Medical Xpress

New atlas of genetic function maps complexities of immune system and immune diseases

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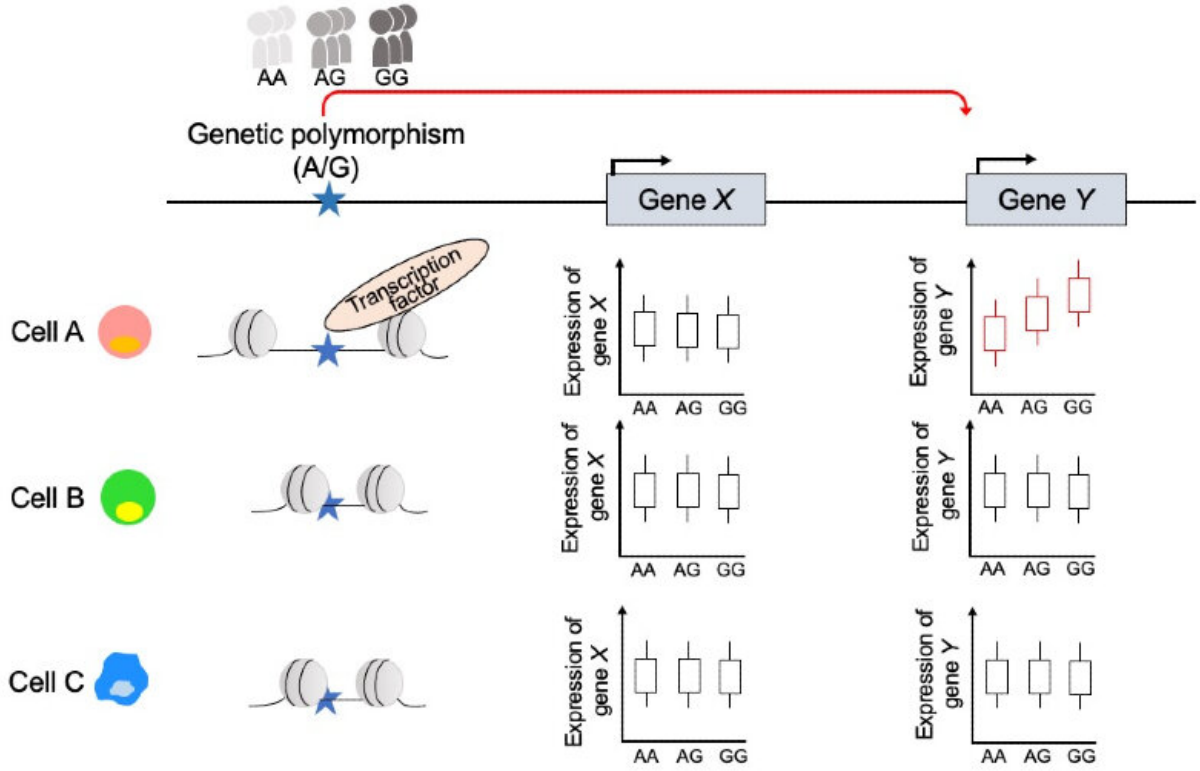

Each person only has one genome, but different parts of the genome are active in different cell types. In the example above, a region of regulatory DNA (blue star) is active only in Cell A. This regulatory DNA controls expression level of Gene Y. Different people have different variations of that regulatory DNA sequence (AA, AG or GG genetic polymorphisms), which lead to different expression levels of Gene Y (top right red graph). This type of data was used to build the ImmuNexUT database, which will allow experts to understand how DNA

sequence differences lead to changes in gene expression and cause different immune system diseases. Credit: Mineto Ota, Creative Commons By Attribution 4.0

Researchers in Japan have compiled a first-of-its-kind genetic database for autoimmune and autoinflammatory diseases. This resource will allow experts to more deeply understand how immune disorders develop and plan future drug discovery projects. Scientists also hope this atlas of immune-related genome data may eventually be applied to investigations of infectious diseases like COVID-19.

"To understand diseases, a deep comprehension of the function of genetic variants is essential. With this data set, we can connect the data about changes to DNA sequence associated with a disease to genes and cell types that are important for disease pathogenesis," said University of Tokyo Project Research Associate Mineto Ota, M.D., Ph.D., a clinical rheumatologist and expert in functional genomics. Ota is lead author of the study recently published in *Cell*. The project was completed with collaborators at RIKEN research institution and Chugai Pharmaceutical Co., Ltd.

Many prior research projects have compared the full genome sequences of patients with medical diagnoses to those of healthy people. Any DNA sequence variants identified in these genomewide association studies are then considered "associated" with the disease.

Many variants identified in association studies are not located in genes, the basic units of heredity, but rather in portions of DNA that regulate the "on" or "off" expression of genes. Most of the human genome is not genes, but this regulatory DNA. Experts might know that a portion of DNA is involved in gene regulation, but not understand exactly how or

what it does or even what genes it regulates.

To uncover the function of regulatory DNA, a different type of genome study called expression quantitative trait loci (eQTL) analysis attempts to connect differences in DNA sequence to differences in gene expression. With eQTL data, researchers can make more informed guesses about the purpose of regulatory DNA sequences, how variants in the regulatory sequence might affect expression of the genes it regulates and how those differences in gene expression cause disease.

Other immune-focused eQTL studies have been performed, but prior research efforts included only healthy volunteers and examined a limited number of cell types.

"Inflammatory conditions create very different physical characteristics in immune cells compared to the same cells in a healthy condition. The genetic variants associated with immune conditions may only function in the diseased state, so for this type of genetic study, it was very important to get samples from real patients," said Ota.

The research team sequenced the full genomes of 79 healthy volunteers and 337 patients diagnosed with any of 10 different categories of immune-mediated diseases, including rheumatoid arthritis, systemic lupus erythematosus and systemic sclerosis. All volunteers had Japanese ancestry.

Understanding immune-mediated diseases is challenging because although each disease is clinically distinct, there are many overlaps and patients with the same diagnosis may show very different symptoms.

"Due to all this diversity, there's a limit to how much you can learn studying one immune-mediated disease at a time. But if we study 10 diseases together, it gives a bigger picture about these types of diseases,"

Ota explained.

After completing full genome sequencing, researchers isolated 28 different types of immune-related cells from volunteers' blood samples and measured gene expression in those cells.

The database created through this research was named the Immune Cell Gene Expression Atlas from the University of Tokyo (ImmuNexUT).

"We see that each immune cell type has distinctive eQTL results in the atlas, which can tell us how gene regulation differs between cell types and exactly which cell type is important for developing which disease," said Ota.

ImmuNexUT is now the largest eQTL data set built using volunteers of East Asian ancestry.

"In this field so far, large-scale genomic and functional genomic studies have been mainly conducted with European donors, although population diversity is critical for precise understanding of the genomic functions. This eQTL atlas of Japanese subjects is also meaningful for overcoming this European-centric bias and further investigating the functions of DNA variants in combination with European data sets," said Ota.

Researchers hope the ImmuNexUT database will continue to grow and eventually lead to better outcomes for patients.

More information: Dynamic landscape of immune cell-specific gene regulation in immune-mediated diseases. *Cell*. DOI: 10.1016/j.cell.2021.03.056