SCIENCE NEWS of the week

First Gene-Hypertension Link Found

Researchers have pinpointed a tiny genetic defect in a strain of rats prone to high blood pressure, suggesting that a similar mutation may underlie certain forms of hypertension in humans. The finding represents the first known link between a specific genetic error and high blood pressure.

Molecular geneticists performing the work caution that hereditary high blood pressure — whether in rats or people — almost certainly results from a combination of genetic defects and environmental factors. They say significant hurdles remain before they'll be able to sort out the various contributing factors.

Nonetheless, the new finding confirms many scientists' suspicions that hypertension can result from defects in a critical molecular pump that regulates salt concentrations in cells. In the long run, it could lead to the development of genetic tests capable of spotting susceptible individuals, and possibly to novel therapies.

"This is a very important finding," says Michael Horan, associate director for cardiology at the National Heart, Lung and Blood Institute in Bethesda, Md. "Whether this exact genetic flaw is important in humans remains to be seen. But finding it in an animal is a good first step."

Horan notes that high blood pressure — which affects 58 million Americans, or about one-third of the adult U.S. population — is a potent risk factor for stroke, heart disease and kidney disease. "If we can make inroads in hypertension, we'll be making inroads for a whole sphere of very serious diseases," he says.

The work was performed by Victoria L. M. Herrera and Nelson Ruiz-Opazo of the Boston University School of Medicine. They investigated an enzyme called sodium- and potassium-dependent adenosine triphosphatase (Na^+,K^+-ATPase) in two strains of rats — one that becomes hypertensive in response to a high-salt diet and one that retains normal blood pressure despite a high-salt diet. Na^+,K^+-ATPase is a protein embedded within the cell membranes of many types of animal cells. It pumps sodium ions out of cells and hauls potassium ions in, creating a sort of ionic tension, or chemical gradient, across cell membranes. In addition to maintaining proper water volumes and acidity levels within cells, this gradient provides the electrochemical energy to drive a host of important cellular activities, including sugar transport, nerve firing and muscle contraction.

With its obvious role in maintaining salt balance and its abundance in blood-pressure-regulating organs such as the heart, kidneys and blood vessels, some researchers have hypothesized that Na^+,K^+-ATPase might play a role in hypertension. Herrera and Ruiz-Opazo isolated segments of Na^+,K^+-ATPase genes in hypertensive and nonhypertensive rats and analyzed the DNA sequences. They found one significant difference: Hypertensive rats bear a DNA mutation that leads to the amino acid leucine getting substituted for the amino acid glutamine at position 276 in the 1,023-amino-acid-long protein.

The change, while seemingly minor, apparently causes big problems. It occurs in a region of the protein that must regularly change shape to perform its ion transport work. The leucine substitution makes the protein segment water-repellent, interfering with its flexibility. In a series of experiments with radioactive ions, Herrera and Ruiz-Opazo showed that mutant Na^+,K^+-ATPase pumps ions less efficiently than normal Na^+,K^+-ATPase.

The work, described in the Aug. 31 SCIENCE, provides a plausible genetic mechanism for some varieties of high blood pressure. "An alteration in Na^+,K^+-ATPase ion transport would affect the [sodium-potassium] electrochemical gradient and conceivably contribute to changes in renal function, vessel wall resistance, or cardiac rhythmogenicity and contractility," the researchers say.

The finding represents a "very significant" advance, says the University of Cincinnati's Jerry B. Lingrel, who led a successful effort to clone part of the human Na^+,K^+-ATPase gene in 1987. "To find a real defect in a gene like this that appears to correlate with differences in hypertension is very exciting."

The enzyme "may be important in some families and not in others," he says, adding that the discovery will spur a search for this or similar mutations in people with high blood pressure. About one-third to one-half of U.S. hypertensives have a form of salt-sensitive high blood pressure similar to that seen in the experimental rats.

Herrera says the mutant gene "might just contribute to salt sensitivity or it might contribute to hypertension [directly]." To clarify the extent to which the gene causes high blood pressure independent of other contributing factors, she plans to mix and match Na^+,K^+-ATPase genes in genetically engineered rats.

"Ideally, we'd like to put a mutant gene into a wild-type rat and see what happens to its blood pressure, or put a wild-type gene into a hypertensive rat and see if we can reduce blood pressure despite a high-salt diet," Herrera says. "Experiments like those . . . would really help nail this thing down." — *R. Weiss*

Geneticists to arthritics: A gene's the rub

An inherited form of premature arthritis sometimes results from a minor typographical error in the genetic code for a joint-cushioning protein, according to new research. The disease, called primary osteoarthritis, can start to affect victims in their second or third decades of life, leaving them hobbled by midlife with limited, painful joint movement in the elbows, knees, hips and fingers.

Scientists estimate that as many as 6 million arthritic Americans can blame their disability at least in part on defective DNA, but they remain unsure how many of these people bear the newly pinpointed genetic glitch. Although the investigators found the mutation in all nine arthritic individuals of the one family they thoroughly studied, they note that other families with a history of the disease may harbor different genetic misspellings. But if the defect causes a large proportion of cases, its discovery could help clinicians identify people who have inherited the faulty gene, allowing early intervention.

Darwin J. Prockop of the Jefferson Medical College in Philadelphia and his colleagues examined DNA from 19 individuals spanning three generations of a family with a propensity for primary osteoarthritis. Affected family members harbored an identical error within a gene on chromosome 12, they report in the September PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES (Vol.87, No.17). The gene contains instructions to make Type II procollagen — the precursor of Type II collagen, which is the major ingredient of joint-surface protective linings. The gene was normal in all 10 unaffected family members and in 57 other unaffected people tested. Studies of 10 other families with inherited osteoarthritis remain largely inconclusive.

The researchers suggest that the mutation ultimately weakens collagen's triple-helical structure, making it susceptible to degeneration after only a few decades of normal wear and tear.

Although no effective drug therapy so far exists, Prockop says early detection of the faulty gene could help people "tailor their careers and exercise habits" to minimize arthritis-accelerating stresses.

— *R. Weiss*