OncoArray Links Dozens of DNA Variants to Risk for Common Cancers

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Over the last decade, genome-wide association studies (GWAS) have begun to identify common inherited genetic differences, or variants, that influence disease risk. Now, researchers with the NCI-supported GAME-ON initiative and OncoArray Network are on their way to completing the latest round of cutting-edge studies of inherited risk factors.

These researchers have recently published studies identifying dozens of new genetic variants associated with the risk for developing cancer.

A recent study published in Nature Genetics, for example, found 10 new variants associated with lung cancer, and studies published in Nature and Nature Genetics found 72 new variants associated with breast cancer.

In the case of breast cancer, 10 of the risk variants are associated specifically with the risk of developing estrogen receptor-negative disease, which tends to have a poor prognosis and for which few genetic influences were previously known.

The latest results to come out of the OncoArray Network, published June 11 in Nature Genetics, identified 63 additional genetic variants associated with risk for prostate cancer.

The GAME-ON, or Genetic Associations and Mechanisms in Oncology, initiative was funded by NCI beginning in 2010 to provide a comprehensive look at genetic variants that influence the risk for five common types of cancer and then investigate the underlying biology of how those variants contribute to risk.

The OncoArray Network was formed by scientists from the GAME-ON initiative and other disease-based consortia to develop a new, more useful custom genotyping array. This new array was used to test for DNA variants across hundreds of thousands of people and several different cancer types.

The types of common variants identified each have a small effect and “are not necessary or sufficient” on their own to cause cancer, said Stephen Chanock, MD, director of NCI’s Division of Cancer Epidemiology and Genetics. They “contribute to the complexity of cancer,” Chanock said.

Ultimately, the aim of GAME-ON was to help researchers better understand the biological causes of

the cancers being studied and how multiple risk factors, each with a small effect, stack up to make some people more likely to develop cancer.

With this information in hand, researchers may, for example, be able to identify specific groups of people who might benefit most from earlier screening for a given cancer or who might safely put off screening for a few years, said Stefanie Nelson, PhD, a program director in NCI's Division of Cancer Control and Population Sciences, who administers GAME-ON grants.

Screening for cancer is "not easy," she said. "If we can help clinicians shift their focus to those most at risk, that would be really helpful."

Strength in Numbers

A spur for GAME-ON was to try to develop promising leads obtained from the first wave of GWAS, which are used to identify DNA variants that are associated with risk of a disease. Starting just over a decade ago, Chanock and other researchers began to use GWAS to link DNA variants located throughout the genome to cancer risk.

GWAS studies reveal markers—signposts that highlight a region of the genome as potentially important for disease risk. The next step is to painstakingly map and explore those regions, trying to pinpoint the actual DNA variations that may trigger cells to evade normal checks on growth and become cancer.

Before GWAS came along, geneticists typically tried to work out how genetics influences cancer risk by looking for altered genes in families with an unusually high rate of cancer. In contrast, GWAS research derives its strength from numbers—testing DNA from huge numbers of unrelated people both with and without cancer.

GAME-ON and its spin-off project, the OncoArray Network, brought together genetic and detailed clinical information from hundreds of thousands of patients to try to locate the changes in DNA that contribute to the development of cancer—a process that occurs over years—and analyze the interplay between genetics and factors such as weight, height, tobacco use, alcohol consumption, vitamin D levels, and hormone use.

GAME-ON and OncoArray collaborators hail from around the world and from many disciplines—including epidemiology, statistics, genetics, and molecular biology. They conduct research at more than 350 institutions in 60 countries and have published more than 400 scientific articles, including some of the largest genetic association studies of cancer.

Economies of Scale

Working with network researchers, the company Illumina produced a customized DNA microarray for the OncoArray project. The array includes more than half a million variants across the genome.

Some variants were chosen because researchers already had reason to believe they might be linked to cancer, while others were distributed evenly throughout the genome to allow for the

discovery of new regions associated with cancer risk. Researchers in the network were able to use the array for only $40 a sample.

OncoArray was a huge project taking years and a great deal of coordination, said Christopher Amos, PhD, a biomedical data scientist at the Baylor College of Medicine and Dartmouth College.

“The cost was exceptionally low. That was part of the impetus,” Amos said.

By forming such a large collaboration, the OncoArray Network was able to develop a high-density microarray manufactured for a price that allowed for large-scale study. The initial plan for the network was to test 410,000 people for over 500,000 markers, but the number of people tested with the array has surpassed that goal.

Studies reporting OncoArray findings began to be published last summer and will continue to be published over the next few years.

The chip is a “phenomenal resource that can be used to study all kinds of cancers,” Amos said. Genetic epidemiologists and any researchers “who want to investigate the biology of cancer risk” could use the array, Nelson said. Researchers could also use the chip to see how much cancers in different tissues overlap genetically.

Amos points out that the OncoArray Network drove technology development in an additional way; the project’s large number of samples prompted Illumina to create a new microarray format that can test twice as many DNA samples at a time compared with the previous format—24 instead of 12.

Dozens of research groups contributed DNA to be genotyped using the OncoArray chip, which was crucial to detect rarer variants. For lung cancer alone, researchers from 30 different projects contributed patient DNA, Amos noted. The DNA was tested at eight genotyping centers, and the data from the genotyping centers were pooled and analyzed at three central sites—the University of Southern California, Dartmouth, and Cambridge University.

In accordance with a tradition of open sharing of data among genomic researchers, all network participants have agreed to deposit research results into NIH’s Database of Genotypes and Phenotypes to allow for public access to the data.

Next Steps

The GAME-ON and OncoArray studies have been “sort of a treasure hunt,” Nelson said. They have linked dozens of variants for the first time to the risk for developing cancer, shining a spotlight on regions of the human genome that had never before been linked to cancer risk.

The new risk variants found by the GAME-ON and OncoArray Network scientists are located throughout the genome. The variants are not clustered together, and few of them are within genes. Instead, almost all of them are within sites of the genome that appear to be important for controlling the activity of genes, Chanock said.

Variants found through GWAS together can account for a little less than half of the familial risk for breast cancer, Chanock said. When rare mutations are added to the mix, it may now be possible to explain as much as two-thirds of a woman's familial risk for breast cancer.

Much remains to be understood about the newly identified variants that have been linked to risk for different cancer types, Chanock cautioned, noting that researchers can explain the function of only about 5 percent of the regions.

While biologists try to understand how specific variants influence cancer risk, epidemiologists are using the results from GAME-ON and the OncoArray studies to develop models that predict cancer risk in individuals and are starting to test those predictions in large group studies.

The outlook seems particularly promising for estimating the risk for prostate and breast cancer. Trials are evaluating whether genetic profiles can help improve screening for these cancers.

A study in the United Kingdom, for example, is evaluating the use of genetic risk profiles to decide who should be screened for prostate cancer and to interpret screening results. As part of another large study, researchers are assessing whether genetic profiling can help improve breast cancer screening, Amos noted.

Chanock calls these kinds of studies an effort at "precision prevention." The goal, he said, is less overtreatment and more successful intervention, possibly when the disease is still precancerous.

"This GWAS age is very exciting," said Chanock. But, echoing Winston Churchill, he said, "The most we can say is that it's the end of the beginning, not the beginning of the end. We have a long way to go."

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