

Press Release:
The Rett Syndrome Protein Surrenders
Some of its Secrets

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Discovery of a mutant gene responsible for a disease is a milestone, but for most conditions, it may be only a first step towards a treatment or cure. Understanding Rett Syndrome, an autism spectrum disorder, is further complicated by the fact that the implicated gene controls a suite of other genes. Two papers, published in today's *Nature Neuroscience* and *Nature*, reveal key steps in how mutations in the gene for methyl CpG-binding protein (MECP2) cause the condition. The Rett Syndrome Research Trust (RSRT) funded this work with generous support from partners Rett Syndrome Research Trust UK and Rett Syndrome Research & Treatment Foundation.

Rett Syndrome is a single-gene neurological disorder that affects girls. Development slows during the first year of life, then regresses, as toddlers lose speech, mobility, and hand use. Many girls have seizures, orthopedic and severe digestive problems, as well as breathing and other autonomic impairments. Most live into adulthood and require total, round-the-clock care. Rett Syndrome affects about 1 in 10,000 girls born each year.

The papers result from a collaboration between the labs of Adrian Bird, Ph.D., Buchanan Professor of Genetics at the Wellcome Trust Centre for Cell Biology at the University of Edinburgh, and Michael Greenberg, Ph.D., Department Chair and Nathan Marsh Pusey Professor of Neurobiology at Harvard Medical School.

The Bird and Greenberg labs have been working together since 2011 as members of the MECP2 Consortium along with Gail Mandel, a Howard Hughes Investigator at Oregon Health and Sciences University. The Consortium, launched by RSRT with a \$1 million lead gift by RSRT Trustee Tony Schoener and his wife Kathy, fosters novel alliances among leading scientists to interrogate the molecules at the root of the syndrome.

Professor Bird discovered the MeCP2 protein in 1992. In 2007, he showed that affected brain cells in a mouse model of Rett Syndrome can regain function, even in late stages of the disease, suggesting that the disorder is curable. Despite this unexpected breakthrough the function of the Rett protein remains elusive.

In search of the function, the Bird lab set out to identify the key domains of the protein. Mutations found in individuals suffering from Rett led them to their answer. By focusing only on "missense" mutations, which alter a single amino acid, the researchers were able to hone in on two key domains where the mutations aggregated. The first was the well-known methyl binding domain (MBD) which is the site where MeCP2 binds to methylated DNA, thereby modulating the expression of downstream genes. The second key domain is where MeCP2 binds to a molecule called NCoR/SMRT, a large multi-protein machine that shuts down genes. The Bird lab coined this domain the NCoR/SMRT Interaction Domain (NID).

"Further proof of the importance of the MBD and the NID came from mining the genomes of 6503 healthy people. The result was the exact mirror image of the situation seen in Rett. All along the MECP2 gene normal people have non-disease causing alterations, known as polymorphisms. However, no alterations of any kind could be found in the MBD and the NID, indicating that these domains are prized real estate that cannot be tampered with," said Matthew Lyst, postdoctoral researcher and lead author on the *Nature Neuroscience* paper.

The most frequent Rett mutation in the NID is at amino acid # 306. When the researchers recapitulated the mutation in mice, the animals suffered symptoms similar to girls with Rett. At fault: loss of the interaction between the MeCP2 and NCoR/SMRT proteins and further evidence of the importance of the NID.

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“We knew that MeCP2 binds to the genome at methylated sites, but nothing more than that. We now know that its function depends on the ability to bring NCoR/SMRT co-repressors to the DNA,” Prof. Bird summed up.

The Nature paper continues the story through another amino acid location, 308, which is very near the 306 mutation in the human version of the gene. Sensory input leads to the addition of a phosphate group at the 308 site and this alters the ability of the MeCP2 protein to interact with the NCoR/SMRT co-repressor, thereby affecting the expression of downstream proteins. The Greenberg lab created mice with a mutation at 308 that are unable to attach a phosphate group. As a result, genes that MeCP2 normally controls are mis-regulated.

“The MeCP2 308 mice have reduced brain weight, motor system abnormalities, and lower seizure thresholds that correspond to the deceleration of head growth, motor system impairments and seizure disorders found in Rett. This suggests that the modification of 308 is critical for the normal function of MeCP2 and its disruption might contribute to Rett,” said Daniel Ebert, postdoctoral researcher and lead author on the Nature paper.

Whether the phosphates are added to MeCP2 depends on activity of the neuron. The Greenberg lab has found that in early life, sensory input leads to modification of MeCP2 at multiple sites, including 308. These changes appear to be critical for proper brain development, and their absence in Rett Syndrome may begin to explain what goes wrong in the brains of girls with this devastating disorder.

Each step deciphered in the genetic choreography behind Rett Syndrome is a step towards treatment. “To design an effective small molecule therapy, one needs to understand the underlying mechanisms of how MeCP2 functions and how mutations in MeCP2 lead to disease. Both papers published today make significant progress by providing compelling evidence for dysregulation of the MeCP2-NCoR interaction underlying key aspects of Rett Syndrome,” said Prof. Greenberg.

What still isn’t known is which genes the co-repressors target. And that will be the next leap in traveling the road from a mutant gene to a little girl who wrings her hands, has seizures and can’t talk or walk. Discovering the other molecular events might reveal intersecting or redundant genetic pathways that drug developers can tweak in the search for treatments.

“I am very pleased with the collaborative effort that has resulted thus far from the Consortium. To achieve this amount of progress over such a relatively short period of time attests to the abilities of the Consortium members to freely exchange ideas, and to encourage one another while at the same time providing critical evaluation of the work as it progresses. I look forward with great anticipation to future discoveries,” said Monica Coenraads, co-founder and Executive Director of RSRT and mother to a teenaged daughter with the disorder.

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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.