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EMBARGOED for release until 8:30 a.m. Pacific Standard Time on Friday, Feb. 14, to correspond with presentation at the annual meeting of the American Association for the Advancement of Science (AAAS), held in Seattle at the Washington State Convention and Trade Center and the Sheraton Seattle Hotel.

Editors, reporters, please note: This release was adapted from one distributed in October 1996 at the annual meeting of the American Society of Human Genetics.

GUILT BY ASSOCIATION: NAILING CULPRIT GENES

STANFORD – A relatively unused technique for finding common disease-predisposing genes should ultimately surpass the approaches currently in vogue, according to a statistical study by Neil Risch, professor of genetics at Stanford University School of Medicine.

This method – called association analysis – will be especially useful in understanding the genetic basis of complex disorders, in a particular gene increases disease risk only moderately or else mutiple genetic factors are involved.

"Using this technique, it should be feasible in the next decade to test each of the estimated 100,000 human genes for possible links with every disease," Risch said.

Risch will present his findings on Friday, Feb. 14, at the morning session (8:30 to 11:30 a.m.), "Complex Traits: Where Are the Genes?" at the annual meeting of the American Association for the Advancement of Science, held in Seattle.

In the study, he created mathematical models to compare association analysis with linkage analysis – the method used to map most genes until now. Risch compared the number of people who would have to be studied by each method in order to identify disease genes with varying properties. "The data showed that linkage analysis requires sampling far more people to generate the same amount of information," he said.

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Scientists have used linkage analysis to find genes for many disorders, including Huntington's disease and Alzheimer's disease. This approach, which is part of a process called "positional cloning," identifies disease genes by their chromosomal location, gradually zeroing in on them among their neighbors in the genome. Researchers compare the co-inheritance of known landmarks, or genetic markers, in the genome with the disease state of family members. They locate the disease gene by finding the markers closest to it – those most highly correlated with inheritance of the disease.

"The nice thing about linkage analysis is that you can find genes involved in disease by using only a limited number of genetic markers along the various chromosomes," said Risch. "Even if you're some distance away, you still detect a signal that's strong enough to see where the gene resides. With association studies, you could be at the gene next door and still have no signal."

But the problem with linkage analysis is that it depends on having that strong signal, which occurs only if the gene is the predominant cause of disease, Risch explained. "If the gene is one of many factors that lead to the disease, the signal won't be loud enough to detect, even if you're very close," he said.

Association tests are more powerful in such cases because they give clear-cut answers to specific questions, Risch explained. Scientists ask directly whether affected individuals have a certain characteristic, and get a yes or no answer. They find out whether there are relative differences in the frequency of a particular genetic variant, or allele, in people with and without disease.

"This approach gives a loud signal," said Risch. "It's much more powerful. You get more information than by trying to find some attribute that is shared by affected individuals. A limitation of association studies, however, is that you need to be on top of or very close to the implicated gene to have a signal."

Association studies have already been done when researchers have had an idea of what causes a particular condition. For instance, earlier this year scientists in New York used this approach to find a mutation that decreases a person's risk of HIV infection. They knew that a certain protein interacts with the cellular molecule that allows HIV to enter the T cells of the immune system. So they looked at the gene for this cofactor in different people and found something startling.

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"What they saw was that a piece was missing from this particular gene in some people," Risch said. "Individuals who have two copies of this defective gene – and as a result lack the cellular protein it encodes – are resistant to HIV infection."

In this case, the mutation is beneficial. But the same approach can be used to detect genes that cause disease: Researchers can ask whether there is an association between a particular genetic variant and disease.

"The HIV story is a case in which one gene predisposes people to resistance," said Dr. David Cox, professor of genetics and co-director of the Stanford Human Genome Center. "But the same approach can be used for conditions with multifactorial causes. In these cases, certain combinations of genes predispose people to disease. The question is which genes differ between normal and diseased populations. That's how you figure out which alleles and patterns of alleles are associated with disease."

"The key to this method is that you need a candidate gene," Risch said. "Instead of gradually getting closer to the disease gene, you ask, 'Is this it?' "

Although linkage analysis has succeeded in identifying genes with a strong influence on disease, "there are a lot more genes with small effects on disease, and those are what we're turning to now," he explained.

The genetic variations that cause complex diseases are widespread. "These variations are very common, and they've been in the human population for a long time," said Richard Myers, professor of genetics and director of the Stanford Human Genome Center. "They probably contribute to common diseases like autoimmune disease, psychiatric disease and cancer, which often are not thought of as being genetic. Getting these diseases probably requires the inheritance of multiple genes and some interactions with the environment as well."

"The main limitation to association analysis is identifying candidate genes," Risch said. "But with information from the [international] Human Genome Project, we could test all genes that often vary within a population. The Genome Project will have an enormous impact on mapping disease genes by association studies because it will identify many, if not all, variants."

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Myers agrees. "The Human Genome Project has released people from standard ways of thinking and doing things by stimulating technology," he said. "The development of high-throughput, accurate and cheaper ways to manipulate and analyze DNA has had a profound effect. We can generate orders of magnitude more results and information at far less expense. The standard approach was to figure out what was possible. But the Genome Project has expanded people's imaginations, allowing them to think on a grand scale, asking and answering questions they would never have dreamed of before.

"It is likely that within a few years we'll be able to find all of the common variants, and maybe some of the rare ones as well," Myers said.

Testing every genetic variant for possible associations with complex diseases is a daunting prospect, given that every human chromosome carries some 100,000 genes. "The technological difficulty of so many tests would be a serious problem in linkage studies, where you have to test everyone individually," said Risch. "But in an association study, we can throw everyone's DNA into one of two pots. Put all of the affected individuals into a soup together, and all of the unaffected controls into a different soup. The gene that is causing a particular disease will have a different frequency in each of those two pots."

2/10/97 –rs– AAASRisch