

Quebec Feels the Power of Genomics

By his own admission, physician-scientist Vamsi K. Mootha is no Lance Armstrong. But when he saddles up this summer for a bike-a-thon in Canada, he'll likely get a hero's welcome.

Using a sophisticated technique of his own invention, Mootha recently isolated the genetic mutation behind a fatal disease prevalent in French Canadian children from an isolated corner of Quebec. Based on his finding, scientists believe a treatment for the disorder—called Leigh syndrome, French Canadian type (LSFC)—is now within reach. So local families have fresh reason for hope. As one way to honor Mootha for his work, the grateful community insisted that he join its annual LSFC-fundraising bike ride this summer.

Rare elsewhere in the world, LSFC is common in the Saguenay/Lac-Saint-Jean region of Quebec. Most of the 300,000 French Canadians who live there trace their origins to some 100 families who settled the region in the early 1800s. At least one member of those founder-families carried the genetic mutation for LSFC, and today, 1 in 23 of their local descendants possesses it. One out of every 2,000 children born there has LSFC, a rate comparable to cystic fibrosis and other more common diseases in the United States.

When both parents carry the mutant gene, they have a one-in-four chance of bearing a child with LSFC. The child appears developmentally delayed in infancy and then most often dies before age six from metabolic shock induced by a cold, a viral infection or other common physical stresses resulting in a lactic acid buildup in the bloodstream. Most parents do not realize their children even have LSFC, or that they themselves are carriers, until a child becomes sick.

Mootha began doing research on mitochondria (the sites of cells' energy production) at Harvard Medical School and at the National Institutes of Health (NIH), where he was an HHMI-NIH research scholar. While a clinical resident in internal medi-



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cine at Brigham and Women's Hospital in Boston, he continued working on mitochondrial biology at the Dana-Farber Cancer Institute with HHMI investigator Stanley J. Korsmeyer.

Mootha's next step as a scientist was in the fall of 2001, when he arrived at the Center for Genome Research at the Whitehead Institute for Biomedical Research as an HHMI physician postdoctoral fellow. At the suggestion of institute director Eric S. Lander, a prominent researcher in the Human Genome Project, Mootha began to work with an in-house team studying LSFC.

Whitehead researcher John Rioux, a French Canadian who had previously directed a project to map another genetic mutation found in Quebec, invited Mootha

to apply his knowledge of genomics and mitochondrial biology, which was believed in part to underlie LSFC, to find the gene mutation causing LSFC. Rioux's team, including groups from McGill University in Montreal and the University of Toronto, had already identified the chromosomal region where the mutation would likely be found, but the area was still enormous, containing 2 million base pairs. The researchers estimated that given the available resources, sequencing all those base pairs to locate the gene in carriers of the disease would take nearly two years.

Mootha had a better idea: Conduct a "neighborhood analysis," using a computerized technique of his invention to find associations among the expression signatures—

the active state as indicated in microarray experiments—of different genes. Mootha's method is essentially an efficient search algorithm that exploits similarities in those signatures across vast sets of publicly available data such as those generated by the Human Genome Project, gene expression profile sources and proteomics datasets.

Mootha used his computer-based, integrative genomics method to reduce the 2 million candidates to 5,000 likely base pairs—a far more manageable target—with in a week. “It was such an incredible moment when the research assistant, Katie Miller, showed me the site of the mutation,” recalls Mootha. The excitement was just beginning.

Within those base pairs, a single mutated gene, *LRPPRC*, stood out as a likely suspect. Mootha and his colleagues tested the gene in patients, parents and control subjects and, less than four months later, proved it was indeed the cause of LSFC. Published in the January 21, 2003, issue of the *Proceedings of the National Academy of Sciences*, the finding rated national news coverage in Canada.

Meanwhile, a provincial government program has begun to screen families from the Saguenay/Lac-Saint-Jean region for the LSFC mutation. Rioux leads a Whitehead Institute effort to clone the gene in mouse models of the disease and begin testing therapeutic compounds. “We are confident,” he asserts, “that we'll have an effective treatment in the next 5 to 10 years.” And although the team's research has been marked by elegance of technique, high speed and demonstrable results, it has another distinguishing characteristic. “This was very different from any other disease project I'd been involved in,” Rioux says. “Usually the subjects are anonymous, but we got to know them and their parents, who really took a leading role in energizing the research groups.”

One of those parents was Pierre Lavoie, a local factory worker who lost two children to LSFC. Also a competitive athlete—an age-group winner of the renowned Ironman of Hawaii world championship triathlon—Lavoie embarked on a whirlwind bike tour of the region to raise LSFC awareness; he covered a phenomenal 650 kilometers in 24 hours. Lavoie's trek was transformed into a regular event in which he

collects donations for LSFC research en route. LSFC researchers also get involved: Last summer, Rioux rode with Lavoie in the last 150 kilometers—and Mootha is next.

When he elected to conduct laboratory research after completing medical school, Mootha worried that he would wind up “doing abstruse work with no relevance.” In light of his work on LSFC, he can set that concern aside. In fact, his technique has significance far beyond its immediate promise for the afflicted community in Canada; it is already being applied to other,

more common disorders such as diabetes and Crohn's disease.

Putting on his other hat when reflecting on his LSFC work, Mootha says that “as a physician, it was very gratifying to see how basic work actually impacts the population with the disease.” And thinking ahead to his ride with the LSFC bike-a-thon, Mootha observes that “I didn't figure that getting on a bike would be part of my scientific career.” Nevertheless, his place of honor with Lavoie and company will only underscore the relevance of that career. —MARC WORTMAN

Stevolution

What's in a name? Ask the National Center for Science Education (NCSE), a group that promotes the teaching of evolution. NCSE, an Oakland-based nonprofit, issued a brief proevolution statement in February that at press time was signed by 378 Ph.D. scientists—all of whom, in a striking example of selection, were named Steve.

“Project Steve” is both homage to the late Stephen Jay Gould and a wry response to a habit of creationists to circulate antievolution statements signed by a handful of carefully selected people with science doctorates. “We did it as a joke, but the antievolutionists are serious,” says NCSE executive director Eugenie Scott.

Several HHMI investigators joined their fellow science Steves (and four Stephanies) in the tongue-in-cheekiness. “I thought it was a rather interesting idea because humor really gets through to people,” says Steven Henikoff, HHMI investigator at the Fred Hutchinson Cancer Research Center in Seattle. “But there is a message there.”

The list counters the creationist argument that evolution is widely doubted in the scientific community. Because Steves make up about 1 percent of the population, this non-random Steve sampling may be seen as the tip of the iceberg, representing tens of thousands of non-Steve scientists. “It suggests that the organizers didn't simply go after some corner of the National Academy of Sciences,” notes signatory Stephen R. Sprang, HHMI investigator at the University of Texas Southwestern Medical Center at Dallas.

Feedback from the science community was supportive, both of the message and the medium. “I've had a lot of e-mail saying that this is hilarious,” says NCSE deputy director Glenn Branch. But the other side wasn't laughing. “I've also had a couple of e-mails,” Branch added, “from creationists who have missed the point, saying, ‘Well, science isn't decided by majority vote.’ We're aware of this.”

HHMI investigator Nipam H. Patel, of the University of Chicago, agrees: “I think it's a nice illustration of how united the scientific community is, and it's a great way to poke fun at what's going on.” Does Patel look forward to a Project Nipam? “Well,” he admits, “we may not get too many signatories on that.” —STEVE MIRSKY



GORDON STUDER