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Single Genetic Defect Links Many Risk Factors for Heart Disease and Stroke

A single change in a person's DNA can contribute to a range of life-shortening risk factors, including high blood pressure, high cholesterol, and other metabolic disorders. A woman with hypertension, low magnesium levels, and a cooperative family allowed scientists to pinpoint the mutation, which affects the genes of the mitochondria — the energy-producing power plants of the cell that are passed from mother to offspring.

The researchers, led by Howard Hughes Medical Institute investigator Richard P. Lifton, who is at Yale University School of Medicine, published their findings October 22, 2004, in *Science Express*, an online component of the journal *Science*. Gerald I. Shulman, another HHMI investigator at the Yale School of Medicine, was also an author on the paper. The researchers are hopeful their discovery could help unravel the complex genetic and environmental factors that cause a range of metabolic disorders.

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— **Richard P. Lifton**

"Epidemiological studies over the last 20 years have shown that hypertension, high cholesterol, high triglycerides, low magnesium, diabetes, insulin resistance, and obesity tend to cluster with one another, but not in a simple way," said Lifton. "Not everybody who has any one of these traits has all of the others. The pattern of inheritance is complicated, and there hasn't been a clear understanding of what's driving this relationship."

Various combinations of these abnormalities affect up to a quarter of the U. S. population, and they are contributing to a public health epidemic of heart disease and stroke.

Lifton said that the woman with hypertension and low blood magnesium levels proved to be the key to tracing the genetic cause of the array of pathologies. Since low magnesium occurs infrequently in the general population, the researchers tested her for known mutations that they had previously associated with that trait.

"When we spoke to her, what stood out was that she said that a number of other family members also had low magnesium," said Lifton. "That suggested that she might have a new disease, because all the known genetic causes of low magnesium were autosomal recessives that would not occur so widely."

The woman told researchers that a number of her female relatives had the same problem. Further study of the family revealed a high frequency of high blood pressure and cholesterol.

"That's when the real saga began," said Lifton. "The family was extraordinarily cooperative, and we eventually studied 142 relatives. When we looked at the pattern of these pathologies, we found there was a whopping excess of affected individuals on the maternal lineage."

Such a pattern immediately suggested a defect in the mitochondrial genome, because those genes are uniquely passed from mother to offspring, unlike the rest of the cell's genome, which is contained in the nucleus.

Detailed sequencing of the mitochondrial genomes of family members revealed a specific mutation in all affected people. That defect was the substitution of a single DNA unit, or base, in the gene that coded for a specific transfer RNA (tRNA) in the mitochondria.

Transfer RNAs are critical carrier molecules that ferry amino acids during the construction of proteins in the cell. During the translation of genetic material to a protein, a tRNA latches onto a specific amino acid that it was designed to carry and transports it to the site of protein synthesis. There, it docks precisely with the messenger RNA that is the protein's blueprint and unloads its amino-acid cargo, which can then be incorporated into the elongating protein chain.

The defective base the researchers pinpointed was in the gene for the tRNA that transports the amino acid isoleucine. That defect distorted the docking region of the tRNA, preventing it from recognizing and attaching to the messenger RNA to deposit its isoleucine cargo. Thus, the faulty tRNA could lead to defects in a vast array of proteins that normally contain isoleucine, thereby contributing to a broad range of cellular malfunctions.

Once the researchers determined that a mitochondrial defect caused the diverse traits, they reexamined the family members for other problems known to be linked to mitochondrial malfunction. Indeed, they found an increased prevalence of hearing loss, migraine headaches, and weakened heart muscle, which are all known to be associated with genetic mutations in mitochondria.

"What's unique about this study and this family is that there has never before been a report of a common genetic link among any of the three traits we found—low magnesium, hypertension, and high cholesterol," said Lifton. "This raises the general question of whether the more common forms of these traits might arise from abnormal mitochondrial function as well."

Lifton noted that although about half of the family members had each of the three traits, "they occur randomly in the family members, despite the fact that everybody has the same mutation. So our suspicion is that there are either genetic or environmental modifiers that dictate which specific outcomes will result from the mutation," he said. "But it was particularly striking that the complex pattern of clustering that we see arising from this single mutation has many of the hallmarks of the kinds of clustering that we see in the general population."

The discovery of the genetic defect could open new avenues for basic research and treatment, said Lifton, and could help explain why problems such as hypertension increase with age. The mutation could, for example, link hypertension to the age-related decline in mitochondrial function, which was identified by Shulman. Shulman's work has shown that this decline can lead to insulin resistance, a major contributor to type 2 diabetes.

Lifton has no illusions that defining the mechanisms underlying such linkages will be easy. "We have identified this defect and linked it with these traits, but there remains a complex black box in between," he said. "We don't know the mechanism that links the two."

A better understanding of this mechanism could yield new treatments, said Lifton. He speculated that the genetic defect might produce clinical pathologies by crippling the energy-production capability of the mitochondria. Alternately, it might increase the production of reactive oxygen species that cause wear and tear on blood vessels, contributing to high blood pressure and other problems.

Differentiating between the two possibilities is important, he said, because each would suggest a very different therapeutic approach. "If it proved to be the former mechanism, you would want treatments to try to rev up mitochondrial energy production," Lifton said. "If it was the latter, treatments might aim at using antioxidants to prevent damage caused by reactive oxygen species."