Using the Canary of the Mind to Find Genes Causing Brain Malformations
by Joel Schwarz

For centuries miners brought canaries into coal mines and used them as a warning alarm to detect the build-up of toxic gas. Today developmental biologist Kathleen Millen, Ph.D., is using what she calls a "canary of the mind" to search out genes that cause early malformations in the brain that can lead to developmental delays and disabilities. Her “canary” is the cerebellum, a small region located between the brain stem and spinal cord. Her specific focus is congenital malformations of the cerebellum - structural birth defects that are relatively common and visible on brain imaging studies such as magnetic resonance imaging (MRI).

Millen is a professor of pediatrics, a researcher at the Center for Integrative Brain Research (CIBR) at Seattle Children’s Research Institute and a research affiliate of the Center on Human Development and Disability (CHDD). Her work is directed at the cerebellum because its structure is relatively simple to understand and can be used as a model for the rest of the brain. The cerebellum has a beautiful folded and layered structure making it easy to identify disruptions of its pattern. “In addition, there are only nine types of neurons in the cerebellum and we know how they are interconnected, unlike the thousands of kinds of neurons found in other parts of the brain such as cerebral cortex. Since developmental mechanisms are similar in all parts of the brain, the cerebellum is a relatively simple entry point for understanding brain development,” she said.

Cerebellar malformations occur in one out of 5,000 human births and are linked to intellectual disabilities, a subset of patients with autism spectrum disorder (ASD), and motor deficiencies. About 10 percent of children with ASD have a cerebellar malformation and Millen believes that the same genes that cause these malformations are related to this subset of ASD patients. Dandy-Walker malformation is the most common form of cerebellar malformation and represents specific malformation in the cerebellar vermis in the center of the cerebellum. “Clinicians are aware of it and tend to diagnose all malformations of cerebellum as Dandy-Walker. So it is often misdiagnosed,” said Millen. “However, we are finding that almost anything that can go wrong will go wrong during cerebellar development. We are finding more and more types of cerebellar...”
malformations as we look for them. They can occur by themselves or in the context of other brain malformations.” Dandy-Walker is often marked by a bump on the back of the skull and an unusually large fluid collection. It is most often detected by prenatal ultrasound and can best be seen on MRI scans. The clinical outcome for Dandy-Walker “is all over the map with individuals being severely affected to those not affected at all. We can’t tell the outcome based solely on the brain scans because if there are no other birth defects the probability of a child with Dandy-Walker being severely affected is 50-50,” she said.

To help parents and clinicians understand what the odds are that a child will develop serious cognitive or movement problems Millen has become a gene hunter. She and colleague William Dobyns, MD, professor of pediatrics, a researcher at CIBR, and a CHDD research affiliate, have identified and published findings about three genes that are associated with Dandy-Walker. Findings about a fourth gene they found are awaiting publication. Millen believes there are probably 20 or more genes involved with this one brain malformation. In their collaborative work, Dobyns sees patients and is sent brain images from around the world to identify brain malformations. Millen and Dobyns then use genome technology to find genes that may be damaged. Then Millen develops a strain of mice with these same genetic disruptions to identify the causative gene and the related abnormal developmental biology that contributes to brain birth defects.

Finding these genes is a slow, expensive process. It took Millen and Dobyns five years to identify the first two Dandy-Walker genes and four years to find the third. Today, Millen said it costs approximately $50,000 and takes about 18 months to make a mouse model of a human gene defect to see if it contributes to a disorder. “If you have five candidate genes that is potentially a lot of time, work and money. Today, we make a best guess among the candidate genes and if we are wrong we have to start to work over again,” she said. Millen uses mouse models of brain disorders because the rodents’ cerebellum have exactly the same nine types of neurons, the same circuitry and the same layering as do humans.

The pace and cost of identifying genes suspected of being involved in brain disorders could change radically next year. “We aim to have a high through-put laboratory where we analyze 50 genes a year to see if they cause brain malformation. Considering it took five years to identify the first Dandy-Walker gene, if we assess 50 genes a year that would be extraordinary,” said Millen. Her lab would use a technique called RNA Interference Technology which temporarily cripples the function of a gene but does not kill it. With it, Millen said it will be possible to see if a mouse has a disease for $2,000 in just six weeks. “We will be able to test 25 candidate genes for the cost of one with current technology, making mouse models of human disease faster and cheaper. We are on the cusp of making this work and ultimately we will be able to test more than one gene with the same technology. When this is working we could, for example, check if two gene defects are needed to cause disease instead of just one. Our goal is to become a resource to CHDD, the broader UW community and Children’s Hospital.”

Figure 2: Mouse brain MRI. Horizontal image of an adult mouse brain. The mouse cerebellum is the folded structure located at the bottom of the image. Since mouse and human brain development is similar, the mouse provides an excellent model system to decipher the underlying disruptions that lead to human structural birth defects of the brain.