Mutations linked to repair of chromosome ends may make emphysema more likely in smokers

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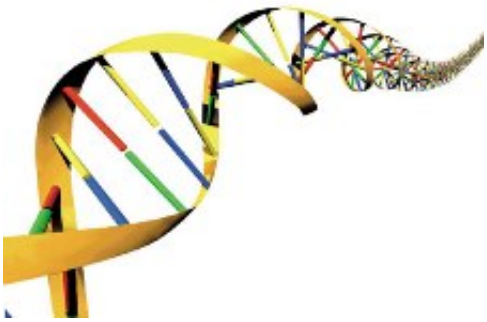

Mutations in a gene that helps repair damaged chromosome ends may make smokers—especially female smokers—more susceptible to emphysema, according to results of a new study led by Johns Hopkins Kimmel Cancer Center researchers.

The mutations are one of a few genetic factors directly linked to chronic obstructive pulmonary disease (COPD), including emphysema, since the 1960s, says Mary Armanios, M.D., associate professor of oncology at the Johns Hopkins University School of Medicine.

Specifically, the alteration occurs in the telomerase reverse transcriptase (TERT) gene, which helps produce an enzyme called telomerase.

Telomerase maintains and repairs the "caps" that protect the ends of chromosomes from degradation during cell division. Telomeres gradually shorten with age and act as a sort of cellular clock in cells. Mutations in TERT lead to excessively shortened telomeres.

Using genetic data gathered in COPD studies funded by the National Institutes of Health, Armanios and colleagues found TERT mutations in three of 292 smokers with emphysema. The researchers then looked at a sample of 50 Johns Hopkins patients with syndromes linked to telomere shortening. Among 39 nonsmokers, there were no cases of emphysema. Among smokers, seven of 11 patients, including all six female smokers, had emphysema. Armanios says this suggests that female smokers with telomerase-related mutations may be more susceptible to emphysema.

A report on the research was published Dec. 22 in the *Journal of Clinical Investigation*. Lung disease is the third leading cause of death in the U.S., and the main risk factors are aging and smoking. However, only about 10 percent of smokers develop COPD, according to Armanios. "Not everyone who smokes gets emphysema, so our study is part of a bigger effort to find out why some people get it and others do not," says Armanios, who notes that other studies have shown that young women who smoke may be more susceptible to emphysema.

The researchers had some clues about telomerase genes from earlier studies, including one in which Armanios and her colleagues identified the impact of shortened telomeres in mice as a risk factor for emphysema after being exposed to cigarette smoke. The scientists previously had noted a link between telomerase mutations and a severe hereditary lung disease called idiopathic pulmonary fibrosis.

Patients with emphysema often suffer from other health problems, including osteoporosis, liver disease and cancer. These disorders are common in people with shortened telomeres as well. The new study, says

Armanios, "may now give us an explanation for why people with emphysema have these systemic problems. If we know that they have a telomerase mutation, it may help us take care of them in a more sophisticated way and delay the onset of those diseases."

Armanios and colleagues published a study last year showing that telomerase mutations may lead to more complications during lung transplants for people with idiopathic pulmonary fibrosis.

In the current study, only 1 percent of the smokers with severe emphysema carried the TERT mutation, but Armanios says this is comparable to the percentage who carry another known genetic factor related to COPD—a mutation in the alpha-1 antitrypsin gene.

The researchers only looked at mutations in two telomerase genes but will now search for mutations in other telomere-regulating genes that might also predispose people to lung disease. "There are many genes that regulate the telomere, so it's likely that more than 1 percent could be impacted by these predisposing factors," says Armanios.

More information: - *J Clin Invest.* DOI: 10.1172/JCI78554. www.jci.org/articles/view/78554

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