Press Release:
Length Matters Rett Syndrome May Result from Overexpression of Long Genes

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Mutations in the methyl CpG binding protein 2 gene (MECP2) are the cause of the devastating childhood neurological disorder Rett Syndrome. Despite intense efforts spanning several decades the precise function of MECP2 has been difficult to pin down. Research primarily funded by the Rett Syndrome Research Trust (RSRT) and the National Institutes of Neurological Disease and Stroke (NINDS), and published today in the journal Nature reveals important information that could lead to new treatment approaches. The study, led by Michael Greenberg, Ph.D., Chairman of the Department of Neurobiology at Harvard University, shows that MECP2 dampens the expression of long genes.

In the early 1990s, Adrian Bird of the University of Edinburgh discovered the MeCP2 protein and proposed that it functions as a repressor of downstream genes. Since then, much effort has been focused on identifying these genes in the hopes that they could potentially become drug development targets. However, the results from numerous labs over the past 15 years have yielded long lists of genes with very little overlap, making it difficult to come to a consensus as to how mutations in MeCP2 lead to neurological dysfunction.

Today's publication sheds new and important light on this puzzle. Researchers Harrison Gabel and Benyam Kinde of the Greenberg lab set out to analyze various gene expression datasets in search of a common theme. This led them to an intriguing finding: the genes disrupted in Rett Syndrome are exceedingly long. The median size gene is about 20,000 nucleotides long, but about 10% of genes are greater than 100,000 nucleotides in length and some extend for more than one million nucleotides. It is the genes that are longer than 100,000 nucleotides that are the most affected in Rett Syndrome.

All of our cells contain the same genes. What differentiates a liver cell from a heart cell from a brain cell are the particular genes that are either silenced or active and the degree of activation, also known as expression.

The researchers in the Greenberg lab found that across all analyzed datasets, and in studies of different mouse brain regions, in the absence of MECP2 the expression of long genes is increased. Furthermore, they found that the longer a gene was, the more it increased. While the increase in expression is modest – only about 3 to 10% – it applies to thousands of genes and therefore might have a significant impact on the function of the brain.

The scientists gathered additional data in support of the gene length hypothesis. They found that in the biological mirror image of Rett, the MECP2 Duplication Syndrome, long genes are under expressed. They next analyzed long gene expression in mice of different ages. Although pre-symptomatic mice showed detectable overexpression, the effect was more dramatic in symptomatic mice. The researchers also found that the degree of increased long gene expression correlates with disease severity: mice with more severe Rett-like symptoms displayed more overexpression. Finally they looked at gene expression in autopsied brains of individuals with Rett. Just as in the mice models they found that long genes were overexpressed.

Greenberg's lab also found that the disruption of long gene expression appears to be a distinctive signature of Rett Syndrome and related disorders. "When we analyzed gene expression data from other neurological disorders that do not have similarities to Rett Syndrome, we did not see the same effects on very long genes," said Gabel.

The data from the Greenberg lab converge to suggest that Rett Syndrome may result from a relatively subtle yet widespread overexpression of long genes with functions important for the brain while the Duplication Syndrome could be due to under expression of these same genes.

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"Interestingly, we found that while all cell types in the body use short and medium length genes, there is more expression of long genes in the brain than elsewhere in the body. This fact could help explain why Rett is mostly a neurological disease," says Kinde.

Last year the labs of Mark Zylka and Ben Philpot at the University of North Carolina at Chapel Hill discovered that a class of drugs called topoisomerase inhibitors reduces the expression of long genes. This begged the question of whether these drugs could be helpful in Rett Syndrome. Indeed the Greenberg lab found that adding low doses of the drug topotecan to cultured cells lacking MeCP2 normalized levels of long genes. Testing of the drug in mouse models of Rett is now underway.

"MECP2 is one of the most complex problems I have worked on in my career. We persevere because I believe strongly that understanding how this protein works will help us to treat this devastating disorder. It's gratifying to imagine that we, a basic science lab, may have opened the door to a novel way to think about treating Rett and MECP2 disorders. This research was funded primarily by RSRT through the MECP2 Consortium, an unconventional collaboration between our lab and the labs of Adrian Bird and Gail Mandel. We have benefited tremendously from the many conversations with our colleagues in these two laboratories and look forward to aggressively pushing this work ahead," said Michael Greenberg.

Benjamin Philpot at the University of North Carolina, who was not associated with the study, adds, "The work from the Greenberg lab provides further compelling evidence that long genes may be preferentially altered in neurodevelopmental disorders, and in particular in Rett Syndrome and MECP2 Duplication Syndrome. Their tour-de-force project used multiple mouse models, across developmental progression of the phenotypes, as well as human data to convincingly demonstrate a close association between disease severity and the dysfunction of long genes. Thus, this important basic research discovery lays a therapeutic groundwork for treating Rett Syndrome."

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.

Citation: Disruption of DNA methylation-dependent long gene repression in Rett Syndrome

Funders: The primary funder of this work is the Rett Syndrome Research Trust and NINDS; other funders include Damon Runyon Cancer Research Foundation, William Randolph Hearst, HHMI, Gilliam Fellowship to Dupont-Warren Fellowship in the Department of Psychiatry at Harvard Medical School.

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rett syndrome research trust

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 the MECP2 Consortium

The MECP2 Consortium, launched by the Rett Syndrome Research Trust in 2011, fosters novel alliances among leading scientists to interrogate the molecules at the root of Rett Syndrome and apply these discoveries to treatments. Consortium members include Adrian Bird of the University of Edinburgh, Michael Greenberg of Harvard University and Gail Mandel of Oregon Health and Sciences University.