Profile of Christopher A. Walsh

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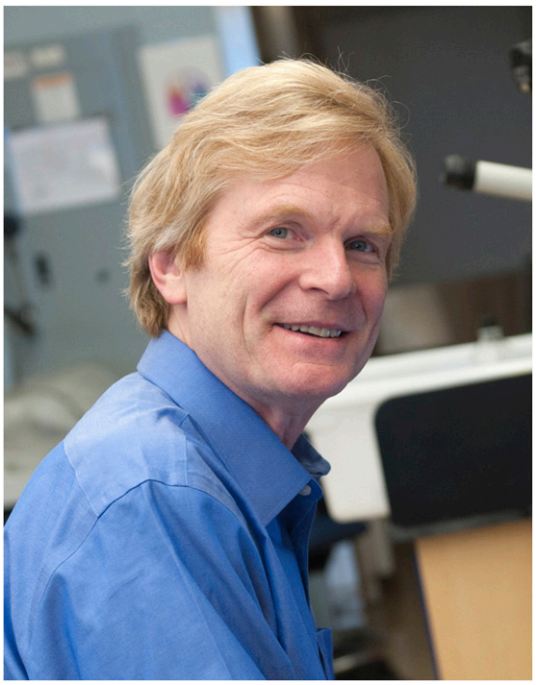
When Christopher A. Walsh was still a teenager, his parents gave him a choice of either skipping a year of high school or a year of college. Deciding to forgo his high school senior year, Walsh found himself, just a month after turning 17, a freshman at Bucknell University with no clear idea of the subject in which he wanted to major.

A couple of months before college, Walsh received a letter inviting him to take an honors psychology course. Intrigued, Walsh enrolled in the class, which was taught by Alan Leshner, who later went on to direct the National Institute of Drug Abuse. "He was a totally inspiring and entertaining lecturer, and I just got really excited about studying the brain," Walsh says. Walsh also took organic chemistry that first semester and realized he loved it. "I feel like that's what I've been doing ever since, a combination of chemistry and psychology," says Walsh.

Over a distinguished career, Walsh has studied the genes and mechanisms mediating the development of the brain, specifically the cerebral cortex, the part of the brain responsible for human traits, such as intelligence, creativity, and language. His research has helped identify genes involved in human brain development and those underlying disorders associated with cerebral palsy, seizures, and autism.

Walsh, who holds appointments at Boston Children's Hospital and Harvard Medical School, is a Howard Hughes Medical Institute Investigator and was elected to the National Academy of Sciences in 2018. His Inaugural Article uses cutting-edge technology to address questions about cerebral cortex development (1). "It's about the sequence of formation of the cells that form our organ of consciousness," says Walsh. "This paper has a lot of personal meaning to me, since it uses the most modern technology to address issues that have engaged me since my PhD and postdoc years."



Christopher A. Walsh. Image credit: Boston Children's Hospital and Katherine C. Cohen (photographer).

Tracking Neuron Development

Walsh's interest in studying the brain led him to The University of Chicago, where he obtained MD and PhD degrees. For his doctoral thesis, he studied the sequence of formation of neurons in the retina. Among other things, Walsh described the timing and pattern of formation of cats' retinal ganglion cells, and examined how this process related to the outgrowth of retinal axons (2–4).

Walsh's doctoral advisor, Ray Guillery, was one of his early scientific role models. "I can trace my interest in the interplay of development and genetics to his interests," Walsh says. "In many ways my career is an outgrowth of his influence on me."

During his doctoral degree studies, Walsh would develop expertise in "birth-dating" neurons in the brain, a technique that serves as a forerunner to some of his later work, including his Inaugural Article (1). Unlike cells in other human tissues, neurons stop dividing after their formation during embryonic development. "You can think of a neuron as having a birth date, which is defined as the day during fetal development on which that cell stops dividing," says Walsh. "Part of mapping the development of the brain is just

This is a Profile of a member of the National Academy of Sciences to accompany the member's Inaugural Article on page 13886.
First published June 15, 2020.

understanding the sequence of when different things are formed," he says. "That's what the Inaugural Article is about."

After his PhD, Walsh trained as a neurologist at Massachusetts General Hospital and did his postdoctoral training with Constance Cepko at Harvard Medical School. During this time, Walsh went from studying the lineage of neurons in the retina to those in the cerebral cortex of rats. Cepko and Walsh developed a way to label progenitor cells of the cerebral cortex using barcoded retroviral markers, using the markers to track clones of sibling cells in the brain (5–7). "We found that a single family of cells scatter their daughter cells all over the entire cerebral cortex from one end to the other," says Walsh. "I was completely unprepared for that intellectually, and it was so gratifying because we had spent years developing a method to see something that you would never have been able to see otherwise, which was amazing," he says.

It was at Massachusetts General Hospital that Walsh met Joseph Martin, who was the chairman of neurology there when Walsh was a resident. "He was another huge influence, and a tremendously wonderful mentor," Walsh says. Martin would go on to become Dean at Harvard Medical School, where Walsh would become a faculty member in 1993. "As the Dean there, he was also very influential to my faculty development," says Walsh.

As a new faculty member at Harvard, Walsh applied his research on cortical development toward understanding human genetic diseases.

Brain Development in Human Disease

Soon after setting up his own laboratory, Walsh decided to focus on human neurological disorders. "I had been trying to find a way of combining my interest in the development of the human brain with work that had some relevance to people and to disease," says Walsh. Many neurological disorders are a result of mutations in the genes that help construct the human cerebral cortex, and their underlying mechanisms remain unclear. "What we found was that we could identify the genes directly without having to understand the mechanisms first," says Walsh.

The initial breakthrough came when Walsh attended a meeting in Venice, Italy and heard a talk by Peter Huttenlocher, one of his former teachers at medical school. "Peter presented this family with a developmental disorder of the brain," says Walsh. "I realized that I could study this family using brain scans to define anatomical abnormalities as a way of defining whether they were sick or not, and combining that with genetics," he says. "That was just a pivotal moment, and my palms were sweating, my heart was racing when he was presenting it, and I just couldn't wait to talk to him and to try to collaborate with him."

Walsh's collaboration with Huttenlocher resulted in the mapping and cloning of the *FLNA* gene, which is responsible for Huttenlocher's periventricular nodular heterotopia (8). By then, Walsh had already mapped another disease gene that he named *doublecortin* (*DCX*), which causes "double cortex" syndrome in humans (9). "That was the first human disease gene that we ever identified, and it was gratifying because it's something we worked on for 5 years, searching through the wilderness of the genome without a map," says Walsh.

Spurred by these early successes, Walsh went on to study other genetic disorders. "I went on to clone dozens more human disease genes because each one brings a similar level of satisfaction, to be able to relate a problem that a child has to a very specific single change out of 6 billion base pairs in the genome," he says.

Walsh's interests eventually led him to investigate the basis of genetic intellectual disabilities and autism spectrum disorders. "The autism research was an attempt to do work where there was a greater possibility of developing therapies based on genetics," he says. His approach to studying autism stemmed from previous work focused on studying recessive genes in families from Arabic countries of the Middle East, in which parents had shared ancestry. "We thought we could make a unique contribution to understanding autism by specifically focusing on recessive causes of autism, which is difficult to study in the United States," he says. Walsh and his colleagues were able to identify many inherited mutations that cause a high risk for autism.

More recently, Walsh has become increasingly interested in basic biology, resulting in work that addresses questions raised early in his career (1). "My Inaugural Article combines my interests in human genetic mutations that confer risk and in understanding the basic biology of the brain," he says.

Back to Barcodes

Walsh's Inaugural Article (1) harkens back to his postdoctoral work using barcodes to track and elucidate the lineage relationships among neurons. "The general idea was to use DNA mutations that occur in neurons," he says.

Walsh was able to detect these mutations using methods he developed five years ago for sequencing the genome of a single brain cell and comparing it to a neighboring brain cell (10). "We found that there's about a thousand spots where they differ," he says.

Some of the mutations occur during brain development. "Every cell division introduces a few mutations, and so that represents a permanent map of where all of the different cells in the body come from, their lineage," says Walsh. To his surprise, Walsh found that additional mutations continued to accumulate with age even in neurons that do not undergo cell division. "We found that the genome of a single neuron is dynamic and accumulates a new mutation every 2 or 3 weeks," says Walsh. The accumulation of these mutations turned out to be accelerated in some forms of dementia or brain degeneration (11).

Walsh realized that in combination with methods to sequence single neurons, the neuronal mutations could serve as natural barcodes, which could be used to track the development of the neurons. "But there are thousands of different types of neurons, and we

needed a second method to tell which neuron is which, and that's what we've done in the Inaugural Article," he says. The Inaugural Article (1) combines simultaneous identification of cell lineage and transcriptional analysis of cell type. "It's a substantial technical challenge," says Walsh.

August Yue Huang and Pengpeng Li, two fellows in Walsh's lab, developed and used these techniques to simultaneously reconstruct neuronal cell type, cell lineage, and birth-dating in the postmortem human cerebral cortex in a quantitative manner. The proof-of-principle study confirmed some of the developmental patterns expected from previous analyses of mouse brains, while revealing novel cortical patterns of interneuron development in the human brain.

"We've only analyzed a thousand cells in the cerebral cortex, and the human cerebral cortex contains billions of neurons," says Walsh. "We're now trying to find ways of using new technologies to make it faster and cheaper so we can study thousands and, hopefully, hundreds of thousands or even millions of cells," he says.

The findings also raise the possibility of novel applications. "Now we can, in principle, look at Einstein's brain, and you could figure out if the pattern of development of his brain is different from the pattern of development of my brain," says Walsh. "This method could be applied to any brain postmortem, or to any animal where it would be unethical to perform experimentation," he says. This would allow researchers to explore the genetic differences between human and nonhuman brains and answer fundamental questions about how the human brain evolved.

Walsh remains focused on the big questions that intrigued him as a college freshman, always from the standpoint of brain development. "I'm still trying to understand where our unique experience of the world comes from," he says.

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