

A major research study  
hopes to crack epilepsy's  
genetic code. **BY AMY LYNN SMITH**

# THE FAMILY CONNECTION



*While researchers have been able to identify several factors that can lead to an epilepsy diagnosis, 70% of new epilepsy cases have no known cause. And although the treatment for epilepsy has come a long way since the days when people believed seizures were caused by the moon, scientists still know very little about what role genetics play in epilepsy. “Our understanding of epilepsy is very limited, and that affects our ability to provide effective treatments—let alone any cure or preventive strategies,” says Dan Lowenstein, M.D., professor and vice chairman in the department of neurology of the University of California, San Francisco (UCSF). To overcome this restriction, Lowenstein and other experts have joined forces to conduct the largest-ever research study of epilepsy and genetics: the Epilepsy Phenome/Genome Project (EPGP).*

Funded through a \$15 million grant by the National Institute of Neurological Disorders and Stroke, the EPGP was designed to create a better understanding of what causes epilepsy, the genetic components the condition may have, and how doctors can better predict which treatment will work best for each patient.

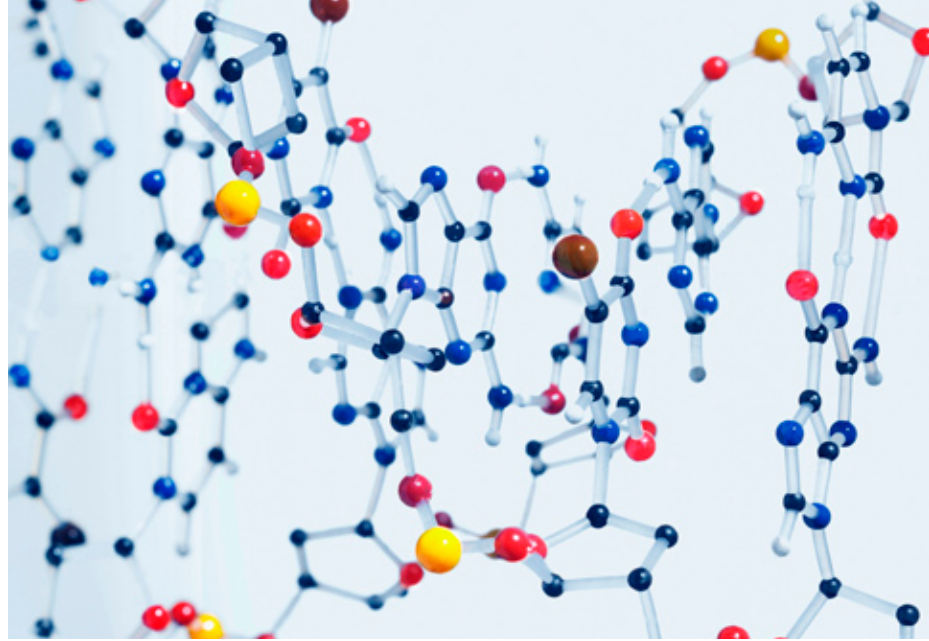
## **ADVANCED STUDIES**

According to Lowenstein, one of the most exciting advances in epilepsy research during the past 15 years has been the identification of altered genes that clearly cause the condition in certain people. But for the most common type of epilepsy, which is idiopathic—meaning it has no known cause—the role of heredity is far less clear. Project researchers seek to explore the theory that multiple genes may be involved in such cases.

“There’s this great unexplored territory in understanding the complex genetics of epilepsy,” Lowenstein says. “Epilepsy specialists from around the country realized that the only way to make significant headway on the question was to organize ourselves in a way that would let us reach out to thousands of patients and their families, and work together to collect and analyze information.”

By taking blood samples and conducting interviews with 5,250 participants, the researchers hope to gather a large enough volume of information to see patterns of subtle genetic differences in people with unexplained epilepsy or certain forms of the condition (see sidebar, page 18). At the same time, the study is considering the unique impact epilepsy has on every person living with the condition, which is where the words phenome (pronounced *fee-nohm*) and genome (*jee-nohm*) come in. “We’re collecting information on the characteristics of an individual as well as on the seizure types he or she

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has—which is known as phenotyping (*fee-no-type-ing*),” Lowenstein says. “And we’re collecting information on how their genes are structured, which is known as genotyping (*jee-no-type-ing*).”

Researchers are also looking for genes that could affect a person’s response to treatment. That’s why the EPGP also includes a review of each participant’s medical records, as well as thorough interviews designed to gather details about the nature of each participant’s epilepsy and how he or she has responded to treatment over time.

Kristen Schardein, R.N., M.S., participant/recruitment director for the EPGP at the UCSF Epilepsy Center, emphasizes that personal information is kept strictly confidential. “None of a participant’s private information will ever be shared with anyone outside of the study,” she says.

## REAL-WORLD RELEVANCE

Through the EPGP, researchers hope to identify genes that can give new insight into what they call the “network dysfunctions” of epilepsy. As Lowenstein explains, seizures are a result of improper functioning of brain networks, so discovering where or why those dysfunctions occur could be useful in developing new and im-

proved therapies. “It’s a long-term goal that’s going to take many years, but identifying these targets could lead to the development of therapies that might be able to specifically treat certain types of epilepsy,” he says.

Another goal of the project is to better predict how an individual will respond to a particular medication—before he or she ever begins taking it. “I have patients whose seizures occur only once every three or four months, so it can take six months to know whether a change to a new drug has any benefit,” Lowenstein explains. “And during that time, they might have to put up with mild to moderate side effects and just hope that the drug stops their seizures.”

The EPGP could also lead to the development of genetic tests to determine whether someone is at risk of developing epilepsy. There’s even the potential to develop therapies that could prevent epilepsy from occurring in the first place—even for people whose epilepsy is caused by a known event, such as a head injury.

“It may be in the distant future, but the possibility of keeping someone from developing epilepsy could be in part because of the insight we’re going to get out of studies such as this one,” Lowenstein says. He emphasizes the critical importance of enrolling qualified candidates in the study—many more of whom are needed. Otherwise the advances researchers hope to make in the understanding and treatment of epilepsy may be unattainable. “From the beginning,” Lowenstein adds, “we’ve seen this project as a huge collaboration among participants, health professionals and scientists that requires all of us to work together to pull it off.” ●

**To learn more about the EPGP or to register to participate, visit [www.epgp.org](http://www.epgp.org) or call 1-888-279-EPGP (3747).**

## Wanted: Siblings With Epilepsy

The Epilepsy Phenome/Genome Project (EPGP) is seeking participants who fall into one of two groups.

**1. People with epilepsy who also have a brother or sister with epilepsy.** Both siblings will be asked to participate. 1,500 pairs of siblings will be enrolled.  
**2. People who have seizure conditions such as infantile spasms, Lennox-Gastaut syndrome, polymicrogyria or periventricular heterotopias.** Both biological parents will be asked to

participate. The EPGP is enrolling 750 of these individuals plus their parents.

Candidates must be younger than 60, with the onset of epilepsy having occurred before age 40.

Participants will need to allow researchers to review medical records. Interviews can be conducted over the phone, and blood samples can be submitted by mail if enrollees don’t want to visit a clinic in their area. The entire process takes between two and four hours.