

Press Release: Adult Brain Requires MeCP2 for Proper Functioning

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Adult Brain Requires MeCP2 for Proper Functioning

A paper published online today in *Science* provides evidence that the Methyl-CpG-Binding Protein 2 (MeCP2) is required throughout life to maintain healthy brain function. The findings are reported from the Baylor College of Medicine lab of Huda Zoghbi, HHMI investigator and Director of the Jan and Dan Duncan Neurological Research Institute.

Mutations in MeCP2 cause the autism spectrum disorder Rett Syndrome, and have been seen in some cases of classic autism, childhood schizophrenia and milder neuropsychiatric conditions such as anxiety and learning disabilities.

Rett Syndrome strikes little girls almost exclusively, with first symptoms usually appearing before the age of 18 months. These children lose speech, motor control and functional hand use, and many suffer from seizures, orthopedic and severe digestive problems, breathing and other autonomic impairments. Most live into adulthood, and require total, round-the-clock care.

Using sophisticated genetic engineering tools, Christopher McGraw, an MD/PhD student in the Zoghbi lab, inhibited production of the *Mecp2* protein in mature adult mice at 9 weeks of age. He characterized the mice and found that by 19 weeks the animals began displaying symptoms reminiscent of the classic Rett Syndrome mice which are missing *Mecp2* protein from conception: impaired gait and locomotion, hind-limb claspings, motor abnormalities, impaired learning and memory. Lethality in both sets of mice took place approximately 13 weeks after removing MeCP2.

Rett Syndrome has been considered a neurodevelopmental disorder, due to the onset of symptoms in early childhood. The appearance of these symptoms after removal of *Mecp2* in adult mice suggests that there may be no discrete time period during which MeCP2 is critical for normal development, and argues against categorizing the disorder as neurodevelopmental.

Joshua Sanes, the Director of the Center for Brain Science at Harvard and Professor in Harvard's Department of Molecular and Cellular Biology, commented on the broader impact of Zoghbi's findings. "This work not only sheds new light on the pathogenesis of Rett Syndrome, but also raises fascinating questions about a central dogma in neuroscience - that genes affecting the brain act differently during the "critical period" than they do in adulthood. In at least some instances, Zoghbi's result tells us, this may not be the case." Sanes was not involved in this work.

The findings are also valuable from a clinical perspective, since they suggest that certain potential treatments for the disorder, such as small molecule drugs, may need to be maintained throughout the lifetime of individuals afflicted with Rett Syndrome.

"Given the parallels between autism and Rett Syndrome with regard to age of onset of symptoms and clinical features, these findings raise the possibility that several autism spectrum disorders might indeed result from failure of maintaining neuronal function rather than alterations of key developmental programs," says Zoghbi.

Monica Coenraads, Executive Director of the Rett Syndrome Research Trust which helped fund this work, and mother of a teenaged daughter with Rett Syndrome, says "Although Rett is a relatively rare disorder, it provides opportunity for broader neurological insights. Huda Zoghbi's new work challenges some central tenets in neuroscience. It is gratifying to see that Rett research is teaching us important lessons about the brain."

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About Rett Syndrome

Rett Syndrome is a genetic neurological disorder that almost exclusively affects girls. It strikes randomly, typically at the age of 12 to 18 months, and is caused by random mutations of the *MECP2* gene on the X chromosome. Rett Syndrome is devastating as it deprives young girls of speech, hand use, normal movement often including the ability to walk. As the girls enter childhood the disorder brings anxiety, seizures, tremors, breathing difficulties, severe GI issues. While their bodies suffer, it is believed that their cognitive abilities remain largely intact. Although most children survive to adulthood, they require total round-the-clock care.

About the Rett Syndrome Research Trust

RSRT is a non-profit organization with a highly focused and urgent mission: eradicate Rett Syndrome and related *MECP2* disorders. In search of a cure and effective treatment options, RSRT operates at the center of global scientific activity, funding bold projects that are unlikely to be supported by the NIH or other more traditional funding agencies. RSRT refutes the conventional practice of labs working in isolation, instead seeking out, promoting and funding collaborations and consortia in which scientists work across multiple disciplines. These relationships enable the development and execution of a research agenda that neither academia nor industry could achieve alone. Since 2008, RSRT has provided \$25 million of financial support to: 4 clinical trials testing 3 compounds, 33 scientists in 27 academic institutions and 3 biotech firms. To learn more about the Trust, please visit www.ReverseRett.org.

About Baylor College of Medicine

Baylor College of Medicine (www.bcm.edu) in Houston is recognized as a premier academic health science center and is known for excellence in education, research and patient care. It is the only private medical school in the greater southwest and is ranked as one of the top 25 medical schools for research in *U.S. News & World Report*. BCM is listed 13th among all U.S. medical schools for National Institutes of Health funding, and No. 2 in the nation in federal funding for research and development in the biological sciences at universities and colleges by the National Science Foundation. Located in the Texas Medical Center, BCM has affiliations with eight teaching hospitals, each known for medical excellence. Currently, BCM trains more than 3,000 medical, graduate, nurse anesthesia, and physician assistant students, as well as residents and post-doctoral fellows. BCM is also home to the Baylor Clinic, an adult clinical practice that includes advanced technologies for faster, more accurate diagnosis and treatment, access to the latest clinical trials and discoveries, and groundbreaking healthcare based on proven research.