Gene is linked to lung cancer development in never-smokers

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A five-center collaborative study that scanned the genomes of thousands of "never smokers" diagnosed with lung cancer as well as healthy never smokers has found a gene they say could be responsible for a significant number of those cancers.

In the March 22 on line issue of Lancet Oncology, the researchers reported that about 30 percent of patients who never smoked and who developed lung cancer had the same uncommon variant, or allele, residing in a gene known as GPC5. The research was co-led by scientists at the Mayo Clinic campus in Minnesota, Harvard University, University of California at Los Angeles (UCLA), and MD Anderson Cancer Center. Researchers found in laboratory studies that this allele leads to greatly reduced GPC5 expression, compared to normal lung tissue. The finding suggests that the gene has an important tumor suppressor-like function and that insufficient function can promote lung cancer development.

"This is the first gene that has been found that is specifically associated with lung cancer in people who have never smoked," says the study's lead investigator, Ping Yang, M.D., Ph.D., Mayo Clinic genetic epidemiologist.

"What's more, our findings suggest GPC5 may be a critical gene in lung cancer development and genetic variations of this gene may significantly contribute to increased risk of lung cancer," she says. "This is very exciting."

The research teams scanned and analyzed the genomes of 2,272 participants who have never smoked, nearly 900 of whom were lung cancer patients. It took researchers 12 years to identify and enroll these study participants.

"It has been very hard to do this research because never smokers have been mingled with smokers in past studies, and what usually pops up are genes related to nicotine dependence," Dr. Yang says.

"Findings from this study concern pure lung cancer that is not caused by smoking, and it gives us some wonderful new avenues to explore."

Little is known about the GPC5 gene, except that it can be over-expressed in multiple sclerosis, and that alterations in the genome where GPC5 is located are a common event in a wide variety of human tumors. "It may be that GPC5 holds different roles depending on the tissue type during various disease development and progression," Dr. Yang says.

A never smoker is defined as a person who has smoked fewer than 100 cigarettes in his or her lifetime, and that describes 15 percent of men and 53 percent of women who develop lung cancer -- accounting for 25 percent of all lung cancers worldwide, according to Dr. Yang. In the Western countries, between 10 and 15 percent of lung cancers occur among never smokers, but in Asian countries, 30 to 40 percent of lung cancers are never smokers, she says. "Our suspicion all along is that this is a distinct disease, and that is why we undertook this study," Dr. Yang says.

The research took two years and involved four steps. In the first step, conducted at Mayo Clinic, a genome-wide association study (GWAS) was performed on 377 never smokers with lung cancer, matched with 377 participants without lung cancer, the "control" population. This was the first GWAS ever conducted solely among never smokers, and it

involved scanning the entire genome of every participant, looking for differences among 300,000 markers or so-called single-nucleotide polymorphisms (SNPs). The scan looks at everything -- inside and outside genes, coding and noncoding regions, Dr. Yang says. They found 44 "hits" -- hinting 44 areas on the genome that were substantially different between the lung cancer patients and healthy control population.

Then, to rigorously validate their findings in other populations, researchers launched stage 2. That involved using data from two more GWAS scans in independent populations -- 328 never smoker lung cancer patients and 407 controls at MD Anderson Cancer Center, and 92 never smoker lung cancer patients and 161 controls at Harvard University. From this, the search was narrowed to just two hits. Both of these hits were adjacent to each other on the same gene, which the researchers then identified as a variant of GPC5.

In the third stage of the study, the researchers used a different method to perform genotyping from the method used in stages 1 and 2 to look at the difference between 91 never smoker lung cancer patients and 439 controls at UCLA. "We confirmed the variant-lung cancer association again," Dr. Yang says.

The final stage of the study involved understanding the function of the gene. "We had to understand whether these hits really represented the functional aspect of the gene, so we tested expression level of GPC5 and found it was significantly reduced," Dr. Yang says. They found that the GPC5 transcription level was twofold lower in adenocarcinoma compared to normal lung tissue. "Interestingly, this reduced transcript expression level was not found in lung carcinoid tumors," Dr. Yang says.

Then the researchers looked to see if this reduced expression led to tumor development, which it did in laboratory culture. "If reduction of

expression of this gene leads to development of lung cancer, it suggests that this gene is normally a tumor suppressor," Dr. Yang says. "We believe it helps control the cell proliferation and division, but we need to prove its function in animal models."

They calculated that about one-third of never smoker lung cancer patients in this study had the same variation of the underperforming GPC5 gene. "We hypothesize that this is an important cancer trigger in these patients, and that something else is going on in the remaining two-thirds of never smokers," she says.

"We don't know what that is, but we now have 42 other hits to explore," Dr. Yang says.

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