

The Hunt for Genes and Cures



For Nancy Wexler, Ph.D., the search to find the gene that causes Huntington's disease and a way to cure it has been a lifelong quest.

Her work is not just academic. When she was 23, Dr. Wexler found out that her mother, Leonore, had the untreatable and fatal brain disorder. Because Huntington's disease is "autosomal-dominant"—meaning only one parent has to have the disorder in order for a child to inherit it—there is a 50-50 chance that she and her sister inherited the genetic misprint. Three of her uncles also died of it.

In 1969, she became president of the Hereditary Disease Foundation (HDF), a clinic founded by her late father, Milton Wexler, Ph.D., a psychotherapist. One of the foundation's

most valuable achievements so far was a decades-long study of the world's largest family with Huntington's, in Lake Maracaibo, Venezuela—18,000 individuals in total, 14,000 of whom were related to one woman who died of the disease.

These kinds of genetic studies are helping researchers to understand the roots of Huntington's, as well as other elusive neurological disorders such as Alzheimer's disease, autism, Parkinson's disease, and even stroke.

"We're making steady progress in identifying genes that can cause or predispose people to develop these disorders," says Thomas D. Bird, M.D., chief of the division of neurogenetics at the University of Washington School of Medicine in Seattle. "The past few years were marked by important advances in several different arenas, including new gene discoveries and a

Researchers are successfully teasing out the genetic roots of many neurological disorders, making possible earlier interventions—and maybe even new treatments.

BY CHARLENE LAINO



THE GENE HUNTER

Nancy Wexler, Ph.D. has spent decades compiling a 10,000-person family tree of the world's largest family with Huntington's disease, in Lake Maracaibo, Venezuela (previous page). The people of Lake Maracaibo generously donated 2,000 blood samples that helped Wexler discover the HD gene in 1993.

better understanding of how these genes cause disease.”

Doctors have long known, based on family and twin studies, that neurological disorders can be passed from generation to generation. But with the mapping over the past decade of all 25,000 or so genes that makes us human, scientists are now better able to zero in on the genes that influence the risk of developing a condition.

Dr. Wexler's groundbreaking Huntington's research has not only led to the identification of the gene that causes Huntington's disease, but also to the development of a test that can tell who is carrying the fatal gene prior to the onset of symptoms.

Since 1993, Dr. Wexler, who is also a professor of neuropsychology at Columbia University, has searched tirelessly for new drugs to treat or cure Huntington's, which typically strikes be-

tween the ages of 35 and 45 and causes involuntary movements, severe emotional disturbance and cognitive decline. At present, there is no treatment to halt its inexorable progression, which leads to death after 10 to 25 years.

“We're pretty sure that if you eliminate expression of the mutated [gene variant], that would be a cure,” says Carl Johnson, Ph.D., executive director for science at HDF. “But we're not there yet.”

Blood samples from over 4,000 of the participants also assisted in the mapping of other disease genes, including those involved in Alzheimer's disease, kidney cancer, and dwarfism.

Meanwhile, unprecedented collaborations like the Autism Genome Project, a group of over 120 scientists from nearly two dozen countries, have dramatically increased the number of genetic samples from families with inherited disorders, giving researchers a better shot at teasing out their underlying causes.

Other advances are propelling the search for mutated genes as well. There are new, faster technologies that let researchers analyze the activity of thousands of genes at once. Researchers say the developments will ultimately lead to new treatments.

“If we can better understand the pathways involved in causing disease, we can develop drugs to target these pathways,” says Tatiana Foroud, Ph.D., director of the division of hereditary genomics at Indiana University School

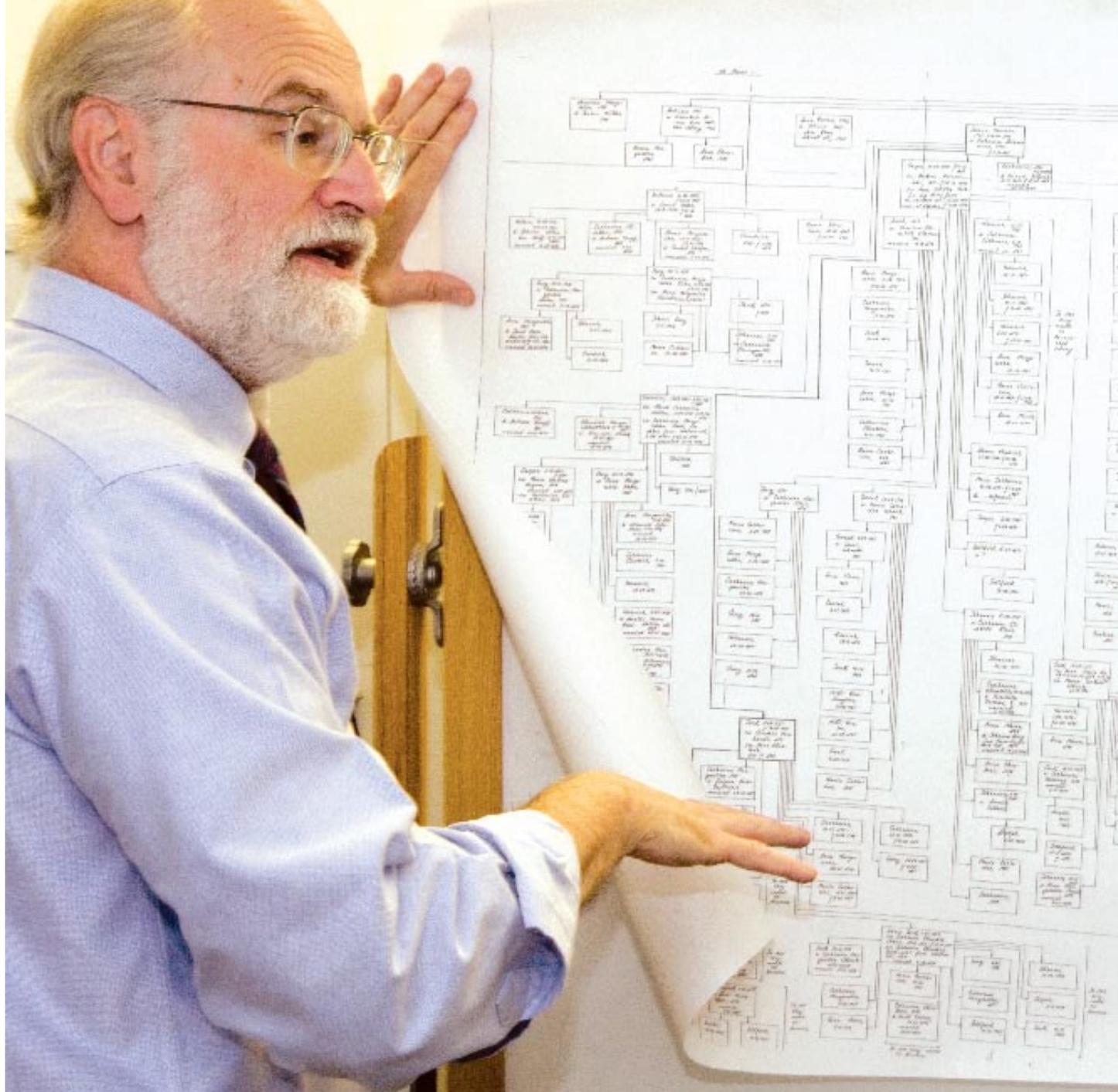
of Medicine in Indianapolis. “Genes give us insight into what is going wrong and where we can jump in to alter it.”

“What we really want to do long-term is identify people at high risk and make an intervention to prevent or delay the disease,” she says.

ALZHEIMER'S DISEASE

Dr. Bird says some of the most exciting research involves studies into the genetic causes of late-onset Alzheimer's disease (AD), the most common form of the memory-robbing disorder.

Age is the most important risk factor for Alzheimer's disease, a progressive, neurodegenerative disease characterized by amyloid plaques and neurofibrillary tangles in the brain.



Amyloid plaques are abnormal clumps of misplaced proteins, and neurofibrillary tangles are tangled bundles of fibers, also composed of misplaced proteins.

The late-onset form of AD develops after age 60, with the number of affected people doubling every five years afterward.

So far only one inherited deviation in the gene from what is normally seen—a variant in the DNA that prevents genes from producing proteins as they normally would—has been identified as a risk factor for late-onset AD. It's a form of a gene called apolipoprotein E (APOE), which helps make a protein that carries cholesterol in the blood. Researchers have found that the e4 variant, known as APOE e4, is associated with an increased number of amyloid plaques deposited in the brain.

Having one copy of the APOE e4 gene variant increases the risk of developing Alzheimer's two- to three-fold, according to Richard Mayeux, M.D., co-director of the Taub Institute for

Research on Alzheimer's disease and the Aging Brain at Columbia University. As head of the northern Manhattan study, Dr. Mayeux has been tracking the rates of Alzheimer's disease and genetic and environmental risk factors among elderly New York City residents since 1989.

One intriguing finding to come out of the study is that although blacks and Hispanics are much more like to carry the mutant APOE e4 gene than whites, whites with the genetic misprint are more likely to develop late-onset AD, he says.

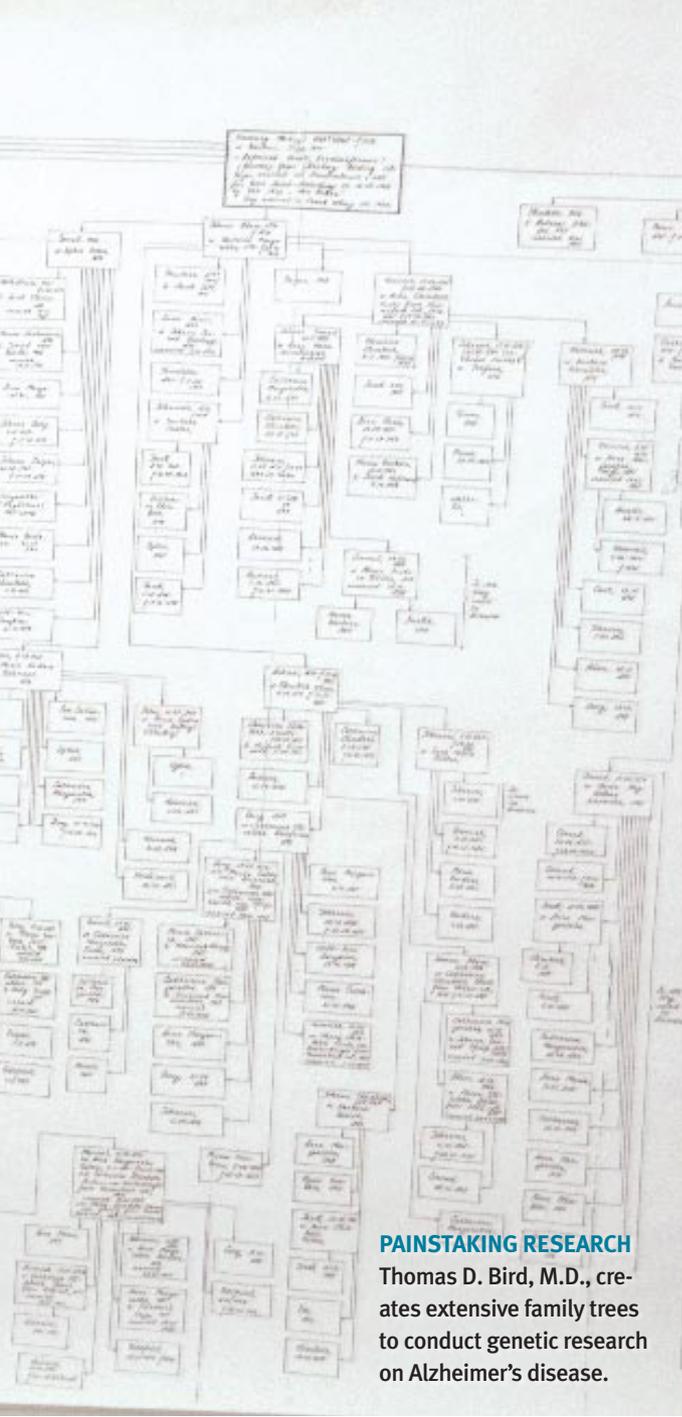
The researchers also found that environmental factors play a big role, with smoking, diabetes, and stroke each raising the risk of AD by up to three-fold.

Earlier this year, Dr. Mayeux and colleagues around the country reported that a mutation in the SORL1 gene may also raise the risk of late-onset AD, although not to as great a degree as APOE e4.

"We think SORL1 is involved in amyloid processing," he

“We think that all these genes and environmental factors interact, so that a person who has several together is much more likely to develop Alzheimer’s.”

—RICHARD MAYEUX, M.D., COLUMBIA UNIVERSITY



PAINSTAKING RESEARCH
Thomas D. Bird, M.D., creates extensive family trees to conduct genetic research on Alzheimer’s disease.

PREPARING FOR THE FUTURE

Cathy* has mixed emotions.

A participant in genetic studies run by Thomas Bird, M.D, the 31-year-old mom of two active youngsters recently tested positive for early-onset familial Alzheimer’s disease (AD).

While she’s worried about whether she passed the gene for AD onto her own children, Cathy says she is glad she got tested.

When her mom was stricken in her forties, there was a dearth of information about early-onset AD, Cathy explains. “It took a number of years to get a proper diagnosis, and even after she was diagnosed, doctors lumped her in with people who have the late-onset form of the disease, which has a much less rapid course. Dr. Bird was our golden ticket, offering a wealth of information about the disease, how it develops, and how to treat it.”

Participation in a clinical trial has helped her entire family prepare for the future—emotionally, medically, psychologically, and financially, she says. “Having a crystal ball lets you get your priorities straight at a time in your life when you’re going full speed ahead.”

Cathy says she would like to share her story with others and become a spokesperson for AD research, but is afraid of genetic discrimination. “Privacy and getting health and life insurance are big issues. But hopefully in a few years I can be more open. We have to get the word out that Alzheimer’s disease is not just an old people’s disease,” Cathy says.

*Not her real name.

says. A faulty SORL1 gene may lead to increased production of beta amyloid, which can damage brain cells and lead to memory loss and other symptoms.

The finding still needs to be confirmed, but according to Dr. Mayeux, SORL1 “appears to be the second late-onset Alzheimer’s disease gene. There are likely to be other important genetic variants that need to be identified before the entire picture is complete.”

No one knows how many genes will ultimately be involved in raising the risk of late-onset AD, but Dr. Mayeux notes that one in 10 victims has a living family member—usually a brother or sister—with the disorder. “There are probably at least four or five more genes out there that are at least as strong a risk factor as APOE e4,” he says.

“We think that all these genes and environmental factors interact, so that a person who has several together is much

more likely to develop Alzheimer’s,” Dr. Mayeux says. “The by and large of it is that AD is a multifactorial disorder.”

Dr. Bird is heading up a large collaborative effort involving 10 medical centers in North America to home in on these other genes as well as environmental factors that may work in concert to raise the risk of developing late-onset AD. The goal is to study 1,000 people with AD who have at least one other family member with the disorder as well as 1,000 people of the same ages who do not have the condition.

“We take blood samples and bank the DNA in a big repository so they are available to anyone who wants to study them,” Dr. Bird says. The effort is well on its way: More than 900 affected families have already been identified and more than 400 tested.

There is a commercially available test for the APOE e4 gene, but neither Dr. Mayeux nor Dr. Bird typically recommend that people take it unless they are part of a clinical trial.

“We want to identify people at high risk and make an intervention to prevent or delay disease.”

—TATIANA FOROUD, PH.D.,
INDIANA UNIVERSITY SCHOOL OF MEDICINE

One reason: APOE e4 is neither necessary nor sufficient to cause late-onset AD.

“Not everyone with AD has the APOE e4 gene, and not everyone who has APOE e4 will develop AD,” Dr. Bird says. Additionally, there are no interventions to help if you test positive, he adds.

EARLY-ONSET ALZHEIMER’S

Early-onset or familial AD, which affects fewer than 2 percent of patients, is inherited and typically develops between the ages of 30 and 60, Dr. Bird says.

Researchers have identified three mutations for early-onset AD: amyloid precursor protein (APP), presenilin 1 (PS1) and presenilin 2 (PS2). If you have a parent with one of these gene mutations, you have a 50-50 chance of developing AD, he says.

If your mother, father, sister or brother developed AD before the age of 60 and have symptoms of the disease, you could consider getting being tested for PS1, the most common form of familial early-onset AD, Dr. Bird says. “The other two variants are so rare that no one has developed a commercial test,” he explains.

There are advantages and disadvantages to being tested. “If the test result is negative, you don’t have to worry. And if it is positive, you can make plans—for your family, finances, and your career.

“The downside is that people who test positive can get very depressed, and so far, doctors have no way of preventing the disorder. People also worry about whether it will affect their chance of getting health or life insurance,” Dr. Bird says.

He has studied people’s responses to genetic testing for early onset AD and found that the majority are glad they had it done, even if it was positive. That said, it’s an individual decision, Dr. Bird stresses.

PARKINSON’S DISEASE

For years, many researchers thought that Parkinson’s disease (PD) was caused by environmental factors—where people live and work, chemicals they were exposed to, or other

nonbiological factors.

The most common degenerative disease after Alzheimer’s, PD affects more than 1 percent of individuals aged 65 and older. It is characterized by resting tremor, slowness of movement, muscle rigidity, postural instability, and impaired balance and coordination.

A landmark study of twins found no evidence of a genetic influence in people diagnosed with Parkinson’s disease after age 50—a group that accounts for 97 percent of victims, says William Langston, M.D., chief executive officer and scientific director of the Parkinson’s Institute in Sunnyvale, Calif. Twin studies are important because identical twins share all their genes, while fraternal twins only share about 50 percent of them. If you compare the rates of a disorder in identical and fraternal twins and find they are the same, you know it’s not genetic, he says.

In people diagnosed with PD before age 50, there was some suggestion of genetic link, but the number of affected twins was so small it was hard to draw conclusions, Dr. Langston says.

Since then, a large Swedish study of twins resulted in the exact same findings. But more recent research has changed that perception, according to Dr. Foroud.

“It’s now clear that Parkinson’s disease is one of those diseases where both environmental factors and genetics are at play,” she says. “Genetics are important.”

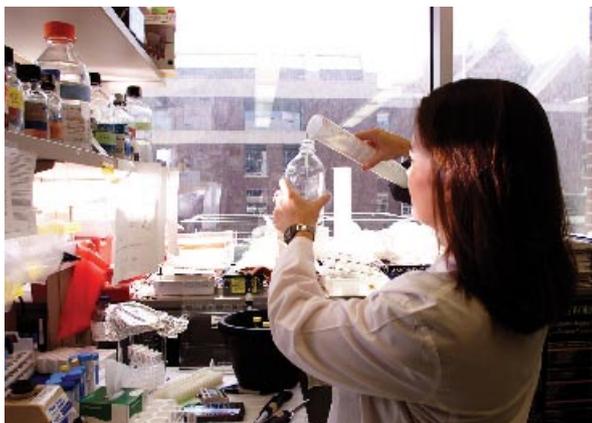
In the past decade, scientists have identified five genes that when mutated, “clearly and indisputably can cause PD,” she says. “A change in the DNA sequence can cause PD even without any environmental factors.”

Four of the five variant genes—parkin, DJ1, PINK1, and alpha-synuclein—primarily cause early-onset PD, which develops before the age of 45 years, Dr. Foroud says. “The last one, LLRK-2, causes PD in people in their 60s and 70s, more the age when we’re used to seeing it.”

Together, all five variants account for fewer than 5 percent of people with PD, while studies suggest that anywhere from 6 percent to 20 percent of PD involves faulty genes.

“We have only just scratched the surface,” she says.

Dr. Langston agrees that there may be a genetic influence and that researchers have yet to pinpoint the right genes. But



INSIDE THE LAB at Indiana University, where Dr. Foroud is conducting genetic research on Parkinson’s disease.



ONE OF THE LUCKY ONES

Seventy-something Pearline Davis of New York City considers herself one of the lucky ones.

As a participant in the long-running northern Manhattan study, Pearline found out that she does not have Alzheimer's disease (AD). Not only that, her memory tested better than many people her age.

Participating in the study, designed to track the rates and risk factors of AD in different ethnic groups, "was good for me," Davis says. "Finding out that forgetting things now and then can just be a normal part of aging helped me physically, mentally, spiritually, even financially."

Davis says the good news propelled her to tell other seniors in her neighborhood "never to give up the fight. The mind needs stimulus and nourishment."

new insights may be in sight: He and his colleagues at the Parkinson's Institute have identified what they believe is the first known family to lose an entire generation to the disease.

Since a family connection to PD is relatively rare and a family with consecutive affected generations is nearly unheard of, studying the family will offer new clues unto possible PD genes, he says. The Institute has already completed a pedigree—a family tree that shows who had the disease through multiple generations. All but one of the affected family members were diagnosed in their 70s or later, so they have the more common, late-onset form of the disease.

After taking blood samples and looking for and eliminating known PD-carrying mutations, the researchers will look for new mutations that may cause the disease.

Dr. Foroud is also involved in an effort to find genes in-

volved in PD. At 50 sites throughout North America, she and collaborators are studying families in which at least two siblings have the disorder.

So far, they have zeroed in on a region on chromosome 2—one of the body's 23 chromosomes that house our genes—that looks suspicious. But they have yet to locate an exact gene.

Even if newly found gene variants turn out to be rare causes of PD, as Dr. Langston believes they will, the findings will help scientists to better understand the causes of non-genetic forms of the disease, he says. Plus, the findings can lead to new treatments.

Dr. Langston says that the findings can also be very important to be families who want to be tested for mutant genes, although he cautions that counseling is a must.

Genetic testing is already available for the parkin and PINK1 genes, but he advises against it. In the case of parkin, there are over 100 mutations that can cause PD, he explains. And PINK1 mutations are carried by fewer than 2 percent of those developing the condition at an early age.

"A mutation doesn't mean you will necessarily get the disease, and we don't know how many people fall into that group," Dr. Foroud says. "And as with AD, there is nothing you can do in terms of preventing the disease. Again, its most valuable use may be for planning."

STROKE

For years, most of the research on stroke also focused on environmental risk factors like diet and smoking, says James Meschia, M.D., an associate professor of neurology at the Mayo Clinic in Jacksonville, Fla. But about 50 percent of stroke risk is unexplained by traditional risk factors, he says. As a result, scientists are searching for genes that may raise the risk of developing stroke.

"The search for a stroke gene is really heating up," says Dr. Meschia, who heads up the Siblings With Ischemic Stroke Study (SWISS). "We're trying to find out why some people still get stroke despite blood pressure control and health lifestyles."

A break came in 2003, when Icelandic researchers discovered that people with a faulty version of the so-called phos-

phodiesterase 4D (PDE4D) gene have three to five times a greater risk of stroke than those without the variant. That makes it at least as great a risk factor as known environmental risk factors like high blood pressure, high cholesterol, and smoking.

The researchers believe that in people with a mutant form of the gene, the muscle cells of the artery walls may proliferate, leading to a buildup of plaque that can block blood flow to the brain, causing an ischemic stroke.

Then in 2004, the same researchers reported that they had linked a variation of yet another gene involved in the buildup of plaque—alternately called ALOX5AP and FLAP—to stroke.

Since then, there have been numerous attempts to replicate the Icelandic findings, which were based on an analysis of an extensive gene database from the geographically and socially isolated Icelandic population. Some were successful, some were not, Dr. Meschia says. For example, early results from the SWISS study showed no link between ischemic stroke and either gene. But Daniel Woo, M.D., assistant professor of neurology at the University of Cincinnati, found that several variants in the PDE4D gene were linked to ischemic stroke in African Americans and whites in the Cincinnati area.

Part of the problem is that researchers may be looking at different variants within a gene, different ethnic populations, or different age groups, Dr. Meschia says.

He believes the ongoing SWISS study, which is open to anyone over the age of 18 who has had an ischemic stroke and has a sibling who has had a stroke, will offer answers.

So far the SWISS investigators have enrolled 243 sibling pairs, toward a goal of 300 pairs. “It’s really the only study of its kind,” he says.

Dr. Meschia is also involved in the Ischemic Stroke Genetics Study, which will compare DNA from people who have had stroke and those who haven’t. “The goal here is to focus on a limited number of candidate genes—in this case, genes related to why platelets clump and form blood clots in arteries. With the mapping of the genome, we can look at genes in ways that were not possible a few years ago,” he says.

No one really knows how many genes will eventually be identified as novel risk factors for stroke, but Dr. Meschia es-

timates there will be at least a dozen. Their identification can lead to new ways to prevent or treat the disorder, he says.

“In the short term, the major reason to identify these genes is to identify targets for drug therapy,” he says. “Genes produce proteins that can be inhibited or stimulated to prevent disease in new ways.”

Equally as important, “novel genes tell you there are novel risk factors,” he says. “Just as when we identified high blood pressure as a risk factor and did studies to show that lowering blood pressure would lower stroke risk, we could develop a panel of tests that could stratify people by risk. Then people with high-risk genes would be counseled to take particularly aggressive methods to lower their chances of having a stroke,” he adds. Those steps generally include a very strict diet and exercise regimen as well as cholesterol-lowering drugs.



FINDING STRENGTH IN PARTICIPATION

JANICE KROGER, a 57-year-old diagnosed with Parkinson’s disease over a decade ago, believes that participation in a clinical trial has helped her prepare for the future.

Since her father also had the disease, Kroger says she wasn’t terribly surprised when she got the diagnosis. Like her dad, she plans to live life to its fullest and not let the shaking, tremors, and other symptoms slow her down any more than necessary.

“I know what this disease can do to you and I’m fighting hard not to let it happen. My hope is that through these genetic studies, researchers will identify something that will stop the disease from progressing,” she says.

“In the short term, the major reason to identify genes is to identify targets for drug therapy. Genes produce proteins that can be inhibited or stimulated to prevent disease.”

—JAMES MESCHIA, M.D., MAYO CLINIC

AUTISM

As with PD, autism spectrum disorders (ASDs) are thought to be caused by a complex mingling of genetic and environmental factors. Studies have shown that when one identical twin has the disorder, the chance of the other twin being affected is 30 percent to 60 percent. But this also means environmental factors must be at play, says Zak Kohane, Ph.D., director of the informatics program at Children’s Hospital in Boston.

Autism spectrum disorders, which affect as many as 1 in 150 U.S. children, are characterized by a range of symptoms, from fairly mild social dysfunction in Asperger’s syndrome to disabling learning and social impairments in severe autism.

The search for mutated genes has been elusive, Dr. Kohane says, “probably because there isn’t really a single gene for autism spectrum disorders, but multiple genes. Each ASD probably involves many different genes, and many ASDs probably require changes in more than one gene.

“Plus, having a genetic disorder is probably not enough to cause autism: There probably has to be exposure to an environmental factor, such as an infectious agent or chemical, in the womb or first few years of life,” he says.

As a result, “the real question is not whether we will find a gene but whether we can develop a set of tests that can diagnose a young infant as being at risk of ASD and help us to figure out if it will be mild or severe,” Dr. Kohane explains.

He is part of a multidisciplinary team at Children’s Hospital that is hunting for the answer. So far, they have studied about 150 of 300 planned children with ASDs—some of whom have a family history and some who don’t—and 300 children without the disorders.

Dr. Kohane believes that studies of the youngsters’ white blood cells may provide clues. The blood cells are being tested for RNA, a relative of DNA that shows whether a gene is turned on and working properly. The researchers believe the gene fingerprints seen in the white blood cells may reflect what is going on in the brain.

Meanwhile, other researchers are starting to pinpoint genetic mutations that may raise the risk of autism. One team,

led by Pat Levitt M.D., at Vanderbilt University in Nashville, Tenn., homed in on a single mutation in a gene called MET, which is known to be involved in brain development, regulation of the immune system, and repair of the gastrointestinal system. All of these systems can be affected in children with autism.

“This is a vulnerability gene,” Dr. Levitt says. “These are not genes that actually cause autism. It raises the risk.”

Earlier this year, researchers with Autism Genome Project reported another new link to ASDs after scanning the largest collection of families with multiple cases of autism ever assembled. The work implicates a region of chromosome 11 and a specific gene called neurexin 1.

Neurexin belongs to a family of genes that help nerve cells communicate, says Dan Geschwind, M.D., a professor of neurology, psychiatry and human genetics at the University of California, Los Angeles, David Geffen School of Medicine.

There also appear to be links on chromosomes 11 and 17, he says.

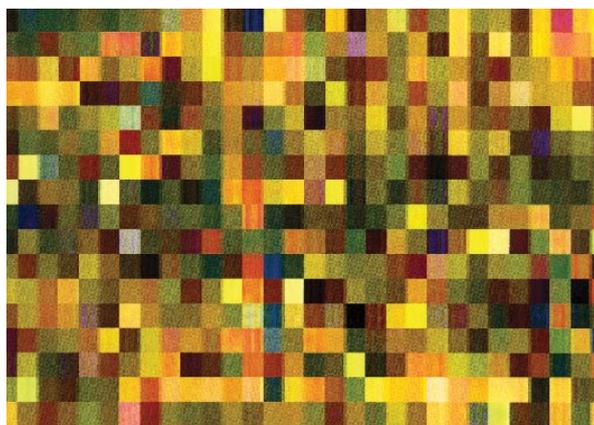
“We’re finding that there are many different genetic causes of autism,” Dr. Geschwind says. “This is a common disorder

for which there are many different genetic changes. A significant proportion of ASD results from rare mutations that are specific to people with ASD and don’t occur in normal people.”

One of the major goals of the research is to identify, as early as possible, children who are at risk of autism, he says. “Then, if they’re at risk, you can intervene early. The brain is more plastic early on, and there is a lot of evidence that the earlier one intervenes, the better the results.”

Indeed, the possibility of early intervention—and a potentially effective treatment down the road—is what drives the search for the genetic link to autism as well as a host of neurogenetic diseases. 

Charlene Laino is a health and science journalist who has written for Reuters, WebMD, and msnbc.com.



ILLUMINATING AUTISM Colored squares on this microarray image indicate genes turned on at varying intensities.



For more information on the programs featured here, see **RESOURCE CENTRAL** on page 46.