PS8 yielded only negative lod scores.

Table 1. Pairwise chromosome 17 lod score data by family. The population prevalence of psoriasis was assumed to be 1%. Penetrance = 0.99.

Family	Recombination fraction							Z_{max}	$\hat{\theta}$
	0.00	0.01	0.05	0.10	0.20	0.30	0.40		
				Locus D17S785					
PS1	−0.01	0.51	1.95	2.37	2.25	1.63	0.76	2.42	0.13
PS2	−4.57	−2.30	−1.20	−0.72	−0.32	−0.13	−0.04	0.00	0.50
PS3	−0.62	−0.32	0.08	0.22	0.24	0.15	0.05	0.25	0.16
PS4	−0.15	0.00	0.28	0.39	0.38	0.24	0.08	0.40	0.14
PS5	−1.88	−1.54	−0.96	−0.63	−0.33	−0.19	−0.10	0.00	0.50
PS6	−3.63	−1.66	−0.92	−0.60	−0.29	−0.14	−0.05	0.00	0.50
PS7	0.26	0.26	0.23	0.19	0.11	0.06	0.01	0.26	0.00
PS8	−1.10	−0.81	−0.38	−0.18	−0.03	0.01	0.01	0.01	0.30
Total	−11.71	−5.86	−0.94	1.03	2.01	1.62	0.73	2.01	0.20
				Locus D17S802					
PS1	0.76	4.47	4.76	4.52	3.65	2.50	1.16	4.77	0.04
PS2	−5.59	−3.12	−1.54	−0.79	0.16	0.05	0.07	0.07	0.36
PS3	0.84	0.82	0.72	0.60	0.38	0.18	0.05	0.84	0.00
PS4	−2.45	−1.19	−0.32	−0.01	0.14	0.12	0.05	0.15	0.22
PS5	−3.36	−1.67	−0.97	−0.59	−0.18	0.00	0.05	0.05	0.40
PS6	−3.10	−1.82	−0.98	−0.59	−0.24	−0.10	−0.04	0.00	0.50
PS7	−3.12	−2.53	−1.60	−1.10	−0.60	−0.33	−0.14	0.00	0.50
PS8	−4.05	−3.21	−1.86	−1.16	−0.50	−0.19	−0.04	0.00	0.50
Total	−20.07	−8.25	−1.79	0.88	2.49	2.23	1.16	2.54	0.23
				Locus D17S784					
PS1	1.36	5.07	5.32	5.03	4.06	2.79	1.30	5.33	0.04
PS2	−0.39	0.03	0.68	0.93	0.97	0.73	0.35	1.00	0.15
PS3	−0.80	−0.49	−0.10	0.04	0.08	0.04	−0.01	0.09	0.17
PS4	2.30	2.24	2.02	1.74	1.17	0.65	0.25	2.30	0.00
PS5	0.37	0.37	0.42	0.52	0.59	0.50	0.30	0.59	0.19
PS6	−3.04	−1.37	−0.68	−0.40	−0.16	−0.06	−0.02	0.00	0.50
PS7	−4.95	−3.70	−2.16	−1.42	−0.74	−0.39	−0.17	0.00	0.50
PS8	−2.98	−2.47	−1.59	−1.09	−0.58	−0.29	−0.11	0.00	0.50
Total	−8.13	−0.32	3.91	5.35	5.39	3.97	1.89	5.70	0.15
				Locus D17S928					
PS1	2.26	2.23	2.08	1.88	1.42	0.91	0.35	2.26	0.00
PS2	−1.75	−1.15	−0.25	0.17	0.44	0.39	0.18	0.45	0.23
PS3	−0.70	−0.71	−0.57	−0.35	−0.13	−0.07	−0.05	0.00	0.50
PS4	−1.88	−1.52	−0.79	−0.32	0.03	0.08	0.05	0.08	0.30
PS5	−1.01	−0.76	−0.32	−0.11	0.04	0.05	0.02	0.05	0.26
PS6	0.17	0.17	0.14	0.12	0.07	0.03	0.01	0.17	0.00
PS7	−4.21	−3.92	−3.06	−2.16	−1.15	−0.58	−0.22	0.00	0.50
PS8	−2.49	−2.12	−1.32	−0.85	−0.38	−0.15	−0.03	0.00	0.50
Total	−9.61	−7.78	−4.09	−1.62	0.34	0.66	0.31	0.66	0.30

The admixture test, as implemented in the HOMOG program (*23*), was significant when tested against multipoint lod score data (α = 0.50). Hence, there was evidence for heterogeneity with 50% of the families being linked. Families PS1 and PS2 showed strong evidence consistent with linkage (posterior probabilities >0.97), whereas families PS4 and PS5 showed less evidence (posterior probabilities 0.94 and 0.76). Families PS3, PS6, PS7, and PS8 appear to be unlinked (posterior probabilities <0.20). When only families PS1, PS2, PS4, and PS5 were considered, the combined maximum two-point lod score for linkage between *D17S784* and a psoriasis susceptibility locus was 8.44 at 6% recombination with the first model and 5.67 at 2% recombination with the second model. There were no apparent differences in clinical presentation observed in the linked and unlinked families.

We also tested for linkage with HLA. There was no evidence for linkage of psoriasis susceptibility with polymorphic microsatellites within and flanking the HLA cluster, or with class II haplotypes (*24*) for any of the families. However, because of the previously reported associations of psoriasis susceptibility to HLA alleles, and in particular to *HLA-Cw6*, the association of psoriasis susceptibility with this allele was examined with polymerase chain reaction sequence-specific oligonucleotide probes (PCR-SSOP) (*25*) in the families. Only two of the families in which psoriasis susceptibility was unlinked to 17q (PS6 and PS7) yielded empirical *P* values for excess sharing of the *HLA-Cw6* allele of 0.027 and 0.004, respectively [for significance empirical *P* value ≈ 0.0001 implies a lod score of 3 (*23*)]. These empirical *P* values were generated with 10,000 replicates and, though not significant, suggest that psoriasis susceptibility in families PS6 and PS7

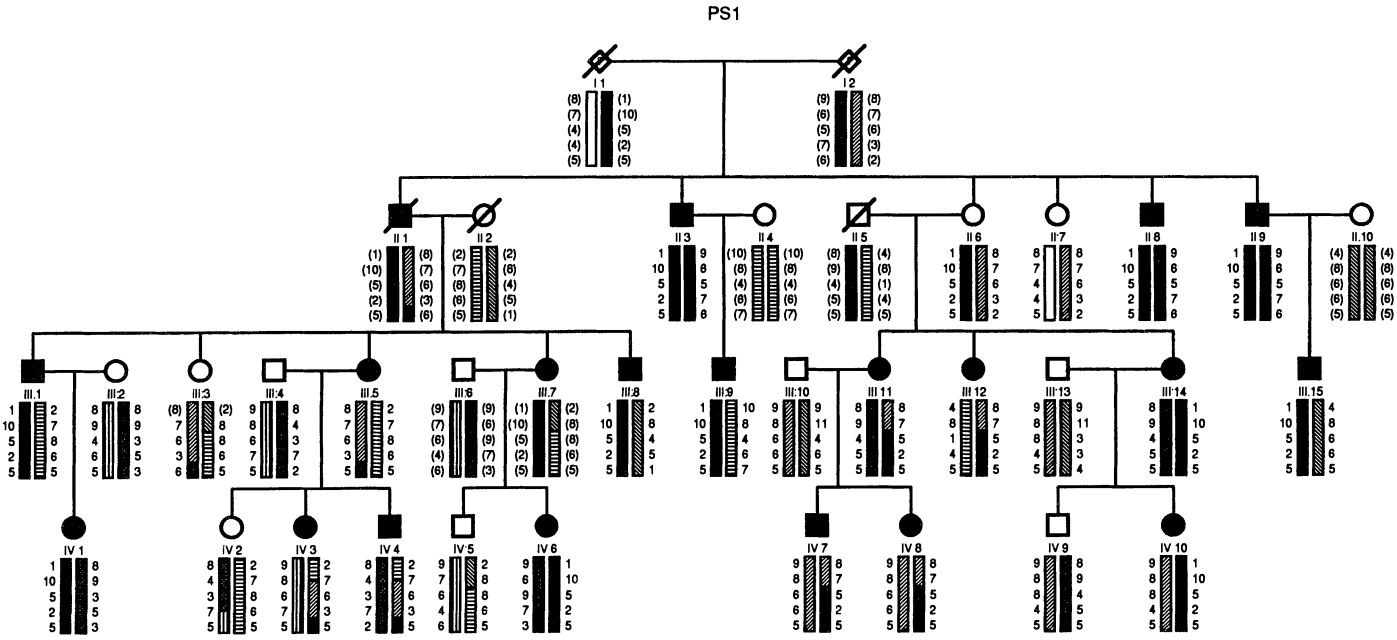

Fig. 2. Chromosome 17q haplotypes for family PS1. Symbols are as described for Fig. 1. The haplotype harboring the psoriasis susceptibility gene is boxed. Loci (from top to bottom) for which genotypes are provided are as follows: *D17S515, D17S785, D17S802, D17S784*, and *D17S928*. Inferred genotypes are indicated in parenthesis.

may be associated with *HLA-Cw6*.

Linkage mapping is used in the study of human diseases to identify regions likely to contain disease genes. These regions can then be isolated with physical mapping approaches such as the cloning of the region in a series of overlapping yeast artificial chromosomes, converting these to cosmids, and using these to select genes by means of a variety of approaches which include direct hybridization to complementary DNA libraries, exon trapping (*26*), and direct selection (*27*). Occasionally linkage mapping reveals several highly probable candidate genes within the mapped region. A gene involved in the activation of T cells was shown by others to lie within this region of 17q. This is ILF, or interleukin enhancer binding factor which, in addition to an inducible T lymphocyte factor (NFAT), binds to purine-rich regions of the interleukin-2 (IL-2) and human immunodeficiency virus promoters (*28*). One could speculate that affected members in families showing linkage to 17q harbor alterations in ILF that may potentially alter its regulation of IL-2 transcription. This could cause inappropriate expression of IL-2 resulting in the inflammatory cascade and hyperproliferation characteristic of lesional skin. It will be necessary to search for mutations in the ILF gene in affected members from 17q-linked families to determine if this is the susceptibility gene.

In conclusion, we have localized a gene involved in psoriasis susceptibility to the distal end of the long arm of human chromosome 17 and provided evidence for genetic heterogeneity. Mapping such genes in affected families is important because it may lead to the identification of genes responsible for sporadic psoriasis. In the linked families, no association between psoriasis susceptibility and *HLA-Cw6* was detected; however, weak associations with *HLA-Cw6* were seen in two unlinked families. HLA alleles were not correlated with age of onset nor with severity of psoriasis in any of the families. At least two unlinked families were not HLA-associated, raising the possibility that there is at least one additional psoriasis susceptibility locus.

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includes the second half of exon 2, intron 2, and exon 3 of the HLA class C genes. The presence of *HLA-Cw6*, and the related allele *-c1.10*, was identified by SSOP hybridization with CI-326 (CTCCAGTGGATGTATGGCT) that detects a codon for Met at residue 97 specific for these two alleles. An additional set of 14 SSOPs spanning other polymorphic codons (70 to 75, 76 to 81, 91 to 97, 95 to 101, 111 to 117, and 151 to 157) was used to distinguish *Cw6* from *c1.10* and to genotype the other *HLA-C* locus alleles. Amplified genomic DNA from 8 homozygous B cell lines carrying *HLA-Cw6* and from 10 B cell lines carrying other C-locus alleles was used to monitor the specificity of the SSOP.

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Long-Distance Neuronal Migration in the Adult Mammalian Brain

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During the development of the mammalian brain, neuronal precursors migrate to their final destination from their site of birth in the ventricular and subventricular zones (VZ and SVZ, respectively). SVZ cells in the walls of the lateral ventricle continue to proliferate in the brain of adult mice and can generate neurons in vitro, but their fate in vivo is unknown. Here SVZ cells from adult mice that carry a neuronal-specific transgene were grafted into the brain of adult recipients. In addition, the fate of endogenous SVZ cells was examined by microinjection of tritiated thymidine or a vital dye that labeled a discrete population of SVZ cells. Grafted and endogenous SVZ cells in the lateral ventricle of adult mice migrate long distances and differentiate into neurons in the olfactory bulb.

During brain development, most neurons are born in the VZ and SVZ. From these proliferative regions, cells migrate to reach their appropriate targets where they differentiate into neurons. The generation, migration, and differentiation of neurons are generally thought to end soon after birth (*1*, *2*). However, in adult birds in which neurogenesis persists (*3*), precursor cells that divide in the walls of the lateral ventricles migrate to distant targets within the forebrain before they differentiate into neurons (*4*). Neurogenesis also continues in the dentate gyrus of the hippocampus and in the olfactory bulb of adult rodents (*5*). In contrast to adult birds, newly generated neurons in adult mammals are thought to be derived from precursor cells that proliferate close to their site of differentiation instead of in the ventricle walls (*5*).

In mammals, proliferating cells persist through adulthood in the SVZ of the lateral ventricles (*1*, *6*), and these proliferating SVZ cells from the brain of adult mice can generate neurons in vitro (*7*). These cells are probably the epidermal growth factor–responsive neuronal precursors recently isolated from the brain of adult mice (*8*). The fate of these neuronal precursors in vivo remains unknown. Whereas earlier work suggested that SVZ cells in adult mammals may differentiate into glial cells or neurons (*1*, *6*, *9*), a recent study indicates that SVZ cells in adult mammals die soon after mitosis (*10*).

To investigate whether SVZ cells from adult mice could differentiate into neurons in vivo, we grafted SVZ cells from adult transgenic mice that carry the reporter gene β-galactosidase attached to the promoter of the neuron-specific enolase (NSE) gene (*11*). This transgene is only expressed in differentiated neurons (*11*). SVZ explants from transgenic animals were stereotaxically grafted into the lateral wall of the lateral ventricle of adult immunocompatible nontransgenic mice (Fig. 1) (*12*). Animals were killed 30 days after grafting, and transplanted cells that differentiated into neurons were detected by X-gal histochemistry (*12*). Cells that were X-gal–positive (X-gal$^+$) were detected only in the graft site and the ipsilateral olfactory bulb (*13*). We found no evidence of X-gal$^+$ cells in the

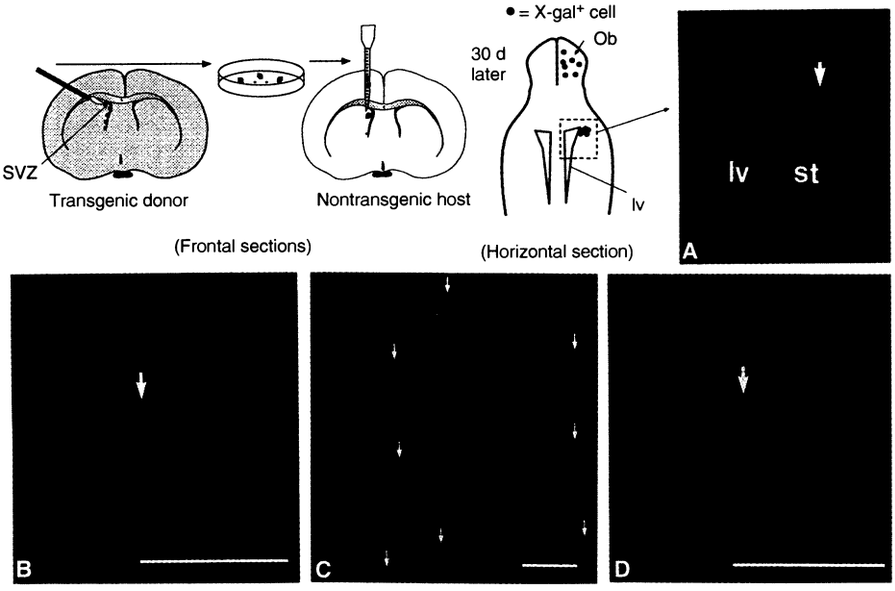

Fig. 1. Transplantation of transgenic SVZ cells close to the lateral ventricle of nontransgenic mice (*11*). X-gal histochemistry produced a blue precipitate in the perinuclear cytoplasm of the NSEp transgenic cells. Cell nuclei stained with Hoechst 33258 appear green. (**A**) Transgenic cells at the site of transplantation (arrow). (B, C, and D) show X-gal$^+$ neurons in the olfactory bulb 30 days (d) after transplantation. (**B**) X-gal$^+$ periglomerular neuron (arrow). (**C** and **D**) X-gal$^+$ neurons (arrows) in the granule cell layer. Ob, olfactory bulb; lv, lateral ventricle; st, striatum. Scale bars, 50 μm.

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