Of Genes and Antigens: The Inheritance of Psoriasis

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Psoriasis is one of a number of autoimmune diseases that display significant HLA associations. In particular, individuals with onset of disease prior to 40 years of age display striking associations with HLA-Cw6 and are much more likely to have a positive family for psoriasis. However, only about 10% of Cw6-positive individuals develop disease, suggesting that other genetic and/or environmental factors must be involved. Several compelling lines of epidemiologic evidence indicate that psoriasis susceptibility is inherited, albeit not in a simple monogenic fashion, and that genetic, rather than environmental, factors are primarily responsible for the variability in inheritance of psoriasis. Taken together, these observations suggest that one or more loci in addition to HLA are necessary for the development of psoriasis. The number of additional loci is likely to be small, because i) the disease is very common ii) substantial excess risk of psoriasis is observed in first degree relatives, and iii) nevoid variants of psoriasis have been reported, suggestive of somatic mutation of a single gene during development. The substantial homogeneity of the psoriatic phenotype and the clear evidence for increased HLA association and heritability in juvenile onset disease indicate that despite its complexity, psoriasis is a common disease whose etiology is amenable to elucidation through the techniques of modern molecular genetics. ***Key words: human genome/gene mapping/autoimmune diseases/epidemiology. J Invest Dermatol 103:150S–153S, 1994***

Psoriasis affects over four million Americans (about 2%) at an estimated annual cost of $1.6 billion per year [1]. Most of the 150,000 new U.S. cases diagnosed annually occur in individuals less than 30 years of age, and 10,000 of these cases are less than 10 years old at diagnosis [1]. At present, the cause of psoriasis is unknown, no curative therapy is available, and all effective antipsoriatic treatments can produce significant side effects. Therefore, an improved understanding of the etiology of psoriasis would be of major benefit for the rational design of new antipsoriatic drugs. In this article, we will review the available data pertinent to the genetic etiology of psoriasis, and explore the implications of this information for the feasibility of identifying psoriasis susceptibility genes through a genetic linkage/positional cloning strategy. This subject has also been recently reviewed elsewhere by ourselves [4,4a] and others [4b].

EPIDEMIOLOGY

Two large-scale true epidemiologic studies of psoriasis have been undertaken, one by Lomholt in the Faroe Islands [2], and one by Hellgren in Sweden [3]. Both of these studies revealed significantly higher incidence of psoriasis in relatives compared to the general population or to the families of spouses, providing strong evidence for the genetic basis of this disease (reviewed in [4]). In a population-based study based on xamination of psoriatic twins identified through the Danish Twin Registry, Brandrup and colleagues found that 63% (18 of 32) of monozygotic (MZ) probands had a psoriatic twin [5], yielding a heritability of 91% according to the method of Smith [6]. A very similar estimate of heritability (91%) was determined on the basis of re-analysis of Lomholt's epidemiologic study of psoriasis in the Faroe Islands [7]. Brandrup and colleagues concluded that [5]

> "the variation observed between individuals with respect to presence or absence of psoriasis is due almost entirely to their gene differences and only to a limited extent to differences in the environment which they experience at home or at work."

A lower estimate of heritability was obtained by Watson and colleagues [8]. However, the Danish study appears to be more reliable as the age of the twin studied was greater, allowing for increased penetrance of disease with age. Recently, a study of psoriasis in Australian identical twins revealed a heritability of approximately 80%, although the concordance rate in identical twins was lower than that reported in previous studies [9].

A number of other epidemiologic studies of psoriasis have been conducted on clinic or hospital-based populations; however, many of these lacked the matched controls necessary for case-control epidemiologic studies. Despite their shortcomings, these studies have provided several insights into the genetic nature of psoriasis. Many of these studies are referenced in Farber, Nall, and Watson's retrospective study of psoriasis in identical twins [10].

There have been many reports of families in which psoriasis is common [11]. In virtually all kindreds reported to date, the mode of inheritance has been reported as consistent with autosomal dominant with reduced penetrance vs. polygenic inheritance, with an equal sex ratio [11]. One of these kindreds, reported by Abele *et al* [12], contained 815 members, of whom 537 were in direct genetic line. In this kindred, of the 402 individuals examined, 44 were affected. Although the pattern of inheritance in this family was inferred to be simple autosomal dominant with reduced penetrance (60%, other studies measuring the frequency of psoriasis in sibships with 0, 1, or 2 affected parents does not fit either a simple autosomal dominant or recessive model, even after accounting for age-dependent penetrance [8,13]. The presence of psoriasis in children of two unaffected parents is particularly difficult to reconcile with an auto-

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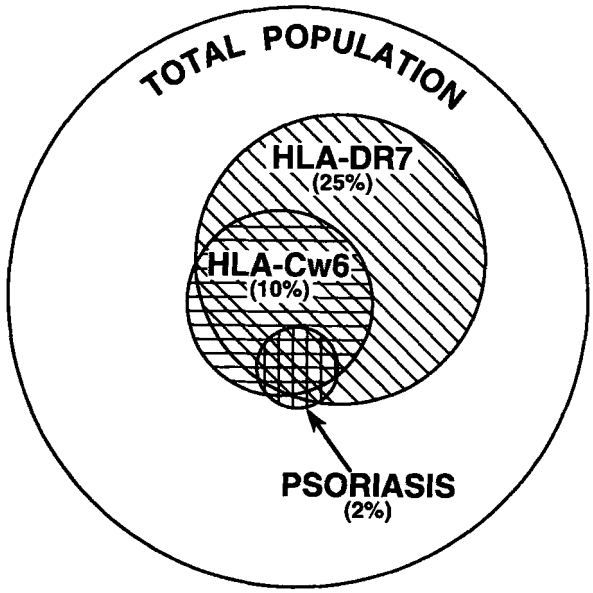

Figure 1. Venn diagram depicting the relationship of HLA-Cw6, HLA-DR7, and psoriasis in the general population. The areas of the *shaded circles* and their intersections are approximately proportional to that fraction of the total population affected by any single or combination of phenotypic traits shown.

somal dominant, single-gene model. The alternative explanation for these data is that psoriasis is determined by more than one factor, which could be environmental, genetic, or both. The former concept is termed polygenic, and the latter, multifactorial inheritance.

Although the identical twin data discussed earlier provides strong evidence for the heritability of psoriasis, it is important to remember that identical twins have been discordant for psoriasis in some 30 to 70% of cases [5,9,10]. Although this could be explained by somatic mutation during development of the T-cell and/or B-cell repertoires, it is also possible that differences in environmental exposure are responsible (ie, infections, stress, trauma, climate, etc.). Given the prominent evidence for immune system involvement in psoriasis, it is not surprising that environmental factors may play a significant role. However, to focus entirely on the environmental aspect of psoriasis etiology would overlook a genetic component that is among the strongest of all the so-called autoimmune diseases, whether primarily manifested in the skin or in other organ systems (reviewed in [4]).

HLA ASSOCIATIONS

Psoriasis belongs to a group of immunopathologic diseases that show significant HLA associations, including insulin-dependent diabetes mellitus, rheumatoid arthritis, multiple sclerosis, thyroiditis, Sjogren's syndrome, celiac disease/dermatitis herpetiformis, pemphigus vulgaris, and the spondyloarthropathies, among others. Many of these diseases are quite common (relative to most monogenic disorders), and display a complex pattern of inheritance in which only a limited number of individuals in the population carrying the susceptibility allele actually develops disease. This relationship is outlined for psoriasis in **Fig 1**. Evidence for the involvement of specific environmental factors (e.g., antigens) exists in several of these conditions, Reiter's syndrome and dermatitis herpetiformis (DH) being two examples that display prominent dermatologic manifestations [14,15]. However, in each condition, disease occurs in only a fraction of those individuals carrying the implicated HLA susceptibility allele and exposed to the offending environmental factor, strongly suggesting the participation of additional genes and/or environmental factors [15–18].

Numerous studies attest to the involvement of specific HLA alleles in psoriasis [19–25]. The serologically-defined class I antigens HLA-B13, B17, B39, B57, Cw6, and Cw7, and the class II antigens HLA-DR4 and DR7 all show increased association with psoriasis in population studies. Of these, the greatest relative risk has been associated with HLA-Cw6 [22]†; however, the percentages of psoriatics positive for HLA-DR7 and HLA-Cw6 are nearly the same (each about 70%, [25]). The difference in relative risk is accounted for by the higher frequency of HLA-DR7 in the general population (about 25%) relative to HLA-Cw6 (about 10%) **(Fig 1)**. This figure also reflects the fact that these two alleles are frequently inherited as a haplotype (that is, on the same parental chromosome). As a consequence, it remains unclear whether it is HLA-Cw6, HLA-DR7, or an allele at some other HLA or nearby non-HLA locus that is the major HLA-linked determinant of psoriasis susceptibility.

JUVENILE ONSET PSORIASIS

The peak age of onset of psoriasis is between 15 and 25 years, and two-thirds to three-fourths of patients experience onset before the age of 40 [25–27]. Henseler and Christophers have used the age of onset and HLA typing data to define two types of psoriasis [25,26]. Type I psoriatics (HLA-Cw6-positive, age of onset < 40 years) are much more likely than type II patients (HLA-Cw6-negative, age of onset > 40 years) to have affected parents (44% versus 0%) and to experience severe and recurrent disease (75% versus 25%) [25,26]. These results suggest that it is reasonable to select probands for juvenile onset disease to identify kindreds in which segregation of psoriasis may be detected.

HOW MANY GENES?

If psoriasis is to be amenable to the techniques of modern molecular genetics, especially the so-called parametric or LOD score methods of analysis, it is important that the number of major genes that predispose to disease be limited. There are three lines of evidence that suggest that this is likely to be the case. The first is that psoriasis is a very common disease, reaching a frequency of 1 to 3% in the Northern European and U.S. populations. If psoriasis were determined by multiple, unlinked genes, each of them would have to be present at high frequency in the population to account for the frequency of the disease. For instance, if 5 independently-segregating, completely penetrant genes of equal predisposing power and equal frequency, **f**, were required, and the population frequency of psoriasis is 2%, then under an autosomal dominant model for each gene $(\mathbf{f})^5 = 0.02$, $\mathbf{f} = 0.46$. In other words, each predisposing gene would need to be present in 50% of the population. Such a multigene model would seem a better fit for an uncommon, HLA-associated disease such as dermatitis herpetiformis, in which the HLA association with DQw2 is virtually complete and yet only a very small fraction (less than 0.03%) of HLA-DQw2–positive individuals go on to develop disease [17–19]. In contrast, in psoriasis nearly 10% of HLA-Cw6-positive individuals develop psoriasis **(Fig 1)**, suggestive of the involvement of only a limited number of independent genetic factors.

The second reason that the number of genes involved is likely to be limited is the relative risk of developing psoriasis in first-degree relatives of psoriatics. Thus, Hellgren's Swedish study [22] found the frequency of psoriasis to be 7.8% in first-degree relatives, and 2.99% in second-degree relatives, compared to 3.14% of age-, sex-, occupation-, and geographically matched relatives of normal controls, and to an overall prevalence of 1.97% in the population examined. Our re-analysis of these data revealed that the odds ratio for developing psoriasis in first-degree relatives was 2.72 (95% confidence interval = 1.53–4.83). If many independent, unlinked genes were all required, the probability of inheriting them all would decrease by $(1/2)^n$, where n is the number of unlinked genes involved, and a relative risk of this magnitude in first degree relatives would

† Lin JD, Auerbach AD, Auerbach R, Allen RG, Mann WR, Olsen DA, Gottlieb AB, Carter DM: Genetic linkage studies in psoriasis (abstr). *J Invest Dermatol* 96:535A, 1991.

be unlikely. However, these considerations do not rule out the possibility of additive or incremental effects of many different genes.

Nevoid psoriasis is an unusual clinical observation that further suggests that only a limited number of genes determine psoriasis. Atherton, Kahana, and Russell-Jones have described a unilateral eruption, distributed along the lines of Blaschko in a two-year-old child, which was histologically indistinguishable from psoriasis, improved by sunlight and anthralin therapy, and worsened after upper respiratory infections [28]. They speculated that the child was a mosaic for the genetic abnormality present throughout the skin of an ordinary psoriatic. Given the correctness of the clinical and histologic diagnosis, it is difficult to imagine how independent mutations in multiple, unlinked psoriasis genes could arise during development to produce such a mosaic. The existence of nevoid psoriasis also points out that at least one of the genes involved in psoriasis must be expressed in the skin itself, rather than in circulating cells of the immune system, because the latter would not be predicted to produce localized involvement.

PSORIASIS MOLECULAR GENETICS

Despite the complexities of psoriasis inheritance outlined above, the recent identification of genes responsible for other diseases such as cystic fibrosis, neurofibromatosis, fragile X syndrome, and Duchenne's muscular dystrophy demonstrate that the methods are at hand for genetic identification of loci that contribute to psoriasis susceptibility [29,30]. That the HLA region is one such locus is essentially a foregone conclusion, based on the well-established disease associations reviewed above. Moreover, linkage anaylsis can do relatively little to refine the location of a disease predisposition gene in a region as small as HLA (approximately three megabases). This technique, as well as related techniques such as sib pair and affected pedigree member (APM) analysis, are likely to have their greatest impact in identifying additional, non-HLA-linked loci. As reviewed above, the available data strongly suggest that only a limited number of major genes in additional to HLA are likely to be involved in determining susceptibility to psoriasis. Therefore it seems reasonable to attempt to identify these genes by genetic methods.

To date, very little has been published evaluating psoriasis susceptibility on the basis of linkage specific genes [21,24,31], and thus far, all studies have focused on HLA. In none of these studies was it possible to convincingly demonstrate linkage of psoriasis to the HLA locus despite the unambiguous evidence of HLA associations. In collaboration with Drs. Tilo Henseler, Enno Christophers, Stefan Jenisch, and Eckhard Westphal in Kiel, Germany, we have been identifying, clinically evaluating, HLA typing, and immortalizing lymphocytes from affected and unaffected members of multiplex psoriasis kindreds identified in Michigan and in northern Germany. Probands have been identified in our clinic populations on the basis of juvenile onset. The minimum criteria for inclusion in the study are 1) three generations available for analysis, 2) at least three affected first-degree relatives, and 3) either a history of psoriasis in at least two of these generations or at least three affected siblings in a single generation. Kindreds collected thus far resemble those previously reported in that apparent autosomal dominance with reduced penetrance is observed. Based on LOD score analysis of these kindreds using four chromosome 6p markers, we have reached conclusions similar to those of previous authors regarding the lack of tight linkage to the HLA region (unpublished data). However, the assumptions that have been used in these analyses may be overly simplistic, as they involve monogenic autosomal dominance, the absence of sporadic cases, linear, age-dependent penetrance, and the absence of imprinting.

Sib pair and affected pedigree member methods offer substantial advantages over linkage-analysis methods, in that no assumptions regarding the model of disease inherited, penetrance, sporadic cases, or other factors are required. [32]. Once such sib-pair analysis of psoriasis was recently published by Suarez-Almazor and Russell [33]. These authors found two identical HLA haplotypes in 13 of 15 affected sib pairs. Although it was not clear whether the sib pairs in this study were truly identical by descent, rather than identical by state, the results were interpreted by the authors to suggest that more than one HLA linked gene may contribute to psoriasis [33]. Although the interpretation of these results is not as yet clear, the excess of individuals identical by descent for two HLA alleles suggests that either more than one HLA-linked gene is required, or that a gene dosage effect involving alleles at one or more loci is present.

In collaboration with the University of Kiel, we have performed HLA class I and class II typing on many of the individuals in our psoriasis kindreds. Thus far, this anaylsis has revealed several examples of inheritance of HLA Cw6 from an unaffected parent with no family history of psoriasis (unpublished data). These results confirm those of two previous investigations [21,24], and strongly suggest that the presence of the HLA Cw6 allele is a necessary but not sufficient condition for development of psoriasis.

FUTURE DIRECTIONS

At present, we are completing the collection of our kindreds, and plan to make use of additional kindreds currently being collected by the National Psoriasis Foundation Psoriasis Tissue Bank as they become available. Future studies in our laboratory will be directed toward scanning the genome for additional, non-HLA-linked susceptibility loci, making use of the rapidly-expanding library of mapped microsatellite markers, as well as recently-developed extensions of sib pair, APM, and LOD score methods for multilocus involvement. In addition, the use of DNA-based methods for HLA typing will allow further dissection of HLA genes themselves for the possible existence of disease epitopes shared between different HLA alleles. These studies should eventually provide significant clues, and ultimately a molecular understanding of, the etiology as well as the pathogenesis of psoriasis.

Note Added in Proof: Evidence for linkage of psoriasis to a locus on distal human chromosome 179 in some, but not all, psoriasis families has recently been reported [33a].

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