Metabolic syndrome linked to cold tolerance

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Researchers from the University of Chicago have discovered that many of the genetic variations that have enabled human populations to tolerate colder climates may also affect their susceptibility to metabolic syndrome, a cluster of related abnormalities such as obesity, elevated cholesterol levels, heart disease, and diabetes.

More than 100 years ago, scientists noted that humans inhabiting colder regions were bulkier and had relatively shorter arms and legs. In the 1950s, researchers found correlations between colder climates and increased body mass index (BMI), a measure of body fat, based on height and weight.

Now, in a study published in the February issue of the open-access journal *PLoS Genetics*, scientists have found a strong correlation between climate and several of the genetic variations that appear to influence the risk of metabolic syndrome, consistent with the idea that these variants played a crucial role in adaptations to the cold. The researchers report that some genes associated with cold tolerance have a protective effect against the disease, while others increase disease risk.

"Our earliest human ancestors lived in a hot humid climate that placed a premium on dispersing heat," said Anna Di Rienzo, professor of human genetics at the University of Chicago. "As some populations migrated out of Africa to much cooler climates, there would have been pressure to adapt to their new settings by boosting the processes that produce and retain heat."

"Thousands of years later," she said, "in an era that combines widespread central heating with an overabundant food supply, those genetic alterations have taken on a different sort of significance. They alter our susceptibility to a whole new set of diseases, such as obesity, coronary artery disease and type 2 diabetes."

The researchers set out to look for correlations between the frequency of genetic variations linked to metabolic syndrome and climate variables in worldwide population samples.

They selected 82 genes associated with energy metabolism – many of them previously implicated in disease risk – and looked for climate-related variations in those genes. They studied genetic variation in 1,034 people from 54 populations, finding widespread correlations between the frequencies of certain genetic variations and colder climates, as measured by latitude as well as summer and winter temperatures.

One of the strongest signals of selection came from the leptin receptor, a gene involved in the regulation of appetite and energy balance. One version of this gene is increasingly common in locales with colder winters. This version of the leptin receptor is associated with increased respiratory quotient – the ability to take up oxygen and release carbon dioxide – which plays an important role in heat production. This allele also has been linked to lower BMI, less abdominal fat and lower blood pressure, and is thus protective against metabolic syndrome.

Other genes that varied according to climate included several involved in heat production, cholesterol metabolism, energy use, and blood glucose regulation.

Not all cold-tolerance-related gene variants protect against metabolic syndrome. Increased blood glucose levels, for example, could protect someone from the cold by making fuel more readily available for heat production, yet it raises the risk of type 2 diabetes. The version of a gene known as FABP2 that became more common as temperatures fell causes increased BMI, promotes fat storage and elevates cholesterol levels. This would protect against the cold, but increase susceptibility to heart disease and diabetes.

"All these genes are likely to be involved in metabolic adaptations to cold climates," said Di Rienzo, "but they have opposing effects on metabolic syndrome risk. We suspect they spread rapidly as populations settled into colder and colder climates at higher latitudes, but in the modern era they have taken on a whole new significance, as the supply of calories from food has mushroomed and the survival advantage of generating more heat has been minimized by technology."

The authors suggest that the search for genes that vary according to climate could provide additional clues about the onset of metabolism related diseases.

"The biological processes that influence tolerance to climatic extremes," the authors conclude, "are likely to play important roles in the pathogenesis of common metabolic disorders… Our results argue for a role of climate adaptations in the biological processes underlying the metabolic syndrome and its phenotypes."

Source: University of Chicago

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