

Press Release:
A Role for Glia in the Progression of
Rett Syndrome

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

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A Role for Glia in the Progression of Rett Syndrome

A paper published online today in *Nature* reveals that glia play a key role in preventing the progression of the most prominent Rett Syndrome symptoms displayed by mouse models of the disease: lethality, irregular breathing and apneas, hypoactivity and decreased dendritic complexity. The discovery, funded in part by the Rett Syndrome Research Trust (RSRT) was led by Gail Mandel, Ph.D., an investigator of the Howard Hughes Medical Institute at Oregon Health and Science University.

Rett Syndrome, the most physically disabling of the autism spectrum disorders, is caused by mutations in the methyl CpG-binding protein (MeCP2). 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. There are several mouse models for RTT in which MeCP2 has been deleted: these mice accurately recapitulate many of the human symptoms.

In a seminal 2007 *Science* paper, Adrian Bird and colleagues from the University of Edinburgh showed that global re-expression of MeCP2 in mouse models dramatically reversed Rett symptoms, even in very late-stage disease. This led to the idea that the damage to neurons in RTT was reversible.

In 2009, Mandel and collaborator Nurit Ballas (Stony Brook University) showed that the MeCP2 protein was present in all types of glia. Glial cells are comprised of astrocytes, oligodendrocytes and microglia. Glia support and interact with neurons in innumerable ways, from providing the structural underpinnings and guidance of axons and dendrites (the neuronal processes that carry information), to creating protective insulation for axons, to providing energy substrates necessary for neuronal function. Until the reports of MeCP2's presence in glia, Rett Syndrome was thought to be caused exclusively by MeCP2 deficiencies in neurons.

Mandel and Ballas and colleagues now show that in a mouse model of Rett Syndrome, re-expression of MeCP2 solely in astrocytes, in male mice at 4 weeks of age and in female mice between the ages of 5 to 7 months, rescues the lifespan, breathing, anxiety, and locomotor activities associated with the global knockout mice.

Mandel states: "The RTT plot now thickens...we need to think about contributions from multiple cell types to this disease. The idea that neurons and glia might serve different roles in Rett Syndrome, in initiation and progression of symptoms, is reminiscent of the situation in another neurological disorder, an inherited form of ALS. Thus, a role for glia may turn out to be a more common theme in many neurological diseases. It will be important to determine if other glial types play roles in RTT, and to further investigate how normal neurons and astrocytes interact, a currently active but controversial area".

First author Daniel Lioy (Howard Hughes Medical Institute, OHSU) comments, "Future studies will focus on trying to identify the key molecules in astrocytes that might mediate the rescue. These molecules may provide new avenues for targeted pharmacological intervention for Rett."

"This new and unexpected result by the Mandel lab reveals important clues regarding the function of MeCP2 and how its absence causes devastation. The Rett Syndrome Research Trust will continue to support high-level exploration with the conviction that understanding how this protein works will open new doors to treatment approaches," said Monica Coenraads, Executive Director of RSRT and mother to a daughter with Rett Syndrome.

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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.