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Single letter in the human genome points to risk for high cholesterol

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(PhysOrg.com) -- Write out every letter in the human genome, one A, C, T or G per millimeter, and the text would be 1,800 miles long, roughly the distance from New York to Colorado. Now, in the search for genes that affect how humans synthesize, process and break down cholesterol, a consortium of researchers led by Rockefeller University scientists has found a single letter among this expanse of code that is associated with elevated LDL cholesterol levels, one of the leading health concerns that has come to dominate the 21st century.

The research, led by Jan L. Breslow, head of the Laboratory of Biochemical Genetics and Metabolism, brings a new level of understanding to an enzyme called HMGCR, the rate-limiting catalytic engine of cholesterol biosynthesis and the target of the much-revered cholesterol-lowering drugs known as statins. For years, scientists have known that HMGCR (the enzyme's full name is 3-hydroxy-3-methylglutaryl coenzyme A reductase) plays a key role in cholesterol metabolism, but there was no evidence that common genetic variants existed in the gene that could affect how people metabolize cholesterol, an artery-clogging fat when produced (or consumed) in excess.

"In fact, HMGCR became the poster boy for how genes without common variation can still be good drug targets," says first author Ralph Burkhardt, a postdoctoral fellow in the Breslow lab.

The work builds upon ongoing research involving the inhabitants of the

Micronesian island of Kosrae, who have a higher burden of risk factors associated with obesity and heart disease. By taking advantage of the growing power of genomic databases and genetic and biochemical techniques, Burkhardt, Breslow and their colleagues showed that a single letter difference, known as a single nucleotide polymorphism or SNP, in the HMGCR gene was linked to higher LDL cholesterol levels in the 4,947 people whose blood was analyzed: a population of 2,346 Kosraeans and a European sample that was included for statistical power.

“At this point, nobody had an idea what biological effect this SNP would have,” says Burkhardt. “So we went on to look for a mechanism, one that could explain how this variant affects HMGCR expression and/or function.”

From the literature, the researchers, including Jeffrey M. Friedman, a Howard Hughes Medical Institute investigator and head of the Laboratory of Molecular Genetics, and Markus Stoffel, now of the Institute of Molecular System Biology in Switzerland, knew that people produce two forms of the HMGCR enzyme: a short form and a long one. Now they've discovered that the SNP in question modulates how much of each form each person produces, and that those with higher cholesterol levels produce more of the long form than the short one. Through a process called alternative splicing, the researchers further showed that when the cell transcribes the HMGCR gene, it skips a region of it called exon 13, leading to the shorter enzyme. This process, they believe, ultimately reduces cholesterol production in the body.

“Genes that affect the synthesis, processing and breakdown of these lipoproteins are closely linked to heart disease,” says Burkhardt. “This research has helped us to better understand atherosclerosis susceptibility and its complex genetic basis.”

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