Lack of 'Trio' Families Thwarts RA Gene Studies

BY TIMOTHY F. KIRN
Sacramento Bureau

SNOWMASS, COLO. — Only the absence of "trio" families prevents major breakthroughs in finding genetic mutations for rheumatoid arthritis, even using the present technology, said Dr. Peter K. Gregersen at a symposium sponsored by the American College of Rheumatology.

Trio families, consisting of the patient and both parents, "are very hard to find, because RA is a late-onset disease," explained Dr. Gregersen, the principal investigator of the North American Rheumatoid Arthritis Consortium, the world's largest effort to identify the genes associated with the development of rheumatoid arthritis. "But [studying trio families] is an extremely powerful way of doing association mapping."

In searching for genes associated with complex diseases such as rheumatoid arthritis, the approach is to survey the entire genome of many individuals and their siblings with single nucleotide polymorphism markers (SNPs) to find regions of the DNA where particular SNPs are shared more frequently among affected siblings than nonaffected siblings.

This process requires enormous numbers of individuals, especially since rates of RA vary among different populations. Dr. Gergersen's consortium currently has about 1,000 sibling pairs, representing almost 800 families and 200 trio families. It has taken a few years to recruit them, and he estimates that they will need "several thousand," said Dr. Gregersen, of North Shore University Hospital, Manhasset, N.Y.

Once the shared SNPs are found, the researchers can plot those SNP regions on the human genome map to try to identify likely candidate genes and refine the search.

A gene found by Dr. Gregersen's group with this method is the *PTPN22* allele. The gene encodes a tyrosine phosphatase inhibitory to T cells, and it appears also to be involved in Graves' disease, systemic lupus, and type 1 diabetes.

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Just in the last couple of years, the technology for this kind of work has all come together: the human genome map, the catalog of SNPs, and a fiber-optic technology for rapidly sorting through SNPs. And the cost of genotyping has dropped dramatically, from about $1 per SNP to "a couple of pennies," Dr. Gregersen said.

But much more work needs to be done to hunt out other candidate genes. Neither the *HLA-DRB1* allele, identified back in the 1970s, nor the *PTPN22* allele accounts for all of the relative risk for rheumatoid arthritis, which has a heritability of about 60%.

The *PTPN22* polymorphism is found in 28% of rheumatoid arthritis patients, versus 17% of the general population.

More than 300 other possible candidate gene regions have been identified already, and others probably exist.

But the sheer volume of the material that needs to be sorted through for this work means that even when the probability of chance associations is extremely low, they will occur often, Dr. Gregersen said.

The use of trio families, where the genotype of an affected individual can be compared with a parent who would have transferred the DNA of interest with the parent who did not, can greatly speed and improve the process.

The work will also elucidate the pharmacogenetics of response to arthritis drugs, an area of research about which there has been a lot of talk, but not much clinical translation so far, Dr. Gregersen said.

Physicians who have an adult patient with a confirmed diagnosis of RA, two living parents, and an interest in participating should have the patient call 800-382-4827.

The rheumatologists who assist are compensated $150 for their time for each patient. They need to confirm the subject's RA diagnosis on a checklist, and draw a blood specimen for overnight delivery. They will also be paid an additional $50 for each blood sample they draw from a parent. For parents not local to the rheumatologist, a phlebotomy service is available, arranged and paid for by the consortium. ■