

Chris Walsh began his scientific career studying chemistry at a small university in Lewisburg, Philadelphia. Now a Professor of Neurology at Harvard Medical School, he has been identified as one of America's top 12 physician-scientists by the Howard Hughes Medical Institute. He gave *Nature Medicine* a brief insight into how he became such a respected neurologist and scientist.

Chris Walsh

Chris Walsh's work is a prime example of how technology has enabled advances in medical research. Clinical collaborators in countries thousands of miles away email magnetic resonance imaging (MRI) scans from selected patients with mental retardation to him, from which Walsh determines linkage to genetic abnormalities. He discusses the diagnosis with colleagues at Beth Israel Deaconess Medical Center in Boston before providing genetic counseling and treatment advice. In essence, he runs an 'Internet clinic'.

Walsh has been selected as one of America's top 12 physician-scientists to receive a new Howard Hughes investigator award (see page 647). He plans to use the money to expand his research to additional countries. "We collaborate with physicians in places such as Australia, Israel and Saudi Arabia, and the new money will help us to expand into countries like India and Kuwait," he says.

Thanks to modern technology, Walsh—a self-confessed homebody—does not have to leave his lab. "I have not yet been to these countries. I am somewhat of a reluctant traveller, since we have two young daughters." His excursions into foreign research labs have been brief. Many years ago, he followed his PhD advisor, Ray Guillery, to Oxford University. Guillery taught him about brain development, which has been at the heart of his work ever since, but Walsh only stayed in the UK for two months. He then worked at the Max Plank Institute for just under a year. "I think it helped me to find myself. I tried hard to appear European, but didn't fool a single person. It took several months for me to be happy to be American and then I realized that I'd be better off at home."

His work takes advantage of genetically conserved populations with a historical sense of community. "A lot of the mendelian disease genes that have yet to be identified are inherited in a recessive fashion and so are caused by genes that

tend to be unique to parts of the world that are a little more communal or tribal, or less mobile than the countries of Western Europe and the States."

Once a gene that causes a particular disorder has been mapped to a locus, families with the same condition can be identified worldwide. But doesn't the location of the initial family within a small community that may not have access to a well-developed healthcare system present a problem? "On the contrary," says Walsh. "I find it easier to get an MRI scan on patients in some of these countries than in England. Right now we're trying to get an MRI on a kid there with a particular chromosome abnormality, and we're having a difficult time getting it because of the National Health Service."



The web doctor

His work stems from an understanding of how the cerebral cortex develops. The cortex is the largest structure in the brain comprising the frontal, parietal, occipital and temporal lobes. During its formation, neurons of the cortex are derived from remote dividing progenitor cells, which must migrate to the cortex

region of the brain. A number of mutations that disrupt specific steps in cortical development have now been identified. These genetic disorders give rise to cortical malformation and result in mental retardation, epileptic seizures and generalized problems of movement and language.

Recently, Walsh's group studied five Palestinian children with varying degrees of mental retardation and epilepsy. Brain MRIs revealed excessive folding and layering within the cortex indicative of bilateral frontoparietal polymicrogyria. Genome-wide linkage screening revealed the locus, and the team is now searching for the responsible gene.

Walsh's work is translational because it combines basic genetic research with clinical diagnosis for patient benefit. And like several of the investigators profiled in the

Nature Medicine series, his career has been heavily influenced by mentors. Fond of science, but unsure what path to take, Walsh majored in chemistry at Bucknell University, a small, local college. "I had the tremendous good fortune in my freshman year of having Alan Leschner as my psychology teacher. He taught there for a short while before leaving for much bigger and better things," says Walsh. Leschner was the director of the National Institute on Drug Abuse and is now the publisher of *Science*.

Thereafter, Walsh pursued a combined MD-PhD degree at the University of Chicago, which he describes as "very intellectually stimulating" for someone studying neuroscience, not least because the medical school is across the street from the philosophy department. It was here that Walsh became interested in studying cortical malformations. "I'd been trying for a long time to combine my interest in basic science with my interest in patient care. I got very good advice from Joe Martin, now the Dean of Harvard, when he was the Chair of my residency program. He kept telling me that the way to combine basic science is through human genetics, but I couldn't think of how to do this." Walsh started his own lab at Beth Israel in 1993 and went to a conference where one of his old medical school teachers presented a family with brain malformations. "The light went on," he says. "I needed to identify the genes required to put the brain together, and this was essential to neurology to figure out what these unusual symptoms were."

Is he himself a good mentor? He strives to be. In addition to his lecturing responsibilities and a role on the Harvard MD-PhD training program steering and admissions committees, he is an advisor for a dozen students in the program. "Nothing would make me happier," he admits, "than if someone walked up to me at the annual neuroscience meeting—as I did to Dr. Leschner eight years after he taught me—and told me 'I would not be at this meeting if I had not taken your class.'"

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