

# GENETICS AND ANKYLOSING SPONDYLITIS SUSCEPTIBILITY: THE NEXT STEP—THE TASC STUDY

By Dr. John D. Reveille



One of the indisputable facts about ankylosing spondylitis (AS) is that hereditary factors play a critical role in its cause. We have known for many years that AS and the related conditions associated with spondyloarthritis (such as psoriasis, iritis or uveitis, and inflammatory bowel disease) occur more frequently in family members of AS patients than in the general population. For nearly 35 years we have known that one hereditary factor, HLA-B27, is extremely important in susceptibility. The significance

of HLA-B27 became even clearer with the development of the HLA-B27 transgenic rat in 1990, a model that continues to teach us about the immunology of this disease.

Genetic investigations in the 1990s were focused on finding susceptibility genes in families for many diseases such as diabetes, rheumatoid arthritis and lupus using a technique known as genome-wide scanning with DNA markers called microsatellites, which allowed an examination of the human genome much like mile markers on a superhighway. Accordingly, in 1998 the Spondylitis Association of America collaborated with Dr. John Reveille at the University of Texas Health Science Center at Houston to launch the AS Family Genetic Project. SAA's efforts led to the National Institute of Arthritis, Musculoskeletal and Skin Disease (NIAMS/NIH) providing funding for Dr. Reveille and the SAA to establish the North American Spondylitis Consortium (NASC), a collaboration between ten academic medical centers in the US and Canada aimed at collecting family data and performing genetic analyses in the susceptibility to AS.

During the period that NASC was funded, between 1999 and 2004, data from nearly 400 AS-affected sibling pairs was collected. A genome-wide association study was completed and published that identified, in addition to the major histocompatibility complex on chromosome 6, several other genetic regions on other chromosomes, whose importance was magnified when the NASC data was pooled with the data from the British and French scans. In addition, several candidate genes were examined, some not confirmed and some, such as interleukin 1, a cytokine that is very important in inflammation whose gene is found on chromosome 2, that have now been recognized as adding to HLA-B27 in the risk for AS.

Recent advances in genetic analysis have led to new approaches in unlocking the genome. Today, computerized chip technology has

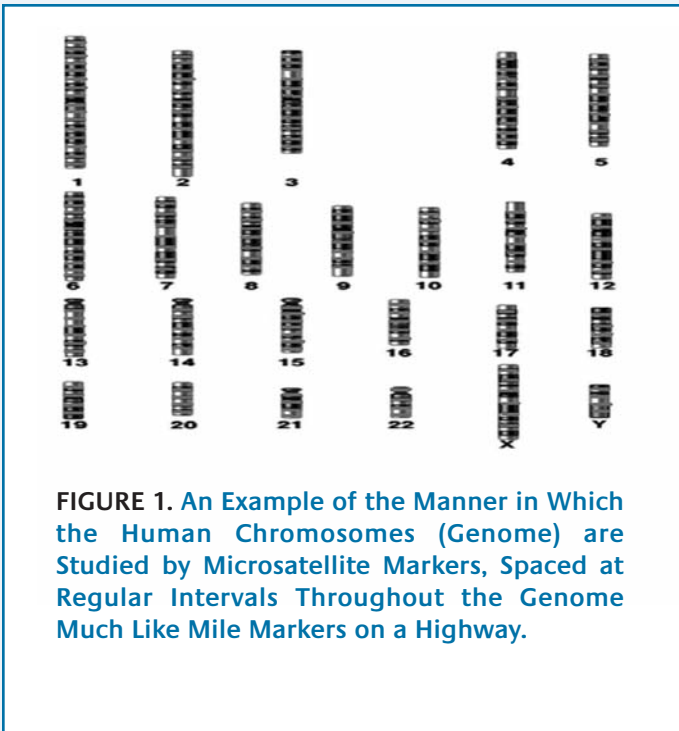
**Recent advances in genetic analysis have led to new approaches in unlocking the genome. Today, computerized chip technology has allowed dissection of the human genome not just with 400 markers, the limit of the previous microsatellite technology, but to up to 1,000,000 markers. The challenges presented by this approach include its expense (more than could normally be covered by an NIH grant) and that large numbers of patients (in the thousands) and healthy controls are required.**

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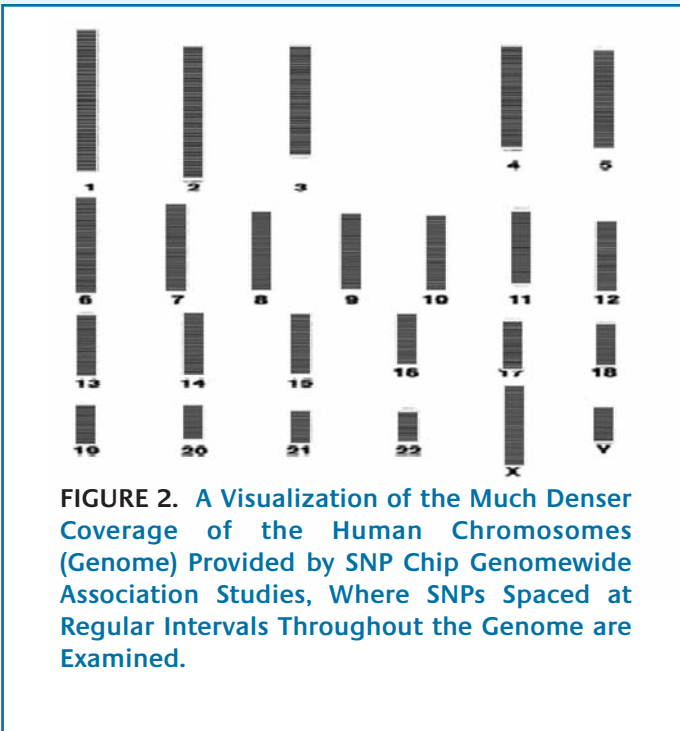
Recognizing that this new technology was necessary to achieve the cure, we have entered into a partnership that involves not only US investigators and the SAA, but also parallel efforts in the UK, with whom we have already established a working relationship in pooling data from our previous genome-wide scans. This new team transcends NASC and is called TASC (the Triple A--Australian-Anglo-American--Spondylitis Consortium), which has been funded for five years by NIAMS.

TASC is headed by myself and co-Principal Investigator, Dr. Matthew A. Brown, who has joint appointments at the Wellcome Trust at the University of Oxford and at the University of Queensland in Brisbane, Australia. The TASC Project consists of four projects, aided by two core facilities.

The first project will use SNP chip technology to study 317,000 single nucleotide polymorphisms (SNPs) scattered throughout the genome in 1,000 UK and 1,000 US AS patients compared to 3,000 UK controls (provided at no cost by the Wellcome Trust Case Control Consortium) and 1,000 US controls (provided by Dr. Peter Gregersen of North Shore Hospital, one of the external advisors to TASC). This scan is already nearly half done, and will be finished by early 2008. Genes found to be associated with AS in both the UK and US groups will be further studied in additional cohorts of 1,000 new UK AS patients and



**FIGURE 1. An Example of the Manner in Which the Human Chromosomes (Genome) are Studied by Microsatellite Markers, Spaced at Regular Intervals Throughout the Genome Much Like Mile Markers on a Highway.**



**FIGURE 2. A Visualization of the Much Denser Coverage of the Human Chromosomes (Genome) Provided by SNP Chip Genomewide Association Studies, Where SNPs Spaced at Regular Intervals Throughout the Genome are Examined.**

500 US AS patients (coming largely from the membership of SAA) who are being presently being enrolled. Project 1 will include Drs. Reveille and Brown, as well as Dr. Paul Wordsworth, representing the Wellcome Trust Case Control Consortium from Oxford, England.

Project 2 focuses on using the data from the SNP chips in Project 1 to examine genes impacting disease severity. Genes in a living person work in conjunction with and are affected by a variety of non-genetic factors, such as socioeconomic status, ethnicity, education, psychological and behavioral factors, personal habits such as smoking, drinking and exercise, and other medical problems such as obesity, high blood pressure and diabetes. Consequently, this project will examine both genetic factors and non-genetic factors and their impact on prognosis in AS, including radiographic severity, functioning, disability, and quality of life. This project will be overseen by Dr. Michael Weisman at Cedars-Sinai Medical Center, in conjunction with Drs. Reveille, Michael Ward from the NIAMS/NIH Clinical Center, Millicent Stone from the Bath Royal United Hospital, Dr. Perry Nicassio, a noted psychologist from UCLA, and Thomas Learch, a bone and joint radiologist from Cedars-Sinai. Overall, 900 patients from Cedars-Sinai, UT-Houston, the NIH and UCSF will be enrolled.

Project 3 focuses on the immediate family members of patients with AS and the spectrum of related diseases that occurs in them, including inflammatory back pain, arthritis, uveitis, inflammatory bowel disease and psoriasis, as well as defining the genes associated therewith. It is headed by Drs. Reveille, Weisman and Tammy Martin at Oregon Health and Science University.

Genetic and environmental factors don't work in a vacuum, but in

networks together. Previous statistical methods proved inadequate to account for these interactions, requiring the development of new statistical paradigms, which is the focus of project 4. The project will be headed by Dr. Momiao Xiong at the University of Texas at Houston, a statistical geneticist, in conjunction with Dr. Lon Cardon of Oxford University.

Overseeing TASC will be an Administrative Core, headed by Drs. Reveille and Brown, in conjunction with Laura Diekman, the TASC Program Manager, Omolade Ogun, SAA Research Coordinator and Laurie Savage, SAA Associate Executive Director, who will oversee the SAA's nationwide recruitment of patients and families. The genetic analyses and blood samples will be handled by the Laboratory Core, overseen by Drs. Xiaodong Zhou at UT-H and Dr. Matthew Brown at the University of Queensland.

TASC has already yielded some exciting new discoveries, which will be detailed in a subsequent issue of Spondylitis Plus, and the genome-wide association study will be complete by early next year. The genes we are identifying will need further characterization and validation in additional patients, and the SAA continues to play a critical role in this effort. SAA's partnerships with members of the research community have had success that few other advocacy organizations can claim. The TASC study will forever be a testimony to the generosity, hard work and commitment not only of the researchers, but also the SAA membership, who remain the community to which we are responsible. You have been critical contributors to this research, and we hope you will continue to partner with us in the very exciting work that lies ahead as the genetic basis of AS susceptibility and the determinants of prognosis and outcome are dissected.