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****UT Southwestern researchers find new information about diabetes susceptibility

Dallas -- Gene studies of patients with Type I (juvenile) diabetes have led to new knowledge about which Caucasians are susceptible to developing the disease.

Drawing upon an exceptionally large bank of volunteers, Dr. J. Donald Capra and associates at The University of Texas Southwestern Medical Center at Dallas have found a pattern of dominant inheritance at work in passing on the disease, as well as new information about specific inherited genes called alleles that determine "dominant susceptibility" and "dominant protection."

The study by Capra, professor of microbiology, and his UT Southwestern associates is slated for publication in the June 28 issue of The New England Journal of Medicine.

Use of a large data pool of DNA material from 266 diabetic patients and 203 controls was important in clearing up some previously misunderstood concepts about predictive tests for genetic susceptibility, Capra said. Up to this point, studies on the genetic predictability of the disease have been limited in scope due to the small number of patients in any one study. The founding of the North Texas Diabetes Registry four years ago made Capra's study possible.

The UT Southwestern studies used certain nucleic acid compounds called oligonucleotides to "type" DNA in cells. The oligonucleotides are used as gene "probes" to explore and seek out the "homes," or positions, of certain inheritable characteristics on the genes of a particular chromosome.

The DNA tissue-typing studies are correlated with the classic

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human lymphocyte antigen (HLA) tests done with antibodies. HLA-DR3and HLA-DR4 alleles have long been associated with increased susceptibility to Type I diabetes in Caucasians. HLA-DR analysis, however, had certain limitations as a predictor of developing Type I diabetes.

Capra said that two major new findings resulted from studying the HLA-DQ allele, which lies adjacent to HLA-DR. The new findings make prediction much more accurate. First, individuals who inherit the "dominant protection" gene, a beta-chain allele called DQw1.2, rarely develop insulin-dependent diabetes. Second, the protective effect of the DQw1.2 allele prevails over the effect of the dominant susceptibility gene, called DQw8, if both are inherited.

An identical twin of a patient with Type I diabetes has a 50-50 chance of developing the disease. Capra said the fact that only a 50-50 correlation can be made in twins with identical DNA proves that diabetes is more than just a genetic disease.

"Many diseases, such as diabetes, are associated with specific histocompatibility or transplantation antigens," he said. "These are molecules that are involved in the recognition of an invading pathogen -- like a virus -- as foreign, and they trigger the body's defenses against it. In the case of Type I diabetes, the immune system is activated to attack the pancreas' beta cells because an unknown and presumed environmental agent has caused beta cells to be recognized as 'non-self.'

"We want to know what's happening before the process that damages the pancreas is complete and the patient presents in a diabetic crisis," Capra explained. "We want to know what triggered the process. Was it water from a well in North Denton or the bite from a particular mosquito? Could it have been a certain cold virus?"

Once the process is understood, scientists can attempt to develop measures to counter the disease, he added. One possibility might be the development of a vaccine. Another might be the use of immunosuppression to prevent the destruction of the pancreas by the immune system.

Recent studies with cyclosporin, commonly used as an anti-

rejection drug for transplant patients, have shown promise in Type I diabetes. However, most researchers have concluded that the side effects outweigh the benefits. Future approaches may include the use of FK 506, a new anti-rejection drug currently in experimental trials.

With newer techniques such as the DNA typing described in the New England Journal article, experts can predict the development of Type I diabetes at a rate that is five times as accurate as formerly. "We would like to be able to pinpoint an individual's predisposition with the same 50-50 certainty as identical twins," Capra said.

He said the population at large can be divided into three groups with the new gene-probe test. "For the first group, we can say with almost certainty that they will never get the disease," he said. These people, he explained, have inherited the gene that confers dominant protection.

A second group, about a third of the population, has five to 10 times the normal risk because members of this group have inherited the gene for dominant susceptibility. The third group, also about a third of the population, falls into an intermediate position, neither particularly protected nor particularly vulnerable.

Capra believes that until predictability approaches 50-50 -- the highest possible for the disease -- most physicians will be unwilling to use the test widely with children. However, the new information derived from the studies represents a major step toward the goal of broad testing.

Capra, known internationally for his work in microbiology, soon will be named to the Edwin L. Cox Distinguished Chair in Immunology and Genetics. Working with him on the project were Drs. Robert Giles and Peter Stastny, UT Southwestern faculty members, and Marie Hoover, now at the University of Kentucky, as well as graduate student Jeanine M. Baisch and Tracy Weeks, a research technician at GeneScreen Inc. Capra credits Baisch with "doing most of the work." Assisting the study through her work with the North Texas Diabetes Registry, which provided DNA samples, was clinical nurse specialist Marilyn Alford.

Funding for the project was from the Juvenile Diabetes Foundation, the Greenwall Foundation and Dallas Biomedical Corp.

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Families with at least one child having diabetes can get information on the diabetes registry by calling (214) 879-6121.

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NOTE: The University of Texas Southwestern Medical Center at Dallas comprises Southwestern Medical School, Southwestern Graduate School of Biomedical Sciences and Southwestern Allied Health Sciences School.