Surprising pair of diabetes genes debuts

In 1861, an East Prussian couple emigrated to Detroit, bringing with them four sons, five daughters, and a secret that would last for more than a century. The secret was the cause of a rare form of diabetes that afflicted four of the couple's nine offspring and at least 74 of more than 360 known descendants.

That family secret is now out in the open.

In the Dec. 5 NATURE, researchers who have painstakingly studied this lineage reveal the identity of a mutated gene responsible for the family's unfortunate excess of diabetes. The long-awaited success actually stems from the finding of another inherited diabetes gene in other families, which the same research group also describes in NATURE.

Mutations in the two genes do not appear to be responsible for the more common, noninherited forms of diabetes. Nonetheless, researchers believe that the genes and the proteins they encode, which regulate the activity of other genes, could offer insights into treating or preventing all types of diabetes.

"It's quite a nice piece of work. It draws attention to two proteins that clearly play a role in preventing diabetes," comments Simeon I. Taylor of the National Institute of Diabetes and Digestive and Kidney Diseases in Bethesda, Md.

In 1958, the diabetes-prone East Prussian descendants came to the attention of Stefan S. Fajans of the University of Michigan Medical Center in Ann Arbor. Fajans, who has gathered data on six generations of the lineage, found that family members suffered non-insulin-dependent diabetes mellitus (NIDDM), also called type II diabetes.

Yet the disease, which stems from an inability to control glucose concentrations in the blood, strikes unusually early in this family: It appears during adolescence or by the age of 25, rather than after age 40. This rare, inherited form of NIDDM is known as maturity-onset diabetes of the young, or MODY.

A research group headed by Graeme I. Bell of the Howard Hughes Medical Institute at the University of Chicago then joined with Fajans to take on the challenge of finding the responsible gene. In 1991, Bell and his colleagues localized the gene to a region on chromosome 20. That large span of DNA contained so many candidate genes that the search stalled, however.

Consequently, Bell's group began to study other families prone to early-onset NIDDM. In 1992, the researchers found that several of the families possess a mutant chromosome 12 gene that produces a defective enzyme involved in insulin's response to glucose (SN: 5/2/92, p. 300). From their studies of still other MODY families, the researchers concluded that the disease could result from a mutated gene somewhere on chromosome 7.

Bell's group has now identified mutations in a chromosome 7 gene called *TCF1* as the cause of those families' diabetes. This discovery immediately made the researchers suspicious that a related gene, *TCF14,* which resides on chromosome 20, causes diabetes in the original MODY family studied by Fajans. Indeed, Bell's group quickly found mutations in *TCF14* among family members with the disease.

These two diabetes genes encode transcription factors, proteins that bind to DNA and regulate the on-off activity of other genes. These particular proteins, called HNF-1alpha and HNF-4alpha, control genes in liver cells and in other tissues, including the pancreas, where the glucose-regulating hormone insulin is made.

Little is known about how the transcription factors might ultimately influence glucose concentrations, says Bell, noting that their involvement in diabetes comes as a surprise. "If you asked me to make a list of genes that could be responsible [for MODY], neither of these would be on my list," agrees Taylor.

HNF-4alpha controls the production of HNF-1alpha, so Bell suspects that mutations in each protein's gene trigger diabetes through a common pathway.

He and Taylor agree that the proteins, particularly HNF-4alpha, which is activated by an unknown molecule, are appealing targets for drug designers seeking to treat or prevent diabetes. The likely strategy, they say, will be to create or identify compounds able to influence the diabetes-preventing genes that the two proteins control.

— J. Travis

Smart materials for tiny robotic rovers

One day, an army of robotic insects from Earth may invade Mars or other planets with orders to search for signs of extraterrestrial life. Small and agile, they could clamber over rocks, burrow into soil, and slip into crevices inaccessible to larger space rovers.

At the Materials Research Society meeting in Boston this week, Sarita Thakoor of the Jet Propulsion Laboratory (JPL) in Pasadena, Calif., described her group's work on a device that could become part of the limbs of such robotic explorers; a current robotic prototype measures 6 by 10 centimeters. The device, a thin sandwich of materials called a flexible microactuator, would bend when stimulated by electricity or light and could also be used as a component of miniaturized instruments.

At the heart of the JPL group's device are materials known as piezoceramics. Light or electricity rearranges their chemical structure, causing them to expand or contract. Thakoor and her colleagues want to produce the microactuators by depositing thin piezoceramic films on polymer sheets and fibers.

Actuators currently made from piezoceramics employ a bimorph structure, Thakoor says. Two different piezoceramics are bonded together so that "when you put on an electrical voltage, one of them contracts and the other expands," she explains. "You get a big bending moment and a high displacement."

These bimorphs are only about 200 micrometers thick. Nevertheless, that thickness limits their range of motion. In JPL's design, on the other hand, a thin film of piezoceramic is deposited on an equally thin polymer to make a device only 2 micrometers thick. This microactuator is more flexible than a bimorph and responds to a much smaller stimulus.

The microactuator's small size also makes it a promising component of miniaturized scientific instruments that the robots could carry. The microactuator could respond to computer instructions to make adjustments in measurement devices, such as infrared spectrometers. It could also find its way into more earthly applications, such as medical diagnostics and devices.

At this stage of the project, the main challenge is to find polymers that can withstand the high temperatures needed to crystallize the piezoceramic films. Researchers usually deposit the films on hardy, rigid materials such as silicon or gallium arsenide, Thakoor says. One promising polymer is polybenzoxazole, she reports. That material's exceptional strength and stability compare well even with fiber-reinforced composite materials.

Thakoor and her colleagues seem to be making good progress, says Glen R. Fox of the Ecole Polytechnique Federale in Lausanne, Switzerland. "I thought it was interesting work." Fox presented a study on coating fibers with piezoelectric materials.

He adds that when thin films are deposited on polymers, the device may become unstable as the temperature changes. Polymers usually expand more than ceramics when heated. "Since the coating is rather thin, there's a likelihood that you'd get cracking," Fox says. Choosing a polymer wisely, however, can avoid that problem.

Ultimately, the JPL group would like to use piezoceramic materials that bend in response to light instead of electricity. That way, robotic limbs could be stimulated from afar without the need to connect electrodes to the microactuators.

— C. Wu