

## Louis Ptáček receives the 2015 ASCI/Stanley J. Korsmeyer Award

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### News

Channelopathies encompass a diverse set of diseases that are caused by mutations in genes encoding ion channel subunits or their regulators. The first recognition of a channelopathy came from Louis Ptáček (Figure 1), whose lab cloned a mutated muscle sodium channel gene found in a family with hyperkalemic periodic paralysis. His subsequent work extends far beyond channelopathies, as he has continued studying a number of inherited, familial disorders. Ptáček's research has identified a wide range of genes that are mutated in patients with migraine, epilepsy, cardiac arrhythmias, neurodegeneration, and circadian rhythm disorders. This year, the ASCI honors Ptáček's outstanding work using human genetics to provide fundamental insights into the molecular mechanisms that drive disease pathophysiology. The JCI recently spoke with Ptáček about his path to success as a physician-scientist. JCI: Your undergraduate degree is in mathematics. How did you become interested in studying medicine? Ptáček: I had a lot of different interests. I was always moving forward but following my heart. I loved math, so I studied math. But medical school was attractive to me, in part, because it seemed to open so many doors. I knew that as a physician, I could pursue research or become a clinician or work in industry. I also liked the idea of helping people. At that time, I didn't really know what I [...]

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*JCI:* Your undergraduate degree is in mathematics. How did you become interested in studying medicine?

Ptáček: I had a lot of different interests. I was always moving forward but following my heart. I loved math, so I studied math. But medical school was attractive to me, in part, because it seemed to open so many doors. I knew that as a physician, I could pursue research or become a clinician or work in industry. I also liked the idea of helping people. At that time, I didn't really know what I wanted to do, but it seemed that there were many different kinds of things I could pursue as a physician.

*JCI:* How did you decide you wanted to specialize in neurology?

Ptáček: For me, so much of this choice was about role models. Some people may say, "I've wanted to be a neuroscientist since I was 3 years old," but I don't think that's how it works for most people. I had great experiences in medical school working in neurology, working in internal medicine, and working in general surgery, of all

things. And so, until not so long before I had to put in applications for residencies, I didn't know if I was going to be a surgeon or an internist or a neurologist. In the end, I just felt like I identified most closely with the neurologist, and I've never looked back.

*JCI:* When did you decide you wanted to incorporate research into your work?

Ptáček: Much later than the average physician-scientist, I would say. I always



**Figure 1. Louis Ptáček is the recipient of the 2015 ASCI/Stanley J. Korsmeyer Award for his work studying the genetics of ion-channel defects and familial circadian rhythm disorders.** Image credit: Ying-Hui Fu.

had the impression that I would do something academic, but I didn't really know what that meant because I hadn't worked in a biomedical research lab as a student. As a resident, I started exploring opportunities for the future and became very excited about the revolution that was coming in human genetics. I was inspired in large part by the man who became my postdoctoral mentor at the University of Utah, Raymond White, who I consider to be the father of modern human genetics.

His lab was conducting research in building human genetic maps, using them to localize (and then clone) human disease genes and trying to understand the disease pathophysiology at a molecular level. This really appealed to me.

*JCI:* How did you come to study that first patient and family with hyperkalemic periodic paralysis that led to your discovery of the *SCN4A* sodium channel mutation?

Ptáček: While I was still a resident, I spoke with some people in Ray White's lab and expressed an interest in studying human genetics. David Viskochil, an MD/PhD in Ray's lab, referred my first hyperkalemic periodic paralysis patient to me. I saw her and enrolled her in my study while I was a resident. I went on to see exactly 100 people in that family (including her), 40 of whom were affected with this really rare disease. The amazing thing is that, very quickly, I became one of the world experts because, with this family, I had seen more hyperkalemic periodic paralysis than 99.9% of all neurologists.

This same family was actually the first family ever described with hyperkalemic periodic paralysis, back in 1951 by Frank Tyler (1). Of course, there were more offspring included in my 1991 study (2), because a number of years had passed since the initial report, but it also includes some of the same people from Dr. Tyler's report. At that time, Frank was still on the faculty at the University of Utah, and he became one of my clinical mentors.

Ray White was very generous, and he allowed me to use the human subjects protocol in his laboratory that enabled me to get consent to draw blood. His lab was extracting DNA from the blood and banking it, so I was collecting the family while a resident and received help from Ray's lab in securing the DNA. Then I started talking to people in his lab and around the campus to figure out how I would go about mapping and cloning the gene because I didn't have any experience with that. Utah, at that time, was a great place for human genetics, and I benefited from this

remarkable environment where I could ask for help from many of the world leaders in the field of human genetics. Once I figured out what I had to do, it was up to me to get the job done. It was partly my tenacity and hard work, but also the remarkable environment in Ray's lab and the department that were critical for my success. As with all things, there was also a certain amount of good luck along the way that helped me accomplish things that, with a little less luck, might not have gone so well.

*JCI:* From this initial discovery of the genetic cause of hyperkalemic periodic paralysis, you've gone on to study a number of channel genes that affect the pathogenesis of a diverse set of disorders, such as epilepsy, migraine, and cardiac arrhythmias, along with a number of familial mutations in circadian rhythm disorders. How did you come to work in such far-reaching areas of study?

Ptáček: This represents the joy and the power of being a physician-scientist. When I'm mentoring young people, I emphasize to them how much you have to focus in the beginning to make progress in one direction, but then as things work out and one has success, we have the luxury of branching out a little bit.

When I was beginning, I thought about nothing except hyperkalemic periodic paralysis. My first goal was to collect that large Utah pedigree, but then I began to see some other patients and have patients referred to me from around the country and around the world. But it all began with hyperkalemic periodic paralysis. Once I cloned that gene, there were a number of other related muscle diseases that I thought might be caused by the same or similar genes. So I broadened my clinical scope from just hyperkalemic paralysis to several different muscle diseases, including paramyotonia congenita, potassium-aggravated myotonia, myotonia congenita, and then I marched through systematically cloning the genes and the mutations that caused those diseases.

As a neurologist, I was always interested in epilepsy and migraine because migraine affects 15% of the population and epilepsy affects about 3%–4% of the population. Even in my first paper in 1991, I recognized that hyperkalemic periodic paralysis was a great model not only for other episodic muscle diseases, but also cardiac arrhythmias, epilepsy, migraine, and episodic ataxia. So initially, we studied the muscle diseases, and then epilepsy and migraine and other things. Eventually, other colleagues came to me because they knew I was doing genetics and would bring me families with other kinds of diseases. This is how we came to clone the gene for the neurodegenerative disease, spinocerebellar ataxia type 7; later, we studied families with spinocerebellar ataxia type 4.

A colleague at Utah, Christopher Jones, also brought me the first family I studied with a circadian rhythm defect. I knew nothing about circadian rhythm genetics or biology of sleep more generally, but I found it remarkably interesting, and nothing — absolutely zero — was known about the genetics of the circadian clock in humans. A lot was known in *Drosophila*, but in humans and in mammalian systems in general, there was almost nothing known, and so that was just too good an opportunity to pass up. Like everything else with me, it was a patient who came into a clinic that led me down the path of studying genetics of circadian rhythms and sleep, even though it's completely different and fundamentally not related to periodic paralysis or channelopathies.

*JCI:* What excites you most about your current research?

Ptáček: We're closer than ever to completing the circle and going back to patients with new therapies. Based on the first two circadian genes we cloned, and very mechanistic biochemistry and molecular biology studies done with my collaborator Ying-Hui Fu about clock regulation in humans, we are now doing a huge screen of a small compound library looking for jet lag drugs.

We've made so many animal models, and we continue to make many animal models of human mutations, so we're really able to probe very deeply. I think we've done this as well as anybody else, taking human disease genes and mutations to build really fantastic models that have allowed us to study what's going on at a molecular level and in the brains of mice with different circadian phenotypes, for example. Only through better understanding of the biology and the pathophysiology can we have a real hope for doing something new and different in terms of being able to help patients with different clinical phenotypes.

The track from first beginning to study a family with a genetic phenotype to making a difference in treating patients is an extremely long, hard road. And I think we are getting closer and closer to the end of that road in some of the projects that we're working on, but only after 20–25 years of work.

*JCI:* What does winning the Kornsmeier award mean to you?

Ptáček: It is, of course, a tremendous honor. I'm quite humbled when I look back at those who have won it before me. I met Stan [Kornsmeier] at several meetings and had always admired him as a remarkably intelligent and thoughtful individual who really embodied this concept of translational, basic science/patient-oriented research. It's people like him that I have always emulated. It's a great honor, and it just reinforces all the excitement and wonder that I feel for this remarkable field that I found myself in. I'm very humbled by it all but also very gratified.

### Sarah Jackson

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