Epidemiology of Ankylosing Spondylitis: IGAS 2009

JOHN D. REVEILLE and MATTHEW A. BROWN

ABSTRACT. The International Genetics of Ankylosing Spondylitis (IGAS) meeting was held in Houston, Texas, July 25, 2009. Sixteen investigators from Asia, Australia, Europe, and North and South America presented the status of their respective cohorts of patients with ankylosing spondylitis (AS). They also reviewed a proposal to examine their patients by single-nucleotide polymorphism (SNP) genotyping on an Illumina Infinium microarray SNP genotyping chip in a case-control cohort exceeding 12,000 samples. This chip will type 200,000 SNP selected from the most strongly associated variants identified in genome-wide association studies of inflammatory diseases, including inflammatory bowel disease, psoriasis, and ankylosing spondylitis. (J Rheumatol 2010;37:2624–5; doi:3899/jrheum.100891)

Key Indexing Terms: ANKYLOSING SPONDYLITIS GENETICS, METAANALYSIS GENOME-WIDE ASSOCIATION STUDY ETHNICITY

The implementation of gene chip technologies has allowed genome-wide association studies (GWAS) in large populations, the results of which have greatly extended the knowledge of the genetic basis of human disease. In ankylosing spondylitis (AS), despite family studies suggesting regions on chromosomes 2, 10, and 161, in addition to the overwhelming effect of the major histocompatibility complex (MHC; primarily reflecting HLA-B27), prior to 2007 no other non-MHC gene had been identified that could be widely replicated. The first non-MHC gene to be identified and validated on metaanalysis was interleukin 1A on chromosome 2q2.

The first GWAS in AS, involving patients from the UK with a replication cohort from the USA, identified 2 new genes in AS susceptibility that have been extensively replicated in other cohorts and locales, namely endoplasmic reticulum-associated aminopeptidase 1 (ERAP1) and interleukin 23 receptor (IL23R)3. A subsequent, more comprehensive scan in a larger cohort of patients from the UK, US, and Australia revealed additional genes, including “gene deserts” on chromosome 2p15 and 21q22, anthraxin receptor 2, and interleukin 1 receptor 24. This ERAP1 association has been extensively confirmed in nearly all ethnic groups5,6,7,8.

Emerging data from other groups, however, have shown that these genetic associations, although well replicated in patients of European Caucasian ancestry, do not all extend to other ethnic groups. The association of IL23R with AS, although seen in studies from the UK, US, Canada, Spain, and Portugal6,9,10,11, is not associated with AS in China or Korea8,12.

What became abundantly clear from these studies and other studies of complex genetic diseases is the need for very large discovery and replication cohorts to successfully identify the genes and genetic networks involved in AS susceptibility.

To address this need, the International Genetics of Ankylosing Spondylitis (IGAS) consortium was established in 2002 with the goal of coordinating international efforts in gene-mapping studies in AS. An initial meeting was held at Keble College, Oxford, UK, and meetings have since been held approximately yearly. IGAS has initiated many collaborations, including a metaanalysis of linkage scans1, as well as a large-scale prospective metaanalysis of interleukin 1 gene variants and AS2.

At the Houston IGAS meeting in July 2009, presentations were made by research groups (Table 1) that described a broad range of approaches to the challenge of gene mapping. Several groups described the development of AS case or family cohorts in different ethnic groups in East Asia (China, Korea), South America (Argentina, Brazil, Columbia), European (Britain, France, Holland), and North American (Canada, USA). This represents a major increase in research activity in the field over the past decade. Ongoing research topics include association and linkage studies for gene mapping, clinical studies investigating the relationship between the disorders comprising spondyloarthritides and their determinants, studies of determinants of AS outcomes and disease severity, pharmacogenetic studies related to tumor necrosis factor-antagonist response and antibody development to biologic therapies, and genomic and proteomic profiling studies.

To harness the potential of the different IGAS cohorts, agreement was reached regarding the involvement of IGAS
with the Wellcome Trust Case-Control Consortium-initiated “Immunochip” study. The Immunochip Consortium has developed an Illumina Infinium microarray SNP genotyping chip that will type 200,000 SNP per sample, at a cost per SNP of about 0.02 cents ($US 39/sample). The chip has been designed with content including SNP selected from the most strongly associated variants identified in GWAS of the autoimmune diseases, including rheumatoid arthritis, type 1 diabetes, systemic lupus erythematosus, celiac disease, autoimmune thyroid disease, and the seronegative diseases Crohn’s disease, ulcerative colitis, psoriasis, and AS. This will allow both deep replication of disease-specific GWAS data and additionally facilitate the identification of pleiotropic genes associated with more than one autoimmune disease. It also contains SNP designed to permit imputation of the classical HLA loci, killer cell Ig-like receptors (KIR) and leukocyte immunoglobulin-like receptor (LILR) genes, and dense SNP maps around known genome-wide significant disease-associated loci to permit fine mapping.

IGAS has agreed to use this chip to study a case-control cohort that currently includes about 12,000 samples. Control genotype data will also be available from over 20,000 samples from the Immunochip Consortium. AS genotyping will be performed outside Brisbane to ensure generalizability of the data. Analysis will be coordinated centrally by Dr. David Evans at the University of Bristol, UK. While the primary aim of the study is the analysis of the combined IGAS cohort for gene identification and fine mapping, IGAS agreed on a series of subanalyses looking at genetic determinants of disease subsets (including age at disease onset, presence of uveitis, functional and radiographic severity), and ethnic-specific analyses and comparisons. The study genotyping will be complete by the end of 2010, and a preliminary analysis will be presented at an IGAS conference being organized by Prof. Huji Xu in Shanghai, China, in March 2011.

REFERENCES