

GENETEAMWORK

Barrow physicians and scientists are teaming up to learn more about disease through genetic research and to develop better patient care

Researchers and physicians at Barrow are spending more and more time on genetic research. What they're learning is helping Barrow provide better patient care.

Take the case of cerebral cavernous malformations (CCMs). CCMs are clusters of very weak blood vessels in the brain that are prone to leaking blood. When they hemorrhage, CCMs can cause seizures, strokes and, in rare cases, death. CCMs occur in about one of every 250 people.

By the late 1980s, Joseph Zabramski, M.D., a neurosurgeon at Barrow, suspected that CCMs might have a hereditary basis. That's because he was treating several Hispanic families with a higher-than-normal prevalence of the disease.

Martha Valdivia and her family are a classic example. The Phoenix woman suffered her first seizure, caused by CCMs, at the age of 17. Her grandmother, brother and several cousins have also experienced symptoms caused by CCMs. The worst case was her younger sister, who began having strokes in her early 20s, underwent six operations to remove CCMs and died in her early 40s.

Interested in finding the cause of the disease, Dr. Zabramski began sending blood samples from his CCM patients to Eric Johnson, Ph.D., a "gene hunter" working on a CCM project at the Marshfield Clinic in Wisconsin.

"Barrow is one of the premier places for collecting DNA because of its large patient base. Dr. Zabramski was able to collect from well-characterized families," says Dr. Johnson. "It was clear very early on that the physicians at Barrow took research very seriously."

Drs. Johnson and Zabramski say that searching for a gene is like searching for John J. Smith in the United States. First, you must determine the state this particular John Smith lives in, then the city, the neighborhood and finally the street.

Using DNA samples from patients, statistical analysis, computer modeling and mapping, Dr. Johnson and other researchers identified the long arm of Chromosome 7 as the "state" in which the faulty gene resides. As their research continued, they gradually narrowed their search.

Then, in Jan. 1999, Dr. Johnson joined Barrow, where he continued his research into CCMs. Later that year, Dr. Johnson and other members of the CCM1 Consortium - which included scientists from Barrow, Duke University, the National Institutes of Health and the National Library of Medicine - announced that they had found the cause of hereditary CCMs: the gene known as KRIT1.

Their discovery has changed the way surgeons like Dr. Zabramski view CCMs. Doctors used to consider CCMs a structural vascular problem present at birth. But the discovery of KRIT1, which is similar to a tumor-suppression gene, suggests that CCMs may actually be a type of vascular tumor that can occur after birth.

"Now the theory is that CCMs occur when KRIT1 fails to suppress the proliferation of the cells that line small blood vessels. The cells divide unnaturally and form something similar to a vascular tumor," Dr. Johnson explains.

Understanding the genetic cause of CCMs enables Dr. Zabramski to provide better patient care. For instance, he has learned which CCMs should be removed and which can be simply monitored.

"Earlier, when you saw a lesion, you took it out because you thought that would take care of the problem. Now we know CCMs can develop at any time so there is no reason to remove asymptomatic ones," says Dr. Zabramski. "But once a CCM has bled outside the lesion capsule, the risk of recurrence is very high, so we usually remove it."

When a patient is diagnosed with the inherited form of CCMs, Dr. Zabramski provides information to other family members so they can receive testing if they wish. Barrow researchers have developed a simple blood test to identify carriers of the faulty gene. Early diagnosis and treatment can help prevent the strokes and seizures that can harm brain tissue.

Martha underwent her fourth surgery in 1998. Dr. Zabramski removed the CCMs that were causing symptoms but left one asymptomatic lesion. During the last year, Martha has had only one seizure. Although left with some memory problems, Martha is now taking classes at Glendale Community College.

Martha is thankful for Barrow's research into CCMs. It has given her an understanding of her seizures and a certain amount of reassurance - her two grown daughters have been examined and show no signs of the problem. With the knowledge brain specialists now have, the future also looks brighter for her four grandchildren, she says.

"Dr. Zabramski has been a blessing for many people with problems like mine.