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Genetic variant could identify those more susceptible to lung cancer

Lyon, France, 11 May 2020 – A group of international researchers have identified a mutation involved in a person's susceptibility to lung cancer. The research consortium, led by Baylor College of Medicine (USA), Dartmouth College (USA), Memorial Sloan Kettering Cancer Center (USA), and the International Agency for Research on Cancer (France), reports that this mutation could help to identify certain populations who are at greater risk of developing lung cancer. These findings were published today in the journal *Nature Communications*.[1]

The combined efforts of the researchers identified a genetic variant that changes the protein sequence of the *ATM* gene, which is involved in the repair of DNA damage. The *ATM* gene has previously been implicated in a rare syndrome that includes cancer susceptibility, but susceptibility to lung cancer had not been clearly recognized as part of its effects until this genetic variant was identified.

"We know that *ATM* genetic variants are involved with susceptibility to different types of cancer, of which breast cancer is the most studied, but it was really unexpected to see such a strong genetic effect in lung cancer. There's something unusual about this genetic variant and how it acts," says Dr Christopher Amos, senior author of the paper, associate director of quantitative science at the Dan L Duncan Comprehensive Cancer Center, and director of the Institute for Clinical and Translational Research at Baylor College of Medicine.

Because the research involved studies from countries around the world, the researchers were able to trace the population origins of this genetic variant. It was found almost exclusively in individuals of Ashkenazi Jewish descent.

"That the variant is found mostly in one population is consistent with something that geneticists call a founder effect," says Dr Xuemei Ji, first author of the paper and an instructor at Dartmouth College at the time of the research. "Founder effect variants are used in breast cancer screening programmes, particularly in Ashkenazi Jewish populations. This *ATM* variant has a similar prevalence to those. There has been a lot of progress in techniques for lung cancer screening in recent years, so this finding may be really useful for targeted lung screening. Understanding the biological processes in which this *ATM* variant acts may also lead to new therapeutic options."

The expansive nature of this study also enabled the researchers to consider how this variant influences risk across the histological subtypes of lung cancer. Surprisingly, tobacco smoking, which is the predominant cause of most lung cancers, may not be the only player with this *ATM* variant. The

[1] Ji X, Mukherjee S, Landi MT, Bosse Y, Joubert P, Zhu D, et al. (2020). Protein-altering germline mutations implicate novel genes related to lung cancer development. *Nat Commun*. Published online 11 May 2020, https://doi.org/10.1038/s41467-020-15905-6.

researchers found that this genetic variant seemed to be involved in patients with lung cancer who did not have a history of tobacco smoking, in women, and in patients with a particular subtype of lung cancer – lung adenocarcinoma.

“Although most lung cancers occur in smokers, unfortunately lung cancer does occur, rarely, in never-smokers and, for reasons that are not entirely clear, occurs disproportionately in never-smoking women with this type of lung cancer,” says Dr James McKay, senior author of the paper and head of the Genetic Cancer Susceptibility Group at the International Agency for Research on Cancer. “We hope that this finding may help us to understand that enigma a little more.”

The researchers stressed that even though these genetic variants may prove very useful in identifying those who are more susceptible to lung cancer, avoiding tobacco smoking at all levels is the best thing to do to avoid this devastating disease.

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