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Future of Disease Gene-Hunting Studies Questioned

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WHEELING, W.Va., April 16 -- Disagreements within the medical community on the utility -- or futility, as some see it -- of genome-wide association studies reached a new prominence this week.

Four "Perspective" articles in the April 16 issue of the *New England Journal of Medicine* hashed out the pros and cons of whether these expensive genomic studies continue to be worth pursuing.

Even the defenders of such studies do not dispute that, thus far, they have failed to realize early promises that genomics would revolutionize clinical medicine.

When focused on common chronic disorders such as type 2 diabetes or cardiovascular disease, these studies have uncovered a vast array of genomic variations associated with disease.

But these variants confer relatively modest increases in risk and are found in only small portions of the population. Most of the incidence of chronic diseases still cannot be attributed to genetics.

"The great majority of the newly identified risk-marker alleles confer very small relative risks, ranging from 1.1 to 1.5," wrote two Harvard School of Public Health researchers, Peter Kraft, Ph.D., and David J. Hunter, M.B., Sc.D, M.P.H., in one of the *NEJM* articles.

Although Drs. Kraft and Hunter argued that genome-wide association studies remain valuable, they acknowledged that those discovered to date do not have much diagnostic utility, even when combined.

David B. Goldstein, Ph.D., of Duke University, argued forcefully that the research community would do better to focus its efforts elsewhere.

He suggested that if there were any common gene variants responsible in a major way for chronic diseases, they would have been found already.

"I assume that all SNPs [single nucleotide polymorphisms, one-base variations in the genome] yet to be discovered have weaker effect sizes than the weakest so far found," he said.

Dr. Goldstein said future genome-wide studies would likely identify an increasingly broad array of SNPs with decreasing associations with any given trait or disease.

One outcome, he said, would be that most genes would end up labeled as "height genes" or "type 2 diabetes genes."

To the extent that common chronic diseases are under genetic control, he said, it is more likely that rare but powerful mutations are responsible.

"Either way, it's hard to have any enthusiasm for conducting genome scans with the use of ever larger cohorts after a study of the first several thousand subjects has identified the strongest determinants among common variants," Dr. Goldstein said.

But two other Perspective articles argued against abandoning such studies now.

Joel N. Hirschhorn, M.D., Ph.D., of Harvard and MIT, disagreed with Dr. Goldstein's contention that large numbers of weakly-associated SNPs were useless in understanding chronic diseases.

He noted that, in several diseases, genomic loci identified in genome-wide studies have pointed to a relatively small number of biologic pathways.

"The genetic variants that are associated with age-related macular degeneration strongly implicate components of the complement system," Dr. Hirschhorn wrote. "Loci associated with Crohn's disease point unambiguously to autophagy and interleukin-23-related pathways. . . . This clustering into biologic pathways is highly nonrandom."

A similar point was asserted by John Hardy, Ph.D., of University College London, and Andrew Singleton, Ph.D., of the Laboratory of Neurogenetics in Bethesda, Md.

"As a risk allele at a genetic locus comes into focus, it provides clues to other risk loci and mechanisms by which variability at the same locus or on the same pathway can contribute to disease," they wrote.

They also suggested that ongoing projects such as the HapMap haplotype database collaboration may allow more information to be extracted from genome-wide association studies.

Wrote Dr. Hirschhorn, "I predict that by the 2012 American Society of Human Genetics meeting, genome-wide association studies will have yielded important new biologic insights for at least four common diseases or polygenic traits -- and that efforts to develop new and improved treatments and preventive measures on the basis of these insights will be well under way."

Dr. Hirschhorn reported relationships with Correlagen, Ipsen, Pfizer, and Novartis. Other authors reported no potential conflicts of interest.

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