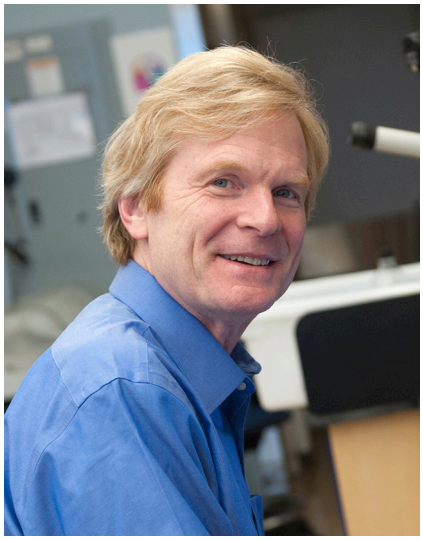
# Christopher A. Walsh

Christopher Walsh studies how the human brain develops with an appreciation for how basic science is informed and enriched by patients. In this interview, Dr. Walsh shares how mapping a genetic mutation united his scientific passion with his clinical training and advises that ideas are cheap but experiments are golden.

Christopher A. Walsh is Chief of Genetics and Genomics at Boston Children's Hospital, a Professor at Harvard Medical School, and an HHMI Investigator. He completed his MD and PhD at the University of Chicago with Ray Guillery; he then trained as a neurologist at Massachusetts General Hospital and did postdoctoral training with Dr. Constance Cepko at Harvard Medical School, developing barcoded retroviral libraries for cell lineage tracing. He started his own lab at Beth Israel Deaconess Medical Center in 1993 and moved to BCH in 2006. Dr. Walsh studies genetic, developmental brain diseases of children to understand how the human brain develops. Some of these genes regulate neurogenesis, and unexpectedly, some disease genes were targets of the evolution that distinguished the human brain from other species. His lab has sequenced genomes of single neurons from the human postmortem brain to develop a cell lineage map of the human brain and to understand the effects of age, disease, and degeneration on the neuronal genome. Dr. Walsh is a member of the American Academy of Arts and Sciences, the National Academy of Medicine, and the National Academy of Sciences.



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Boston Children's Hospital and Harvard Medical School

**_Neuron_ is marking its 30th anniversary this year. Which _Neuron_ papers have struck you as truly elegant or inspired and why?**

Wow—over the 30 years there have been so many. Recently, Paul Thomas's paper (Pederick et al., 2018, Neuron *97*, 59–66.E5) showed that abnormal cell sorting occurs in mice heterozygous for the X-linked PCDH19 mutation, which in humans causes epilepsy and intellectual disability in females while males carrying the mutation are normal. This resolves a conundrum in human genetics that has fascinated me for years, and it is always neat to find out just how crazy biology can be. But I also enjoy the way *Neuron* has helped define the field and the times, either with the review issues or by hosting articles that disagree over major findings.

**What future direction in neuroscience are you most excited about?**

We live in a time of incredible technological innovation in all areas of neuroscience, but I would say I am most excited about the tools, like advanced sequencing methods, that allow us to study the human brain directly—whether at an imaging, cellular, or molecular level. The Human Connectome project has allowed us—after more than a century—to finally validate and actually improve on Brodmann's subdivision of the human cortex, which has been in textbooks unaltered for literally a century. Single-cell RNA-seq allows us to interrogate neural cell types in humans with almost the same accuracy as in other species and to find human-specific neuronal types. There is nothing more exciting than combining a new technology with the ability to interrogate age-old questions that have been sitting there since the ancients. This is also amazing to me because such an ability to study human tissue directly, with a similar level of rigor to that which we apply to mice, seemed an impossibility when I was training; also because, like many neuroscientists, I ultimately got into the field wanting to figure out the human brain.

**How would you like to see neuroscience evolve over the next 30 years?**

The strength and attraction of neuroscience is its diversity in almost every dimension—in terms of technology, model systems, points of view, and background training. I think the future of the field depends upon seeing that intellectual diversity reflected significantly better in the population diversity of the scientists in the field in terms of gender and equality in terms of jobs and promotion.

**What is your guiding philosophy for running your lab?**

My success relies on attracting the best people that I can and then supporting their great ideas, so my lab's success has reflected the good ideas that were dragged in by students and postdoctoral fellows. In terms of project selection, I try to remind people that the greatest science in history—Newton, Darwin, Cajal, Hodgkin and Huxley, Watson and Crick, Hubel and Wiesel, Brenda Milner, Wieschaus and Nusslein-Volhard, Brenner and Horvitz and Sulston—all involve simple description and categorization, typically using a new technology, followed by proposing a model to explain the observations. Nothing much more complicated than that. We are not smart enough to figure out Nature, but instead have to let it come to us; hence the importance

of new tools. Genetics helps because it reveals nature as it really is, rather than as we hypothesize it might be.

**What is your personal philosophy?**

I am the 7th of 8 children, and we all get along remarkably well; I guess I owe that to my mom, who always said, "You never know where you next friend will come from." And I try to follow that in science. Although I am no extrovert, and consider myself poor at networking, the enjoyment of science comes from sharing it with others and meeting new people.

Fortunately I am lucky to have had several role models—Ray Guillery, Connie Cepko, and Joe Martin, among others—who have all abundantly illustrated that you can reach the highest levels of success in science without having to compromise in any way your identity, integrity, or rigor and without having to be mean or duplicitous to others. I try to emulate their examples.

**What are the questions that inspire your lab?**

Where do we come from? The development of every baby is an intimate replay of the process of biological creation from a single cell that leads to a new person, similar to others but different. On the one hand, this structure is defined by genes we inherit from our parents, and they from our ancestors, and which have been ruthlessly selected by ancient evolutionary forces. And yet, that biological tool is specified to be constantly changing in response to diverse stimuli. How do we reconcile genetic determinism with synaptic plasticity? Moreover, I see from meeting patients that there is a stunning diversity of possible brain structures that are consistent with someone we recognize cognitively and behaviorly as human and just like us. How is that possible?

**Do you have a favorite anecdote from doing science that you'd like to share (perhaps a key discovery moment)?**

Here I am, chief of a medical genetics division, yet I consider myself a developmental neuroanatomist whose entry into human genetics began quite by accident. Interested in cerebral cortical development, my first trip upon starting my lab was a pilgrimage to the Jackson labs thinking I would work on mouse mutants; I was disappointed to find at that time only one or two with abnormal cortical development. Just 5 months later, at a meeting in Venice, I heard a talk by one of my teachers from medical school, Peter Huttenlocher. He presented a family with an inherited malformation of the cerebral cortex (periventricular heterotopia), which he already suggested was X-linked and lethal to males. Listening to him, I had one of those rare moments in science where I literally felt my heart race and my palms sweat and my head ache, and I could not contain myself from wanting to run down to the stage to ask him to collaborate before anyone else could. Here was a mappable genetic mutation that united my scientific passion with my clinical training. Fortunately, the idea of actually mapping and cloning the gene seemed to come as a complete surprise to Peter, and our wonderful collaboration was born. This led, in turn, to a long history of human genetics research.

**What has been the highlight of your career?**

One of the early highlights was as a postdoc with Connie Cepko, when we labeled cerebral cortical progenitor cells with retroviral markers. Fully expecting to see perfect radial columns of clones in cortex, as Connie had seen in retina, I found it impossible to say where one clone ended and the next began because cells seemed lightly scattered all over the place. Connie's response was that we simply needed better technology, and she encouraged me to develop barcoded libraries of retroviruses to allow us to trace clones no matter where in the brain they went. Who at that time could have imagined that many clones (especially inhibitory interneurons) literally scatter over the entire cerebral cortex? Finding that was incredibly validating.

But human genetics is also wonderfully addictive. It allows you to take an unknown disorder—wondering for years, "How in the world could that ever happen"?—and then search and search until you boil it down to a single base change of a gene, typically one you have never heard of or imagined could do anything like what it turns out to be doing. So cloning doublecortin (*DCX*) and *FLNA*, the gene for Peter Huttenlocher's family, were great highlights as well.

**Who were your key early influences?**

After skipping my senior year of high school and never having experienced scientific research, I came to college with no idea what to do. First semester of college, I took Psychology 101 with Alan Leshner (later Director of NIDA and publisher of Science); he was an amazingly entertaining, engaging, and challenging teacher who amazed us about the wonders of the brain and behavior. I got my first taste of college neuroscience research with Owen Floody. But my PhD thesis advisor, Ray Guillery, was my first role model, and I feel much of my research project on genes and the brain ultimately derives from his pioneering work on genetic regulation of visual connections. Joseph Martin was my Chair while I was a resident at MGH, and has had so many influences on my career that I cannot count them all.

**What's your favorite experiment?**

From our own work, I would have to choose single-neuron whole-genome sequencing. The idea that you can take the genome of a single human neuron, amplify it a million times over, and then sequence essentially the whole darn thing and call mutations just like in regular DNA samples—and find that the patterns of mutations are accurate and actually make biological sense—astounds and amazes me. And the capper is that each neuronal genome has its own genetic barcode, just like those retroviral libraries from so many years ago, so that every human brain carries a permanent, forensic lineage map of every cell division that created it.

**What motivated you to become a scientist?**

I think there were many steps, as I gradually obtained a more realistic idea of what it means to be a scientist, but one story stands out.

At the end of my freshman year of college, I didn't get the fellowship I had wanted, to stay at college for the summer, but my brother-in-law got me a summer internship with Dr. Sadek Hilal, the Chairman of Neuroradiology at the Neurological Institute of New York at Columbia. That summer, they installed Columbia's first CT (computed tomography) brain scanner. Near the end of the summer,

I went down there to see what was up, and I saw Dr. Hilal lift up a grainy Polaroid print of an early CT image of the human brain, wagging it back and forth in the air to dry off the chemicals. He looked at us, gestured at us with the photo, and said, "This will revolutionize neurology." At the time I had no idea what he was talking about, but it definitely struck me that science could be really cool.

**What is your view on big data-gathering collaborations as opposed to hypothesis-driven research by small groups?**

Large groups will always tend to outcompete individual scientists, and so, like it or not, large collaborations are here to stay. I find collaborations are almost invariably key to having success and having fun, and large descriptive projects utilizing new technology can be expected to generate not only novel datasets but typically also new and unexpected insights.

On the other hand, I wonder whether large team science might change the face of science and attract different people to science over time. Cajal describes several key aspects of scientists that are not all positive: independent judgement, the ability to concentrate for long periods, and a passion for reputation that he compares to the motivation of great artists. Large groups ruled by committees could impair some aspects of individual autonomy and discovery that I think drive many scientists—not just of Cajal's day, but I think today as well. So it will be interesting to see how this plays out.

**What do you think are the biggest problems/challenges that science as a whole is facing today?**

"Seven-eighths of all science is wrong." This quote, from Dr. Jay Goldberg, a member of my PhD thesis committee, came at our journal club decades ago when I was a second-year graduate student. At first, I could not sort out whether I was more angry or more crestfallen. And anyway, how could he tell it was seven-eighths rather than three-fourths or five-sixths? And why am I trying to do science if it is mostly wrong?

Much attention has been paid recently to the fact that, indeed, more than half of major studies in biology are not replicable when they are tested. However, it is worth noting that this has not changed from Jay's time thirty years ago. I am dubious that science today is inherently more competitive or more money-driven or corrupt than in olden times. I think most errors reflect not merely the overly optimistic use of statistics, but more importantly, our inability to imagine how complicated and wondrous biology is—and that is not our fault. But it is important that our shiny new tools don't blind us to how poor we are at developing hypotheses about how the world works. This is where the importance of description comes in, because if we just describe what we see, we cannot go far wrong.

**In your opinion, what are the most pressing questions for the field?**

There are some disease conditions that just stare us in the face and appear to taunt us with the fact that we don't yet seem to have the right paradigms for understanding them. Among these I would include schizophrenia, Alzheimer disease, and dyslexia.

**What advice do you find yourself giving to your students and postdocs?**

(1) Read Cajal. His writing is endlessly entertaining as literature and is still current today, and he will remind you that you are engaged in a noble and timeless pursuit. As he is almost painfully blunt about the shortcomings of himself as well as his contemporaries, he will also remind you that science has always done by imperfect humans—above all, himself. I think he can be quite inspiring to young students that they may someday also be an imperfect human doing great science.

(2) Ideas are cheap; models are cheap; experiments are golden. Scientists have long been known to put too much faith in their model and not enough faith in their data. Believe your data, not the model that is popular with you or with the community. All models will be wrong sooner or later.

(3) But then, always propose a new model, even though you know that models won't last. Models are an essential part of learning and classifying, and we need them in order to learn.

(4) Do simple experiments. You can always make them complicated later. Do the fastest experiment you can that will convince you whether the line of investigation you are pursuing is worthwhile or not, so you don't waste time on a dead end. Don't fear failure; just get to failure as fast as you can, and if it turns out that you don't fail, then you are in great shape. Then after you have convinced yourself that a result looks promising with a quick experiment, do the experiment all over again, with the greatest of care and all the controls, to convince yourself and others.

**How do you find inspiration?**

As a parent, I get inspiration from meeting disabled children and their families. Raising a child with an intellectual or social disability is the defining event in the adult lives of the parents, around which all the rest of their adult lives will revolve—their work plans, their family plans, their travel plans, their retirement plans, everything. I am constantly impressed by the resilience and dedication and love of such parents. And I am reminded that my wife and I could have easily been in their position, leaving me wondering whether I would be able to respond as positively as these parents have.

I am also inspired by how little you learn from looking at an MRI picture of a human brain about what a child will look like and act like when you meet them, and how miraculously much many children can achieve even with very abnormal-appearing brains.

**If you could ask an omniscient higher being one scientific question, what would it be and why?**

I would ask her what the neurophysiological representation of the human experience of conscious self is, because I am not sure that we have a good plan for the technological developments necessary to tackle that problem.

**Do you have a role model in science? If so, who and why?**

As a younger sibling I have always looked up to those older than me, and eyed their choices to see whether they would fit me, so role models have always been important. Among my grad school teachers, Ray Guillery was my principal role model, because he was a scientist and an intellectual and taught me that you could achieve great success in science without sacrificing your life, your family, or your integrity. He and his wife, who also worked, raised four great kids. He would come in to lab after the kids went to school, work a full day, walk home for dinner, and read science and referee papers after dinner at home. He would work evenings and weekends at times, but he was not crazy. He showed that science was a great way to have an endlessly fulfilling career and raise a well-adjusted family at the same time.

Joe Martin, my department chief during residency and mentor at many stages of my career, shared many of these same virtues, but he hooked me on thinking about the relationships between genetics, human disease, and human behavior. He is also a model to me of leadership, team management, and integrity.

**What do you do when you're not in the lab?**

I exercise slowly but determinedly, garden badly, and cook not quite so badly. I find that science is so much fun that it is hard to maintain a hobby that out-competes it. Every few weeks, my many siblings and I have a scheduled sibling conference call to catch up on family news. This started by accident, but I recommend it to anyone who has a far-flung family.

**Did you encounter particular difficulties? How did you overcome them?**

Science has by no means always been easy for me, especially the social aspects of it. There have been times that I feared I would not succeed, or I was involved in frightening differences with people more powerful than me that kept me up at night fearing my reputation or career would suffer. At those times, I found support from people who knew me both in and out of science, especially my wife, Ming Hui. Support often came from colleagues in science that I had not expected, or even thought that I knew all that well, reminding me of my mom's advice: "You never know where your next friend will come from." The key to successful networking in science is to find some balance between being friendly to others and not letting yourself be a doormat. Sort of like real life, I guess.

**What career paths did you consider other than a scientist?**

As a physician-scientist who completed a neurology residency, I continued to see patients for a decade or so after residency was complete, and I still see patients occasionally. Medicine can also be a fulfilling profession, but there was never much doubt in my mind that the lab was the right place for me.

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