PROFILES

Christopher Walsh: Solving mysteries of the mind in the Middle East

BY **EMILY SINGER**

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Gold mine: Christopher Walsh has found that intermarrying families in the Middle East offer a rich genetic resource to study diseases.

At first glance, the waiting room at the Ministry of Health Hospital in Muscat, Oman, may look different than that of your average American hospital.

Men dressed all in white and women in black burqas wait in separate rooms, even if they are members of the same family. But talking to these families soon reveals just how similar they are to their American counterparts, says **Christopher Walsh**, a neurologist who has studied neurodevelopmental disorders in the Middle East for nearly 10 years.

Recalling one father seeking treatment for his child with autism, Walsh says, "His questions could have been the same as those I might hear from suburban parents at a Boston hospital."

Since 2004, Walsh's team has traveled regularly to the Middle East, carefully phenotyping children with autism.

"We met considerable skepticism initially that 'autism' would mean the same thing in Arabic cultures as in European or American cultures," says Walsh. "Our results indicate that it is highly similar if not exactly the same."

In fact, unpublished evidence from Walsh's lab suggests that there is some overlap between the genes that carry recessive mutations in Middle Eastern children with autism and those found by other scientists to have *de novo* structural variations ? which occur spontaneously in the sperm or the egg of the parent.

Walsh's scientific journey to the Middle East began a decade ago with his quest for patients with recessive genetic disorders. After scanning the literature, Walsh called Saad Al Shahwan at the Armed Forces Hospital in Riyadh, who had published a paper about a recessive condition in which the brain was malformed, called "lissencephaly with cerebellar hypoplasia."

As Al Shahwan explained to Walsh, in many Middle Eastern countries intermarriage between first and second cousins is a common social custom. And as a result, recessive genetic disorders occur more frequently and are easier to identify.

"If you go to a genetics clinic in Saudi Arabia, more than 98 percent of families have parents that are related," says Walsh, who is chief of genetics at Children's Hospital Boston. "You can track the gene back to a common grandparent or great-grandparent, which means you can get lots of information from one family."

Genetic resource:

Over the past decade, Walsh has traveled to Turkey, Saudi Arabia, Jordan, Dubai and Oman, working with doctors there to find families in which children suffer from different disorders.

His team has collected more than 1,500 DNA samples from families with children affected by an assortment of neurological diseases, including mental retardation, epilepsy, cerebral palsy, brain malformations, and degenerative diseases.

"The vast majority of them are genetic, but we do not know the genetic cause as yet," says Walsh. "The diversity of genetic brain conditions to which humans are subject still amazes me."

Walsh's team has so far identified 12 genes linked to brain developmental disorders, including several types of mental retardation and malformations of the brain that are linked to epilepsy and cerebral palsy. "This work has given us great insight into the development of human cerebral cortex," says **Daniel Geschwind**, a neuroscientist at University of California, Los Angeles.

Walsh knows full well all that can go wrong with the brain: brain folds important for language that grow abnormally tiny, clumps of neurons can get stuck in the wrong part of the brain, triggering learning disabilities and seizures.

"Anything you can imagine can go wrong has gone wrong," he says.

These days, he's applying his approach to autism, which is characterized by impairments in language and social function. "Autism is a disorder that seems to be telling us something very important about how the brain works," says Walsh.

Language and social abilities are the most recent cognitive functions that have appeared in human evolution, he notes, "And those are the abilities that are disrupted in autism."

Tough task:

Identifying the genetic bases for autism has not been not easy, however.

Autism is thought to be the result of many different genetic variations, each of which may be extremely rare. Even large, genome-wide association studies ? which dramatically boost the power of genomic studies by scanning the DNA of thousands of people ? have yielded variations that explain only a small proportion of autism cases.

"Disorders that are genetically heterogeneous are hard to study because no two genes are the same in two kids," says Walsh. "One family will lead us to one chromosome, and another will lead us to a different one."

Walsh is a physician scientist, and runs a joint clinic specializing in children with difficult neurological cases. He completed a residency in neurology in 1989 and a fellowship in genetics at Harvard University in 1992 before launching his own lab at Beth Israel Deaconess Medical Center in 1993.

Within the first five years, his team had uncovered several genes linked to neurodevelopmental disorders in American, European and Australian families.

Suspecting that there were myriad disorders yet to be discovered, he began searching for disorders linked to recessive mutations, meaning that the disease only develops when someone has two disabled copies of the gene.

"When you identify a recessive mutation, the connection between the mutation and the syndrome is clearly established, so it gives a good place to start for functional studies," says Geschwind.

Walsh's careful work characterizing these disorders has required both the clinical finesse of a physician and the deep knowledge of brain development that came from his animal research.

As a post-doctoral researcher at Harvard Medical School, he published seminal work demonstrating how far neurons migrate in the developing brain in rats. His lab now develops mouse models of the genes that they identify in human brain disorders in order to understand their mechanism of action.

Common pathways:

With that combination, Walsh has shown that disruptions in multiple genetic pathways can lead to the same outcome ? such as mental retardation.

"He has shown that even common diseases are a collection of rare diseases," says **Huda Zoghbi**, a neurologist at the Baylor College of Medicine in Houston, Texas.

For his work on autism, Walsh has so far collected DNA samples from about 200 families, some of which have up to four children diagnosed with autism, and is expected to publish the first set of results in the next few weeks.

Still, the search has only just begun, Walsh says.

"It will take more than five years to understand even half of the families we have recruited so far, to say nothing of other families that may enter research," he says. Although there is no cure for autism, the researchers offer the families genetic counseling and customized genetic testing.

As he has in the past, Walsh plans to decode the role that the genes he identifies play in the brain. In that regard, his approach gives him an advantage over most autism researchers, who focus on finding more common variants.

"Will we need to perform gene therapy for each gene we find, or do they organize into pathways, with many genes in a pathway potential affected by a smaller set of drugs?" asks Walsh. "I am hoping for alternative number two, and our recent work suggests that this might be the case."