Laser gene-mapping yields clues in diabetes

As difficult as geneticists found it to pinpoint the gene for Huntington's disease and the gene for cystic fibrosis (SN: 7/10/93, p.20), those searches seem simple compared to the quests for the genetic bases of more common disorders, such as diabetes and schizophrenia. Several genes and environmental factors seem to play a role in the development of these illnesses, making it difficult to tease out specific causes.

A refinement of a gene-mapping technique now promises to simplify these quests and has already enhanced the understanding of type I, or insulin-dependent, diabetes. "We have proved for the first time that type I diabetes is a polygenic disease," says John A. Todd of the University of Oxford in England.

Other studies had indicated that a form of a gene responsible for an immune-system molecule called HLA class II and a version of the insulin gene were important in this disease. The new data confirm HLA's key role — HLA genes account for about 40 percent of an individual's risk of developing type I diabetes. The insulin gene seems no more important than about a dozen other genes, Todd said last week at the Jackson Laboratory in Bar Harbor, Maine, during the Short Course in Medical and Experimental Mammalian Genetics.

If these findings hold up, then testing for this HLA gene may help identify people at high risk of getting this disease, he adds.

To home in on a gene, scientists first identify ever smaller sections of the chromosome on which it resides. For several years, gene mappers have used DNA signposts called microsatellite repeats as markers to delineate these sections.

To streamline the analysis of these markers, Todd's group labeled 300 of them with fluorescent dyes. These markers divide the human genome into sections of 20 million nucleotides. As the labeled DNA sections migrate down a gel, a laser detects each one's color and sizes it more accurately than a person could, Todd explains. Then a computer stores and analyzes the data, comparing an individual's genome to those of other family members, Todd's group reports in the July NATURE GENETICS.

From these comparisons, the researchers compiled a "suspect list" consisting of all sections of DNA that show up in diabetic children more often than expected. When compared to lists generated from 100 families with diabetic members, "you begin to find out which sequences are cropping up all the time," Todd says.

Eighteen suspect sections, not counting those with the insulin and HLA class II genes, appeared on multiple lists. The team is checking the 18 against the genetic makeup of another 100 diabetic families.

The two sections evaluated so far do appear in these families, Todd notes. However, he expects that many of the 18 will prove uninvolved in diabetes and that new suspects will crop up.

Using dyes, a laser, and automated data analysis makes this mapping technique 10 times more efficient than existing ones, Todd says. These refinements make practical whole-genome screens that evaluate all of an individual's chromosomes at once. — *E. Pennisi*

Changing hepatitis C evades immune system

For the first time, researchers report that the human body produces antibodies against the hepatitis C virus. However, the rapidly mutating virus can outwit that line of defense to produce a chronic infection of the liver. The new findings hint at the difficulties in fashioning a vaccine that will shield people from multiple forms of this wily virus.

Patrizia Farci of the National Institute of Allergy and Infectious Diseases in Bethesda, Md., and her colleagues wanted to see if they could shield chimpanzees from the hepatitis C virus, a microbe that can cause a chronic inflammation of the liver.

Perhaps the least well known of the viruses that trigger this disease, hepatitis C can be spread through exposure to infected blood or body fluids, sharing needles with an infected person, and in some cases, transplantation of an infected organ (SN: 8/17/91, p.103).

The researchers reasoned that antibodies — proteins made by specialized immune cells — would circulate in the blood of an infected person. They therefore obtained plasma, the clear portion of blood, from a volunteer who had become infected with hepatitis C during a blood transfusion in 1977. (Blood is now screened for hepatitis C, and the risk of contracting the disease through a blood transfusion has declined.) The team also had access to the strain of virus infecting this patient during the acute phase of the illness.

In one experiment, the researchers injected a chimp with a strain of the acute-phase hepatitis C virus and with plasma collected from the volunteer in 1979. In the Aug. 2 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, team members report that they blocked infection in this chimpanzee. Those findings show that the plasma obtained from the volunteer in 1979 contained antibodies that successfully neutralized the early form of the hepatitis C virus.

However, the researchers found they could not guard against hepatitis when they injected two other chimps with a mixture of the same virus and plasma taken from the recruit in 1990. At that point, the volunteer had already developed a chronic form of the disease. Scientists know that at least 50 percent of people infected with hepatitis C go on to suffer from this debilitating chronic disease, which can lead to liver cancer and death.

The virus present in the patient's blood in 1977 appeared very different from the virus recovered in 1990, the scientists found. Genetic analysis revealed that a section of the virus' outer coat differed by more than 28 percent between the 1977 strain and the 1990 strain.

These findings offer the reassuring news that the human body appears to manufacture protective antibodies against hepatitis C, at least at first.

The worrisome news is that hepatitis C appears to change so drastically that an effective vaccine may require a broad scope of action. Researchers will have to design a vaccine to protect against the early form of the hepatitis C virus as well as the later forms, perhaps a very difficult task. — *K.A. Fackelmann*

Salts add tightness to DNA supercoils

Within the watery world of living cells, DNA molecules do a tortuous dance. First the chainlike strands wind themselves into helices. Then they bend and twist again, folding into gnarled supercoils.

At first glance, each strand resembles a tangled braid. In fact, the DNA supercoil is a carefully articulated knot that ties itself up according to rules governing its geometry and electrical forces acting on it from the liquid surroundings.

To understand more completely how DNA supercoils and the forces that make the strands writhe, Tamar Schlick, a mathematician and Howard Hughes Medical Institute researcher at New York University, and her colleagues have developed a computer model that links knot theory to biochemistry.

Addressing a meeting of the Society of Industrial and Applied Mathematics in San Diego last week, Schlick explained that her computer simulations reveal the influence of salt concentrations on the tightness of DNA's supercoils.

Because dissolved salts carry an electrical charge, they can alter the shape of certain molecules with which they come in contact. Such behavior shows up clearly in the computer simulation, Schlick says.

While biochemists have known for some time that salts cause DNA's coils to