Genome-Wide Association Studies Provoke Debate and a New Look at Strategy

By Rabiya S. Tuma

Genomewide association studies (GWAS), which began with hopes of quickly uncovering the genetic underpinnings of disease and personalizing treatment and risk prediction, are now the subject of debate in both academic journals and the general media.

GWAS use microarrays to scan thousands of tissue samples from patients with a particular disease and compare the results with samples from healthy individuals, the goal being to find common genetic variations associated with the disease. The problem is that the results so far have not lived up to the promise. Critics point out that although hundreds of single-nucleotide polymorphisms (SNPs) have been found to be associated with one or another disease, the magnitude of risk associated with a SNP is small in most cases. Finding them has not led to rapid drug development or a meaningful improvement in the ability to predict risk. And critics contend that continuing to spend vast amounts of money on these studies is not likely to change that picture, which reflects the genetics and biology of complex diseases.

GWAS defenders acknowledge that the approach was initially oversold with promises that it would personalize medicine in
the near future, but they insist that genomewide association studies are providing valuable information about biological pathways involved in diseases, including cancer. The key to evaluating the approach, they say, is using a narrower lens and asking about its value in specific contexts—and recognizing that much work remains.

There are three main reasons to do these studies, according to Stephen J. Chanock, M.D., chief of the translational genomics laboratory at the National Cancer Institute in Bethesda, Md. The first is discovery of regions that were not previously known to be associated with a disease or human trait; the second is predicting outcomes or response to therapy; and the third is direct-to-consumer clinical and public health applications.

“Domain one has been wildly successful,” Chanock continued. “In domain two, we are starting to scratch the surface. Domain three is where people like myself are extremely worried about the overly-aggressive marketing or pushing of these tests, without all of the rigor we would expect. These tests could be transformative but they are not there yet.”

Looking only at Chanock’s first domain, identifying new loci associated with disease, John P. Ioannidis, M.D., Ph.D., comes to a similar conclusion. “I think we have been pretty successful actually,” said Ioannidis, who leads genetic epidemiology research at Tuft University’s Center for Genetic Epidemiology and Modeling in Boston and the University of Ioannina School of Medicine in Greece. That is, GWAS studies have probably been more successful than earlier genetic epidemiology studies “when almost everything that was being discovered could not be replicated in subsequent studies,” he said. Ioannidis estimated that GWAS studies have identified about 400 high-quality associations with complex diseases, including up to 100 with cancer. These associations tend to have stronger statistical support than other kinds of genetic epidemiology studies, he said.

Data from genomewide association studies may also provide insight into the etiology of diseases that have been otherwise impene-
Not everyone, however, is convinced that the prediction problem will be so easily overcome. Ioannidis points out that accumulating many small-effect variants may allow scientists to predict individual risk for those people whose genome carries lots of “bad” variants and thus are at one end of the risk spectrum or whose genome carries lots of “good” variants and are at the other as the end. But that approach is unlikely to do much for most people who fall in between those extremes.

As for the likelihood of finding rare alleles that individually account for a larger proportion of total risk, Ioannidis agrees that the possibility exists, but that it is unclear how many of these will be found. “It may be that some interesting stuff is hiding in the more rare variability, but this is more of a speculation now than knowledge,” he said. “What we do know is that when we try to expand coverage to more rare variants or other types of variability, such as copy number or structural variants, it is going to be even more difficult in terms of statistical approaches to get the same level of robust support as we get for the common variants that we have targeted today.”

Even if the variants can be found that account for a substantial proportion of risk, researchers will need to test their predictive value in prospective clinical trials before they can be used in the clinic regularly. And that raises another challenge in Chanock’s view. Many of the high-quality studies and associated tissue collections that have been assembled over the past 20 years have already been used in genome-wide association studies. In breast and prostate cancer, for example, he estimates that 75% of the high-quality sample collections have already been used in these studies. That means few collections are available for replicating initial observations or learning how best to use them clinically.

“What we need looking forward are studies that will let us follow up and refine the observations, to get us to the endpoints to be able to say, ‘Yes, these are the single nucleotide polymorphisms in breast cancer that are really important when considering whether a 40 year old woman should go to every-2-year mammograms or every year, or whatever,’” Chanock said.

Now that the day-to-day realities of research have eclipsed some of the initial hyperbole about genomewide association studies, all of the experts interviewed agree that the next steps are not going to be entirely straightforward. “We still have to exploit the maximal utility of this technology,” Ioannidis said. “But I think we can say this is not really easy ...it is going to be one step at a time.”

And though the discovery of particular associations may still make headlines, Houlston emphasized that they are only the start. “Genome-wide association studies are a means to an end, not an end in themselves,” he said. “That is the point.”

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