Making sense of fMRI: CHDD core service helps researchers refine analyses for more accurate results

The advent of functional magnetic resonance imaging, or fMRI, has been a boon for scientists who study the brain and its functioning. Employing existing MRI technology that produces images of soft tissue in any part of the body in a noninvasive manner, fMRI takes the technology to a new level, producing visual images of brain functioning, most commonly by detecting minute changes in blood oxygenation in specific regions. The higher oxygenation levels indicate areas of greatest neural activity as the person in the MR scanner performs various assigned mental tasks that activate brain areas for working memory, episodic memory, face perception and language and reading skills, as well as physical tasks like finger tapping.

Functional MRI scans generate an immense amount of data, producing brain images in thin slices from top to bottom. When information from many individuals is combined as researchers compare brain activity in healthy volunteers with that of individuals with various neurodevelopmental and neurodegenerative disorders, an even greater volume of information is created. Data must be aggregated and analyzed using sophisticated computer and statistical techniques to produce composites that reveal differences between subjects and controls. The accuracy of the composites allows scientists to begin drawing conclusions about, for example, the differences in brain response in children with and without autism who are shown an image of a face, or in children with and without learning disabilities as they perform specified reading and language tasks.

As researchers at the University of Washington increasingly utilize fMRI in their brain studies, the Center on Human Development and Disability has expanded its core services to assist them. One unit of CHDD’s Neuroscience Core is its Brain Imaging Component, which facilitates the use of various imaging techniques including conventional MRI, fMRI, and a third form of magnetic imaging, MR spectroscopy. Important services provided by the core include guidance in data analysis and development of specialized techniques tailored to the research needs of individual investigators affiliated with CHDD.

Clark Johnson, Ph.D., is a member of the core and expert in fMRI data analysis. A research associate professor in the School of Nursing, he assists CHDD researchers in refining their studies to achieve the most accurate results. He works closely with CHDD research affiliate Elizabeth Aylward, Ph.D., a professor of radiology and CHDD’s coordinator of experimental design and image analysis. Todd Richards, Ph.D., also a CHDD research affiliate and professor of radiology, works closely with Johnson to develop methods for analyzing fMRI images.

Goal number one for these investigators is to identify and control for confounding variables, to make the scans as accurate as possible. Confounding variables, or covariates, that affect brain function might include such factors as the time of day the scan takes place, medications taken, the number of cups of coffee ingested, tobacco use, and the amount of sleep the night before.

“First we need to figure out whether these are, in fact, confounding factors,” said Johnson. “If they are, we need to control for them in order to be precise about our measurements. If they’re not controlled for, these confounders add variability. Since we’re talking about very subtle effects, variability can mean the difference between discovering an effect and not finding one. This is an area that I don’t believe anyone has done a lot of work on.”

Working with Richards and other colleagues, Johnson and Aylward hope to develop a simple one-page questionnaire that individuals will complete before being scanned. They will work in a small group and then with a larger group of UW researchers to reach consensus on the important confounding factors that research subjects should report on. While research participants can provide infor-

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mation on a number of variables, they do not have the ability to report on some factors, such as blood chemistry.

Aylward and Johnson hope then to start asking researchers who run fMRI studies at the UW to begin gathering data on confounding variables. If consensus among local researchers can be reached regarding the most important variables, Johnson and Richards hope to present their results at a national level, mapping and publishing new analysis strategies.

“With variability, you lose the ability to make precise statements,” said Johnson. “The whole point of doing a study is to be able to say something concrete. When you have variability, it makes the whole picture fuzzy.”

“If you were comparing weight-loss diets and you didn’t know that one dieter ran three miles a day and the other sat around and ate bonbons, you couldn’t properly evaluate the diets,” said Aylward. “The same is true in brain research, whether it’s for autism, learning disabilities, fetal alcohol syndrome, speech and language, Alzheimer’s or traumatic brain injury, all areas being investigated by CHDD researchers. At this point we don’t even know the variables. We want to get rid of as much ‘slop’ as we can. We need to ask our subjects questions in order to reduce the variability, to be able to say, yes, there is a difference between people with autism and people without. If we figure out what questions to ask and get rid of the confounding variables, it will help us determine true differences between brains, or in the same brain before and after treatment; for example, after a three-week intervention for learning disabilities. It’s also important to know how brain activation changes between two scans of the same individual even if there is no intervention. We’re trying to reduce the variability so we can determine with confidence whether it’s actually the treatment producing the effect.”

Aylward cautions it is important not only to ask the questions, but to choose research subjects judiciously. “If we decide smoking is an important factor, then either we don’t include smokers in our pool of subjects or we choose people who haven’t smoked a cigarette in, say, the last six hours. We can get better at choosing our sample for explicit control, and/or we need a statistical method to control for confounding factors after the fact. It’s partially an organizational challenge: we have to reach consensus about what data should be collected and then get investigators to share data with us. We’re going to request that they ask their subjects such questions as how many cigarettes did you smoke? how many cups of coffee did you drink?—whatever it is that we, by consensus, determine affects brain activation.”

“This is a wonderful example of the benefits of CHDD and its core services,” said Johnson. “On one hand, the researchers come to the core to gain valuable assistance with their research, but they can also collectively contribute to the core by virtue of doing their work and sharing their data.”

A second goal that Johnson, Richards and Aylward have set is what they call Best Practices. “fMRI is really the Wild West of statistics,” said Johnson. “There are new developments practically every week, and there is a need for an ongoing effort to incorporate those that have merit and settle on the best way to do statistical analysis. We have all this data; now let’s figure out the best way to analyze it.”

“This goal is similar to our goal for covariate analysis,” said Aylward. “When fMRI started, no one thought we could use these covariates to make data more understandable, or get results that might otherwise be lost because we weren’t controlling for the confounding factors. We have immense computational capacity and we need to agree on the best way to analyze data.”

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Advocating for change: CHDD’s Community Disability Policy Initiative and the Washington DD Council

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carcely more than a generation ago, families with a loved one with a developmental disability typically received little support. Children with severe developmental disabilities often could not attend schools. In many instances, people were sent to state institutions for life.

With the passage of the Developmental Disabilities Assistance and Bill of Rights Act in 1970 and the subsequent establishment in every state and U.S. territory of Developmental Disabilities Councils, Protection and Advocacy Systems, and University Centers of Excellence in Developmental Disabilities (UCEDDS), remarkable changes have taken place. The National Association of Councils on Developmental Disabilities lists signs of progress:

• There is a societal expectation that children with developmental disabilities will grow up in families, not institutions, and families will receive needed supports
• The number of people with developmental disabilities in state institutions has dropped significantly
• Infants and toddlers receive needed services as early as possible to give them the best start on life
• Children with developmental disabilities go to school, often in their own neighborhoods
• Young adults with developmental disabilities learn to work in real job settings
• Adults with developmental disabilities have jobs in increasing numbers and live in their own homes
• People with developmental disabilities are becoming more valued and contributing members of their communities.

Significantly, said Sherrie Brown, J.D., Ed.D., the advent of Developmental Disabilities Councils has helped people with developmental disabilities and their families become advocates for themselves, advancing legislative and social agendas. Brown is the representative of the UCEDD at the Center on Human Development and Disability to Washington’s Developmental Disabilities Council. She succeeds Cecile Lindquist, a longtime CHDD staff member and advocate.

At a recent DD Council meeting, Sherrie Brown introduced women publishing an illustrated oral history of the efforts of a group of families to effect change for their children with developmental disabilities. The book, *Becoming Citizens: Family Life and the Politics of Disability*, will be published next fall. The project, the brainchild of Kathi Whittaker and the Seattle Family Network, chronicles the lives of families who raised children with developmental disabilities in the Seattle area between 1940 and 1980. “The book not only documents what happened in the past,” said Brown, “but it shows how all of us can make things happen. That’s the message for everyone in the DD advocate community. These families lobbied the legislature and didn’t give up. But they’re growing older, and it’s important to pass the torch to new advocates. The DD Council has continued to support that effort.”

The Washington State DD Council meets every two months in locations around the state. A primary role is to make public policy recommendations to the Governor and policy makers. The council comprises thirty-three members appointed by the Governor; at least sixty percent must be individuals with developmental disabilities, parents or other family members, or guardians. Also on the council are representatives of service providers and principal state agencies that provide funding or services.

In representing CHDD on the council, chairing its Health and Education Work Group, and heading CHDD’s Community Disability Policy Initiative (CDPI), Brown advances CHDD’s mission to work on systems change in collaboration with individuals who have developmental disabilities and with advocacy groups. The effort involves ongoing dialogue to identify issues that the community considers appropriate for CHDD assistance in re-

The DD Council includes self-advocates, family members and representatives of state and other agencies that provide services to people with developmental disabilities.
Mosaicism and methylation: CHDD investigator and colleagues make advances in understanding fragile X

Affecting an estimated one in 4,000-6,000 males and about half as many females in all ethnic groups, fragile X syndrome is the most frequent inherited cause of cognitive disability. It is caused by an inherited mutation in the gene \textit{FMR1}, discovered in 1991 on the long arm of the X chromosome.

Since females have two X chromosomes and hence two copies of \textit{FMR1}, females with the mutation usually have a properly functioning copy of the gene when the normal copy is on the active X chromosome. The normal copy can partially compensate for the mutant one. With just one X chromosome, males with the mutation typically have more severe symptoms than females. Associated physical features include enlarged ears, a long face and connective tissue problems. Some males exhibit speech disturbances, hand biting or flapping, and autistic behaviors. Both sexes can carry a "premutation" version of the gene that can further mutate and cause mental retardation in later generations.

Fragile X syndrome involves a mutation called a trinucleotide repeat expansion, in which a specific combination of the building blocks of DNA—in this case the nucleotides CGG—repeat themselves beyond a normal threshold of about 30 repeats. It also involves inappropriate methylation of DNA, when the repeat size increases beyond about 200. DNA methylation is a process by which a methyl group—one carbon and three hydrogen atoms—is added to a DNA nucleotide, shutting down the activity of a nearby gene. In most cases this shutdown is needed for normal function, as in the inactivation of the second X chromosome in females, or in the inactivation of genes as stem cells differentiate during fetal development and become, for example, blood cells, skin cells or neurons.

In fragile X syndrome, however, there is excess methylation, or hypermethylation, of the \textit{FMR1} gene, silencing it and disabling or compromising its ability to create FMRP, a protein needed by brain cells for normal cognitive function. The proportion of somatic cells in which \textit{FMR1} is hypermethylated appears to influence the degree of mental retardation.

Recent advances in the University of Washington laboratory of Charles Laird, Ph.D., are contributing to an increased understanding of the mechanisms involved in fragile X syndrome. Laird is a UW professor of biology, adjunct professor of genome sciences, research affiliate of the Center on Human Development and Disability, and director of the Fragile X Research Center, a federally funded research program involving laboratories at the University of Washington, the Fred Hutchinson Cancer Research Center, and the University of California at Davis.

His research focuses on \textit{FMR1} mosaicism, found in more than 20 percent of individuals with fragile X, in which different cells of one individual contain different forms of the mutation. Some people have different sizes of the repeat expansion in different cells in both methylated and unmethylated states, a condition called methylation mosaicism.

In the last year, Laird and colleagues have made significant advances in two areas of research that will enhance scientific understanding of the fragile X gene and its mechanisms, especially methylation mosaicism. One advance is a refinement of the polymerase chain reaction (PCR) to analyze DNA samples, including those used for pre- and postnatal diagnosis. The second advance is in the area of epigenetics, laying a new theoretical foundation for how methylation states are propagated as cells divide.

**Polymerase chain reaction**

“It is extremely difficult to quantify the degree of mosaicism in an individual,” said Laird. “In the last year our lab has made a quantum improvement in making PCR more accurate in quantifying the methylation state of a gene.” PCR is a simple and inexpensive method of amplifying or generating unlimited copies of any fragment of DNA; it has been in widespread use since the mid-1990s.

In some fields, said Laird, quantifying methylation is very important. In oncology, for example, it is important to look at mosaicism between normal cells and cancer cells in an individual. “In our field of fragile X as well as in other epigenetic diseases, quantification is important in understanding cell/cell mosaicism. We think it will allow us to better understand a patient’s prognosis and why symptoms vary in adults.”

However, there are at least two problems with employing PCR in such analyses: contamination and redundancy. The first problem involves the unintended amplification of contaminants from previous patient samples. The other, template redundancy, involves amplification of such a small sample of methylated and unmethylated cells that it can produce a skewed estimate of the degree of mosaicism. “If you keep amplifying DNA from a sample of three or four cells, you often get an inaccurate result,” said Laird.

To resolve these problems, two of Laird’s colleagues suggested solutions that
work in tandem. R. Scott Hansen, Ph.D., research assistant professor of medical genetics and a CHDD research affiliate, suggested adding a “molecular barcode” to each genomic fragment prior to PCR amplification, in the form of a sequence of nucleotides called a random sequence identifier.

The other solution is a technique of molecular “batch-stamping” suggested by Brooks Miner, a research scientist in Laird’s laboratory. “It is basic but profound,” said Laird. “By ‘stamping’ a gene sequence with a sample number and date using a molecular technique, we gain virtual certitude as to its identity. It’s an elegant method of keeping track of which cell is which; it will be important both for clinical purposes in disorders like fragile X syndrome, as well as in analyzing rare DNA, for example in forensics or ancient DNA samples.”

Laird and colleagues published their new PCR techniques in the Sept. 30, 2004 online issue of Nucleic Acids Research, vol. 32, No. 17. Application of this method to single-stranded PCR is being undertaken by Megan McCloskey, a research scientist in the Laird lab.

Epigenetics

Cells contain not only genetic information, but epigenetic or “beyond the gene” information as well; i.e., modifications to genes other than changes in the DNA sequence. If these modifications do not take place properly, some genes may be switched on or off incorrectly, with major consequences. Faulty modifications are implicated in a number of epigenetic disorders, including fragile X syndrome, Rett syndrome, Angelman syndrome, Prader-Willi syndrome, several types of cancer, and perhaps other diseases.

Epigenetic information is encoded in two ways: one is by means of the proteins that bind to DNA. The second is at the chemical level through the methylation of DNA. Adding these methyl groups alters how a gene interacts with important interpreting or transcribing molecules in the cell nucleus. “With regard to fragile X, the important epigenetic component is whether the fragile X gene is expressed, and the best molecular test is to determine whether the control region of the gene is methylated,” said Laird. “This is the basic clinical test used in pre- and postnatal diagnosis, in early childhood, and even among parents of fragile X children. It’s the molecular test that helped in the discovery of the gene in 1991. One of the first indicators was whether there was abnormal methylation at a particular site on the X chromosome.”

Laird and colleagues’ research lays new theoretical groundwork for how methylation states are propagated as cells divide. “We know it happens,” he said. “The question is how does a cell control methylation so that it is propagated during division?” This knowledge is clinically important for fragile X, since methylation of the gene largely determines whether the individual will be mentally retarded.

Last year, the researchers published a paper in the Proceedings of the National Academy of Sciences (Jan. 6, 2004), showing their new method of PCR-amplifying double-stranded DNA. “This is extraordinarily difficult but very useful,” said Laird, “because we can now look at the transition states of methylation—when the DNA replicates and the cell divides. The moment of DNA replication is the moment at which the transition states of methylation occur. We presented the technique and estimated the fidelity of two different methylation processes, one called maintenance methylation, and the other, de novo or new methylation.”

Maintenance methylation occurs when methylation on the “parent” DNA strand is passed to the “daughter” strand during replication; it occurs with about 95 percent efficiency. De novo methylation can occur in the daughter strand in the absence of parent strand methylation. “We were able to estimate the probability that the daughter strand would become methylated even though the parent strand was not,” said Laird. “In our January 2004 paper, we estimated that it occurs with an average efficiency of 10 to 20 percent per methylation site. The de novo methylation can effectively compensate for the less than 100 percent efficiency of maintenance methylation and thereby keep these genes sufficiently methylated to be inactive.

“Previously, we didn’t have a way to estimate methylation fidelities with enough statistical power to make subtle distinctions, for example between the methylation of mutated and normal fragile X genes in females. We can now estimate quite specific rates of methylation, both maintenance and de novo.” Laird’s lab is pushing into new territory using a mathematical model developed with the help of Brooks Miner and mathematical biologists Diane Genereux and Carl Bergstrom. Data from doublestranded methylation analysis are provided by other researchers in the lab, including Miner, Dr. Reinhardt Stoger and Alice Burden.

Translating such basic research may lead to clinical advances for individuals with fragile X in two important ways, said Laird. “One is a deeper understanding of what mosaicism means in fragile X, and at what cellular levels it occurs. Mosaicism can be estimated in part using the existing clinical technique. Then, in cases where there is a serious question, our methods could be applied to a more precise understanding of the degree of mosaicism and its correlation with severity of retardation.”

The second area of clinical relevance, said Laird, is in clarifying the relationship between fragile X syndrome and FXTAS (fragile X-related tremor/ataxia syndrome), a late-onset parkinson-like disorder affecting older men who are carriers of the FMR1 premutation. The disorder was characterized last year by Laird’s colleagues at the University of California at Davis, Randi and Paul Hagerman, who estimated that some 30 percent of carriers may develop FXTAS later in life. “Are there mosaic individuals who are at risk for mild symptoms of both fragile X syndrome and FXTAS?” asked Laird. “Our work provides a way to more fully understand what is happening in the mosaic cells.”

Beyond fragile X, said Laird, a greater understanding of mosaicism and the pattern of methylation, using mathematical modeling, will have important implications for all epigenetic diseases.
With advancing age, many of us face increasing health challenges and difficulties in obtaining adequate health care. Such difficulties are compounded for individuals with developmental disabilities, their families and caregivers, as they seek comprehensive and appropriate health care services and strive to maintain health and quality of life.

The Center on Human Development and Disability has long had a mission to promote the health and welfare of people with developmental disabilities as they age, through its Adults and Elders Program, which emphasizes community health care. The program was headed by Douglas Cook, Ph.D., for many years until his recent retirement.

The program is now directed by Kathleen Watson, Ph.D., R.N., a post-doctoral fellow in biobehavioral nursing whose area of interest is health and healthcare across the lifespan for people with developmental disabilities. The Northwest Center, a non-profit community agency serving individuals with developmental disabilities, provided partial support for her work. Her interest is not only professional; she has a grown daughter with a developmental disability. With her expertise and abilities of the groups related to training programs in eastern and western Washington, Watson has updated and expanded four training modules developed by Cook. She is offering training sessions to various groups, ranging from the large staff of a group home agency to a married couple who both have developmental disabilities.

“The Division of Developmental Disabilities (DDD) is consulting with us regarding priorities and needs,” said Watson. “With my nursing background, I come at the subject from a slightly different perspective from Doug’s.”

The four training modules include:

- Supporting People with Developmental Disabilities During the Aging Process
- Toward Healthy Aging: Promoting Health Through Lifestyle Changes
- Getting Good Health Care
- Medications: Promoting Safe and Appropriate Use

Each is a hour-long PowerPoint presentation that can be expanded and adapted according to the needs, interests, expertise and abilities of the groups receiving the training. Working with the DDD and the Community Residential Services Association (CRSA), an organization of residential care providers, Watson contributed to two day-long health-related training programs in eastern and western Washington.

She recently presented a training session to the board of the United Friends Group Homes. “Many board members are parents, and one of their big concerns is what happens to our children as we grow older?” she said. “What happens when our children become ill and can no longer be cared for in the group home? Are they going to end up in institutional care, the thing we’ve tried to avoid all their lives? Unfortunately, I don’t have an answer for that.

“We have a whole cohort of people with developmental disabilities living longer lives than ever before. They’re coming along at the same time as we baby boomers are, adding to the stress on the health care system and on funding systems like Medicare and Medicaid. Most people with developmental disabilities are insured by Medicaid, which many health care providers don’t accept because reimbursements are low.

“Then there are the challenges of treating people who may not be able to communicate their health history, who may have behavior issues, who have physical problems that may make the exam take longer, and the problem of lack of knowledge on the part of health care providers who haven’t worked with people with developmental disabilities.”

The training modules are largely focused on giving residential caregivers and family members knowledge and tools to advocate for the good health and health care of the people in their charge. Self-
advocates are also encouraged to participate in the training. Emphases include promoting and maintaining health and making lifestyle changes like increased exercise and physical activity, improved nutrition, and avoiding tobacco use and alcohol abuse. “Lifestyle issues are important for all of us,” said Watson, “and they affect this population more. We have achieved so much—deinstitutionalization, better housing, vocational training and increased self-worth—but we have to concentrate on basic issues like diet and exercise, and on basic health promotion strategies through screenings such as Pap tests, etc.”

People with developmental disabilities often experience greater health challenges than the rest of the aging population, noted Watson, who offers a training module on health-related changes during the aging process. For example, people with Down syndrome experience more rapid aging, their immune systems don’t function as well, they have an increased incidence of Alzheimer’s dementia, they have more joint problems and earlier risk for osteoporosis, and many have heart abnormalities. People with cerebral palsy or fragile X syndrome experience a wide range of health problems. People with Prader-Willi syndrome have obesity and cardiovascular problems stemming from an overwhelming urge to eat. People with seizure disorders may suffer the cumulative effects of long-term use of medications, and increased trauma from falls resulting from seizures.

Watson recently developed the new training module on medication usage. “The Division of Developmental Disabilities has a big focus on medication use,” she said. “There is concern about psychoactive medications—not only those used for mental health and behavioral concerns, but for seizures as well. Some care providers are not sufficiently aware of side effects and drug interactions. Medication side effects may be seen as negative behaviors in a person with a developmental disability; side effects are treated with more medication and it turns into a spiral. Our goal is to educate people about the drugs, their intended uses, the common side effects and when to seek help.”

More information is on the web at depts.washington.edu/aedd.

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“This is an ongoing challenge,” said Johnson, who offers fMRI researchers training sessions in the use of specialized statistical software called FSL. Working with Richards, he has compiled a best practices document, a thick binder focusing on FSL, which is a comprehensive library of functional and structural brain analysis tools written mainly at the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) in the United Kingdom. FSL is free software that runs on Windows or Linux, and Johnson is available to help investigators load it onto their own computers.

“In a sense, Clark is putting together a cookbook for us,” said Aylward. “He’s saying, ‘here are the steps that I as a research methodologist think make the most sense.’ Stephen M. Smith, the statistical expert from Oxford who directs the research and implementation of the statistical software we are using, has expressed an interest in our efforts. At some point we would like him to review our best practices document with an eye towards generating some consensus both among participating UW researchers and with the broader community of scientists as to the best ways to analyze data.

“When we compare the results of our study with studies done elsewhere, or even when two of us do studies here at CHDD and we don’t get the same results, the best practices document gives us a way to go back and determine that one of us controlled for this variable and the other didn’t, so our results were different,” explained Aylward. “It will help with documenting what we did and did not control for. It will help us in interpreting differences between our studies here at CHDD, but perhaps more importantly, in interpreting unexpected differences between studies at different institutions. At this point, we don’t even know what data to collect to be able to say why results are so different.”

“Right now, we have a lot of very bright people who are pretty much taking their own course through the morass of how to do this analysis,” said Johnson. “By utilizing the FSL software and making the right choices in running analyses, we’re attempting to find a robust set of selections that will pass critical review and not generate artifacts.”

“Clark and Todd are doing the legwork and the brain work to figure out, from probably 10,000 choices that you could make in running your analyses, which ones make the most sense, and why they make sense,” said Aylward.

The colleagues hope that research centers across the country might reach consensus on what data to collect. “Centers will probably continue to use a variety of data analysis programs, but we can at least all talk about the covariates that we want to use and try to make sense out of which variables matter,” said Aylward. “The list of covariates will probably never be finalized. It’s obvious that investigators are thinking about it, but in terms of everyone understanding, for example, what the effects of smoking three cigarettes are on an fMRI scan, that is not yet being done.

“When you see the brain scans produced by fMRI, with the brightly colored blobs on them, it’s hard to appreciate how incredibly complex they are, and how a little decision to analyze one way rather than another way can dramatically change your conclusions,” she said.

“It can make the difference between finding nothing and finding something,” said Johnson, “between finding something real or just an artifact. fMRI is like a brand new powerful microscope that’s never been available before. We still don’t know how to control it effectively and how to use the results. We’re trying to change that.”

Visit the CHDD website at depts.washington.edu/chdd
New research affiliates welcomed at CHDD

Dr. Adam Geballe is a professor of medicine and adjunct professor of microbiology at the University of Washington, and a member of the Divisions of Human Biology and Clinical Research at the Fred Hutchinson Cancer Research Center. His M.D. is from Duke University. His research focuses on translational control of gene expression, both viral and cellular. His laboratory investigates gene-specific and global translational controls that influence the timing and extent of expression of human cytomegalovirus proteins. Congenital infections by HCMV are a leading infectious cause of mental retardation, hearing loss, other disabilities and even death in newborns. Geballe is also studying translational regulation of \textit{FMR1}, the gene responsible for fragile X syndrome. They are investigating the mechanism by which CGG repeat expansions in \textit{FMR1} premutation alleles inhibit translation.

Dr. Shanrong Zhang is a research assistant professor of radiology at the University of Washington. He holds a Ph.D. from the Changchun Institute of Applied Chemistry, Chinese Academy of Sciences. Zhang is working to develop new contrast agents for use in molecular resonance imaging, mainly focusing on “smart” contrast agents for molecular imaging that are capable of reporting on certain biological indices such as pH, oxygen pressure, glucose levels and temperature. He also investigates highly specific agents that focus on such targets as brain tumors, and novel contrast agents that permit MR radiologists to manipulate imaging contrasts at will. An area of particular emphasis is agents to help diagnose and treat medulloblastomas, a common and serious childhood brain tumor. Current treatments for such tumors can lead to significant acquired neurologic deficits.

“The DD Council is interested in helping young adults with developmental disabilities learn to advocate for themselves and effect change,” she said. “Citizens, with or without developmental disabilities, can make social and political change; that’s the message that is so important for everyone in the DD community. It doesn’t necessarily take a lawyer or an expert. All of us can influence the political process, even if not as quickly as we would like.”

A major focus in the field of developmental disability has been on special education for children, she noted. “There have been great successes, although certainly plenty of room for improvement. But what happens after public education, as the adolescent makes the transition to adulthood? Although transition issues have long been recognized as critically important to help young people move successfully into the post-secondary world, there is a concerted effort at expanding transition services, which can include helping young adults with DD prepare for and find meaningful employment, and live and navigate independently in the community. Another avenue is to help people with DD advocate for change themselves; to help them gain a voice; to help them know they can vote, impact the legislative process and advocate for systems change.”

University of Washington
Center on Human Development and Disability
Box 357920
Seattle, Washington 98195-7920