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Press Release: MeCP2 Goes Global – Redefining the Function of the Rett Syndrome Protein

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

MeCP2 Goes Global – Redefining the Function of the Rett Syndrome Protein

A paper published online today in Molecular Cell proposes that Methyl CpG binding protein 2 (MeCP2) impacts the entire genome in neurons, rather than acting as a regulator of specific genes. Mutations in MeCP2 cause the autism spectrum disorder Rett Syndrome as well as some cases of neuropsychiatric problems including autism, schizophrenia and learning disabilities.

The discovery of MeCP2's global reach was made in the laboratory of Adrian Bird, Ph.D. of the University of Edinburgh. Bird's seminal contributions in the Rett Syndrome field include cloning the MeCP2 protein in the early 1990's and the dramatic reversal of severe symptoms in fully mature mice models of the disease published in Science in 2007. He is a Trustee and Scientific Advisor of the Rett Syndrome Research Trust, a nonprofit organization intensively focused on the development of treatments and cures for Rett Syndrome and related MECP2 disorders.

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.

Historically, MeCP2 has been viewed as a classic transcription factor, but Bird's data establishes MeCP2 as one of the most abundant neuronal nuclear proteins, with levels 100 to 1,000 times higher than typical transcription factors. In fact, there are nearly as many molecules of MeCP2 in the nucleus as there are nucleosomes, the fundamental repeating structural units of chromatin which in turn make up chromosomes. To put this in perspective, there is enough MeCP2 to cover nearly the entire genome.

Peter Skene, a post-doctoral fellow in the Bird lab and first author of the paper confirmed via chromatin immunoprecipitation and high throughput sequencing that this huge abundance of MeCP2 meticulously tracks the DNA methylation pattern of the cell. As a result, Skene observed that most regions of the genome bind to MeCP2, calling into question the previously assigned role of this protein as a target-specific transcription factor. This may explain why few clear gene targets for MeCP2 have been identified in the last decade.

"The brain contains many types of neurons with different functions, but interestingly it appears that the pattern of MeCP2 binding to chromosomes is broadly similar in all of them. This raises the possibility that the neuronal defect brought about by mutations in this gene affect all neurons in a similar way. If there really is a generic defect shared by many neurons, then the causes of Rett Syndrome may be less complicated than we feared. This idea now needs to be tested by further work," said Professor Bird.

In line with its genome-wide distribution, the scientists found that MeCP2 globally impacts the packaging of the DNA in the cell. Histones are proteins which act as spools around which DNA is wound. This winding, or compaction, allows the 1.8 meters of DNA material to fit inside each of our cells. There are two classes of histones – core histones and linker histones. Core histones form the spool around which DNA winds – resembling beads on a string. The linker histones, such as histone H1, seal the DNA onto the spool formed by the core histones. In this way linker histones act as a padlock to hold the DNA in this structure and stop inappropriate access to the DNA outside of genes. In the absence of MeCP2, the amount of linker histone H1 doubles, suggesting an attempt to compensate for the lack of MeCP2.

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The Bird lab also found an increase in histone acetylation in MeCP2-deficient neurons, but not in glia. These chemical modifications lead to an unwinding of the chromatin spools and potentially leave the DNA open for inappropriate expression. This suggests that the role of MeCP2 is to globally suppress the genome.

“Consistent with MeCP2 coating the entire genome, we observed global changes in the chromatin composition and activity. In the absence of MeCP2, we discovered an increase in the spurious transcription of the so-called ‘junk DNA’ which lies between genes. This suggests to us that rather than targeting specific genes, MeCP2 functions on a genome-wide level and may act as the watchdog of the neuronal genome,” said Skene.

“RSRT is pursuing two parallel approaches to interventions for Rett Syndrome. One is to find assays for MeCP2 function and then screen for anything that fixes the defect. The other is to understand as much as possible about what MeCP2 does in the brain and then design rational treatments. Understanding that MeCP2 acts in a global manner rather than as a gene-specific regulator gives us a new perspective on the molecular basis of Rett Syndrome that will aid in guiding drug development and other treatment modalities,” comments Monica Coenraads, Executive Director of RSRT and parent of a child with the disorder.

For an in-depth interview with Adrian Bird please visit the RSRT Blog.

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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**.

Our Partners

Our partners in supporting this work are parents' organizations worldwide including **Reverse Rett (UK)**, **Rett Syndrome Research & Treatment Foundation (Israel)**, **Skye Wellesley Foundation (UK)**, **Rett Syndrome & CDKL5 Ireland**, **Rett Syndrom Deutschland**, **Stichting Rett Syndrome (Holland)**.

Our U.S. partners that helped make this research possible include **Girl Power 2 Cure**, **Eva Fini Fund at RSRT**, **Kate Foundation for Rett Syndrome Research**, **Rocky Mountain Rett Association**, **Anastasi Fund**, **Claire's Crusade**, **New Jersey Rett Syndrome Association**, **Rett Syndrome Association of Massachusetts**, and the **MECP2 Duplication Syndrome Fund** at RSRT.