'It's awful because the time is going. At least, for my daughter it's going, because she's been ill for so long. She's the oldest of all the Lafora patients. She's 29. She'll be 30 next April. And I am very, very scared.' — Vera Faludi

Gene hunters race

LAFORA
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Fortunately, their eldest daughter, Joanne, was already 19 and seemed to have escaped the disease. But did she carry a gene for it? Could she ever have children? And what about their youngest daughter?

For a while, the Gellels carried on as usual. What else could they do? Diane never complained. When Sam arrived home from work, she would flash him a wonderful smile. But the signs were there. One symptom is myoclonus jerks – involuntary twitches of muscles.

"She used to write so well," Mr. Gellel says.

"Now, all of a sudden, her pencil will fly away, the pen will fly away, the fork will fly away. It gets worse and worse and worse. It was really terrible."

By the late 1990s, Diane was having seizures almost every day. She could no longer walk or speak. Her parents and two sisters could only watch, powerlessly. Shortly before Christmas, 2000, the seizures began to slam into her thin body with barely a pause. One of the particular cruelties of Lafora disease is how closely it adheres to its own rigid script. Patients tend to die at age 23, when seizures cause them to aspirate their stomach contents, causing a florid pneumonia and death. That is exactly how Diane died on Jan. 12, 2001.

But the terrible script did not end there.

Not long before Diane died, her younger sister, Amanda, had a seizure. She was 13.

"I think I knew it in my heart that Amanda had the same disease," Mr. Gellel says.

"Don't ask me how, but I knew."

Sometimes, as his daughters slept or did their homework, he would stare at their slender fingers and toes, noting the similarities in their features. He would pray to himself, *Jesus, not this one, too.* But when he called the hospital for Amanda's test results, he knew his prayers were in vain.

"I said to the doctor, 'Listen, you have to tell us, yes or no. Whatever it is, we're going to have to know.' I know he didn't want to say on the phone."

The doctor hesitated a moment, thinking. "She has Lafora," he finally replied.

Lafora disease is one of medicine's black widow spiders. Exotic and lethal, such diseases kill so few people almost nobody considers them a threat.

These orphan diseases include Prader-Willi syndrome, which causes people to eat themselves to death. Or kuru, once linked to cannibalism. Or Fibrodysplasia Ossificans Progressiva, in which the body grows a second skeleton, turning muscles, tendons and ligaments to bone, as in the mythical story of Medusa turning men to stone.

The list of rare ailments exceeds 6,000. Of course, the definition of "rare" varies. In Europe, a disease is deemed rare if it afflicts one person in 2,000. In Japan, it's one in 2,500. Americans call a disease rare if it affects one person in 1,325.

Lafora is rare even by those standards. It afflicts less than one in a million people, a macabre lottery in reverse.

Yet when all these rare diseases are gathered into one pool, they cause more suffering than so-called common diseases, such as lung cancer or stroke.

"Collectively, rare diseases are not rare," says Peter Singer, director of the University of Toronto Joint Centre for Bioethics. "A rare disease is only rare if you don't have it. If you've got a rare disease, it's not rare to you at all."

But as Dr. Singer points out, the rarity of some diseases makes it hard to obtain research funds, which makes it difficult to get scientists or drug companies interested in finding cures. Then there is the question of ethics. Is it fair to spend scarce funds on even scarcer diseases?

This is the dilemma now faced by medical science. The DNA pioneers, after racing to complete the Human Genome Project and pinpointing the genes that cause disease, are confronted with the more difficult task of trying to cure them. Who will spend tens of millions to cure a handful of children? "In some cases, the disease is so rare that after you find the gene, nobody works on it anymore," the University of Toronto's Dr. Scherer says.

Almost everyone knows someone who has had breast cancer or a stroke or Alzheimer's disease. But who ever heard of Lafora?

Even in neurological circles, it is described in textbooks but rarely witnessed.

Berge Minassian, an Armenian-born neurologist, saw his first Lafora seizure in 1994 during a routine housecall to an Iranian immigrant family in Los Angeles, where he was working as a medical resident.

"It was very distressing," he recalls.

"In a typical seizure, the patient loses consciousness, but what you see [with Lafora] is a very powerful shaking of the limbs, the arms and legs back and forth. The patient falls to the floor and just continuously bangs on to the floor and on to things until the seizure stops. The patients usually bite their tongues, pee on themselves, and if they have food or anything in their mouth, they choke on it. There is a lot of saliva."

The spectacle reminded Dr. Minassian of a religious experience. "Epileptics over the centuries were seen as being possessed," Dr. Minassian says. Paintings of Jesus expelling the devil from possessed people routinely portray people who look to be in the throes of an epileptic seizure. In fact, the word epilepsy in Greek means "being seized."

Dr. Minassian knew from his textbooks that, in the latter stages of Lafora, patients might have 100 seizures a day. He could scarcely comprehend such misery. He resolved to help find a cure for Lafora. That meant finding a gene.

In 1992, doctors treating Diane Gellel at the Montreal Neurological Hospital asked Mr. Gellel and his wife to go on a blood-gathering expedition. The Gellels had originally emigrated to Toronto from Malta, a tiny Mediterranean island with fewer than 400,000 people. Diseases like Lafora tend to arise from consanguineous mating – in bald terms, cousins marrying cousins, even if they are distant cousins.

"Lafora is a recessive disease," explains clinical geneticist Eva Andermann, who asked the Gellels for the blood.

"In all cases of recessive disease, the parents are both healthy but they're each carrying a version of the recessive gene."

While the odds of a child getting two Lafora genes are remote, they rise sharply if you marry someone with your own genetic background, Dr. Andermann says. A Lafora carrier who marries a stranger has a minuscule chance of fathering a child with the disease. The number rises to one in eight if he marries his first cousin.

"Anybody who's on an island with a few thousand people and their families have been there for several generations, there's no way that they're not related in some way," she says.

'I think I knew it in my heart that Amanda had the same disease'

Such islands need not be surrounded by water. Dr. Andermann and her husband, neurosurgeon Frederick Andermann, had found a small cluster of Lafora cases in Quebec. Because most Quebecers are descended from a small number of settlers who arrived from France in the 17th century, they comprise a kind of genetic island. This is known as the founder effect. Dr. Andermann suspected the Gellels' family tree might hold the same Lafora gene that plagued her Quebec families.

So Sam Gellel and his wife, Rita, returned to their native Malta to collect blood from their parents and grandparents for testing. The notion he may have married a distant cousin clearly makes Sam Gellel uncomfortable.

"There is nothing you can say," he says, shrugging. "Malta is very small. I never knew my wife before. But they say that if you go back a few generations, probably her grandmother and my grandfather were related or something like this."

In late 1992, researchers in Dr. Eva Andermann's lab in Montreal began the painstaking search for genetic clues in the blood samples. But because of a fluke, they failed to detect the culprit gene. Discouraged, they sent the samples to Toronto's Hospital for Sick Children, where a group of scientists was building a global reputation for finding disease genes.

Berge Minassian had just arrived to take up his post as a staff neurologist.

Gonzalo Rodriguez-Lafora, a neuropathologist born in Madrid, Spain, is recognized as one of the great pioneers of science. He trained in Munich alongside Alois Alzheimer at the turn of the century. In 1910, while studying the brain tissue of a U.S. Civil War veteran who had suffered seizures and dementia, he found it contained tiny bodies, which some scientists describe as "squashed pearls," in the brain cells. These bodies now bear his name, as does the disease.

For close to 50 years, scientists have suspected Lafora bodies are caused by problems with carbohydrate metabolism, because they contain an abnormal sugar molecule called polyglucosan. The bodies build up in the neurons, much the way amyloid plaques accumulate in the brains of Alzheimer's patients.

"After 13 or 14 years of accumulation, the seizures start," Dr. Minassian says. "Now, in terms of family dynamic, once the prognosis is made of progressive epilepsy like this, it's pretty horrible, because there is nothing anyone can do to stop it.

"And because the disease starts late, by that point the family has had other children. In other genetic conditions, when the disease starts early, it's equally terrible for the patient, but the family can be counselled and they take measures not to have subsequent children. We've had Lafora families with six or seven affected kids," he says.

One of the first breaks in treating the disease came in Montreal in 1981, when pathologist Sterling Carpenter discovered Lafora bodies could be found in the skin of patients. It wasn't a perfect method. It sometimes failed to diagnose the disease. But compared with taking a tissue sample from the brain – not a trivial procedure – it was a step forward. Other neurodegenerative diseases, including Alzheimer and Creutzfeldt-Jakob disease, require a brain tissue sample for diagnosis.

Doctors used the Carpenter test to diagnose Diane and Amanda Gellel.

Shortly after his arrival at the Hospital for Sick Children in 1996, Dr. Minassian enlisted one of Canada's brightest researchers to his cause, geneticist Stephen Scherer. A boyish, tireless worker, Dr. Scherer is one of the world's top gene hunters. During the early 1990s, university researchers used to remark, "finding one disease gene gets you tenure." Dr. Scherer, 39, has found more than a dozen. He was intrigued with Dr. Minassian's quest.

"Berge was the one who really got us interested in the project," Dr. Scherer says.

"He sees the [Lafora] families. And he sees how devastating it is."

In the late 1990s, genomics was advancing at unbelievable speed. Screening for a single gene once took years. Using powerful new computers and sequencing machines, it could now be done in a matter of weeks, and labs around the world were racing to be first to find disease genes. Indeed, one of Dr. Minassian's friends was leading a search for Lafora genes in a Spanish lab.

"I often get asked, 'Do you have Eureka moments in genetics?'" Dr. Scherer says.

"And mostly in science, you don't. But when you identify a disease gene, you do. It's really wonderful. It's amazing."

Late in 1997, they began combing through the DNA from four Lafora families. One of them was the Gellel family.

After narrowing the candidates down to a few hundred genes, Dr. Minassian and Dr. Scherer used a "brute force" method, sequencing every gene in the suspected region. The Christmas holidays came and went, but they didn't stop working. They were close. One night, around 1 a.m., with his feverish baby daughter keeping him awake in the next room, Dr. Minassian kept poring over sheets of DNA data. Something seemed to be missing. Maybe the sample was screwed up.

KEVIN VAN PAASSEN / NATIONAL POST

Sam and Rita Gellel are seen with a portrait of their late daughter, Diane, at their Mississauga home. Diane had Lafora disease, an incurable form of epilepsy, which causes constant seizures and leads to dementia as patients lose their memory, powers of speech and sometimes their vision.