One Alzheimer's gene leads to another

In the 1760s, with an invitation from Empress Catherine the Great beckoning, thousands of Germans emigrated to farm the plains near Russia's Volga River. When World War I erupted, many of the so-called Volga Germans fled Russia for the United States.

In recent years, scientists have scrutinized DNA from these descendants of the Volga Germans. A small number of the families suffer from Alzheimer's disease much earlier—sometimes before age 50—and more often than the general population does. Investigators hope that unearthing the genetic flaw that produces these early-onset familial cases of the neurodegenerative disorder will help them understand the more common, seemingly random cases that emerge as people age.

Aided by the recent disclosure of an early-onset Alzheimer's gene in another group of families, researchers have now discovered that most of the Volga Germans with Alzheimer's owe their affliction to a mutation in another gene, one found on chromosome 1. With this gene in hand, researchers may have completed the roster of genes, now numbering three, responsible for the rare, familial forms of early-onset Alzheimer's disease.

"I think this might actually do it," says Gerard D. Schellenberg of the Veterans Affairs Medical Center in Seattle, one of the leaders of the Volga German collaboration, which is publishing its results in the Aug. 18 SCIENCE.

Over the last few years, Schellenberg and his colleagues have homed in on the location of the Volga German Alzheimer's gene by comparing the DNA of family members with and without the disease. By matching the inheritance pattern of the disease to that of pieces of DNA with well-known locations, they concluded that their Alzheimer's gene rested in a region of the long arm of chromosome 1.

Schellenberg's group had just begun the painstaking process of looking at every gene in that region, when a shortcut surfaced. Last month, a group led by Peter H. St. George-Hyslop of the University of Toronto announced the discovery of a gene on chromosome 14 that also causes early-onset Alzheimer's disease (SN: 7/8/95, p.23). Rudolph E. Tanzi, Wilma Wasco, and their coworkers at Massachusetts General Hospital in Boston, collaborators with St. George-Hyslop on that work, decided to see if the protein produced by the chromosome 14 gene were similar to any known proteins.

They searched a public computer database that contains information about expressed sequence tags (ESTs), short spans of DNA that represent portions of genes. One EST, says Tanzi, popped up as a match; its DNA sequence was similar to a part of the sequence needed to make the protein encoded by the chromosome 14 gene. Schellenberg, Tanzi, and the rest of the collaboration then fished out the full gene the EST had come from, a gene found right in the chromosome 1 region that Schellenberg's work had pointed to.

In seven of the nine Volga German families they've studied, researchers have found that family members with Alzheimer's disease have the same mutation in the chromosome 1 gene. This suggests that the families shared an ancestor with the genetic flaw.

Researchers continue to look for mutations in the chromosome 1 and 14 genes to see if they will explain all the early-onset cases. They've also started to explore the function of the two proteins made by these similar genes and how, when mutated, the genes contribute to Alzheimer's.

For instance, Steven Younkin of the Mayo Clinic in Jacksonville, Fla., told SCIENCE NEWS he already has preliminary evidence that mutations in the chromosome 14 gene may prompt cells to increase their secretion of one type of beta-amyloid. This protein, many researchers contend, may produce Alzheimer's disease by forming abnormal deposits in the brain that kill neurons.

"This field is on fire. It's just amazing the speed [with which results] are coming in," comments Younkin. *— J. Travis*

Tiny structures molded in capillaries

With the size of microelectronics seemingly shrinking by the month, scientists must search for better ways of fabricating tiny circuits, machine parts, manipulators, and optical devices.

Photolithography—a technique that uses lasers and light-sensitive chemicals to etch surfaces—has satisfied existing needs for the most part, particularly where metal, glass, and silicon come into play.

Plastics present other difficulties, especially as conductive polymers increasingly find their way into the microelectronic domain. To facilitate the use of polymers in the land of Lilliputian machinery, Enoch Kim, Younan Xia, and George M. Whitesides, all chemists at Harvard University, propose a new method for building polymer microstructures and etching plastic surfaces.

Their technique, reported in the Aug. 17 NATURE, allows them to cast tiny features in microscopic molds, filling them with liquid polymers by way of capillary action. Called MIMIC—for micromolding in capillaries—the new method employs a flexible master mold laced with a network of channels that forms patterns when placed on a substrate, the scientists explain.

No method exists for filling such narrow channels directly, the researchers note. However, when thin liquid polymer seeps into the tiny canals, capillary action pulls the plastic juice into the network.

Once the polymer has set and cured, hardening into a malleable plastic, the researchers can remove the patterned microstructure from the master and reuse the mold. The result is a layered, textured surface on which stand distinct, three-dimensional features.

"In this MIMIC process, we're doing the same type of thing that people do with photolithography," Kim says, "except that we can do this in a chemistry lab without any elaborate lithographic instruments."

"This process is much simpler and less expensive than traditional photolithography," he adds. For instance, photolithography requires two steps to form and pattern a film, whereas MIMIC requires only one—since forming and patterning a polymer film occur simultaneously.

Unlike standard lithographic methods, MIMIC permits a manufacturer to retain the master mold and make hundreds of subsequent copies, Kim notes. In addition, the technique works on many kinds of surfaces and materials, not just the flat films to which most lithographic techniques have traditionally been limited.

"The process is quite flexible," Kim says. Moreover, the ability to reproduce three-dimensional patterns and films of varying thickness distinguishes MIMIC from standard microlithography.

"Whitesides' recent work is very important," says Calvin F. Quate, a physicist at Stanford University. "I suspect that he's onto something. He'll probably find an interesting application for this technique."

As part of MIMIC's development, the research team will apply the patterning technique to other types of materials, observing both the method's advantages and limitations—particularly for patterning conducting polymer microcircuits and tiny optical systems.

Though in an early stage of development, MIMIC might one day find its way into the manufacture of computer chips or polymer diodes, Kim says.

"But that's still a long way off," he notes. "This process is still in its infancy."

— R. Lipkin