Alopecia Areata Registry: An Overview

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The National Alopecia Areata Registry was awarded as a five-year contract by NIAMS to promote research on the genetic basis of alopecia areata. The registry is Web based and can be accessed online at http://www.AlopeciaAreataRegistry.org. Samples of DNA, lymphoblast lines, and sera, as well as epidemiology and quality-of-life data, are being collected from well-characterized individuals, multiplex families, and sib pairs for future research studies and investigators. Keywords: hair/T-cell/HLA/autoimmune. JID Symposium Proceedings 8:219–221, 2003

Alopecia Areata (AA) is an organ-specific, T cell-mediated autoimmune disease in which hair follicles surrounded by lymphocytes have abnormal keratinocyte differentiation resulting in breakage of antigen hairs and in baldness (Madani and Shapiro, 2000). Studies suggest that the process is generalized in the scalp, although patches appear to be localized (Nutbrown et al, 1995). It is estimated that in the United States over 2 million persons may be afflicted with the disease (Safavi et al, 1995).

Clinically, AA can present as patches of baldness on the scalp or in other areas, such as the beard, which are reversible (Madani and Shapiro, 2000). There is a spectrum of phenotypic severity that culminates in total hair loss on the scalp (alopecia totalis, AT) or total loss of all scalp and body hair (alopecia universalis, AU).

AA has long been associated with other autoimmune diseases (Cunliffe et al, 1969; Du Vivier and Munroe, 1975). Although most consider AA to be a sporadic event, about 20%–50% of the afflicted give a positive family history of AA and autoimmunity in other family members is not infrequently encountered (Duvic et al, 2001). It is hypothesized that the release of inflammatory cytokines mediates this process and may be regulated by neuropeptide hormones.

The predisposition to autoimmune diseases is associated with histocompatibility antigens (HLA) (Marrack et al, 2001). AA has been associated with specific class II histocompatibility antigens, including HLA-DR-4 and HLA-DR-5 and associated DQB*03 alleles, in studies of unrelated patients versus controls (Duvic et al, 1991; Welsh et al, 1994; Kavak et al, 2000; Duvic et al, 2001). HLA alleles may differentiate between clinical phenotypes, in that the patchy and persistent form of AA is significantly associated with the HLA-DRB*1104 allele of DR-5 whereas 80%–90% of all patients with severe AT/AU were found to carry HLA-DQ*03 alleles (Welsh et al, 1994; Colombe et al, 1995). Family studies using transmission disequilibrium testing have supported the hypothesis that AA is associated with the HLA-DR and DQ loci (Duvic et al, 1995; De Andrade et al, 1999; Duvic et al, 2001).

Given the lack of Mendelian inheritance and the phenotypic variation displayed by individuals with AA, the hypothesis that AA is a complex genetic trait that depends on the cooperation of a number of genes acting in concert is most attractive at this time. An environmental trigger is likely to initiate the onset of AA, as only a 55% concordancy rate was observed among sets of identical twins who nonetheless all carried predisposing DQB*03 alleles (Jackow et al, 1998). Given the need for the collection of a large number of AA subjects for further linkage and association studies, dermatology investigators from five sites applied for and were awarded an RFA to establish the National Alopecia Areata Registry, to be funded by NIAMS.

BACKGROUND OF THE ALOPECIA AREATA REGISTRY

Following a peer review process, the Alopecia Areata Registry was awarded to a collaborative group by NIAMS on September 23, 2000. Five experienced hair disease investigators, representing the major geographic areas of the United States, competed for this registry from among other groups representing other skin diseases. The structure proposed for the AA registry, shown in Fig 1, is a central site for specimen and data collection plus four subsites where patients can be examined and enrolled across the country.

The purpose of the national AA registry is to collect epidemiology data, quality-of-life information, and sera and DNA samples from well-characterized selected patients examined at each site. The project involves the development of information and questionnaires for the registry, the use of consent forms, and a Web-based front end connected to a Microsoft database with appropriate measures to ensure confidentiality of the patients involved. Institutional Review Board approval was required from each of the five involved institutions, and an OMB exemption was required for collection of data.

The diagnostic criteria and severity for AA have been described and published by a subcommittee of the National Alopecia Areata Foundation (Olsen et al, 1999). The degree of scalp hair loss (0–5), nail involvement (0–2), and body hair loss (0–2) will be recorded for each patient accepted for long-form entry. AA lesions should exhibit patches and broken hairs and be devoid of tinea. The diagnosis of AA will require the exclusion of other forms of alopecia by the use of appropriate cultures,
biopsies on occasion, and lab tests such as RPR or ANA. Patients who present at less than six months of age will be suspected as having mutations in the hairless gene.

**STRUCTURE OF THE ALOPECIA AREATA REGISTRY**

Following the award, a steering committee, composed of the principal investigators from each of the sites, was established to oversee the operation of the registry. An external advisory board of senior scientists was also selected and appointed. The steering committee developed two questionnaires to be used to collect information from the registrants. At the central site, a Microsoft SQL server database was constructed to contain patient questionnaires and collect all the data from them. A laboratory database was constructed to decode and store the samples and link them to the database information. An administrative database was set up for the subsites to use for calling in patients in their regions for examination.

Institutional Review Board review for the registry protocol, questionnaires, and informed-consent forms was obtained from each of the five sites. The first questionnaire is a self-administered, short-intake form consisting of demographic information, AA type, and personal and family history of autoimmune diseases. Consent for the short form requires patients to read the introduction to the registry and choose to register online. The short questionnaire went on line in fall 2000. It is widely available to all persons with AA, having been posted on the Web at http://www.AlopeciaAreataRegistry.org. In addition, the short-form questionnaire may be printed out from the Web site, filled out by hand, and mailed back to the registry for entry at the central site. We encourage dermatologists to print out the short form and give it to their AA patients or have them read the registry information brochure.

The data from the short form goes directly into the central SQL server database. An administrative database allows partitioning of the data where it can be seen regionally by each subsite coordinator. This will allow scheduling of interested patients and families who will come to the site to fill out a longer form, have an examination, and have samples of blood drawn and sent to the central site for processing. Prior to filling out a long form and being examined, each patient will be required to sign a written consent provided at the center.

Patients who belong to one of the categories listed in Fig 2 are prioritized for the second tier of the registry. Multiplex families (three or more affected members) and affected sib pairs or twins plus their first-degree relatives will be of highest priority for genetic studies. In addition, simplex families and single AA patients with the more severe phenotype (AT/AU), patchy and persistent AA, or transient AA will be registered for sample collection for association studies.

The registry will enlist the help of local dermatologists in collecting data and samples from multiplex family members who may not be able to travel to a central site. Patients who are not able to travel may be consented by phone and may have their blood drawn locally after being examined by their dermatologist. The data from the long form and from a quality-of-life questionnaire will be entered by hand into the database and linked to a pedigree program. Each registrant and his or her family members will be given unique patient identifiers. Digital photographs documenting the extent of the disease will be taken and stored. Each site will collect information regarding biopsy results and laboratory tests from each patient who has long-form registration.

Blood samples will be collected from each long-form entrant and processed for sera, white cells, and lymphoblast cell lines, from which genomic DNA will be prepared. An unrelated spouse or accompanying person will also be enlisted for samples to serve as an unaffected control.

**UPDATE ON REGISTRATION**

The registry has been open since fall 2001, and 686 individuals have completed the short-form registration online or by hand. Of the registrants, 396 listed their phenotype as AT or AU; 118, as AA (82 with patchy persistent AA and 36 with transient AA). There are 78 multiplex families, 64 simplex families, and 27 sib pairs registered to date. Long-form data gathering from and blood sampling of 70 individuals have been accomplished from the central site and from the two other sites that have completed IRB approvals.

Of note, the registry Web site, AlopeciaAreataRegistry.org, has had over 2000 hits, averaging 2000–3000 per month, or 60 per day. Seventy percent of the visitors are from the United States, 8% are international, and the remainder are unknown. AOL and Atomz are the most commonly used internet providers, at 8% each.

**PUBLICIZING THE ALOPECIA AREATA REGISTRY**

For the registry to be a success, there must be widely distributed information available, and we enlist the help of all dermatologists in spreading the word to their patients and in reaching underserved portions of the population. Advertisements have been
placed in the major dermatology journals as of November 2002. The details of the registry have been presented at the winter and summer Academy meetings, at the SID meeting, at the International Hair Research Society meeting, and at local medical society meetings. A brochure containing the contact information should contact one of the participating sites listed.

Using the Registry for Research

Investigators are encouraged to use the registry for conducting AA research projects. They may apply by filling out a form to be provided online and reviewed by the steering committee. Priority will be given to projects that are funded by NIAMS, NIH, or NAAF grants. Confidentiality will be maintained for all participants of the registry.

Information about the Registry

The Alopecia Areata Registry is a five-year, NIAMS-funded registry established to collect epidemiologic and quality-of-life data and samples for genetic research leading to a better understanding of the pathogenesis of Alopecia Areata and, hopefully, to improved therapy for this common disease. Persons desiring more information should contact one of the participating sites listed.

REFERENCES

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