FAST BREAKING PAPERS - 2008

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Robert M. Plenge talks with *ScienceWatch.com* and answers a few questions about this month's Fast Breaking Paper in the field of Molecular Biology & Genetics.

Article Title: Two independent alleles at 6q23 associated with risk of rheumatoid arthritis

Authors: Plenge, RM, *et al.*
Journal: NAT GENET
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(addresses have been truncated)

SW: Why do you think your paper is highly cited?

There may be four reasons. The first is that our study represents one of the first genome-wide association study (GWAS) in patients with rheumatoid arthritis (RA). The second is that two independent alleles at a single locus (6q23/TNFAIP3) were identified that contribute to risk of one disease, in this case, RA. This is an emerging theme in genetic studies. Third, we investigated technical and genetic biases that may be introduced into GWAS that use a common set of "shared controls." And fourth, this region is associated with other autoimmune diseases (notably systemic lupus erythematosus).

Also see: Robert R Graham, *et al.*, "Genetic variants near TNFAIP3 on 6q23 are associated with systemic lupus erythematosus," *Nature Genetics* 40(9): 1059-61, September, 2008.

Stacy L. Musone, *et al.*, "Multiple polymorphisms in the TNFAIP3 region are independently associated with systemic lupus erythematosus," *Nature Genetics* 40[9]: 1062-64, September, 2008.

SW: Does it describe a new discovery, methodology, or synthesis of knowledge?

One novel RA risk locus was identified as part of this study. In that sense, it represents a new discovery.

SW: Would you summarize the significance of your paper in layman's terms?

We do not understand the fundamental mechanisms that cause RA. Genetics offers one approach to understanding which biological pathways are involved in disease risk. Our study tested approximately 30% of common genetic variation in the human genome, and found one locus (two different genetic variants) that contributes to risk of disease. Both variants are near a biological candidate gene, TNFAIP3, which is involved in TNF signaling —and important inflammatory cytokine in RA.

SW: How did you become involved in this research, and were there any problems along the way?

"We still cannot explain the entire genetic burden of RA."

I had an interest in studying rheumatoid arthritis specifically because, as a practicing rheumatologist, I see patients with this disease. I quickly came to learn that, for many patients with RA, the disease can be quite disabling.

I became involved in this research because of opportunities created by others—clinical researchers who had collected thousands of RA patients and controls, and geneticists who established technological and statistical advances to study 100,000 SNPs (single nucleotide polymorphisms) across the genome. Without the efforts of many people before me, our study would not have been possible.

There were challenges encountered while conducting our study. The most substantial challenge was that we used first-generation genotyping technology (Affymetrix 100K array) and calling algorithm (DM), which we now know are fraught with biases. We had to overcome these biases to convince ourselves that the signal we observed was a true positive association.

SW: Where do you see your research leading in the future?

There are three important avenues of research:

1. We still cannot explain the entire genetic burden of RA. More RA risk genes need to be identified.
2. We don't understand how these gene variants predispose RA. Functional biological studies need to be done.
3. We don't understand how these discoveries will be translated to patients. Clinical outcome studies for relevant phenotypes (e.g., response to treatment) need to be done.

SW: Do you foresee any social or political implications for your research?

As with all genetic studies, there are social and political implications.

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Keywords: rheumatoid arthritis, genome-wide association study, two independent alleles at a single locus, autoimmune diseases, systemic lupus erythematosus, single nucleotide polymorphisms.

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