Psoriasis Vulgaris: A Genetic Approach

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Evidence for a genetic contribution in psoriasis comes from direct examination of a large segment of the population in an isolated island environment, epidemiologic and questionnaire studies presented to psoriatic patients, twin studies collected from the literature and from twin registries, and split-sibship analysis. The concordance of psoriasis in monozygotic twins was 65–72%, whereas psoriasis in dizygotic twins was 15–30%. Determination of concordance in older twin pairs from a national twin registry in Denmark revealed nearly 90–100% heritability.

In order to link psoriasis with known markers within the human genome, serologic studies have been carried out with a variety of blood group and polymorphic protein antigens. A weak association with the MNS and Lewis Blood Groups Systems (relative risk, 3.5) has been identified. Stronger associations with class I B locus and class II D locus genes (relative risk, 8–12) have also been determined by studies of the human lymphocyte-antigen system. Finally, a strong association with HLA Cw6 has been determined; this marker is thought to be in linkage disequilibrium with B and D locus genes previously associated with psoriasis. The relative risk of developing psoriasis in HLA Cw6 positive individuals is about 24.

A few large kindred have been reported in the dermatology literature. These support the hypothesis of autosomal dominant inheritance with penetrance of approximately 60%. In cooperation with The National Psoriasis Foundation, we have now identified over 90 families with psoriasis in three generations. We have begun the process of ascertainment, the construction of family trees, and the collection of leukocyte DNA for linkage analysis with established restriction fragment polymorphisms (RFLP). Our initial assessment is being directed to four RFLP that span approximately 30 centiMorgans of the short arm of human chromosome 6. Although karyotyping is uncommonly done in patients because of psoriasis, we now seek evidence of translocations of chromosome 6 in association with psoriasis. *J Invest Dermatol 95:2S–4S, 1990*

The new tools of DNA manipulation and restriction fragment length polymorphism (RFLP) analysis allow remarkable localization within the 3-billion-basepair human genome [1–4]. The application of this methodology when the cause of a disease is unknown has led to stunning recent advances [5]. Muscular dystrophy, cystic fibrosis, Huntington disease, neurofibromatosis (both the central and peripheral types), and a host of other human diseases are yielding to the power of the new genetics. In a few instances, the defective gene or gene product has been localized (e.g., dystrophin).

Since the original description of psoriasis vulgaris by Robert Willan in 1801, this relatively common disease in most parts of the world has been recognized to have a hereditary component [6,7]. It is my purpose to review here information that favors a genetic contribution to psoriasis. I will then review our approach for the study of polymorphic DNA markers in families with psoriasis in three or more generations. Many such families are now available for study.

CENSUS AND EPIDEMIOLOGIC STUDIES

The problem of ascertainment, actually determining that cutaneous lesions represent psoriasis, is critical to all studies of the genetics of this disease. Most valuable therefore are the census-with-examination studies of Gunnar Lomholt published in 1964 and based on hispersonal examination of approximately one third of the population of the Faroe Islands in the North Atlantic Sea [8]. Lomholt determined that the prevalence of psoriasis among relatives of psoriatics significantly exceeded that of the general population in the Faroe Islands. Other large surveys by Hellgren and by Watson, et al [8] further verify that the prevalence of psoriasis in first-degree relatives exceeds the prevalence of the entire population. Many who have written about the genetics of psoriasis concur that approximately 30% of patients give a clear-cut history of first-degree relatives being involved, whereas 70% of cases are sporadic and have no known relatives with psoriasis.

Recent studies by Henseler and Christophers have emphasized two populations of psoriatics based on age at onset [9]. Psoriasis of early onset (with a mean age of approximately 16–20 years) is much more likely to be familial, whereas psoriasis of later onset (mean, 55–60 years) is more likely to be sporadic and non-familial.

No data for psoriasis support X-linked inheritance. Most accounts have favored simple autosomal dominant inheritance with decreased penetrance or some form of multifactoral inheritance.

SEROLOGIC STUDIES

A systematic survey of blood-group antigens, polymorphic protein components (such as haptoglobin or GC blood group), and HLA cell-surface markers has been carried out. Recently, chromosome markers for each of the blood-group antigens has been determined and are shown in Table I. The only antigens showing some association with psoriasis are those of the Ss and Lewis Blood Group Systems, alpha-1 antitrypsin variants, and HLA antigens [10]. The blood-group markers associated with psoriasis gave a relative risk of only 3.5, whereas HLA Cw6 has been assigned a relative risk of 14–24 in various reports and is thought to be in linkage disequilibrium with HLA-B13, -B17, and -B37.

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Table I. Chromosome Markers for Blood-Group Antigens

Serologic	Human Chromosome
ABO	9q
MNS[a]	4q 28–32
Kell	Xp 21
Lewis (Le)[a]	19
Duffy	1q
Rhesus (Rh)	1p 36–34
Haptoglobin (Hp)	16q 22
Group-Specific (Gc)	4q 12
HLA-A	6p
HLA-B[b]	6p
HLA-C[b]	6p
HLA-D	6p

[a] Relative risk, 3.5.
[b] Relative risk, 14–24.

FAMILY STUDIES

A few large families have been described in the literature and referenced in McKusick's Mendelian Inheritance in Man [8]. The large families of Ward et al (Utah), Abele et al (North Carolina), and Soltani (Illinois) give the immediate impression of an autosomal dominant inheritance pattern with somewhat reduced penetrance. Both sexes are equally affected.

In cooperation with The National Psoriasis Foundation, Inc. information was provided via the NPF Bulletin and through a questionnaire to members joining the foundation. We sought to identify families with psoriasis in three or more generations of living individuals in whom we might collect leukocyte DNA for further analysis. Our initial written request was somewhat detailed and technical and produced only 12 families in the first 18 months. However, a more simplified manner of presenting the material has allowed the accumulation of nearly 80 additional families within the past few months. This now provides ample material for study and sufficient meioses for calculation of recombination events.

TWIN STUDIES

Isolated reports in the literature of concordance or discordance for psoriasis among identical or dizygotic twins has been collected by Farber and his co-workers [7,11]. These authors added 46 additional cases of twins from the epidemiologic database at Stanford University. There was 65% concordance for psoriasis among 117 monozygotic twin pairs. By contrast, there was only 30% concordance among 112 dizygotic twin pairs. The authors discussed the bias inherent in this type of data collection. One would anticipate twice as many dizygotic twin pairs as monozygotic and they argue that authors are more likely to present concordant data in the literature than discordant.

Brandrup et al have recently presented information from the Danish twin registry on individuals born in 1891 through 1920 [12]. For disease with late onset of expression, such data may provide more accurate information and be a more complete means of ascertainment. Brandrup and co-workers concluded that 72% of monozygotic twins and 15% of dizygotic twins in their series were concordant for psoriasis. With 2–3% prevalence of psoriasis in the population, they concluded heritability was 90–100%.

REVERSE GENETICS

Others have studied selected probes in the HLA region of 6p. Olerup and associates used cDNA probes of the DQ and DR beta chains in 35 patients with psoriasis [13]. In this limited material, they determined that there was no greater association to the DQ than to the DR locus.

Ozawa et al studied 13 patients with psoriasis and six healthy controls each of whom had at least one allele of HLA-Cw6 [14]. They were unable to identify an HLA Cw6 RFLP associated with psoriasis. However, some controls lacked a fragment in the alpha 1–alpha 2 domains of Cw6 ($p < 0.005$), suggesting that its presence may confer susceptibility to psoriasis.

The sudden influx of many multigenerational families with psoriasis should overcome one of our earlier handicaps and allow us to investigate many meiotic events and determine if a suitable marker is within a 1% recombination fraction of a putative psoriasis gene. We have selected four probes that span approximately 30 centiMorgans on the short arm of human chromosome 6 to study in highly informative families. If such a marker does become available, then the laborious endgame analysis begins for research for the psoriasis gene itself. This is sometimes facilitated by assessment of translocations within the region under study or by chromosome walking or jumping. This technology is becoming increasingly accessible and the suitability of probes increasingly more numerous so that one can with some confidence anticipate that in two or three years many new techniques as well as existing ones will be available.

Perhaps the genetic study of psoriasis will parallel the recent breakthroughs in the genetic analysis of insulin-dependent diabetes mellitus. By DNA sequence analysis of variable regions of the HLA-DR locus, the encoded amino acid at codon 57 is critical to protect or permit development of the disease [15].

In addition, recent studies of the nucleotide sequence of the HLA antigens in pemphigus vulgaris have shown susceptibility linked to the DQ beta 1.3 allele as assessed by sequence-specific oligonucleotide probes [16,17]. Perhaps similar studies extended to psoriasis will provide insight about the structural requirements for susceptibility to this disease.

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