Rett Syndrome
Bradley Ching and Ke Wang

Rett syndrome is an X-linked neurological disorder that is a leading cause of mental retardation among females. The progression of the disease consists of normal neonatal development followed by a regression period during which neurodevelopmental signs such as mental retardation and decline of motor abilities start to appear. The developmental progress of Rett patients is within normal range for the first 5–6 months of life. Between 6 and 18 months, development begins to slow or arrest and this stagnation period is followed by a period of regression occurring between 1 and 3 years of age. Common symptoms of the regression period include loss of hand use, decline in verbal and non-verbal communication skills and irregular breathing patterns. From age three to around age ten, the symptoms of the patient stabilize. However, movement and breathing difficulties persist through this phase. The symptoms worsen following this stage and the patient usually loses the ability to walk and suffers from severe breathing problems. With extensive care, patients may survive into adulthood, although they are severely mentally retarded.

Since Rett syndrome is an X-linked dominant disorder, it is mainly observed in females. Males with Rett syndrome rarely survive past two years of age. Mutations in the MECP2 gene are associated with approximately 80% of the female Rett syndrome patients. MECP2, or methyl-CpG-binding protein 2, is located on the q arm of the X-chromosome at position 28 and encodes a ubiquitous protein that is thought to act as a transcriptional repressor and silencer. MECP2 is expressed in all tissues and is thought to help regulate the methylation of DNA and mediate transcriptional repression. The methylation will occur at CpG sites which is involved in long-term silencing of genes in order for development and the repression of certain viral genomes. It is thought that both histone deacetylation, which is the way in which transcriptional repression is relieved, as well as DNA methylation are both linked by MECP2. MECP2 expression occurs during neuronal maturation and therefore its mutation can disrupt normal synaptic formation.

The expression of the mutated MECP2 gene in females is complicated because of the phenomenon of X-chromosome inactivation. Because males only possess one X chromosome, the inactivation of one X chromosome occurs in females in order to equalize the amounts of X-linked gene products produced by females and males. Different cells can exhibit different patterns of X-chromosome inactivation. Thus the severity of Rett syndrome symptoms depends on the proportion of cells that have inactivated the normal X chromosome. These are the cells that end up expressing the mutated MECP2 gene. Since the X-inactivation pattern of one individual may differ from another, a spectrum of Rett phenotypes exists for female patients. This spectrum was studied in detail by Huppke et al, who compared the development of 120 female Rett syndrome patients and found a broad range of symptoms. Those with the most severe symptoms never showed a period of normal development—they were never able to sit, walk, speak and completely lost hand function towards the end of their lives. However, some Rett patients only showed minor neurological symptoms and were able to count numbers, sing songs and ride bicycles.

Exactly how MECP2 mutation causes deviation from normal brain development remains an enigma. Many theories and models have attempted to explain this enigma. A
popular theory is that the deficiency of a gene silencer such as MECP2 could lead to the over-expression of genes that suppress the development of the brain. But exactly which neurodevelopmental processes are disrupted is not known. To date, our knowledge on the functional consequences of the MECP2 mutation is limited.

It has been shown that the MECP2 mutation preferentially affects the development of gray matter, reducing the development of axons and dendrites and suppressing the branching of the dendrites with relative preservation of neuronal number. Since the dendrites and axons serve as connections between different neurons (Figure 1), the failure of these connections to develop and expand would result in a greater packing density of the neurons and lead to smaller overall brain volume. It has also been shown in Rett patients that the densities of neurotransmitter receptors, which function in signal transduction across synapses, decrease over the course of their lifetime. These results suggest that MECP2 mutation slows down the rate of synaptic development. Normal MECP2 function must therefore involve facilitating synapse proliferation through silencing genes that suppress the formation of synapses.

The theory that Rett syndrome is caused by the failure to suppress synaptic pruning genes that antagonize synaptic formation is also supported by clinical evidence. Since the regression phase of RTT is found to coincide with the timing of synapse proliferation in the human cerebral cortex, the failure for this proliferation to occur in RTT patients can account for their dramatic symptoms shown during the regression phase. These dramatic physical symptoms appear in the patients since there is an opposition between two powerful genetic programs, one for synaptic proliferation and the other for synaptic downgrade. An analogy was made for the consequences of this opposition. If the emergency brake is engaged while driving a car, signs of this opposing force can soon be seen through appearances of screeching tires, odor and smoke. A similar process in the brain can also lead to unimaginable physical impacts on the patient. The period of stability that follows the regression phase may indicate that the two

![Figure 1: Illustration of two neurons forming a synapse](image)
opposing forces do not persist since the genetic program for synaptic proliferation is eventually down-regulated.

Brain-derived neurotrophic factor (BDNF) was identified as the first mammalian target gene for MECP2, although its role in Rett syndrome pathogenesis remains unknown. There is a continuing debate concerning the exact role of the BDNF protein in the literature. Since MECP2 serves as a transcriptional repressor of BDNF, it has been hypothesized that MECP2 mutation would lead to higher levels of BDNF, which in turn would lead to excessive synaptic pruning and the reduction of dendritic trees. Therefore BDNF has been hypothesized to play an integral role in the downgrade of synapses. However, recently Chang et al demonstrated the surprising finding that BDNF protein levels in the whole brain of MECP2-null mice is decreased to approximately 70% of the wild-type level, thus contradicting the assertion that MECP2 mutation leads to higher levels of the BDNF protein. The exact biochemical pathway in which the MECP2 protein is able to affect the BDNF gene is unclear. It is known that the MECP2 protein binds to the promoter and functions as a repressor. It is possible to remove the repressor via phosphorylation.

In order to test whether Rett symptoms were influenced by the concentrations of BDNF, Chang et al manipulated BDNF expression in the postnatal brains of MECP2-deficient mice. When the BDNF gene was deleted from the MECP2 mutant brain, the Rett phenotypes of the mice worsened. The observed symptoms following the deletion included smaller brain size, hand-clasping, earlier onset of locomotor activity and earlier lethality. Chang et al also over-expressed the BDNF gene in the brains of another group of MECP2-deficient mice. Following the genetic alteration, the mice exhibited an increased life-span, increased brain weight and improved locomotor activity. These results show that increased expression of the BDNF gene rescued some of the main symptoms of RTT and suggest that the manipulation of BDNF levels can have significant therapeutic meanings for RTT patients.

However, the decreased levels of the BDNF protein exhibited by the MECP2-null mice still remains paradoxical, since MECP2 is believed to act as a transcriptional repressor. Thus less MECP2 should activate the BDNF gene and lead to more BDNF proteins. However, it should be noted that the expression of BDNF is also dependent on neuronal activity, which has been shown to decrease in the MECP2 mutant brain. When the neuronal activity is low, the promoter region of the BDNF gene is not activated and transcription cannot occur even though the repressor MECP2 is absent. Therefore the effect of reduced neuronal activity overrides the lack of suppression by MECP2 in the MECP2-deficient brain, resulting in lower levels of the BDNF protein. In the future, the researchers hope to identify the downstream targets of BDNF that overlap with the affected targets of MECP2 mutation in order to elucidate the exact molecular mechanisms through which the BDNF gene affects the progression of RTT.

Currently, there is no cure for Rett syndrome. All of the available treatments are targeted to treat symptoms in order to increase quality of life. Things such as improving a patient’s communication skills, or allowing them to more adequately deal with their disability are the goal of most therapeutics. Things such as the reduction of seizures, treatment of GI problems with diet and other calming activities are usually considered very beneficial for individuals with RTT. The family of the diagnosed individual is also
given lots of counseling so they are better able to understand and deal with the disease that has affected their loved one.

Since the MECP2 mutation which causes Rett syndrome is inherited in an X-linked dominant manner, it is important to explore its patterns of inheritance. Even though it is a genetic disorder, the vast majority of cases are a single sporadic mutation. This is due to the fact that many individuals who are stricken with the RTT causing mutation are unable to reproduce, therefore ending the genetic line. Those individuals with the mutation who are functional enough to reproduce most likely have a mild version of Rett due to their specific pattern of X-inactivation. For this individual, the inheritance is similar to all other X-linked dominant disorders. Since this mutation is lethal to males, with the majority of them not living past the age of 2, there has never been a situation where a male proband has reproduced. Any offspring of an affected mother will have a 50% chance of inheriting the condition.

Due to the wide variety of symptoms, the mother of a Rett affected child should consider genetic testing since it could be that she has an extremely mild version of Rett. If the mother is found to have the mutation, those individuals who are directly related to her may want to consider genetic testing, as it could have been possibly passed down from the previous generation. For mothers with the MECP2 mutation, prenatal testing can be done via chorionic villus sampling at about 10-12 weeks gestation. In order to properly test for Rett, the familial mutation in the MECP2 gene must first be identified.

References:

1 Saywell et al. (2006) Brain magnetic resonance study of MECP2 deletion effects on anatomy and metabolism. Biochemical and Biophysical Research Communications 340: 776-783.


