Scientists find that chromosomal abnormalities are associated with aging and cancer

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(Medical Xpress) -- Two new studies have found that large structural abnormalities in chromosomes, some of which have been associated with increased risk of cancer, can be detected in a small fraction of people without a prior history of cancer. The studies found that these alterations in chromosomes appear to increase with age, particularly after the age of 50, and may be associated with an increased risk for cancer. These studies were conducted by two consortia, one led by scientists at the National Cancer Institute (NCI), and one by Gene Environment Association Studies (GENEVA) which is sponsored by the National Human Genome Research Institute (NHGRI). NCI and NHGRI are both parts of the National Institutes of Health. The results of the studies were published online May 6, 2012, in *Nature Genetics*.

Mosaicism, the type of structural abnormality in chromosomes that is described in these studies, results from a DNA alteration that is present in some of the body's cells but not in others. A person with mosaicism has a mixture of normal and mutated cells.

“These two studies provide large population-based evidence that genetic mosaicism increases with age and could be a risk factor for cancer. This last point raises an important issue with respect to the stability of a person's genome and suggests that detection of genetic mosaicism could be an early marker for detecting cancer, or perhaps other chronic diseases,” said Stephen Chanock, M.D., co-author and chief, Laboratory

of Translational Genomics, Division of Cancer Epidemiology and Genetics, NCI.

Scientists began observing an unexpected frequency of structural abnormalities in chromosomes during quality control checks of data from genome-wide association studies (GWAS) conducted in the GENEVA consortium and similar programs at NCI. These studies involve comparing hundreds of thousands of common differences across individual patients' DNA to see if any of those variants are associated with a known trait, such as cancer. At first, these abnormalities were thought to be errors or outcomes of laboratory procedures. But they were found consistently at a low frequency, so the scientists wondered with what frequency these structural abnormalities occurred in the general population.

Previously, NCI investigators had reported that genetic mosaicism was observed in a population-based study in Spain. Since there were no accurate estimates of the frequency of mosaicism in the general population, NCI investigators looked at large mosaic chromosomal abnormalities in 31,717 cancer cases and 26,136 cancer-free controls from 13 GWAS. Similar analyses were conducted by investigators at the University of Washington, Seattle, collaborating with NHGRI and NCI investigators in the GENEVA consortium. The 16 GENEVA studies included participants of all ages and have been focused on several different chronic diseases, but only a small proportion of these studies focused on cancer as the primary outcome.

The NCI-led study observed that genetic mosaic abnormalities were more frequent in individuals with solid tumors (0.97 percent vs. 0.74 percent in cancer-free individuals). The NCI study also observed mosaic chromosomal abnormalities in slightly less than 1 percent of the study participants, but noted that the frequency of detectable genetic mosaicism increased with age. This was consistent with GENEVA

results that found genetic mosaicism increased in those over the age of 50.

The GENEVA investigators studied blood samples of over 50,000 participants and identified genetic mosaicism abnormalities in 404 of the participants, most of who were over age 50. They found genetic mosaicism abnormalities in 0.2 percent of people younger than age 30. From age 30 to age 50, mosaicism frequency rose; it increased sharply over age 60, with up to a 2.5 percent frequency above age 75. Past analyses suggest that mosaic abnormalities are often detectable in later life because they arise and accumulate over time and/or because the descendants of mosaic cells expand in numbers throughout the body and are more readily detected at older ages, the scientists say.

“Repeated collection of blood samples may play a major role in helping determine how genetic mosaicism rises quickly at older ages. This is supported by observation of our only GENEVA subject who was sampled twice — once at age 66 and again at age 72. While no mosaic abnormalities where detected in the earlier sample, the later sample contained five mosaic abnormalities, each on a different chromosome,” said Teri Manolio, M.D., Ph.D., director, Office of Population Genomics, NHGRI.

In both studies, scientists observed an increase in the detection of genetic mosaicism in patients with hematological cancers (leukemia, lymphoma, and myeloma), for which DNA was collected at least one year prior to diagnosis, compared to cancer-free individuals. Results from the NCI study showed that risk of leukemia was also substantially higher among people with these chromosomal alterations while the GENEVA study showed that the risk of acquiring a hematological cancer diagnosis was 10 times higher for people who had mosaic chromosomal abnormalities. The results of both studies suggest that mosaicism, observed in older people, may be an asymptomatic condition — not often causing overt

illness — that may predispose them to hematological cancer. However, GENEVA and NCI scientists stress that the event numbers analyzed are small, and additional studies are needed across a broader diversity of populations to establish the clinical significance of these findings.

NIH scientists say these findings will have important implications for the design and analysis of molecular studies of cancer, as well as ongoing studies looking at the characterization of cancer genomes, such as NIH's The Cancer Genome Atlas and the International Cancer Genome Consortium.

NIH scientists recommended that additional analyses be conducted in groups of currently healthy people so that investigators may follow them over time for health outcomes. They also said that researchers may want to collect multiple DNA samples over many years to explore disease and treatment effects. Additional studies with subjects, sampled at multiple ages, will be invaluable in the evaluation of the origin and stability of mosaic abnormalities.

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