Press Release:
New Data Uncover Common Molecular Pathways Between Rett Syndrome, Autism and Schizophrenia

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Media Contact:
Monica Coenraads
Executive Director, RSRT
monica@rsrt.org
203.445.0041

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The laboratory of Huda Zoghbi, where the discovery that mutations in the gene *MECP2* cause the severe childhood neurological disorder Rett Syndrome was made, has taken yet another step toward unraveling the complex epigenetic functions of this gene, implicated also in cases of autism, bipolar disease and childhood onset schizophrenia. The November 11 issue of *Nature* reports that removing *MECP2* from a small group of neurons that typically make the inhibitory neurotransmitter, GABA, recapitulates many symptoms of Rett as well as numerous neuropsychiatric disorders.

The identification of the genetic basis of Rett allowed the development of a number of mouse models of the disorder, accurately reproducing the range of symptoms seen in humans. These are considered to be among the best existing models of neurological disease.

While removing *MECP2* from every cell results in full-blown Rett symptoms, the Zoghbi lab during the past few years has been using genetic tools to knock out the gene from distinct subsets of specialized brain cells called neurons, in an attempt to correlate certain neuronal populations with specific symptoms.

GABA (gamma amino butyric acid) is the main inhibitory neurotransmitter in the brain. Neurons releasing GABA regulate the nervous system by acting like traffic lights on the brain's information highway. Zoghbi and Hsiao-Tuan Chao, a postdoctoral fellow in the lab and lead author of the study, use this analogy to describe the action of GABA in allowing for a balanced level of neuronal activity by controlling the strength and timing of information transfer. Surprisingly, Zoghbi, Chao and colleagues found that removing MeCP2 from the small number of GABA-producing neurons reduced production of the neurotransmitter by about 30%. This reduction reproduced many symptoms of Rett including the paw-clasping that mimics the classical hand-wringing stereotypies. After a brief period of apparently normal development, the mice display brain hyperexcitability, impaired respiration, and loss of muscle control and strength and premature lethality. Learning, memory and sensory responses are also altered. Interestingly, the mice engaged in repetitive movements reminiscent of compulsive behavior seen in a number of neuropsychiatric disorders.

The study raises a number of important points. It implicates GABA as a key player in Rett and suggests that boosting the activity of GABA -producing neurons may help to alleviate the severity of some symptoms. It also begs the question: If a 30% reduction in GABA causes Rett symptoms, could a more subtle perturbation of 10% or 20% lead to certain neuropsychiatric disorders? This study suggests a possible pathway which can now be explored to answer the question fully.

"This study revealed to us the critical role of MECP2 in modulating the levels of GABA in inhibitory neurons and pinpointed all the neuropsychiatric symptoms that develop when the function of inhibitory neurons is compromised. Identifying the cellular and chemical basis of such symptoms is a first step in efforts aimed at understanding and, one day, treating such disorders." - Huda Zoghbi.

Dr. Zoghbi, who was first drawn into Rett research through her clinical experience at Baylor College of Medicine, is a Howard Hughes investigator and a Rett Syndrome Research Trust Scientific Advisor.

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Monica Coenraads, Executive Director at the Rett Syndrome Research Trust which helped to fund this work, says *"The field of Rett research has benefited incalculably from Huda Zoghbi's dedication and perseverance. Her latest results suggest that GABAergic pathways are ripe for exploration not only as therapeutic intervention for Rett Syndrome but also for a much wider class of neurological disease."*

About Baylor College of Medicine

Baylor College of Medicine 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.

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 gastrointestinal 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

The Rett Syndrome Research Trust (RSRT) is a non-profit organization with a highly personal and urgent mission: a cure for Rett Syndrome and related MECP2 disorders. In search of a cure and effective treatment options, RSRT operates at the nexus of global scientific activity. We enable advances in knowledge and drive innovative research through constant engagement with academic scientists, clinicians, industry, investors and affected families. These relationships catalyze the development and execution of a research agenda that neither academia nor industry could achieve alone. 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. Since 2008, RSRT has awarded $34 million to research projects. To learn more about the Trust, please visit **www.ReverseRett.org**.