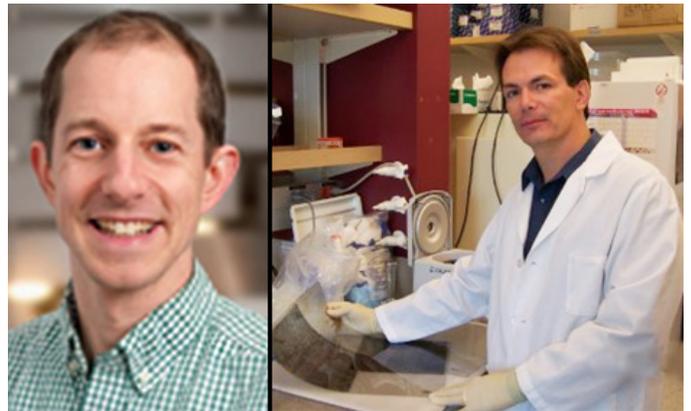




Defining an Autism Subtype through Genetics

by Kate Forster

Research in genetics is continuing to shed light on autism spectrum disorder (ASD), a neurodevelopmental disorder that has so far proven very difficult to understand. The major problem is the vast heterogeneity of this disorder, which makes it difficult to find any meaningful subtypes. In an effort to solve some of this puzzle, Raphael Bernier, Ph.D., associate professor of psychiatry and behavioral sciences and CHDD research affiliate, and Evan Eichler, Ph.D., professor of genome sciences and CHDD research affiliate, collaborated with researchers from 13 institutions worldwide. In addition, two postdocs in Eichler's lab, Bo Xiong, Ph.D., and Holly Stessman, Ph.D., performed much of the experimental work. The research team focused on a specific gene called CHD8 to identify a specific subtype of autism. By focusing on CHD8, the hope was to better understand specific molecular mechanisms underlying this genetically-defined ASD subtype, identify developmental patterns, and perhaps develop novel treatments. This work was published in the July 2014 edition of the journal, *Cell*.



Raphael Bernier, left, and Evan Eichler identified that a mutation in the CHD8 gene causes a specific autism subtype. This is one of the single most common genetic mutations observed to be contributing to autism.

This team of investigators carried out studies on 6,176 children who were diagnosed with autism and their families. At the UW site, the CHDD Behavioral Evaluation Center was used for behavioral assessment. The researchers found that 15 of the children had the CHD8 mutation. When the findings were compared among all the institutions, a common pattern of symptoms emerged. "These 15 children all had head circumferences that were approximately at the 97th percentile for their age, which means they were quite large," said Eichler. "They also all had wide-set eyes, sleep disturbances, and significant gastrointestinal problems." The researchers also found that a mutation in the CHD8 gene always correlated with a diagnosis of autism. "CHD8 seems to be a master regulator gene for autism," said Bernier. "It's connected to a vast majority of other genes that we've identified as playing a role in autism." While 15 comprises only about 0.05% of the children studied, it is one of the single most common genetic mutations observed to be contributing to autism. It also speaks to the heterogeneous nature of the disorder.

Zebrafish Modeling

Bernier, Eichler, and the team of investigators supported their finding by using zebrafish modeling. Zebrafish are commonly used in research because of their regenerative abilities. When researchers disrupted the CHD8 gene in the fish embryos, the fish developed larger heads and wide-set eyes. The

researchers also observed that the fish had gastrointestinal problems when they fed them florescent pellets and those pellets took much longer to move through their digestive system compared with the controls.

Genetic Sequencing

Up until recently, genetic sequencing, the method used to identify the CHD8 mutation, has been prohibitively expensive to perform. As a result, it has been nearly impossible to perform genetic sequencing on a scale large enough to find patterns of genetic mutations that correlate with physical and behavioral symptoms which, oftentimes, can be quite subtle. Comparing the genes of a large number of subjects becomes necessary when you are dealing with a heterogeneous disorder such as autism, which can be caused by a number of different genetic mutations. In 2012, Jay Shendure, Ph.D., associate professor of genome sciences at UW, developed molecular inversion probes (MIPs), technology that can rapidly and cost-effectively resequence genes with a high level of sensitivity and specificity, as shown in the figure below. "This made it possible to do genetic sequencing on a very large scale and ultimately prove the importance of the CHD8 mutation," said Eichler.



Clinical Implications

Genetic sequencing presents a shift in how scientists study autism, and the implications for this discovery are far-reaching. As clinicians care for a child with a disorder that they know is genetically linked, they can be aware of the specific symptoms to watch for. This would allow them to personalize their approach and provide care that is specific to a given individual. Parents who have children with the CHD8 mutation have also started to benefit from this discovery. Parents of children with autism are frequently bewildered by the clinical diagnosis and are often confused and upset when considering possible causes. For this subtype at least, they can rest assured that there is a cause, and it is genetic. Families who were part of this study have already started to establish a community where they support each other and share experiences and resources. Looking forward, scientists can work on developing targeted treatments that are specific to the CHD8 gene mutation. "We're still a few years away from this," said Bernier. "But we at least have a protein we can start working on now."

Genetics is transforming the way we think about autism and how to treat it. "Once we have a better understanding of the likelihood of having a genetic mutation," said Bernier, "we can start doing early screening and then early intervention. Maybe then we can ameliorate autism symptoms. Through behaviorally-based treatment, we know that we can make an impact very early on. Early intervention makes a very big difference."

CHDD is an interdisciplinary center dedicated to the prevention and amelioration of developmental disabilities through research, training, clinical service, and community outreach. CHDD includes the University Center of Excellence in Developmental Disabilities and the Eunice Kennedy Shriver Intellectual and Developmental Disabilities Research Center.

CHDD Outlook

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

© 2015 Center on Human Development and Disability, University of Washington