

New mom's heart arrhythmia triggers novel genetic discovery

Five members of the Bleau family share a common gene defect that was previously unknown to cause an irregular heartbeat

By Shelley White



Wanda Bleau, far left, and her daughters continue to learn about the genetic roots of her atrial fibrillation.

When most new moms bring their baby home from the hospital, their biggest concerns are getting used to changing diapers and trying to get a little sleep in between feedings. But just days after giving birth to her first child, Chantel Bleau of Windsor, Ont., felt like she was having a heart attack.

Chantel, who was 24 at the time, says she had first started to feel symptoms – a tightness in her chest – while in labour.

“I was in labour [a] very long [time], about 18-and-a-half hours, and I kept saying, ‘I’m not feeling well,’ and everyone kept saying, ‘You’ve been in labour a long time; you’re probably just sore,’” says Chantel, now 33 and a mother of two. She was sent home with her husband and newborn, Sophie, but the chest discomfort didn’t improve.

“It almost felt like someone had punched me really hard in the chest,” she says. “I was having trouble breathing, going up and down my stairs, but again, I thought, I just had a baby two days ago. And then it got to the point where my husband had to bring me into the hospital.”

Chantel was admitted to the cardiac unit at her local hospital, and after a battery of tests the cardiologist on call determined that her symptoms were not a heart attack but a heart arrhythmia. Chantel was diagnosed with atrial fibrillation (AFib), a condition involving an irregular heartbeat. It’s a condition that affects approximately 350,000 Canadians but is usually more common in older people.

Although atrial fibrillation itself is not usually life-threatening, it can contribute over time to the weakening of the heart muscle, severe symptoms limiting activity and exercise, or the development of a life-threatening event like a stroke.

“It was terrifying, to be completely honest. I was a brand-new mom and that’s what I was

focusing on and then I had that thrown in there,” says Chantel.

It was a traumatic event that would prove difficult to forget. “Even now, I get a little bit of heartburn and I get nervous,” she says. “It never goes away and it’s been almost six years.”

But it was also an experience that led to a medical discovery. Chantel’s atrial fibrillation was revealed to be an inherited arrhythmia caused by a single gene common to several members of her family, a discovery that has furthered medical science’s understanding of the genetic roots of heart disease.

Putting the puzzle pieces together

Wanda Bleau, Chantel’s mother, remembers first feeling chest discomfort as a busy mom of three in her early 30s.

“I was always short of breath and always tired and my chest always felt heavy,” says Wanda, now 54, also from the Windsor area. “But at that time, I thought it was more anxiety because it was around the holiday time and I was rushing around buying teachers’ gifts and that kind of thing.”

After a visit to the doctor’s office, Wanda was sent to the hospital to have tests, but she says nothing really came of it. “Back then, you went to doctors, you had tests done. Nobody really got too excited about it, and neither did I.”

Her symptoms continued on and off, but her true diagnosis didn’t come for another 23 years.

“I have to thank Chantel for it. Because it started with her,” says Wanda. “She was the one who started the process to give us all more education and more awareness of what’s going on.”

Chantel had been referred to Dr. Lorne Gula, a cardiologist at University Hospital in London, Ont., who began asking questions about whether anyone else in the family had symptoms similar to hers. Chantel noted that her mother had been plagued by an irregular heartbeat for years. “So then it was my mom and then we started following that along, and it was her brothers and my grandma – my mom’s mom – and he said, ‘Wait a minute, I’m starting to see a pattern,’” says Chantel.

Dr. Michael Gollob is a cardiologist, scientist and Chair of the Peter Munk Centre of Excellence in Molecular Medicine at the Peter Munk Cardiac Centre (PMCC). He first became aware of the Bleau family when he was contacted by Dr. Gula, who knew that Dr. Gollob did genetic research in the area of cardiac arrhythmias and cardiomyopathies.

“I reviewed the cases and it was clear there was commonality to their clinical picture, and we said, ‘Let’s try and discover the genetic cause,’” says Dr. Gollob.

The family agreed to take part in a genetic study helmed by Dr. Gollob. “For me personally, it’s education,” says Chantel. “I have two small kids, and if this is a hereditary thing I want to make sure they are taken care of. So I was completely on board.”

Genetic analysis of the family revealed that five family members – Chantel and Wanda, plus Chantel’s two sisters and one of Wanda’s brothers – share a defect in a novel gene not previously known to cause atrial fibrillation: the atrial-specific myosin light chain gene, or MYL4. The findings were published in the medical journal *Nature Communications* in April 2016.

Dr. Gollob points out that there are two main types of genetic diseases – those in which multiple genetic differences occur along one or more molecular pathways, incrementally promoting a disease process, and those in which one rare genetic variant is responsible. “The type of genetic disease that we found in the Bleau family is where a single gene is enough, if it’s defective, to cause a bad clinical condition,” he says.

The Bleau family’s genetic connection is unusual, adds Dr. Gollob, because they have a muscle disease of the heart that is specific to the top chambers of the heart, the atria. “A genetic disease of that form has never been described that is specific to the top chambers,” he says. “There are genes specific to the bottom chambers of the heart [ventricles], but this was the first that described the top chambers. At this point, we think it’s not a common cause for AFib, but we’re attempting to quantitate how many people have this gene as their cause.”

Atrial fibrillation is a condition

that can sometimes go unnoticed for years, because while some people experience symptoms, others do not. Symptoms can include feeling that your heart is racing or “fluttering,” chest pain or discomfort, shortness of breath or extreme fatigue. Atrial fibrillation can be diagnosed through devices such as an electrocardiogram (ECG), a Holter monitor (a portable ECG machine carried around for 24 hours or longer to record your heart rhythm) and stress tests (running tests on your heart while exercising on a treadmill).

Medication can be used to control AFib, and healthy lifestyle choices are also an important way to avoid complications in patients with AFib. High blood pressure, high cholesterol, diabetes and obesity can worsen the outcome for patients affected by the condition, so addressing any risk factors, maintaining a healthy weight and engaging in regular exercise can reduce risk. However, overindulgence in endurance exercise can also trigger development of atrial fibrillation in some individuals.

Chantel, Wanda and Ashley Bleau (Chantel’s sister) all say they try to maintain a healthy diet and exercise regime to control their atrial fibrillation, but the lack of energy and fatigue associated with the disease can make it challenging. Ashley, 26, was found to carry the MYL4 gene defect after being tested last year as part of the study. She only recently began experiencing symptoms of atrial fibrillation, and she says the condition now impacts her ability to exercise.

“I was pretty active before all this, and I can’t even go to the gym anymore for more than five minutes,” says Ashley. “I just can’t control my heart rate. It gets too high and I can’t bring it down, so now I just do walks – that’s about it.”

Chantel says she has struggled to keep her weight under control, and as the mother of two active children, it can be tough to focus on her own needs. “After two kids, I’m doing the best I can,” she says. But knowing that her atrial fibrillation has a genetic cause has helped her understand her condition better.

“Being educated about it has helped me deal with it personally,” she says. “In my generation, it’s talked about so much: how to

eat, how to live, how to exercise. I think people need to realize it's not always your fault."

Exploring the genetic roots of cardiovascular disease

Uncovering the genes that are the root causes of cardiac conditions is not just about scientific discovery, says Dr. Gollob. It's also about discovering a treatment or even a cure.

"When we find a gene that's involved in promoting a disease, that gene tells us a lot about the biological process that leads to the disease pathology," says Dr. Gollob. "No. 1, we've identified a gene that makes a protein in an important pathway that may lead to pathology. That protein may then become a target for drug development in therapy to attenuate a disease process or eradicate it altogether."

In the case of the Bleau family study and others like it, step one is finding the genetic cause, says Dr. Gollob, and step two is conducting future research that could identify novel drugs that may intervene in the molecular pathway.

"I see it as a 'bedside-to-cell-to-bedside' type of translational research study, where we identify a clinical disease, we identify the gene at the cellular level that causes the disease, we understand the physiology of that gene and the protein that it makes, and then we say, 'Can we now go back and target that molecular pathway of the protein to offset the disease process?'"

Dr. Gollob notes that when a molecular pathway is identified, it could be beneficial in all patients with atrial fibrillation, not just one family with one particular gene.

"That particular gene may not be the cause for everybody, but that pathway may be relevant for everybody," he says. "And so a drug that's developed after identifying a pathway may have huge application to many individuals with the same condition."

Dr. Jagdish Butany is the Director of Pathology in the Department of Laboratory Medicine and Pathobiology at the University of Toronto, and he

is a cardiovascular pathologist at the PMCC with more than 30 years of expertise. Dr. Butany says that a "large number" of cardiac diseases have a genetic basis.

"When I started out, genetics was really crude," says Dr. Butany, 72. "We knew that if I was born with a sixth finger, that was genetic. In the beginning, we didn't think very much of the genetic basis of heart disease, but it's been pleasantly surprising to see that almost everything seems to have a genetic basis."

It's a revelation that has helped to explain the sometimes-confounding nature of heart disease – why some people can do everything "right" in terms of lifestyle choices and still have problems, while others can do everything "wrong" and escape the consequences.

"There are people who eat bacon and eggs every day and nothing happens to them. And then there are others who eat one rasher and one egg and they are in trouble; they have to give it up," says Dr. Butany. "And then there are those who live a perfectly normal life, are at university, running, playing soccer and bang, they're dead."

But Dr. Butany also notes that it isn't enough to find an abnormal

gene in one individual.

"It's only looking at five people or 500 people and finding the same gene associated with the same abnormality that you know this likely is the cause," he says. "And having found it, that same gene doesn't always express fully in 10 people who have that abnormality. You may express it very little, while I may have a full-blown abnormality associated to it. So finding a genetic abnormality is one step toward solving the puzzle, but it's not the only answer."

The more people researchers can find who share a genetic abnormality, the closer they can get to solving that puzzle, says Dr. Butany. That's why one of his passions for the past 15 years has been collecting tissue samples in a "biobank" at the PMCC. With the help of Medical Director (PMCC) Dr. Barry Rubin in raising funds for the project, Dr. Butany started collecting samples from patients with cardiac tumours, and about nine years ago he began collecting tissue samples from people with other cardiovascular ailments.

"Now we have material that's potentially of tremendous use. With a biobank, you don't have to



Cardiovascular pathologist Dr. Jagdish Butany, left, and cardiologist Dr. Harry Rakowski are key players in the PMCC's ongoing effort to uncover the genes that are the root causes of cardiac conditions.

wait 10 years to get a reasonable sample of patients. You already have the banked tissue for 15 years that you can use for studies," he says. "[The biobank] is slowly beginning to be used and mined for that purpose."

But as researchers continue to identify faulty genes that are responsible for specific cardiovascular problems, the question then becomes whether it would be possible to screen the general population for that genetic anomaly.

"In the future, when a child is born, we could, at least theoretically, do genetic typing and we may be able to predict that, roughly, at between [ages] 15 and 20 the child might develop leukemia, or at 35 to 50 the child might develop cancer of the tongue, even if [he or she doesn't] smoke or chew tobacco. Or if the child lived to 65, [he or she] develop Alzheimer's. So that sort of roadmap is theoretically possible if we want to go down that road," says Dr. Butany.

Dr. Gollob says that the idea of screening the entire population for genetic abnormalities is just

not an economically feasible approach. "Screening the general population for genes is not something we do, because it would be cost-inefficient and difficult to interpret genetic findings in people who appear healthy. In the future, as we gain a greater understanding of genetic variation in the population and costs of genetic sequencing decrease, we may be able to have our genetic makeup on a 'chip' at birth and manage many conditions with a preventative approach."

Foresight for the next generation

Both Dr. Butany and Dr. Gollob agree that the biggest beneficiaries of diagnosing a condition as having a genetic root are the index patient's first-degree relatives.

"If you screen family members after you've identified an index case in the family with a genetic-based disease, then you have the opportunity to be preventative for those particular family members," says Dr. Gollob.

Chantel Bleau says taking part in the study and learning about the genetic root of her atrial fibrillation has helped her feel more in control of her condition. "Now it's just a way of life for me," she says. Knowing that it is an inherited disease, Chantel says she feels better able to recognize potential symptoms in her children.

"I wasn't diagnosed until I was 24, but knowing what I know now and looking back, I was having symptoms in my teens. So definitely knowing what to look for [in my children] helps me sleep a little better." Dr. Gollob says, "All that Chantel's children need now is a DNA test to see if they carry the genetic defect in the MYL4 gene we discovered. If they do not carry it, they will not get this disease."

Chantel says she also feels good about the contribution that she and her family have made to scientific discovery.

"It feels fantastic to know that they took my DNA and were able to isolate something that they can use," she says. "It's an incredible feeling." 🍷



Dr. Michael Gollob speaks with Genetic Counsellor Melanie Care. The Bleau family took part in a genetic study led by Dr. Gollob.