Seasonal immunity: Activity of thousands of genes differs from winter to summer

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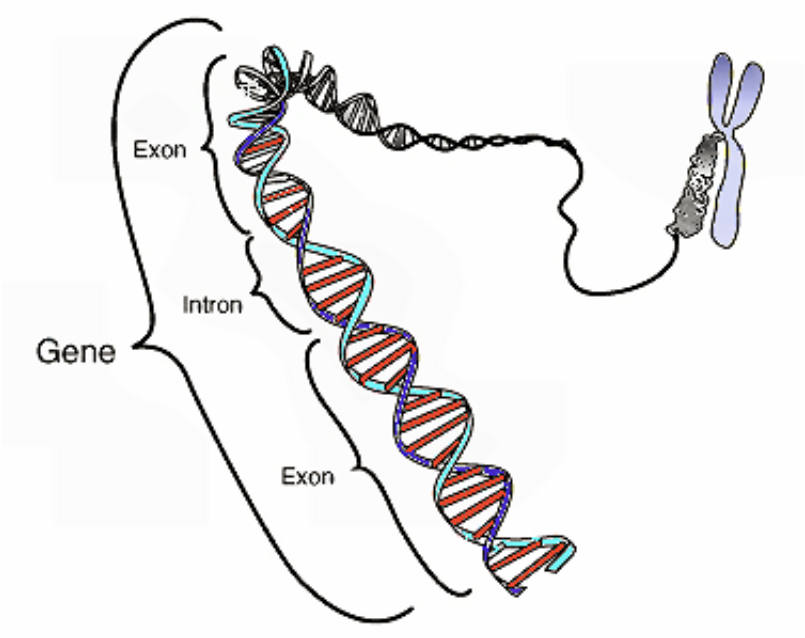

This image shows the coding region in a segment of eukaryotic DNA. Credit: National Human Genome Research Institute

Our immune systems vary with the seasons, according to a study led by the University of Cambridge that could help explain why certain conditions such as heart disease and rheumatoid arthritis are aggravated in winter whilst people tend to be healthier in the summer.

The study, published today in the journal *Nature Communications*, shows that the activity of almost a quarter of our genes (5,136 out of 22,822

genes tested) differs according to the time of year, with some more active in winter and others more active in summer. This seasonality also affects our immune cells and the composition of our blood and adipose tissue (fat).

Scientists have known for some time that various diseases, including cardiovascular disease, autoimmune diseases such as type 1 diabetes and multiple sclerosis, and psychiatric disorders, display seasonal variation, as does vitamin D metabolism. However, this is the first time that researchers have shown that this may be down to seasonal changes in how our immune systems function.

"This is a really surprising - and serendipitous - discovery as it relates to how we identify and characterise the effects of the susceptibility genes for type 1 diabetes," says Professor John Todd, Director of the JDRF/Wellcome Trust Diabetes and Inflammation Laboratory. "In some ways, it's obvious - it helps explain why so many diseases, from heart disease to mental illness, are much worse in the winter months - but no one had appreciated the extent to which this actually occurred. The implications for how we treat disease like type 1 diabetes, and even how we plan our research studies, could be profound."

An international team, led by researchers from the JDRF/Wellcome Trust Diabetes and Inflammation Laboratory in the Department of Medical Genetics, Cambridge Institute for Medical Research, examined samples from over 16,000 people living in both the northern and southern hemispheres, in countries including the UK, USA, Iceland, Australia and The Gambia. These samples included a mixture of blood samples and adipose tissue.

The researchers used a variety of techniques to study the samples, including looking at the cell types found in the blood and measuring the level of expression of the individuals' genes - a gene is said to be

'expressed' when it is active in a particular cell or tissue, usually involving the generation of proteins. They found that the thousands of genes were expressed differently in blood and adipose tissue depending on what time of year the samples were taken. Similarly, they identified seasonal differences in the types of cells found in the blood.

Seasonal differences were present across mixed populations in geographically and ethnically diverse locations - but the seasonal genes displayed opposing patterns in the northern and southern hemispheres. However, the pattern of seasonal activity was not reflected as strongly in Icelandic donors. The researchers speculate that this may be due to the near-24 hour daylight during summer and near-24 hour darkness in winter.

One gene of particular interest was ARNTL, which was more active in the summer and less active in the winter. Previous studies have shown that, in mice at least, the gene suppresses inflammation, the body's response to infection; if the gene has the same function in humans, then levels of inflammation will be higher during winter in the northern hemisphere. Inflammation is a risk factor for a range of diseases and hence in winter, those at greatest risk will likely reach the 'threshold' at which the disease becomes a problem much sooner. Drugs that target the mechanisms behind inflammation could offer a way of helping treat these diseases more effectively during the winter periods.

A particularly surprising finding was that a set of genes associated to an individual's response to vaccination was more active in winter, suggesting that some vaccination programmes might be more effective if carried out during winter months when the immune system is already 'primed' to respond.

During European and Australian winters, they argue, the thresholds required to trigger an immune response may be lower as a direct

consequence of our coevolution with infectious organisms, which tend to be more prevalent during winter. Interestingly, people from The Gambia showed distinct seasonal variation in the numbers of immune cells in the blood that correlated with the rainy season (June-October), during which time infectious diseases, particularly mosquito-borne diseases such as malaria, are more rife.

"We know that humans adapt to changing environments," says Dr Chris Wallace. "Our paper suggests that human immune systems adapt to show different seasonal variation in equatorial regions with fewer distinct seasons compared to regions at higher and lower latitudes with more pronounced differences between winter and season."

It is not clear yet what mechanism maintains the seasonal variation seen in the immune system, though it may be due to environmental cues such as daylight and ambient temperature. Our internal body clock - known as our circadian rhythm - is in part coordinated by changes in daylight, which explains why people in jobs that do not fit with the daily cycle, such as factory shift workers or crews on long haul flights, can be affected by poorer health.

Professor Todd adds: "Given that our immune systems appear to put us at greater risk of disease related to excessive inflammation in colder, darker months, and given the benefits we already understand from vitamin D, it is perhaps understandable that people want to head off for some 'winter sun' to improve their health and well-being."

The research was funded by the Wellcome Trust, the type 1 diabetes charity JDRF and the NIHR Cambridge Biomedical Research Centre.

Professor Mike Turner, Head of Infection and Immunobiology at the Wellcome Trust said: "This is an excellent study which provides real evidence supporting the popular belief that we tend to be healthier in the

summer. Seasonal variation to this extent is a fascinating find - the activity of many of our genes, as well as the composition of our blood and fat tissue, varies depending on the seasons. Although we are still unclear of the mechanism that governs this variation, one possible outcome is that treatment for certain diseases could be more effective if tailored to the seasons."

Karen Addington, Chief Executive of JDRF in the UK, said: "We have long known there are more diagnoses of type 1 diabetes in winter. This study begins to reveal why. It identifies a biological mechanism we didn't previously know of, which leaves the body seasonally more prone to the autoimmune attack seen in type 1 diabetes.

"While we all love winter sun, flying south for the whole of each winter isn't something anyone can practically recommend as a way of preventing type 1 diabetes. But this new insight does open new avenues of research that could help untangle the complex web of genetic and environmental factors behind a diagnosis."

More information: Dopico, XC et al. Widespread seasonal gene expression reveals annual differences in human immunity and physiology. *Nature Communications*; 12 May 2015. nature.com/articles/doi:10.1038/ncomms8000

Provided by University of Cambridge