Teams hunt for vascular and heart genes

The body's powerful renin-angiotensin system regulates blood pressure and salt retention. Now, two new studies add to the knowledge of how genes in that system play a role in cardiovascular disease.

Previously, U.S. and French researchers reported that a gene coding for a protein called angiotensinogen appeared to play a role in the regulation of blood pressure (SN: 10/10/92, p.230). A British team now has more evidence that the angiotensinogen gene may predispose some people to developing hypertension, or high blood pressure.

An estimated 50 million people in the United States suffer from hypertension, a condition in which the heart pumps blood through the body more forcefully than it should. That elevated pressure strains both the heart and the arteries. Left untreated, hypertension can lead to a stroke or heart attack.

In some people, doctors can establish a clear-cut cause for high blood pressure — for example, a kidney abnormality. But in 90 percent of cases, physicians can find no apparent basis for the artery-pounding pressures. Mark Caulfield of St. Bartholomew's Hospital in London began to wonder about the genetic basis of such cases of essential hypertension.

Caulfield and his colleagues studied samples of DNA taken from 63 European families with a history of this disorder. They discovered that 40 of the 63 families shared a distinctive DNA pattern near the angiotensinogen gene, located on the long arm of chromosome 1.

"What the data show is evidence of linkage of the angiotensinogen gene to human essential hypertension," Caulfield says. His team describes its findings in the June 9 NEW ENGLAND JOURNAL OF MEDICINE (NEJM).

The angiotensinogen gene codes for a protein called angiotensinogen. This protein is the raw material used to produce a vessel-constricting hormone called angiotensin II. Scientists suspect that variations in the angiotensinogen gene may somehow lead to chronically narrowed blood vessels.

Some families may pass on a tendency to develop this condition, especially in combination with certain environmental factors associated with high blood pressure, such as a high-salt diet, Caulfield says.

The team did not prove that the angiotensinogen gene itself triggers the elevated pressures. "The present data are entirely compatible with the possibility of linkage to an as-yet-unidentified gene in close proximity to the angiotensinogen gene on chromosome 1," cautions Klaus Lindpaintner of Brigham and Women's Hospital in Boston. Lindpaintner wrote an editorial accompanying the article.

If additional research pinpoints the inherited vulnerability, it may be possible to fashion treatment for hypertension, Caulfield says. His team continues to search the same region of chromosome 1 for a flaw in the genetic code.

In the same issue of NEJM, a team led by Heribert Schunkert of the University of Regensburg in Germany focused on another gene, called ACE, in the renin-angiotensin system. Their population-based study identified 141 women and 149 men with evidence of left ventricular hypertrophy, an enlargement of the heart that can lead to poor pumping ability and heart failure.

The researchers found a statistical association between a particular form of the ACE gene and left ventricular hypertrophy. That association held true for men but not for women. What's more, the researchers found this association just among men who had inherited one copy of that ACE gene type from each parent, says coauthor Beverly H. Lorell of Beth Israel Hospital in Boston.

The ACE gene codes for angiotensin-converting enzyme, a substance that aids in the production of angiotensin II. The researchers speculate that men who inherit a double whammy of the variant ACE gene may end up as superproducers of that hormone. In addition to regulating blood pressure, angiotensin II may spur inappropriate growth of the heart, Lorell speculates. — *K.A. Fackelmann*

Detecting the magnetic force of protons

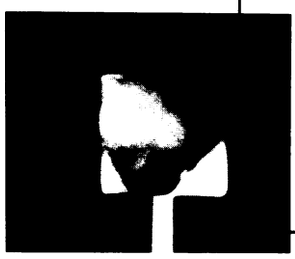
Of the more than 100,000 different proteins known to exist in the human body, most remain poorly characterized. Using crystallographic and other techniques, scientists so far have deduced the structures of only a few hundred of these giant molecules.

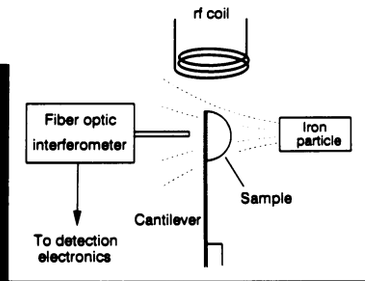
As an important step toward developing a technique for obtaining images showing the three-dimensional atomic arrangement of individual molecules in their natural settings, researchers have now demonstrated that microscopic devices designed to sense minute magnetic forces can be used to detect nuclear magnetic resonance.

Although this achievement falls short of detecting individual protons or nuclei in molecules, it represents a significant improvement in sensitivity and spatial resolution over that of conventional magnetic resonance imaging.

Daniel Rugar and his coworkers at the IBM Almaden Research Center in San Jose, Calif., report their results in the June 10 SCIENCE.

The notion of using nuclear magnetic resonance for imaging individual molecules originated with physicist John A. Sidles of the orthopedics department at the University of Washington School of Medicine in Seattle (SN: 3/7/92, p.150). To demonstrate the idea's feasibility, Rugar and his colleagues subsequently adapted the technology used to measure tiny variations in magnetic forces across a surface to detect a magnetic resonance effect involving the spins of electrons (SN: 3/27/93, p.199).





Rugar et al./SCIENCE

Basic configuration of magnetic force detection apparatus. Left: A small grain of ammonium nitrate rests on the upper portion of the paddle-shaped cantilever, which is 900 angstroms thick and has a neck 5 micrometers wide.

Last year, Rugar and Othmar Züger used their "magnetic resonance force microscope" to measure electron spins and produce images of tiny organic crystals. In the latest development, the researchers have refined their apparatus to pick up the much smaller signals from atomic nuclei.

The key element responsible for achieving this high sensitivity is a microscopic sliver of silicon nitride, which vibrates like a miniature diving board (see image). Interactions between protons in a grain of ammonium nitrate, the magnetic field of a nearby iron particle, and radio waves cause the sliver to vibrate, creating a detectable signal.

"The results . . . demonstrate that [nuclear magnetic resonance] force detection can achieve remarkable sensitivity and spatial resolution," the researchers conclude. "Further advances are expected as progress is made toward more sensitive cantilevers, higher [magnetic] field gradients, and lower temperatures."

"It's a technology that works better the smaller you make it," Sidles notes. — *I. Peterson*