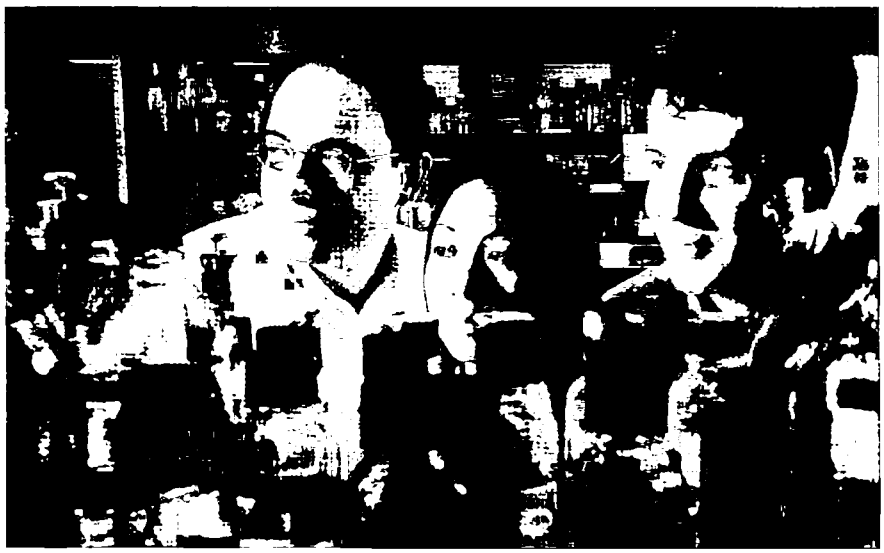
*'I often get asked, 'Do you have Eureka moments in genetics?' And mostly in science, you don't. But when you identify a disease gene, you do. It's really wonderful. It's amazing.' — Dr. Stephen Scherer*

# against Lafora curse



PETER J. THOMPSON, NATIONAL POST

**Berge Minassian, left, Elayne Chan and Stephen Scherer are part of a group of scientists at Toronto's Hospital for Sick Children who have built an international reputation for finding disease genes. Chan's notebook, below, contains some of her research on a Lafora gene.**

"Then it suddenly occurred to me that maybe there's nothing wrong with the DNA," he recalls.

"It's just that there's no gene there. It's deleted."

In healthy people, the gene is called EPM2A. It makes a protein that breaks down the Lafora bodies so they cannot build up in the brain. The Gellel children were missing EPM2A.

Exhilarated, Dr. Minassian leaped for the telephone. It was too late to call anyone at home. He would leave a message at the lab. To his surprise, Dr. Scherer picked up. He was madly writing up a grant application to get funding for the r Lafora gene study.

"We actually got the gene before we got the grant," Dr. Scherer chuckles.

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The World Wide Web has transformed the lives of families with such diseases as Lafora. Once divided by geography, they can now share their experiences with one another. That is how a single adoptive mother from Gutenberg, Sweden, came to know and love a mother of two Lafora children from Rimouski, Que.

"Audette Malenfant and Vera Faludi have never met in person," Dr. Minassian says. "But they are closer than the closest sisters I know because of this ordeal."

In the early 1970s, Ms. Faludi adopted a baby from Ecuador. The child had been left on the doorstep of a convent. She named the baby Jessica. In retrospect, perhaps Jessica was the consanguineous product of incest. It may be why she was abandoned.

A delightful child and teen, Jessica was talkative and popular. "She spent hours on the phone," recalls Ms. Faludi. "She was loved by all."

Then, at 17, things started happening.

"She went from being very normal to dropping things, swerving around with her bicycle," Ms. Faludi says. "Gradually she lost her speech. She began to stutter at first and then she lost her speech."

One day, Ms. Faludi found a scrawled note in Jessica's handwriting. It said, "I can't find my words."

Doctors at Gutenberg's university hospital were initially stumped when they saw Jessica in 1992. But then a skin biopsy showed the telltale Lafora bodies.

Ms. Faludi still gets angry when she describes their reaction.

"They more or less just gave up," she says.

"It was very sad because she's still a person. We had to go into intensive care because she had hundreds of seizures a day. And they just told me to give up and let her go to sleep." The doctors seemed to view Jessica as a living corpse.

One doctor expressed frustration that Jessica was using an expensive lung ventilation machine. If a 35-year-old father came in from a car accident, he warned, he would take it from Jessica. She was not going to be alive long anyway, he said.

"So I took her out of there and cared for her at home," Ms. Faludi says.

Desperate for help, she contacted Dr. Minassian, who put her in touch with Audette Malenfant.

Ms. Malenfant had two children, a boy and a girl. Both had Lafora.

The two mothers resolved to fight the disease together by funding research. Ms. Malenfant held fundraisers. Ms. Faludi sent the pension money Jessica received from the Swedish government. In 1997, she even petitioned the King of Sweden for funds. "He gave me 25,000 Crowns," she says, laughing.

"You'll do anything for your child. It's amazing what you can do."

It wasn't much money, but the researchers were happy to get it.

Touched by the depth of her devotion to Jessica, Dr. Minassian made a trip to Sweden to visit Ms. Faludi. There was something he wished to understand.

"In this case and in others I have always said, 'Why not let go?' Maybe that's the best thing to do."

But when he saw Jessica, lying in bed, smiling at her mother, he understood at once what the Swedish doctors treating the girl had ignored; the glittering spark of life in her eyes.

"The smiles she gives and the reaction to the mom... You think how horrible it would be to let go. Yet it's equally horrible to keep her living and suffering like that."

When the Toronto team announced it had found the Lafora gene, Ms. Faludi allowed herself to hope. Perhaps this meant a cure for the disease.

Then the bad news arrived.

Jessica had the EPM2A gene deletion. But the Malenfant children did not.

There had to be another gene. There were two kinds of Lafora.

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The name, Malenfant, means "sick child" in French. It's not hard to imagine how it originated. But few people have struggled harder to shrug off their family legacy than Audette Malenfant.

"The striking thing is that when you go see Madame Malenfant, she lives a very modest life," says Dr. Minassian.

"Her husband is a truck driver and she does not work... And Rimouski is not a rich part of the country. Yet she was able to raise funds of $10,000 or more [for research]."

When the EPM2A gene deletion was discovered, both children were still alive. They were stricken with Lafora when they were teenagers.

"She was very upset because at one point, Dr. Minassian believed her family was the same as the other non-French-Canadian families," says Dr. Eva Andermann, who helped diagnose the Malenfant children.

The researchers went back to work.

Using samples from several French-Canadian families, they narrowed their search down to chromosome 6. Once again, a race atmosphere began to prevail. One of the graduate students in Dr. Scherer's lab, Elayne Chan, worked doggedly on the project. This time, the breakthrough came earlier in the evening.

On April 11 this year, Ms. Chan dialled Dr. Minassian's cellphone to give him the news. The call found him at a classical music concert. Embarrassed, with audience members casting him dark looks, he quickly turned off the offending phone before she could deliver the news. As he burned in his seat, he waited for the intermission, then rushed into the lobby to call.

*The two mothers have never met, but 'they are closer than the closest sisters'*

The culprit was a mutation to the gene NHLRC1.

"It was a really, really small gene," says Ms. Chan.

"It wasn't in any known genetic databases."

It turns out NHLRC1 makes a unique protein that helps protect against Lafora; the researchers named it malin, after the Malenfants.

"We never would have found it without their help," Ms. Chan says.

Several weeks after the discovery, Dr. Minassian drove up to Rimouski to deliver the news in person.

"I've made it a point every time we discover a gene related to these families that we're very close to, I go and visit them," he says.

In the five years that had elapsed since the discovery of EPM2A, the Malenfants' son, Dantitck, had died at age 27. Only their 25-year-old daughter, Sophy, was still alive. Struggling to speak between her near-constant seizures, she greeted him brightly, "Dr. Min-a-sai-an."

Anxious to hear the news, another Lafora mother, living in Saguenay-Lac-St-Jean, packed her son into a decrepit pickup truck and drove 10 hours to Rimouski, her son having seizures in the passenger seat the whole way. Dr. Minassian took them all to dinner at a restaurant to tell them about the new gene. The mother had planned to drive home afterward.

"Then the boy had a major seizure," Dr. Minassian says.

"The whole restaurant table fell over and [he had] like, major, major convulsions. So Madame Malenfant said to the other mother: 'You cannot go home. Come and stay at my place.'

"At her place there are two bedrooms, one for each child. The boy who had died, she left his room exactly as it was when he died. She had made the bed, but all the pictures and toys were all there and nobody had slept in that bed in the years since the boy died. But ... we all helped this boy into her house — and she put this boy into her son's bed. And it was a very moving thing to see that boy with the very same disease in that same bed."

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"I'm doing OK," Amanda Gellel says haltingly.

Now 18 years old, she is much better than her late sister, Diane, was at her age. The Gellels are feeding her a special diet; since Lafora is caused by carbohydrates building up in the brain, she has no rice, breads or starches. She eats a ketogenic diet that is mostly protein. "Chicken, soup, ground beef, steak — but I don't like steak," she says.

She can't imagine how to describe going through a disease she watched kill her older sister.

"I don't know," she says finally. "I don't know what to say."

Along with the special diet, Amanda is also taking a new anti-seizure drug, Zonisamide. The combination of drug and diet has cut the number of seizures down sharply. She still goes to school most days, and talks on the telephone with her friends, although her speech is impaired.

But the underlying disease is still progressing. Unless scientists can find a way to translate genetic knowledge into a treatment, the terrible scenario will play itself out. "There is a minuscule hope," Dr. Minassian says.

While scientists race to find a cure, the families can only wait as their children get sicker. Mrs. Malenfant could not be interviewed for this story because her daughter, Sophy, was rushed to hospital early in September.

"It's awful," Vera Faludi said by telephone from Sweden last week.

"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."

Dr. Scherer understands. Despite the enviable list of disease genes he and his colleagues have mapped in the past decade, not one has been cured. "It's absolutely frustrating because you know now what's wrong," he says.

"And then you have to figure out how to fix it."

The discovery of the second Lafora gene, NHLRC1, was published this month in the scientific journal *Nature Genetics*. The long list of authors makes it plain this was a team effort. Besides the gene hunters, it lists neurologists who diagnosed the Lafora cases, clinical geneticists, pathologists and the whole army of modern academic medicine. The team also believes a third Lafora gene is lurking in the genome.

One of the most urgent next steps will be to develop animals that get Lafora to test potential cures. In a bizarre twist, researchers found an unlikely candidate. Purebred Miniature Wirehaired Dachshunds suffer a kind of twitching disorder that is a mild form of Lafora. "We don't plan to experiment on the dogs but we'd like to study their brain tissue when they die," Dr. Minassian says. Dog breeders keep much better records of pedigree than most human families, a fact the geneticists love.

One potential Lafora treatment may be to synthesize proteins from the two Lafora genes, since these proteins are either missing or malformed in Lafora patients. This might dissolve the Lafora bodies in the brains.

This approach is called pharmacogenetics, the field of matching therapeutic proteins to an individual's genome.

In some ways, pharmacogenetics is a link between people who suffer such rare diseases as Lafora or Huntington's disease and the wider world at large. Since every human being has a unique genome — except for identical twins — then no two people suffer a disease identically. This is why radiation cures some prostate cancer patients but not others, and why some patients survive SARS while others die.

By the logic of pharmacogenics, all diseases are rare. Lafora is just one of many.

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"OK, so we haven't got the treatment yet," Dr. Eva Andermann says.

"But right now, we can take, for example, the Gellel family. They can now be told whether they're carriers or not. And this is very important. And before they get married, they can find out if they're marrying a carrier.

"If you have two carriers marrying, they can have prenatal diagnosis to make sure they're not going to have an affected child. Depending on people's religious beliefs, if you have a disease that's as bad as this where you know there's no cure, I think there's some justification in having the option to terminate the pregnancy if the child is affected. And all of this was not possible before these genes were discovered."

In 1998, after finding the first Lafora gene, Dr. Minassian tested the Gellel's eldest daughter, Joanne. She has one copy of the gene, so she's a carrier, but she will not get sick. He also tested her husband, Joseph, who is not a carrier.

"It has to be both of them to get the disease, like me and my husband," her mother, Rita Gellel, says.

The news meant Joanne could safely have a family. Two years ago, she delivered a baby boy, the first of generations to come to be absolved of the Lafora curse. His name is Noah.

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