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Team develops new approach to identify genes poised to respond in asthma patients

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In a study published yesterday in the scientific journal *Nature Immunology*, a group at the La Jolla Institute (LJI) led by Pandurangan Vijayanand, Ph.D. identify new genes that likely contribute to asthma, a disease that currently affects over 200 million people world wide.

An organism's genetic material, also known as its genome, can be divided into small sections or 'neighborhoods.' Scientists can determine which genetic neighborhoods in a cell are active, or primed for gene production, by looking for a marker on the genome called an enhancer. An enhancer can increase the production of genes in its immediate neighborhood. The goal of the published study is to find genes whose neighborhoods are active in diseased cells, but inactive in healthy cells. Genes that are in active neighborhoods in diseased cells are likely to contribute to disease, and can potentially be targeted with drug treatments.

In order to find genetic neighborhoods that are active in asthmatic disease, the scientists in Vijayanand's group focus their experiments on memory cells, which develop abnormally in asthma patients. Memory cells are responsible for quickly responding to foreign substances called antigens that the host has been exposed to previously. Air passage inflammation, which characterizes asthma, is mediated by an overactive response to inhaled antigens by memory cells.

By applying his technique in small populations of abnormal memory cells, Vijayanand highlights 33 genetic neighborhoods that are highly

active in diseased cells, but inactive in healthy cells, shifting the focus of asthma research to specific genes that are located in these neighborhoods.

Genome-wide association studies (GWAS) that are less precise, have previously identified 1,500 potential target regions associated with asthmatic disease. According to Vijayanand, these targets are too numerous to study individually, and as a result, the field has remained focused on just a few molecules for discovery of new asthma treatments. Using their approach, Vijayanand's team searched the 1,500 targets for those that have the greatest likelihood of contributing to asthmatic disease. "Our unbiased and hypothesis-free approach has revealed a staggering but manageable number of new molecules that could play a role in asthma, and thus are potentially novel therapeutic targets," said Vijayanand.

Vijayanand and his team completed the study using different amounts of cells from the blood of healthy individuals and asthmatic patients. They did so in order to determine the smallest number of cells that were required for their technique, and found that it works with as little as 10,000 cells, which is significantly less than the millions of cells required to use other methods. Vijayanand envisions using this technique in situations where access to cells is limited, such as tumor biopsy for cancer.

The frequency of asthma is rising across the developed world as well as in several large developing countries. Treatment for asthma usually includes long-term nonspecific medication, as there is no cure at present.

Vijayanand says this study provides information that can be the starting point for many avenues of research and treatment. He says, "our study provides a rich and comprehensive resource that will be useful to the scientific community, enabling investigators to conduct their own

detailed studies of the functional significance of the novel genes and enhancers that we have identified."

More information: The findings were published in a *Nature Immunology* paper entitled "Epigenomic analysis of primary human T cells reveals enhancers associated with TH2 memory cell differentiation and asthma susceptibility."

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