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UAB, Huntsville scientists look to unlock rheumatoid arthritis clues

By Jeff Hansen -- The Birmingham News

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The University of Alabama at Birmingham will lead a five-year, $4.4 million effort to search for genetic links to rheumatoid arthritis in African-Americans.

Dr. S. Louis Bridges Jr., head of clinical immunology and rheumatology at UAB, and Gwendolyn Johnson, a longtime rheumatoid arthritis patient, share a desire to find ways to better diagnose and treat the debilitating illness. (The Birmingham News/Beverly Taylor)

This study will use the power of research called genomics to search for genetic needles in a haystack. Although they're focusing on African-Americans, what the researchers learn could aid all sufferers from rheumatoid arthritis, they say.

UAB's Dr. S. Louis Bridges Jr. and colleagues have the largest collection of blood samples from African-Americans with rheumatoid arthritis in the nation through a National Institutes of Health-sponsored registry. From the blood, scientists can extract DNA, the starting material for the gene hunt.

A major partner in the study is the HudsonAlpha Institute for Biotechnology in Huntsville, headed by Dr. Richard Myers, formerly of Stanford University. Myers has identified genes involved in several inherited diseases, and his genome center contributed about 11 percent of the DNA sequence for the Human Genome project.

Why look for genetic links to a disease?

If you can find them, said Bridges and HudsonAlpha faculty investigator Devin Absher, you can identify genes that maybe involved in causing the disease, or that may protect against the disease. Basic research into these genes can help show how the disease works, and may lead to information to aid diagnosis or treatment. In other words, they are clues that can help solve the mystery of a debilitating illness.

About 30 percent of the risk of getting rheumatoid arthritis is genetic, Bridges said. Previous genome studies with Europeans and Asians have found about 20 to 25 genes involved in the genetic risk.

Bridges expects to find some differences in African-Americans, compared to the other two groups.

His study begins with a simple question: "Are you African-American?" Only those who say yes are included.

Since African-Americans have about 5 to 15 percent European genes, the UAB study will also include some ancestry genetic markers.

The entire study will search through separate DNA samples from 1,600 African-Americans with rheumatoid arthritis and 1,600 African-Americans who don't have the disease. That latter group serves as the "control" in the gene hunt.

Since people get two copies of each gene, one from their mother and one from their father, the hunt has to look at each pair of genes in the human DNA, known as minor and major alleles.

"What we look for is a minor allele with a large difference in between controls and patients," Bridges said. "If you found that, you would have a possible new genetic risk factor associated with rheumatoid arthritis, possibly specific to African-Americans."

The steps of the research show the amazing complexity -- and potential power -- of this kind of genetic hunt.

For every single person in the study, Myers and Absher will search about one million places on the genome, checking which alleles they have. Alleles are distinguished by a difference in a single base of DNA, a marker spot nicknamed a "snip" for SNP, or "single nucleotide polymorphism."

SNPs are identified on a microarray, similar in size to a 1-inch-by-3-inch microscope slide. Each array has millions of tiny glass beads with different SNP DNAs attached. Each SNP is able to bind with single-strand copies of a patient's DNA.

Since the 1 million SNPs are each tested about 15 times, the array actually has about 15 million beads on each slide, Absher said. The extremely expensive microarrays are built using some of the technology used in electronic chip manufacturing.

Through a series of chemical tricks, minor and major alleles will show up as different glowing colors -- red and green -- when the three-day automated steps of the DNA binding are finished. If a patient has one minor and one major allele, the spot will glow yellow.

Each microarray is scanned by a machine, and computers analyze the results, looking for sites that differ between rheumatoid arthritis patients and the controls.

But the SNP is not a gene -- it's merely a mapping marker along the DNA. The gene or genes in question may be nearby, and that will involve a further hunt.

The gene hunt will have two phases.

The first microarrays will be used to analyze 800 patients and 800 controls. This filters out the vast majority of DNA sites that have no relation to rheumatoid arthritis.

Then, Absher said, the most promising 16,000 to 20,000 SNPs identified in the first hunt will be retested with DNA from an additional 800 patients and 800 controls. Scientists will also look for differences among rheumatoid arthritis patients who have bone erosion at their joints and those who don't, and those who suffer a loss of bone density and those who don't.

At the end of this testing, 1 million possible sites may be reduced to just 10 to 15 that truly have a relationship to rheumatoid arthritis.

At that point, the hunt for particular genes can begin.

Bridges' search for genetic links to rheumatoid arthritis is just the second funded grant that involves collaboration between HudsonAlpha and UAB, but there are also about six to 10 pilot collaborations going on.

"There's a new project proposed every few weeks," Absher said. "Our connections with UAB are pretty strong, and are getting stronger."