Disrupted genetic regulation causes common disturbance in metabolism of fat

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The disease familial combined hyperlipidemia (FCH) is a common cause of disturbed metabolism of fat and early heart attacks. Uppsala University scientists have now developed a pioneering method and can show for the first time what genes are regulated by the gene USF1, which is known to cause the disease. These findings are being presented today in the leading journal *Genome Research*.

Familial combined hyperlipidemia is caused by the gene USF1, which in turn regulates many other genes, but until now there have been no techniques for finding which ones. Professor Claes Wadelius, at the Department of Genetics and Pathology, Uppsala University, has devised new methods for analyzing genetic regulation and found a number of genes that govern fat levels and energy conversion. The breakthrough is a result of close collaboration with Professor Jan Komorowski at the Linnaeus Center for Bioinformatics.

How active a gene is is regulated by proteins, called transcription factors, which are bound to the DNA strands. Until now, this has been analyzed in test tubes and only one gene at a time. Claes Wadelius' research team has developed new high-efficiency methods that improve the results in two crucial ways. On the one hand, living cells are now analyzed, not synthetic genes in test tubes. On the other, the entire human genome is analyzed in a single experiment, not merely a genetic fragment.

The method has been used to find genes that have a disturbed function in the common disease familial combined hyperlipidemia. These patients

have elevated levels of cholesterol or other fats, which leads to increased risk of being afflicted by early hardening of the arteries and heart attack. Analyses show that the gene USF1 in turn governs the activities of more than 1,000 genes, several of which determine the body's levels of fat. It also regulates a number of genes that participate in the cell's energy production, which provides new ways of understanding disturbances in metabolism. The new methods are 10-100 million times more efficient that the old ones, and the project involved more than a billion analyses. This places great demands on how we register, store, and interpret data.

"Technological advances are making medical research more of an information science. With these precise new methods for analyzing data we have entirely new capabilities for understanding the causes of disturbances in metabolism. In other projects we are using the same methods to understand new causes of cancer," says Professor Claes Wadelius.

Source: Uppsala University