CHDD OUTLOOK

INSIDE

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Hunting for a gene: CHDD affiliate hopes hereditary disorder will provide clues to more common malady

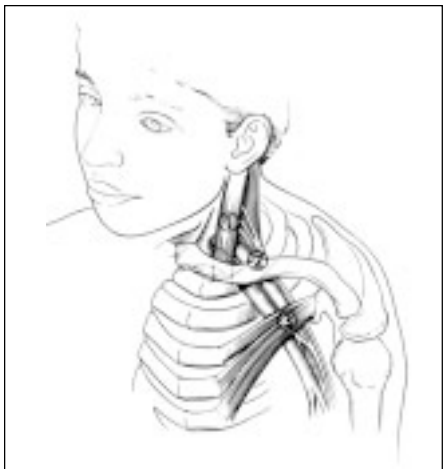
Suppose you are living your life as you normally would when suddenly you wake up with an excruciating pain in your shoulder, pain so severe that you might tell a doctor it felt as if someone was applying an electric drill to the affected area. The pain might be followed by paralysis and a loss of all sensory ability in the arm and shoulder. Then, over a period of weeks or months, you slowly regain function.

If this happened to you, you might be given a diagnosis of idiopathic brachial neuritis. "Idiopathic," meaning no one really knows what caused it. On the other hand, if you came from a family in which others had had similar experiences, your diagnosis would more likely be hereditary neuralgic amyotrophy (HNA), an autosomal dominant genetic disorder producing exactly the same symptoms. But there are important differences between the two disorders, besides the fact that HNA runs in families. The individual with HNA is far more likely to have more than one attack in his or her lifetime, and will likely also have subtle but distinctive facial features—a long face and close-set eyes—that resemble a Modigliani painting. More importantly, while HNA is rare, idiopathic brachial neuritis is not.

Facial features of many people with HNA resemble those of the subjects of Modigliani's paintings.

That's why CHDD research affiliate Dr. Phillip Chance is working hard to identify the gene that causes HNA. He and other researchers in the field hope that by better understanding the inherited form of the disorder, they'll gain insight into what causes the more common, idiopathic variety, and what can be done to prevent or relieve the symptoms of both.

Whatever is causing the pain and paralysis in these disorders has to do with the brachial plexus, Chance says. The brachial plexus is the largest structure in the peripheral nervous system. It is a neural network that's derived from cervical and thoracic nerve routes from the spinal cord.



The brachial plexus is shown in relation to the major muscles (numbered) of the pectoral girdle.

"These form a large structure in the thoracic wall, deep in the armpit, and from this extend the main nerves of the arm," Chance says. "These in turn contain about 100,000 axons, so they carry a lot of information."

The brachial plexus is easily damaged. For example, pulling a baby's arm during a difficult birth may result in dislodging the plexus, which may render the arm permanently useless. Trauma such as gunshot wounds or invasion by cancer can also damage the plexus. In the case of HNA, Chance says, researchers suspect the gene plays a role in the structure of the brachial plexus, or perhaps in its vascular supply.

Chance and his collaborators have been chasing the HNA gene for about five years now. It all started in Philadelphia, where he was located before coming to the UW in 1998. Trained as a neurologist and human geneticist, Chance became interested in HNA and put out the word that he was looking for HNA families.

Families became involved in a variety of ways. He was called to a clinic to meet with one patient, for example, who had had several attacks and who had more than one affected relative. Chance wound up going to Buffalo, N.Y. for the weekend and examining about 30 members of this man's extended family. He took blood samples from which he did two things: 1) he isolated purified DNA for genetic studies and 2) from family members' lymphocytes he established permanent cell lines so he would have a source of DNA or chromosomes for years to come.

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HNA gene hunt

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The research group eventually recruited about 30 HNA families who currently participate in the studies.

"Our first step back in Philadelphia was to find out where the gene was located, by means of a genetic linkage study," Chance explains. "A post-doc in my lab named Joan Pellegrino set out to map the gene and she succeeded in one month."

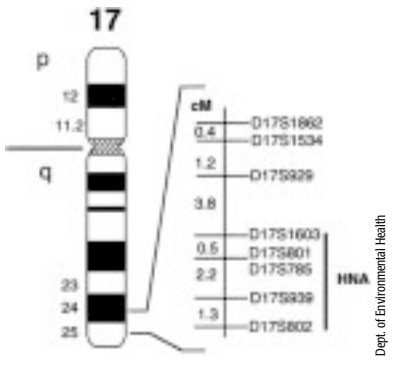
Pellegrino was lucky. Genetic linkage studies are performed by matching markers from the DNA of affected families to particular chromosomes. In the case of HNA, Pellegrino would have had to test markers from all the chromosomes—one through 22 in this case, since the gene is autosomal dominant. But she picked a marker from chromosome 17 that turned out to be tightly linked to the HNA gene in the first two families she studied. This led to the conclusion that the HNA gene is located on chromosome 17.

The research group then studied additional families and identified "key matings" that allowed them to narrow down the location of the HNA gene on the chromosome. Chance illustrates using a family pedigree, or diagram of all the members in an affected family: "For example, we can see that the chromosome 17 which harbors the HNA gene has a 5246635 genotype in most affected family members," Chance says. "But we look here on the pedigree and see someone who has the disorder and while they didn't inherit the 524, they still have the 6635. So what this tells us is that the location of the HNA gene has been narrowed to a smaller region, containing the 6635 genotype."

Chance and his collaborators have now defined a region on chromosome 17 containing the HNA gene that's somewhere between one and two million DNA base pairs.

Chance and his collaborators have now defined a region on chromosome 17 containing the HNA gene that's somewhere between one and two million DNA base pairs. Since the rule of thumb is that every one million DNA base pairs contains about 25 to 30 genes, there are about 50 or 60 genes that are candidates for causing HNA.

Two people in Chance's lab—Dr. Giles Watts, a post-doctoral fellow; and Kathy O'Briant, a research scientist—are doing the day-to-day work of sifting through the genes. A lot of that work involves Internet databases.



This diagram of chromosome 17 shows the region where the HNA gene is located

"They pick sequences that others have mapped to the region and then go back to the online DNA sequence and determine the structure of that gene," Chance explains. "Before you can test a gene as being causative for HNA you've got to know something about its structure and its sequence. That way you can compare the sequence of that gene in a normal person to the sequence in an affected individual."

Once the gene is identified, the next step will be to figure out what it

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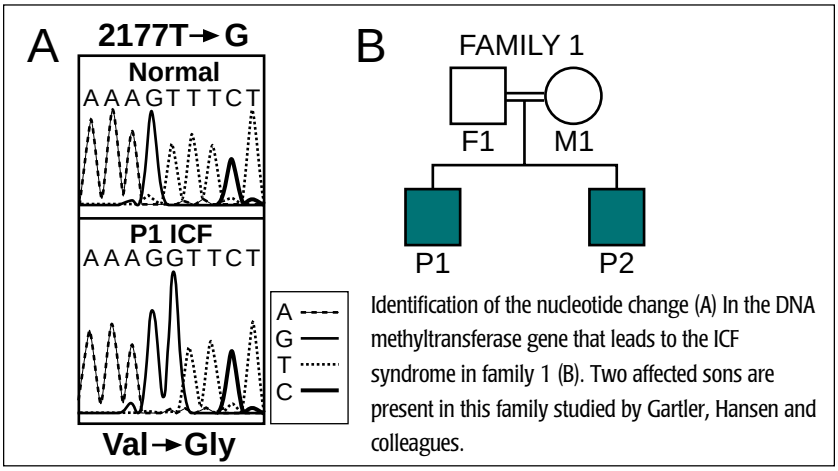
DNA methylation, replication timing may be key to understanding Fragile X syndrome, other genetic disorders

Although fragile X syndrome was identified more than 30 years ago, scientists have been struggling ever since to unravel the puzzle of just what triggers it and how it might be prevented or treated. As with most genetic disorders, the answer is neither simple nor easily pinned down. But recently, researchers have begun to see connections between fragile X and two other inherited diseases—Rett syndrome and immunodeficiency centromeric decondensation and facial anomalies (ICF)—that may lead them to important advances that will be useful in the study of genetic disorders in general. Their research centers on two important processes in the human genome: methylation of DNA and replication timing.

Methylation of DNA, explains CHDD research affiliate Dr. Charles Laird, is a normal process that occurs in many places in the human genome. Essentially, methylation means the addition of methyl groups (carbon and hydrogen) to DNA. Methylation is usually a strong signal to shut down the activity of a gene. Sometimes, this is exactly what's called for. However, when methylation occurs inappropriately, then genes that should be expressed are not, leading to trouble.

"We know that DNA replication is a process with extremely high fidelity," Laird says. "Rates of mistakes are very low—perhaps one in a hundred million. But we think the rate of error in methylation is probably much higher. So one of our goals is to understand how error-prone methylation is, and what the cell is able to do about it."

Fragile X is one of the disorders in which inappropriate methylation is implicated. Individuals with fragile X have a mutation on the X chromosome, a "fragile site," where the following process appears to take place: first, there is an expansion of a particular DNA sequence in the gene called FMR1, resulting in a longer gene. This lengthened gene is more susceptible to methylation, which prevents it from being active even when it is on the "active" X chromosome (most cells in female mammals have only one active X chromosome until the formation of the egg). The result is usually mental retardation in the offspring. Fragile X is, in fact, one of the most common causes of inherited mental retardation.



Identification of the nucleotide change (A) In the DNA methyltransferase gene that leads to the ICF syndrome in family 1 (B). Two affected sons are present in this family studied by Gartler, Hansen and colleagues.

Laird is not the only CHDD affiliate interested in DNA methylation. Dr. Stanley Gartler has devoted much of his long career to studying the inactivation and reactivation of the X chromosome in female mammals. Recently, ICF syndrome studies that he and colleague Dr. Scott Hansen have carried out have identified defects in a gene involved in DNA methylation. In ICF, the problem is a mutation in an enzyme called a DNA methyl transferase, which is responsible for initiating methylation. In this case there is *less* methylation than there should be, leading to certain chromosomes in the centromeric region not being properly condensed. In addition, genes are active that should not be active. The effects of ICF—which is extremely rare—include a compromising of the immune system that leaves the individual vulnerable to such diseases as pneumonia; facial anomalies, although subtle, also occur.

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In Rett syndrome, other researchers have shown that there is a mutation in a gene that encodes a DNA methyl binding protein on the X chromosome. Rett syndrome is fatal embryonically to males; in females it causes a progressive deterioration of gray matter in the brain, leading to dementia and problems with motor control. (Much of the early clinical work in the Puget Sound area on Rett syndrome was done by Dr. Vanya Holm, an emeritus professor of pediatrics who is affiliated with CHDD.)

"The Rett syndrome results show why methylation is so important," Gartler says. "Proteins bind to methylated DNA, and they determine whether genes will be expressed or not."

Laird, Gartler and several other collaborators currently have grants from the National Institutes of Health that focus heavily on methylation. Essentially, they hope to extrapolate from the diseases they have studied in order to better understand the normal process and its role in some genetic disorders. Another aspect

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CHDD researchers ask, 'What effect does childcare have on kids with special needs?'

"Should I put my child in daycare, and if so, where?" is an anxiety-provoking question many parents face—if not right after a child is born, then at some time before that child goes to school. Questions arise about hours, cost and location, but mostly parents worry about the quality of care their child will receive and how it will affect that child's development.

Responding to these parental concerns, many researchers have been studying childcare, especially in the past 10 years. But virtually all of these studies have been limited to typically developing children. When considering children with special needs, researchers have tended to concentrate on questions of access, asking whether daycare operators are willing to accept such children and know how to accommodate their special needs. The result has been a dearth of information on what effects childcare has on children with special needs. That's a gap that CHDD Research Affiliate Dr. Cathryn Booth was anxious to fill.

Note: All of the photos on pages 4 and 5 were taken during home visits as part of the childcare study.

"Although mothers of children with special needs tend not to go back to work as early as do mothers of typically developing children, there are still a substantial number of women with such children who need to work and therefore need childcare," Booth says. "These families are just as anxious to know what effects childcare might have on their children as families with typically developing children."

Since 1995, Booth and co-principal investigator Dr. Jean Kelly have been conducting a longitudinal study on children with special needs in childcare. Sponsored by the Maternal and Child Health Bureau, it is modeled on a similar study of typically developing children for which both researchers are investigators.

That study, sponsored by the National Institute of Child Health and Human Development, is ongoing and has set the standard for looking at childcare in a multi-faceted way. "You can't just ask, 'Is childcare good or bad for children?'" Booth explains. "It isn't that simple. It depends on what kind of childcare, as well as what else is going on in a child's life."

The NICHD study—a 10-site national project—created what it calls an ecological model. It measured many aspects of each child's life—not just daycare—then attempted to measure outcomes in light of all the variables involved.

"We found that in general, what goes on in your family, the quality of life with your family, is about twice as important as what happens in childcare," Booth says.

That doesn't mean that childcare has no effect. "After you consider the effects of the family, if you look specifically at what happens in childcare, it turns out that the quality of childcare is an important positive factor," Booth says. "The higher the quality of childcare, the better the outcomes for children, especially in cognitive and language development. There is also a negative effect for hours in care, so that the more hours a child is in care, the less positive the outcome."

The special needs study Booth and Kelly have been conducting also uses an ecological model, and many of the variables measured are the same. But unlike the NICHD study, which recruited children at birth, the researchers sought children who were a year old. "We wanted to enroll families who were beyond the initial adjustment period," Booth explains.

About half of their subjects were children who had been diagnosed with developmental delays, while the other half were at risk for developing disabilities because of biomedical factors such as low birth weight, respiratory distress syndrome or maternal substance abuse. At-risk children were included with the idea that they were more likely to be chronically ill, medically fragile or more vulnerable to stress; thus, the families' childcare decisions were likely to be similarly affected. Some children in the study were in childcare while others stayed at home with their mothers.

The study began with a home visit, during which mothers were interviewed to obtain some general information about the family, as well as their attitudes toward and plans for childcare. Also during this visit, the children were evaluated using the Bayley Scales of Infant Development, the Bayley Behavior Rating Scale and the Wisconsin Behavior Rating Scale. The purpose of this evaluation was to get a baseline against which later development could be compared.

When the children were 15 months old, they were visited in their childcare setting, if they had one, and also at home. These visits were more than just a quick check of the child-caregiver ratio and safety

conditions in the facility; they were an extended observation of the interaction between the child and the caregiver. Specially trained observers used a standardized instrument known as the Observational Record of the Caregiving Environment to evaluate a number of factors, including caregivers' sensitivity to the child, their level of engagement with the child, their emotional tone in dealing with the child and the degree to which they stimulated cognitive development.

The home and childcare visits were repeated when the children were 30 months old, and they were evaluated using the same instruments employed at 12 months. Also at this age, children came into the lab at CHDD, where they were videotaped during an interaction with their mother and evaluated with an assessment based on the Strange Situation. This is a 25-minute procedure involving brief episodes of increasing stress for the child, including two mother-child separations and reunions. The purpose is to evaluate the quality of the child's attachment to the mother.

The children in the study were evaluated again at age 45 months. The data from that last evaluation is still being analyzed, but Booth and Kelly do have results to report from the 30-month data.

First, Booth says, it is important to separate the delayed group from the at-risk group because the results for each were different. In the delayed group, the researchers found that the higher the quality of care, the better the adaptive behavior in the child at 30 months. And because adaptive behavior had been measured at 12 months, when the children entered the study, this was really about *increases* in adaptive behavior. (The term adaptive behavior refers to functioning in areas such as dressing, eating, playing and toileting.)

"We feel this is important because if children with disabilities have good adaptive functioning, it gives them more opportunities to be in other programs," Booth says. "If you think about what it takes for a caregiver to deal with a child with disabilities in a childcare situation, to the extent that they don't have to do as much one-on-one care, there will be more opportunities that open up."

Significantly, the children in high quality care had an equal level of adaptive functioning as the children who stayed at home.

Another result for delayed children was more surprising. The researchers found that the greater the hours in childcare, the greater the probability that these children would be securely attached to the mother.

"This was the opposite of anything that had ever been hypothesized for typically developing children," Booth says. "In fact, the single thing that started the NICHD study was the controversy about attachment. There had been some studies that showed that insecure attachment was related to lots of hours in care."

The NICHD study found that childcare per se did not affect attachment, but if the mother was already very insensitive, then lots of hours of care or low quality of care increased the probability of insecure attachment.

"We think the result was different for children with diagnosed delays because of stress," Booth says. "It's stressful to be the parent of a child with disabilities. So to the extent the mother and child can have time away from each other, it may give the mother a better connectedness with the child when they are together."

Significantly, the children in high quality care had an equal level of adaptive functioning as the children who stayed at home.

In the at-risk group, the researchers found that the older the children were when they entered childcare, the fewer behavior problems they had and the better behavioral organization during testing, as measured by the Bayley. They also found that the higher the observed quality of care, the fewer behavior problems these children had. Interestingly, the at-risk children were found to have a *greater* probability of secure attachment to the mother if they were in childcare than if they stayed at home. The researchers speculate that this too may be due to stress reduction.

Booth and Kelly will wrap up the study in the next year. In addition to publishing their results in scientific journals, they are also giving talks to groups that are concerned with policy and funding for childcare, pointing out the needs of parents whose children have disabilities.

"We think it's really important to get our results out there," Booth says, "because nobody else has this kind of data." ♦

Fragile X

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of their research keys in on replication timing.

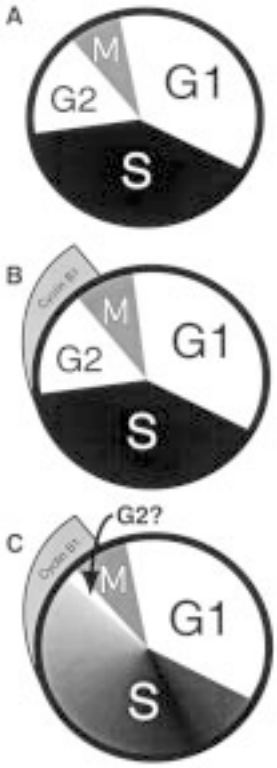
Back in 1987, when Laird first began to study fragile X, he predicted that fragile sites are in part caused by a change in DNA that makes it late in replicating. "Every time a cell divides," Gartler explains, "genes have to double; they have to be replicated. And they aren't replicated randomly. They have a highly ordered pattern. Some genes replicate very early, some late."

Genes on the sex chromosomes are among the latest to replicate even if everything proceeds normally. But now research by an M.D.-Ph.D. student, R.J. Widrow, has confirmed Laird's prediction: the fragile X mutation interferes with the timing of replication under conditions that induce fragile sites. "The mutation takes a gene that is already extremely late in its replication timing during the cell cycle and makes it do that in spades," Laird says.

The problem with late replication is twofold: The gene might not have a chance to "proofread" the replication for errors, or it might not have a chance to complete the replication before the cell divides, which could lead to chromosome breakage.

Laird, Gartler, Hansen, and Widrow published a paper that even questions the accepted beliefs about the normal process of cell division. "The dogma in this field is that the cell cycle is divided into an S phase for DNA synthesis that's flanked by a G1 phase and a G2 phase," Laird says. "G1 is the gap before DNA synthesis and G2 is the gap afterward, then cell division ensues. But in the process of defining this late replication caused by the fragile X mutation, we found that replication is so late we're not sure anymore that there's a discrete G2 phase. We think that some sequences may show replication very close, even up to cell division."

For Laird, this points up the intertwined nature of clinical and basic research. "Here we have a disease that causes mental retardation," he says, "and we try to understand it by consolidating our information, by synthesizing, by hypothesizing models. We then test the models, confirm some of our predictions and reject others, and then begin to question some of our underlying assumptions about cell biology. So the disease is giving us a window into the normal process of cell division."



In this figure, view A shows the classic view of the cell cycle, with four phases: G1, S phase, G2 and mitosis. B is a more recent view, while C is the revision proposed by Laird, Gartler, Hansen and Widrow. Here, low levels of DNA synthesis (shading) are ongoing much later in the cell cycle than previously suspected. In some cells, the existence of a discrete G2 phase is questioned.

Meanwhile, the clinical aspects of searching for a cure have not been forgotten. There is already a drug—5-aza-2-deoxycytidine—that is known to inhibit methylation and theoretically could be used to reactivate the FMR1 gene in individuals with fragile X. But 5-aza-2-deoxycytidine is not specific in its action and could cause damage to the transcription of other genes. That's why scientists like Laird and Gartler are studying methylation in hopes of one day finding a way to counteract problems with it.

"There are several labs that are working hard on these problems," Laird says. "So in the long run we may be able to do something about fragile X—in 10 years, perhaps even sooner." ♦

HNA gene hunt

Continued from page 3

does normally and how the mutation disrupts that function. In addition to its role in the brachial plexus, the gene the researchers seek must also play a role in craniofacial morphogenesis, given the subtle facial features often found in the inherited form of the disorder.

"After you know the DNA sequence in the gene, you can predict what its amino acid sequence would be—its protein structure—and that gives you clues as to its normal function," Chance says.

Chance is hoping the gene will be identified in the next year or two. He and his colleagues are trying to put together a collaboration with a large group in Belgium that has also been working hard to find the HNA gene, with the hope that by combining forces, the search will be speeded up.

Finding the gene, he points out, is really only the beginning of a long process. There are many steps ahead as the researchers ferret out the gene's normal function and how the mutation leads to developing HNA.

"We hope that in the end we'll be able to do something to address not only HNA, but the idiopathic variety of the disorder as well," Chance says. ♦

New initiative targets long-term systems change efforts

Change is hard for people, but it's even harder for systems. Once a system is put in place, it often seems to have a life of its own. Yet systems must change from time to time if they are to continue to serve the purposes for which they were set up, especially when the needs of the system's constituency can change at any time. That's why CHDD has created the Community Disability Policy Initiative.

The Community Disability Policy Initiative (CDPI) brings together people within CHDD for two purposes: (1) to facilitate communication among the individual UAP projects that work to improve systems serving people with disabilities and (2) to collaborate with individuals who have disabilities and with consumer advocate groups in the community to work on an issue of interest to those individuals and groups.

CHDD has long had task forces that work for systems change in particular areas, but this is the first time all of those task forces have attempted to work together. Task forces represented in CDPI include Early Intervention, Assistive Technology, Aging and Developmental Disabilities, Cerebral Palsy, Leadership Training, and Legal Advocacy and Disability Policy. The initiative is co-directed by Dr. Sherrie Brown, who heads the Legal Advocacy and Disability Policy Task Force; and Dr. Doug Cook, who oversees CHDD's Adults and Elders Program.

"We're really just getting started now," Cook says, "but we're pretty clear on what we want to do."

Essentially, they want to learn all they can about planning strategically to effect systems change, then apply what they've learned to a significant policy issue of interest to people with disabilities, their families and the agencies and organizations that serve them.

The next six months are likely to be an information gathering time for initiative participants. They'll be conducting a literature review on systems change strategies, looking especially at methods that have been effective in other locations. And they'll be consulting with community people—both agencies and individuals—to zero in on an important policy issue that is of broad interest. The group has already consulted with the UAP Advisory Board, the Developmental Disabilities Council, the Special Education Coalition, and the Community Advocacy Coalition.

Once an issue has been chosen, Cook and Brown's hope is that CDPI and its community associates will commit to working on it for a five to ten-year period, to ensure enough time to assess its long-range impact and effectiveness. In addition, the goal is to create a Center of Excellence in the policy arena.

Exactly what the group will do once the topic is chosen hasn't been decided, because that decision depends on what the topic is. They anticipate that education—for health care providers and family members—will be part of their activities. Eventually, initiative participants will be involved in research that may lead to change in laws or public policies.

"The internal part of our efforts; that is, the research into systems change strategies, doesn't require funding," Cook says, "but at some point we fully expect to be seeking grants or other kinds of funding to move forward."

Brown hopes that CDPI will one day be a resource both for people within CHDD and in the community. "I would like it to eventually be a resource for people who want help in breaking down a particular barrier in order to improve the lives of people with disabilities," she says.

Cook's vision for CDPI is that it "will lead to better health care for people with disabilities. That's what we're all after, in the long run." ♦

The UAP Activities Guide is now available at the CHDD Website. The guide is a directory of programs, activities and projects currently conducted as part of the University Affiliated Program (UAP) at the University of Washington's Center on Human Development and Disability. We hope the guide will be a good resource for students, professionals, consumers, advocates and others interested in this field.

The UAP at the CHDD is involved in an array of interdisciplinary research, training, clinical service and community outreach activities that address the entire field of developmental disabilities. In the guide you will find a description of each program and project, along with contact information for those most involved with it.

To get your copy of the guide, go to the CHDD Website at http://depts.washington.edu/chdd/. At the bottom of the homepage, click on "CHDD online publications (PDF files)." Then click on "UAP Activities Guide." The guide is a PDF file, which means that when you download it you will have a booklet similar to what you would have had if we had sent you a printed copy. You must have a copy of Adobe's Acrobat Reader—a free program—in order to download a PDF file. To make this easier, we've provided a link to Acrobat Reader on the same page from which you download the UAP Guide.

You can also get the same information contained in the UAP Guide by clicking on "UAP" from the CHDD homepage. By "going electronic," we hope to be able to keep our information current to serve you better. For further information about the UAP Guide, call the CHDD information coordinator, 543-4037. ♦

Two new research affiliates join CHDD in winter quarter

Dr. Ramona Hicks is an associate professor of rehabilitation medicine. She received a master's degree in physical therapy from Stanford University and a Ph.D. in neuroscience from the University of Connecticut. Her research involves investigating ways to improve functional recovery in children and adults with neurological disorders. Recent studies have employed a rodent model of traumatic brain injury to evaluate 1) the effects of neurotrophic factors on cell damage and functional recovery, and 2) the role of the complement system in post-traumatic inflammatory processes. ♦

Dr. Albert La Spada received his M.D. and a Ph.D. in molecular biology from the University of Pennsylvania in 1993, while a recipient of a Medical Scientist Training Program scholarship. He joined the UW Medical Genetics Training Program in 1995 as a clinical genetics fellow. After completing his clinical genetics training in 1998, he spent one year as a neurogenetics fellow with Dr. Thomas Bird. La Spada is board-certified in clinical genetics, clinical & molecular genetics, and clinical pathology. He completed postdoctoral research training as a Howard Hughes Physician Postdoctoral fellow in the laboratory of Dr. Stanley McKnight. La Spada is now an acting assistant professor in the Department of Laboratory Medicine.

La Spada's research focuses on understanding neuromuscular and neurodegenerative disease. In 1991, he discovered the cause of X-linked spinal and bulbar muscular atrophy, finding for the first time that trinucleotide repeats could expand in length to cause an inherited human disease. Since this discovery, 14 more neurological diseases have been shown to be caused by trinucleotide repeat expansions, including Huntington's disease, myotonic dystrophy, and two forms of mental retardation. La Spada's research team is working on understanding why trinucleotide repeats expand to cause neurological disease and how these disease mutations lead to the specific demise of nerve cells. ♦

The CHDD Website

The Center's website has recently updated information on CHDD Research Affiliates, as well as added a University Affiliated Programs (UAP) guide. The **University Affiliated Programs Activities Guide 2000** is a directory of programs, activities and projects currently conducted as part of the UAP. See Page 7 for details on getting the pdf version.

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