REPORT

Psoriasis clinical registries, genetics, and genomics

James T Elder

Ann Rheum Dis 2005;**64**(Suppl II):ii106–ii107. doi: 10.1136/ard.2004.030833

Genetics and genomics are being widely applied in an effort to unlock the secrets of psoriasis. At the same time, an explosion of exciting new biological therapies has brought large numbers of patients into clinical trials. Opportunities exist for synergism between therapeutic trials and genetic/genomic studies of psoriasis (and psoriatic arthritis). This article reviews existing clinical registries of psoriasis, with an emphasis on genetic studies; compares and contrasts the types of information necessary for genetic, genomic, and clinical registries; and considers the impact of patient privacy on the use of registries for both clinical and genetic studies.

Psoriasis is a common and chronic disease of the skin, scalp, nails, and joints, affecting 2% of the US population. It is an immunologically mediated disorder characterised by markedly increased epidermal proliferation and incomplete differentiation, vascular changes, and a mixed inflammatory and immune cell infiltrate of the epidermis and papillary dermis. Psoriasis has multiple clinical presentations, most of which evolve into red, scaly plaques with or without nail disease and arthritis. As a disease influenced by multiple genes and various environmental factors including infections, trauma, and stress, psoriasis is a prime example of a multifactorial disorder. There is now wide agreement that psoriasis is driven by interactions between the innate and acquired immune systems in the skin and joints. However, the root cause of psoriasis remains unclear.

Many laboratories worldwide have turned to genetics and genomics in an effort to unlock the secrets of psoriasis. At the same time, an explosion of exciting new biological therapies has brought large numbers of patients into clinical trials, with many more such trials anticipated in the near future. There is a tremendous opportunity for synergism between therapeutic trials and genetic/genomic studies of psoriasis (and psoriatic arthritis). However, it will be important to proactively meet all pertinent regulatory requirements at the time of study design if these synergisms are to be realised. The objectives of this article are: (*a*) to review existing clinical registries of psoriasis, with an emphasis on genetic studies; (*b*) to compare and contrast the types of information necessary for genetic, genomic, and clinical registries; and (*c*) to consider the impact of patient privacy on the use of registries for both clinical and genetic studies.

EXISTING CLINICAL REGISTRIES

As shown in table 1 of the introductory article on clinical registries by Gladman and Menter in this supplement,[1] there are three basic types of registry: administrative, clinical, and genetic. Remarkably little is available in terms of administrative or clinical registries specific for psoriasis. Non-disease-specific administrative registries such as the Finnish Hospital Discharge Register and the Finnish Cancer Registry have been used to investigate the relationship between psoriasis, its treatment, and cancer.[2] The Dermatology Department of the University of Kiel maintains extensive records of its inpatient population, and these have been used extensively to investigate the relations between psoriasis and other skin diseases.[3] Although patient associations in the USA and elsewhere maintain extensive mailing lists of patients affected by psoriasis, these are usually not accessible for research use because of privacy considerations (see below). In terms of clinical registries, the PUVA Follow-up Study has been particularly prominent.[4] The Food and Drug Administration (FDA) mandates the maintenance of so-called phase IV registries for patients treated with novel and potentially toxic therapies, as exemplified by the ciclosporin A treatment registry.[5] Such registries are now being maintained for all new biological therapies approved for psoriasis. However, these registries are usually maintained by pharmaceutical firms and are not generally accessible for research use.

INFORMATION NECESSARY FOR GENETIC, GENOMIC, AND CLINICAL REGISTRIES

Genetic studies of psoriasis have greatly benefited from the landmark population studies of Gunnar Lomholt in the Faroe Islands and the Danish and Swedish Twin Registries.[6–8] These and other studies have provided the impetus for collection of clinical data and blood samples on thousands of individuals in the USA, Europe, and Asia.[9 10] Results from many laboratories have been shared at a series of international meetings sponsored by the National Psoriasis Foundation, leading to increasing numbers of collaborative studies. One result of such collaboration is the International Psoriasis Genetics Consortium Study,[11] an analysis of 942 sibling pairs and families, which identified very strong evidence for genetic linkage of psoriasis to the major histocompatibility complex (MHC), and possible linkage to chromosomes 10q and 16q. In this study, all collaborating groups agreed to type the same markers, which were then analysed jointly. In another example, published and unpublished genome scans involving different markers have been combined into a single meta-analysis, revealing in addition to strong evidence for MHC involvement, suggestive evidence for involvement of the 4q28-q31 region.[12] This is one of very few studies to combine data from Caucasian and Asian populations.

To date, pedigree based studies have yielded strong evidence for MHC involvement, and reproducible evidence for non-MHC loci, including a possible regulatory variation in the chromosome 17q25 region.[13] Indeed, several of these loci overlap with loci implicated in atopic dermatitis, raising the possibility of skin specific inflammatory genes.[14] However, it is becoming increasingly clear that many of the genetic determinants of psoriasis are common gene variants of distant origin, rather than highly penetrant mutations. Several of these variants may interact with each other and the environment to predispose to psoriasis, psoriatic arthritis and other common diseases. This scenario is known as the "common variant-common disease" model.[15] Under this scenario, linkage analysis lacks sufficient power to detect disease loci due to the limited genetic effect, low penetrance,

and high disease allele frequency of each individual susceptibility gene. Therefore, future studies of psoriasis and psoriatic arthritis will likely rely on analysis of allelic association, rather than genetic linkage, because the former method has much greater power to detect risk due to common variants.[16] These studies will be highly challenging, as they will involve the collection of large numbers of subjects (2000–10 000), and the need to analyse tens to hundreds of thousands of genetic markers due to the shorter range of allelic association as opposed to linkage.[16] Despite these challenges, it is important to note that allelic associations can be studied on cases and controls rather than families, and one could therefore use the same cases typically collected for clinical studies. Controls can be identified from spouses and controls of the case, and/or from other populations provided that they are matched on the basis of sex and ethnicity. This ''paradigm shift'' opens up tremendous possibilities for synergy between clinical and genetic studies of psoriasis and psoriatic arthritis.

Unlike drug treatment studies, clinical information for genetic studies is collected only at a single point in time, and measures of therapeutic response to therapy are usually not recorded. However, the clinical information collected for genetic studies is virtually the same as that collected at the onset of a clinical study of psoriasis or psoriatic arthritis. All that is needed in addition to the baseline clinical information is a blood sample in order to prepare DNA, and such samples are typically collected at the onset of most clinical trials. Other than transfer of information and blood samples from the clinical evaluation unit to the genetics laboratory and the identification of appropriate controls, nothing else is needed.

Genomic studies (that is, gene expression microarray or proteomic studies) are used to distinguish subsets of patients, to identify markers of therapeutic response, or both.[17] Therefore, unlike genetic studies, genomic studies can benefit from taking skin and/or blood samples at multiple time points throughout the course of therapy.

IMPACT OF PATIENT PRIVACY ON THE USE OF REGISTRIES

Clearly, formation of a network for sharing of clinical information and blood samples would be of great benefit to elucidating the genetic basis of psoriasis. Also, with the increasing emphasis on pharmacogenomics by the FDA and elsewhere, it may be of more than altruistic interest for pharmaceutical firms to generate a genetic resource in the course of clinical trials. If this synergy is to be accomplished, three major hurdles must be met:

- improved communication networks
- respect of protected health information (PHI)
- appropriate solicitation of informed consent.

Generally, genetic researchers and clinical trial directors have not previously had common immediate goals. Networks such as the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) offer an exciting opportunity to bring these two groups of investigators together for their mutual benefit. With the passage of the Health Insurance Portability and Accountability Act (HIPAA) in 1996, the respect of PHI is the law of the land in the USA. Basic information such as a subject's name, diagnosis, and address or phone number are PHI and cannot be collected unless they are requested in the context of ongoing clinical treatment of the patient, or unless a waiver of informed consent has been obtained. The major criteria for obtaining a waiver include demonstration of a lack of harm due to the proposed collection of PHI, and a demonstration that the research in question would not be practicable by any other means. Given the large numbers of subjects required for association studies of psoriasis, psoriatic arthritis, and other disorders, these requirements can be met.

Finally, it will be important for genetic investigators and clinical trial organisers to work together to design consent forms that educate the subject about the risks of genetic studies as well as those of a clinical study. Fortunately, risks typical of a family based genetic study (such as the potential for decreased insurability and difficult decisions for unaffected family members about whether or not they should get tested) are largely avoided in a case–control design, as the individuals being sampled already know that they are affected.

CONCLUSION

In summary, it is evident that genetic studies of psoriasis (and psoriatic arthritis) are entering a new phase that will necessitate the collection of large numbers of affected individuals. A unique opportunity exists to coordinate the activity of clinical trials and genetic studies, with potential advantages for both groups. Organisations such as GRAPPA represent a novel way for human geneticists and clinicians to work together for the advancement of knowledge and the improved health of patients.

Correspondence to: James T Elder, Departments of Dermatology and Radiation Oncology (Cancer Biology), University of Michigan; and Dermatology Service, Ann Arbor Veterans Affairs Hospital, Ann Arbor, MI; 3312 CCGC, Box 0932, University of Michigan, Ann Arbor, MI 48109–0932, USA; jelder@umich.edu

REFERENCES

1 **Gladman D**, Menter A. Introduction/overview on clinical registries. *Ann Rheum Dis* 2005;**64**(suppl II):ii101–2.
2 **Hannuksela-Svahn A**, Pukkala E, Laara E, Poikolainen K, Karvonen J. Psoriasis, its treatment, and cancer in a cohort of Finnish patients. *J Invest Dermatol* 2000;**114**:587–90.
3 **Henseler T**, Christophers E. Disease concomitance in psoriasis. *J Am Acad Dermatol* 1995;**32**:982–6.
4 **Stern RS**, Nichols KT, Vakeva LH. Malignant melanoma in patients treated for psoriasis with methoxsalen (psoralen) and ultraviolet A radiation (PUVA). The PUVA Follow-Up Study [see comments]. *N Engl J Med* 1997;**336**:1041–5.
5 **Paul CF**, Ho VC, McGeown C, Christophers E, Schmidtmann B, Guillaume JC, Lamarque V, *et al*. Risk of malignancies in psoriasis patients treated with cyclosporine: a 5 y cohort study. *J Invest Dermatol* 2003;**120**:211–16.
6 **Lomholt G**. Psoriasis: prevalence, spontaneous course, and genetics [published PhD thesis]. Copenhagen: GEC GAD, 1963.
7 **Brandrup F**, Holm N, Grunnet N, Henningsen K, Hansen HE. Psoriasis in monozygotic twins: variations in expression in individuals with identical genetic constitution. *Acta Derm Venereol* 1982;**62**:229–36.
8 **Hellgren L**. Psoriasis: the prevalence in sex, age and occupational groups in total populations in Sweden; morphology, inheritance and association with other skin and rheumatic diseases. Stockholm: Almqvist & Wiksell, 1967.
9 **Capon F**, Munro M, Barker J, Trembath R. Searching for the major histocompatibility complex psoriasis susceptibility gene. *J Invest Dermatol* 2002;**118**:745–51.
10 **Elder JT**, Nair RP, Henseler T, Jenisch S, Stuart P, Chia N, *et al*. The genetics of psoriasis 2001: the odyssey continues. *Arch Dermatol* 2001;**137**:1447–54.
11 **International Psoriasis Genetics Consortium**. The International Psoriasis Genetics Study: assessing linkage to 14 candidate susceptibility loci in a cohort of 942 affected sib pairs. *Am J Hum Genet* 2003;**73**:430–7, Epub 7 July, 2003.
12 **Sagoo GS**, Tazi-Ahnini R, Barker JW, Elder JT, Nair RP, Samuelsson L, *et al*. Meta-analysis of genome-wide studies of psoriasis susceptibility reveals linkage to chromosomes 6p21 and 4q28-q31 in Caucasian and Chinese Hans Population. *J Invest Dermatol* 2004;**122**:1401–5.
13 **Helms C**, Cao L, Krueger JG, Wijsman EM, Chamian F, Gordon D, *et al*. A putative RUNX1 binding site variant between SLC9A3R1 and NAT9 is associated with susceptibility to psoriasis. *Nat Genet* 2003;**35**:349–56, Epub 9 November, 2003.
14 **Bowcock AM**, Cookson WO. The genetics of psoriasis, psoriatic arthritis and atopic dermatitis. *Hum Mol Genet* 2004;**13**:R43–R55.
15 **Zwick ME**, Cutler DJ, Chakravarti A. Patterns of genetic variation in Mendelian and complex traits. *Annu Rev Genomics Hum Genet* 2000;**1**:387–407.
16 **Risch NJ**. Searching for genetic determinants in the new millennium. *Nature* 2000;**405**:847–56.
17 **Zhou X**, Krueger JG, Kao MC, Lee E, Du F, Menter A, *et al*. Novel mechanisms of T-cell and dendritic cell activation revealed by profiling of psoriasis on the 63,100-element oligonucleotide array. *Physiol Genomics* 2003;**13**:69–78.