Saga in the Making

By Valerie Gregg

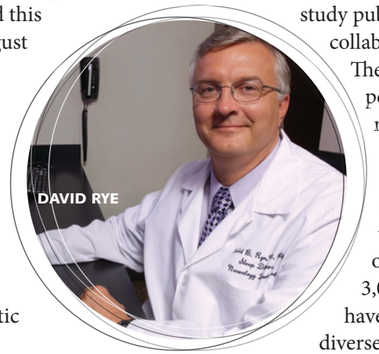
Emory's alliance with a genetic powerhouse in Iceland shakes out the causes of restless legs syndrome and other diseases

Emory neurologist David Rye was about to leave for vacation when he received a call this past spring. "Remember those guys in Chicago that held you up with the sawed-off shotgun?" said Kari Stefansson, CEO and founder of deCODE genetics, on the other end of the phone. **"If you don't get your data over here by Tuesday, you're going to wish they had shot you."**

Rye cut short his vacation, locked himself in his office for four days, and put the finishing touches on the clinical data of Emory patients with restless legs syndrome (RLS). He then jetted to Iceland, headquarters for deCODE, and worked day and night with Stefansson to match the patients' clinical results with their genetic codes.

The result was discovery of a common gene variant responsible for RLS, published this year in the July 19 online and the August 16 print editions of the *New England Journal of Medicine*.

Although collaborating with someone often described as a modern-day Viking can sometimes be trying, the rewards for Emory scientists have been great. Heart disease, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis are all under the genetic microscope for deCODE and Emory researchers.



DAVID RYE

Emory is one of deCODE's most important sources of clinical expertise in neurology, says Allan Levey, chair of Emory's neurology department. While at the University of Chicago as MD/PhD students in the 1980s, both Rye and Levey trained with Stefansson and deCODE co-founder Jeffrey Gulcher. They went their separate ways for a while—Stefansson and Gulcher to Harvard and Levey and Rye to Emory—but stayed in close touch.

They reconnected in a formal way at Rye's home in 2002, when Emory and deCODE signed a formal strategic alliance. In 2003, Levey and other collaborators received a two-year grant of $500,000 from the Robert W. Woodruff Health Sciences Fund—a program that encourages innovative science among health sciences researchers—to assist in starting the Clinical Research in Neurology (CRIN) effort, a data repository of clinical and DNA samples from Emory patients. CRIN now holds nearly 7,000 samples.

The relationship now stretches across several disciplines and has proved fruitful for everyone. This past May, Emory cardiologists Arshed Quyyumi and Viola Vaccarino and Levey co-authored a study published in *Science* with deCODE collaborators, most notably Stefansson. They discovered a gene variant that is perhaps the most significant genetic risk factor for heart disease.

"We provided one-third of the data for this study," says Vaccarino, director of the epidemiology core of the Emory Genebank, a repository of blood samples from more than 3,000 Emory cardiac patients. "We have provided them access to genetically diverse population samples. In turn, deCODE has provided advanced DNA and biomarker testing of these samples at no cost, which has been a huge help to us."

Icelandic origins

Rye's *saga* (an Icelandic word meaning "what is said" or a "story, tale, or history") began in 1997 when he first traveled to Iceland to consider working on a narcolepsy study with deCODE, founded just the year before. The company's mission: to conduct population-wide genetic linkage studies to uncover genetic factors in common diseases.

"When I first saw the setup, I wasn't quite sure it would pan out, but I was intrigued and interested," he says. "The study was very small and very focused. Narcolepsy is not a disease that affects a lot of people.

INFORMATION GATHERED FROM BIRTH IN THE ICELANDIC POPULATION IS PART OF A WIDELY RESPECTED GENETIC DATABASE LEADING TO NEW TREATMENTS FOR DISEASE.

The study got us started and provided a proof of principle. In 1999, other researchers discovered the cause of narcolepsy, but we were all over it quickly and published a paper shortly thereafter."

The original concept behind deCODE was to shake disease-related genes out of family trees. "We look for a cluster of cousins with a certain disease, say restless legs syndrome, and then ask the family to participate," explains Rye. "That allows us to concentrate our efforts on pockets of the disorder where the transmission of an offending gene between generations could be easily tracked. We then match the genetic data to the phenotype—hair color, eye color, height, length of life, or whatever trait or disease we're interested in studying."

Iceland is an ideal place to study the intersection of genetics and disease. The country's fanatic zeal for genealogy—most people can trace their family trees back to the year 1,000 A.D.—and deCODE's concentration of the most powerful genetic fingerprinting equipment in the world have made it the epicenter for genetic study of disease. About 97% of the Icelandic population that has ever lived is now recorded in the national database, and the deCODE campus has grown to include a clinical research center and a biopharmaceutical research center. Translating new discoveries in human genetics into new drugs and diagnostic tools is deCODE's ultimate aim.

It took an act of the Icelandic Parliament to resolve ethical and privacy concerns regarding mapping the genome of the entire country, but deCODE was successful in the end.

"Icelanders can go online, type in their social security number, and within milliseconds, track their family tree back to the 9th century," says Rye. "They had to condense vast amounts of genealogic information into a database. Then came the process of genotyping individuals and matching gene variants in family groups to clusters of disease."

The uniformity of the Icelandic population, totaling only about 300,000, helps isolate and connect genes with clusters of disease. Indeed, phone books in Iceland list people by first names because so many people have the same last names. Emory and other American population samples add power to deCODE's Icelandic data.

ICELAND, HOME OF deCODE GENETICS

"Our U.S. subject samples confirm, validate, and in some instances add information to what is found in the Icelandic population," says Rye. "Essentially, we started capturing as much information as possible, including DNA from patients coming through neurology and cardiology. DeCODE has provided tremendous support with the logistics, just because they have a wealth of experience, having collected more than 140,000 blood samples. The integrity of the process is important to making sure the information is reliable and valid all the way through the process, both clinically and genetically."

DeCODE operates 24/7, crunching more genetic data than all the rest of the world combined, and has found genes for 15 disorders thus far. It has perfected the art of valid information transfer—rendering a clinical diagnosis, taking DNA samples, genetically processing the samples, and ultimately assimilating the data. "The information technology side is spectacular," says Rye. "DeCODE developed its own software from scratch in a high-throughput manner to generate the highest-quality information. That's how they have gotten to this point."

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EMORY RESEARCHERS ARSHED QUYYUMI, VIOLA VACCARINO, AND ALLAN LEVEY COLLABORATED WITH deCODE ON A HEART DISEASE STUDY PUBLISHED IN *NATURE GENETICS*. THE RESULT WAS DISCOVERY OF A COMMON GENETIC VARIANT THAT DRAMATICALLY INCREASES THE RISK OF HEART ATTACK.

Too many clues on the train

Ironically, the usefulness of a thousand years of genealogy no longer matters as much in light of powerful new genomic technology. Most genetic research these days looks forward, not backward, and is less reliant on familial clustering. But because of deCODE, Iceland remains the center of the world for sheer capacity of genome processing. Academic and government scientists are just now starting to catch up in the game of genetic discovery. In turn, deCODE needs more diverse genetic data.

"There are too many clues on this train," says Rye, quoting the book *Murder on the Orient Express*. "They have all this wonderful clinical and genetic data and would benefit greatly from more statistical geneticists and genetic epidemiologists to mine the wealth of information on hand and to manipulate, interpret, and communicate the data to the world. They also need ever larger and more diverse genetic samples."

Because of both new technology and international data samples, results have been coming especially fast and furious in the past year. Emory most definitely is on board.

In January 2006, Quyyumi, director of the Emory Genebank, joined with Vaccarino and Levey in collaborating with deCODE on a study of heart disease published in *Nature Genetics*. A new method of analyzing huge amounts of genetic material yielded the more definitive results published most recently in *Science*. This new technology—genome-wide association on Illumina chips—allows scientists to probe for gene variants in more than 300,000 single nucleotides of the genome.

The result was discovery of a common genetic variant that dramatically increases the risk of heart attack. The variant, an SNP (a single-letter variant in the genome) on chromosome 9p21, was discovered through genome-wide SNP analysis in Iceland and replicated in three cohorts of European descent from Philadelphia, Atlanta, and Durham, North Carolina. The variant is estimated to account for approximately one in five heart attacks in people of European origin, and nearly one in three of early-onset cases, making it one of the most significant genetic risk factors found to date for heart attack. Of more than 17,000 patients and control subjects in the study, more than 20% of participants carry two copies of the variant, conferring a more than 60% increase in the risk for heart attack. Those carrying two copies of the variant are twice as likely as noncarriers to suffer a heart attack before age 50.

ARSHED QUYYUMI AND VIOLA VACCARINO

The Illumina chips at deCODE were also key to Rye's success in tracking down a gene contributing to at least 50% of all RLS cases. He developed the clinical diagnostic tools for RLS to use in the study. To verify RLS diagnoses, Rye made use of a tool that accurately measures the number of times a person's legs twitch during the night. This objective measurement backs up the more subjective clinical diagnoses determined by simply talking with patients. "We wanted our data to be as clean and informative as possible," says Rye.

Graduate student Amanda Freeman and research assistant Joseph "Max" Beck spent a month in a sleep lab that Rye set up at deCODE in the winter of 2003, working through the long, sunless winter days to validate an accelerometer, an instrument attached to the foot to measure the number of movements. "We had to validate the utility of the instrument and then use it to verify our clinical diagnoses," Rye says.

After a patient was diagnosed, nurses interviewed extended family members to trace familial records of RLS. In many cases, these family members were relieved and grateful to have someone recognize their problem and to realize they could receive treatment with medication. That in itself is gratifying to Rye. But finding the RLS gene?

"It is just starting to really sink in," Rye says. "I'm amazed. We've got a slam-dunk. I never imagined that this is how the story was going to end. Yet it is only one chapter of the saga. More questions will arise and even more work will be required to translate these findings into improved patient care."

To learn more about Rye's work with deCODE genetics on restless legs syndrome, view the podcast at www.whsc.emory.edu/multimedia.cfm.