

EDUCATIONAL FORUM International collaboration provides clues to genetic research

“A new and exciting day is dawning in AS.”

THESE WORDS WERE spoken recently by Dr. John Reveille presenting at the SAA Educational Forum in San Antonio, TX. Dr. Reveille, certainly, is fully cognizant of the progress since he has been working closely with the SAA for 7 years to advance research in AS.

As many of our readers already know, having participated directly in the AS Family Genetic Study, much already has been accomplished through the collaboration between the University of Texas, Houston, the Spondylitis Association and the National Institutes of Health. The study set out to identify families with sibling pairs who have AS in order to locate areas on chromosomes where genes causing the disease might be found. Another goal of the study has been to examine at least five candidate genes from these chromosomal areas. A “candidate” gene is one that is located in a chromosome region suspected of being involved in a specific disease. This has been accomplished.

International Efforts to Advance Research

Dr. Reveille went on to explain that the recently developed International Genetics of Ankylosing Spondylitis (IGAS) Consortium has already shown that the way to continue this exponential growth is to pool data internationally. The problem is that AS is caused by several genes acting together with HLA-B27. The effect of B27 is very large, but individually the effect of these other genes is small. Thus very large numbers of sibling pairs and families are required to identify these other candidate genes. One might ask



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that if each of these genes exerts only a small effect on the cause of AS, why should we bother? Well, because they could represent new treatments. Targeting HLA-B27 is not feasible, but these other genes might present targets for

treatment, such as cytokine genes, which make chemicals called cytokines that cause inflammation-TNF is an example of this. Recent analysis of internationally pooled data from the group spanning 5 years of intense effort has already shown significant advances in understanding not only the mechanisms involved in HLA-B27, but also in the smaller, lesser – to-date – observed genes which potentially could lead to a

better understanding of the disease and to the development of new treatments. This international collaborative group includes Dr. Reveille and Dr. Felix (Li) Jin from the U.S. and research groups from Oxford, U.K. and Paris, France.

Causes of AS


As a disease-triggering mechanism, there has been lots of speculation over the years that infection plays a part. To date, such an infectious trigger has not been found in AS. It has been recognized, though, that something in the intestines may be involved in this process. It is thought perhaps that AS starts when the defenses of the intestines start breaking down and bacteria from the intestines pass into the bloodstream directly into the region where the sacroiliac joints are located.

HLA-B27 plays a big part in the overall causation. But it is other genes that are active, too. As previously mentioned, some of these



Interest was high at the SAA Educational Forum held in San Antonio, Texas.

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are “small effect” genes that work in concert with each other. Now, these genes don’t just cause AS, they keep working in terms of how the disease manifests in the individual – for example, age of onset, severity, complications. It would be impractical to develop medicines against B27 – and researchers would not want to turn it off since it plays a very important role in our immune defenses. Each of the B molecules protects and interacts with the environment – particularly to

help against infections. Each B27 molecule seems to confer some resistance or protection against certain infections. For example, several studies published over the past 10-15 years have found that B27 carries a natural defense against the flu and HIV – which means that the immune system deals with the virus more efficiently. Therefore, it is important to recognize the various roles, both individually and in tandem, that these small effect genes play in the cause and

manifestation in AS. The hope is that they can be manipulated to improve outcome through better understanding of the disease and lead to improved, and hopefully lower-cost, medicines able to help a broader spectrum of people with AS.

What Counts?

AS is called a complex genetic disease, because more than one gene is involved. B27 probably accounts for about 40% of the overall risk. Researchers believe there are probably five or six genes involved in susceptibility toward AS since B27 has to be helped along. One thing that has become very clear to researchers both here and abroad, is that it takes very large collections of patients before researchers can reliably find out what the “small effect” genes do – that is compared to “big effect” genes such as B27. And that doing a study with a 100 patients is more likely to produce not only unreliable results, but actually false positives – false results. It is currently estimated that 500-600 patients and 500-600 unaffected people are needed in a study to really be able to pick out the kind of genes that are seen in diseases like AS.

Thus, it was critical that the current IGAS international analysis was able to pool data to form reliable and truthful results given the much higher number of patients involved as a direct result of the collaboration—nearly 600 sib-pairs. This is the future of research in ankylosing spondylitis, and we thank you and look forward to your continued participation and support.

The SAA extends a debt of gratitude toward Dr. Reveille for his ongoing support of its work.

For further reading on genetic advances in AS, please visit www.rheumatology.org abstract numbers 442, 575, 1132, 1133