Elizabeth McNally, MD, PhD, has spent three decades studying the genetics of heart and muscle disease. Her work has yielded new insights into the development and presentation of cardiomyopathy and muscular dystrophy.

Dr McNally’s interests are rooted in her days as an undergraduate student at Barnard College. She earned her medical degree and doctorate in microbiology and immunology from Albert Einstein College of Medicine. She did her internship, residency and cardiovascular fellowship at Brigham and Women’s Hospital, and genetics fellowship at Boston Children’s Hospital. Before joining Northwestern University last year, Dr McNally, a Chicago native, had been at the University of Chicago since 1996.

Among her nearly 200 publications are studies on developing genetic profiling to identify mutations underlying cardiomyopathy, including a collaborative project associating a single mutation with a range of outcomes, and research demonstrating the utility of whole-genome sequencing to find individual mutations in cardiomyopathy patients, and of a supercomputer to facilitate whole-genome analysis.

She has explored how molecular modifiers—focusing on the TGF-beta pathway—change disease outcomes, both in animal models of muscular dystrophy and cardiomyopathy, and in patients with Duchenne muscular dystrophy. Recent work has proposed a novel approach to modulating this pathway. Other studies have identified a new modifier pathway mediating cell repair in striated muscle and elucidated the role of KATP channels in the neonatal heart’s shift to adult metabolism.

In September, McNally became director of Northwestern’s Center for Genetic Medicine, with the goal of transforming how genetic information is used clinically. She plans to capitalize on advances in genetic sequencing, leverage the high heritability of cardiovascular and neurological disease, and navigate the dynamic genetics of cancer, to improve patient outcomes.

What Was Your Childhood Like?
I lived in the northwest suburbs of Chicago and really was not raised in a scientific household—I was very much a girl who played with dolls and took ballet lessons. I was just at dinner with a bunch of my male colleagues, where all the men said, ‘I went to science camp as a kid,’ and the other woman and I said, ‘Yeah, I played with Barbies.’ We had a good laugh over that.

Where Did Your Interest in Science and Medicine Come From?
I was one of five children, and because there were five of us relatively close in age, I think we very much migrated to our own directions in order to have some kind of identity. My older brother was very much into history and things that were not science. I think I gravitated to a scientific direction because I didn’t want to be his little sister trailing behind him.

How Did Your Interest in Genetics Develop?
I didn’t get my first real laboratory research experience until I was between junior and senior year in college. Genetics was just coming on board through Southern blotting and techniques we now consider so dated and arduous.

It was the very, very early stage of being able to think about human genetics and understand that human genomes were different from each other. Even though we could only study one base pair at a time, I was fascinated by this idea of genetic diversity. So my very first project was getting DNA from kids with muscle disease and trying to look at variation in their genes.

That would have been 1982. And all these years later, I’m still doing the same thing. Now I see patients who have these disorders and we sequence their whole genomes and find the single base pair changes that cause their disorder. What’s most exciting is that we are actually now thinking ahead about how
to fix those genetics defects, as well as how do we apply our existing therapies better, based on the genetics.

Was That in the Laboratory of Leslie Leinwand?
Yes. I started in Leslie’s laboratory [she’s now chief scientific officer at the University of Colorado Boulder’s BioFrontiers Institute]; I was an undergraduate at Barnard College. She was a newly hired, junior assistant professor at Albert Einstein, and Leslie was recruited to Einstein because she was one of the early scientists applying new molecular techniques to human genetics. She knew how to isolate DNA out of blood cells and how to digest it properly and separate it for Southern blots. There were few restriction enzymes then, and they were all quite terrible. When I think about it, the chances of finding anything were so remote. But that was the technique at the time.

It was pre-PCR. That’s like saying it was prehistoric.

You Got Interested in Myosin Early. Why?
It was Leslie’s interest. Being a human geneticist, she was interested in studying human genes. Leslie’s lab had just cloned the first fragments of human myosin heavy chain genes when I joined her lab. So the first question was, ‘Is there variability in these genes?’

That idea that our sequences were actually different from each other was not one that people really appreciated. I can remember, vividly, in the 1980s thinking that myosin was way too fundamental to have any variation in it and believing that myosin genes from different people would be identical. That was clearly wrong because there are mutations in those genes. We just would think if you had a mutation in it, you’d be dead, you couldn’t survive.

Why Did You Continue With It?
I decided to join Leslie’s lab as an MD-PhD student. During the time I was in Leslie’s lab, it became the place for molecular cardiology. Mainly because she had started working on the human myosin genes and the importance of these genes to heart function, the lab became full of cardiologists. While I was a graduate student, Leslie’s lab attracted people like Peter Buttrick [now head of the cardiology division at the University of Colorado Denver], Glenn Fishman [now director of cardiology at New York University] and Rick Kitsis [at Einstein, formerly chief of cardiology there]. I was surrounded by it and inundated with it, so it became very clear I would have to become a cardiologist.

When it came time to pick a laboratory for my postdoctoral training I was incredibly excited by all the things that were going on in Lou Kunkel’s lab [Kunkel is now director of the genomics program at Children’s Hospital Boston], which was to look for genes that cause muscle and heart disease.

What Was the State of the Science Regarding Cardiomyopathy?
It was very interesting times. The bulk of my graduate thesis was to define the differences between alpha- and beta-myosin heavy chain. We examined rat sequences because it was very hard to obtain full length cDNAs for such large genes, especially from human hearts. It was really hard to get human hearts with decent RNA. So with the rat sequences, it was the first opportunity to take two highly related sequences and yet be able to point to single amino acids that made the difference between fast and slow myosin.

As I was leaving graduate school I was in the position of having to finish medical school and then do internship and residency. It turned out to be three years during which I was away from science. During that time PCR was invented and became widespread. So quite suddenly, it became possible to rapidly amplify, sequence and examine individual genes. It was a revolutionary time for human genetics.

Around that time the Seidman group [Christine and John Seidman of Harvard, and colleagues] discovered that mutations MYH7, which encodes beta-myosin heavy chain gene, caused cardiomyopathy in humans. They discovered mutations in these genes, the same genes I had worked on during my PhD. They found single-point mutations being responsible for hypertrophic cardiomyopathy. It was an idea that we didn’t think was possible, and yet turns out to be not all that uncommon. It was a very exciting time.

From That Point, How Did Your Research Unfold?
Over the next decade many different genetic diseases became linked to genes and specific mutations. At the same time, it started to become clear that the same mutation had a range of phenotypes. So it’s very important not to be too deterministic with genetics.

Now I see this all the time in patients at my clinic, where a family has a single mutation. With that same single mutation, across the family there are people who have the very severe disease with very early onset, and other people have it really, really mild. That’s been a driving force in research in my own laboratory, to understand what modifies how these genetic determinants express themselves.

How Has the Muscular Dystrophy Research Intertwined with the Cardiomyopathy Work?
You think about dystrophin—this big structural protein that plays a role in stabilizing the surface of muscle and heart cells. People have long had the idea that contraction induces damage to these muscles. If the muscle membrane is fragile, then muscle contraction is enough to tear it apart. As the cardiologist I was always thinking that heart cells similarly face high pressures, so what is it about cardiomyocytes that makes them less susceptible for contraction-induced damage? Couple that with the idea that when skeletal muscle is damaged it can regenerate, whereas in general, cardiac damage produces a large scar.

I still don’t have the answers to those questions. And I still would like to understand why some mutations affect skeletal muscle so much more than they affect cardiac muscle, and vice versa, when in many cases the genes are expressed in both the heart and the skeletal muscle.

What Work Excites You Now?
Human genetic variation is a really important part of what now interests us. We now have the capacity to evaluate human genetic variation. Since about 2007, when next-generation sequencing became more available, it is now possible to really address human genetic variation. We now have a real opportunity to look at human genetic variation in a whole different...
manner, which is computationally intense to do. But we also have the opportunity to link data on human genetic variable to human phenotypes, mostly gathered through medical records, and that provides opportunity to learn about genetic risk for disease.

For cardiology this genotype-phenotype correlation is incredibly important because cardiovascular disease is heavily influenced by genetics. From congenital heart disease, to development of high blood pressure, to vascular disease, to cardiomyopathies, to arrhythmias—all of those have a huge genetic susceptibility to them. That’s why cardiology is a great place to be doing genetics.

Who Would You Consider Your Two or Three Most Significant Mentors?
I’ve had a lot of great mentors. Leslie Leinwand was my graduate school mentor and she was superb—and continues to be. But I had a very unique arrangement, because I did about half of my PhD at Stanford, where I was working in the laboratory of Jim Spudich [now a professor of biochemistry at Stanford]. Jim has remained a wonderful mentor to me.

Lou Kunkel has been a great advisor and wonderful person to continue to talk to. I think I got part of my love for genetics from him, because Lou was one of the very earliest human geneticists, coming up with very creative ways of solving problems before we had the technology to really do it.

Which of Your Own Personality Traits Have Helped Propel Your Career?
I think any scientist would tell you it’s called being stub- born. (Laughs.) You can’t be a scientist if you’re not a little bit stubborn. We have far more failure than we have successes, so part of that is being able to keep going at the same problem and adjusting your approach and adjusting your approach. You have to have that appreciation that it’s hard work but it’s also great fun. Solving the problems and riddles of biology and medicine is pretty satisfying.

What’s Your Workday Like?
I usually work about 12 hours every day, doing all sorts of things. Part of it is because I keep an active clinical practice—even though it’s a small percentage of my time, there are a lot of patients and families with rare diseases, looking for somebody knowledgeable about their disease or condition.

We work a lot with families. Parents may carry a disease and they want to know what the risk is to their children. We’re in this window now we can identify people at risk for developing a disease, based on their genetics. That’s an opportunity to intervene, and some of the things we think about now relate to: When should we start treatment? Can we prevent disease? For those families where there is a risk of sudden cardiac death from irregular heart rhythms, we think about devices as a means to prevent sudden death. But there are other important questions, like are there exercise recommendations or diet recommendations? It’s giving us that opportunity to work with that next generation and change their outcome.

What Do You Do for Fun?
I’m a huge basketball fan. Chicago Bulls. I go to a lot of basketball games.

Of course I am fascinated by the athletes and the genetic variation that exists—thinking, ‘Wow, wouldn’t it be great to have the whole genome sequence on that guy and that guy.’ I see these kids who have real muscle disease and then to look at athletes, it’s an interesting contrast.

In the summer I try to get to Cubs games as much as I can, although they’ve been pretty sad the last few years.

If You Could Master One Skill You Don’t Have Now, What Would That Be?
I would definitely learn to code on the computer. I would learn R [programming language]. I feel like telling every young person I know right now: Learn to code.

I think that’s the future. I see these massive amounts of data we have coming at us, and whatever walk of life you’re in, almost everything is trying to assess large amounts of data. The trick of being able to do that is to instruct computers in the proper way to do that. You can’t do that unless you can code.

Talk About Your Family.
My husband [Steve Kron, a professor of molecular genetics and cell biology at the University of Chicago] is a scientist, too, so we do spend a lot of time working. We don’t have children of our own. But I’m part of my siblings’ families; that’s part of why I love being in Chicago, because I get to be around my nieces and nephews. My sister who lives 10 blocks away from me, she’s got four kids, and my other sister has one, and my brother has two—those are the ones in Chicago; and my other brother has one. And there are many, many cousins. We’re definitely a big Italian family.

How Do You Balance Marriage and Career?
We both very much like the same things. We spend a lot of time working and writing grants and papers and things like that. But we both like to travel, and travel is one of the perks of being a scientist. Seeing the world as a scientist lets you experience so much. We also like good food and good wine and both enjoy going to the Bulls games.

What Advice Do You Have for Young Investigators?
I really believe in encouraging my students to work on collaborative projects and having as many mentors as they possibly can. I obviously had a wonderful experience from doing the same thing.

For the people who are physicians and scientists, I encourage them to try to bring the two sides of their life together. When I trained, science and medicine were much further apart. These days with the progress in translating basic science discoveries, it’s much easier to work on something in the lab and then try to have that relate to something you’re doing in your clinical life.

Do You See Any Special Challenges for Women in the Field?
In certain areas of science and academic medicine, I don’t think women have the same opportunities that men do. I
view it now as part of my responsibility at this stage of my career to point out those inequities and to do what I can to balance the playing field. If you’re an assistant professor you’re not in a position to say that.

My particular issue is women in leadership positions. We’re in this interesting era now where half the medical students are women, more than half the graduate students are women. Even at the assistant professor stage it’s probably very close to 50:50, but when you look at senior people and specifically at leadership, it’s so dominantly male.

For decades we got by with saying, ‘It will happen; it’s just lagging.’ But we’re past that now. It’s time to make an effort and change the diversity of leadership, because we’re moving into the structure where we have a leadership class that doesn’t look like the people it leads.

When You Reach the End of Your Career, What Do You Hope Your Legacy Will Be?
I’ll be happy if we do things that contribute to development of new therapies. In genetics we’re really good at figuring out why something’s broken, but at some level you really want to fix it, too.

Disclosures
None.

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Karen Patterson

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