RETT SYNDROME

TIFFANY OEI

PHYSIOLOGY

X-Linked Dominant disorder.

Most cases are spontaneous so the mutation occurs randomly.

This is gender-dependent and happens mostly in females. Prevalence being 1 in 10,000 – 15,000 females.

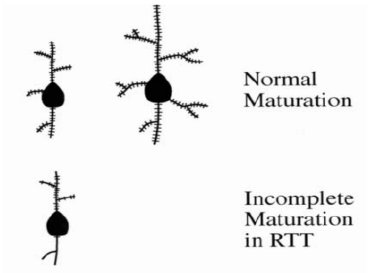
There are only handful of males found with Rett Syndrome which suggests that it is lethal. Due to X-Inactivation being random in every cell of females, if they have one normal X chromosome, they can live with the mutation.

Rett patients do not have neuronal death which means that it is a NEURODEVELOPMENTAL disorder, not a neurodegenerative disorder.

Diagnosis for Rett is symptomatic.

- 6 – 8 months of normal development.
- Stage I : [Early Onset] less eye contact, delays in motor skills, decreasing head growth
- Stage II : [Rapid Destructive Stage] loss of purposeful hand skills and language, repeated hand movements, breathing irregularities, motor movement becomes difficult, head growth stunted
- Stage III : [Plateau] apraxia, motor problems, seizures, cognitive delay, toe-walking; improvements in behavior, less isolation
- Stage IV : [Late Motor Deterioration] reduced mobility, scoliosis, muscle weakness, rigidity

Rett Patients can live into middle age.



MOLECULAR CAUSE

MECP2 (methyl - CpG 2) -> MeCP2 (methyl-CpG binding protein 2) which is found on the long arm (q) of the X chromosome at position 18. The mRNA that encodes for MECP2 are found in a variety of tissues, but was found to be six times more abundant in the brain cells.

CpG sites are where a cytosine nucleotide nucleotide is next to a guanine nucleotide and they are separated by one phosphate.

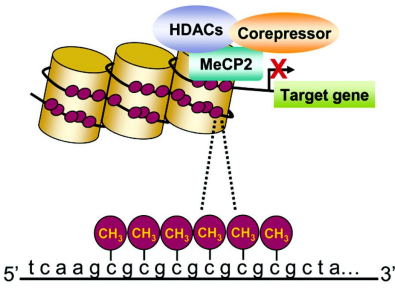
Methylation of CpG sites within promoters of a gene causes silencing of the gene.

Methylation of DNA means a methyl group is added to cytosine and it affects the binding of the protein to a gene.

In this case, DNA is bound by MBDs (methyl-CpG-binding domain) proteins which simultaneously call other proteins to the location such as Sin3 A and histone deacetylases which modifies histones to form compact chromatin which are inactivated.

Symptoms of Rett is caused by a point mutation where C > G changing an amino acid into an early stop codon which truncates the gene. This affects the part of the gene that encodes for MBD and TRD (transcriptional repression domain) which are the key parts in the binding process.

MeCP2 plays a part in gene regulation, especially in turning off a gene. A hypothesis is that it turns off a gene that regulates neuron growth. From the time between birth and adolescence, our brain significantly, however, since the gene regulated by MeCP2 is left "on", it stunts the growth of those neurons.



CURRENT THERAPY

Therapy for Rett patients deals mostly with the symptoms in order to enable them to live as normal of a life as possible
Many Rett patients lose the ability to communicate so parents should respond as best as possible in order to encourage them to respond.
Physical therapy is often needed to help decrease stiffness and at times, splints are needed in order to control the hand movements.
The patients often have trouble with breathing, scoliosis, and epilepsy so medication is needed.
Although Rett patients can live into adulthood, they will never fully develop "normal" skills and life is difficult.

In Johns Hopkins, the Pediatric Clinical Research Unit is initiating a drug trial using dextromethrophan (DM). Glutamate, a chemical that contributes to seizures and behavioral problems found in Rett patients. DM is used to counter the effects and it was tolerated by Rett patients that were infants.

Boston's Children's Hospital approved of a clinical trial called "Pharmacological Treatment of Rett Syndrome by Stimulation of Synaptic Maturation with IGF-1". This is a placebo controlled study to test the efficiency of IGF-1 (insulin-like growth factor 1). It affects the signalling of the BDNF (brain derived neurotrophic factor) protein which is one of the targets of MeCP2. Tests is mice showed that it improved breathing and heart function, lengthened life span, and even restored the functions of synapses. However, it did not improve motor coordination or learning. High doses of IGF-1 were also lethal to the mice.

PROPOSED CURE

Most cures that are being worked on for Rett is focused on restoring the neuron function.

DNA methylation is important for normal development.
In Rett syndrome, because MeCP2 is truncated, DNA methylation does not occur due to the binding sites not being there.
RNA interference (RNAi) is a process where RNA inhibits gene expression by destroying specific mRNA so the mutation is not expressed.
To get the miRNA in, we would use VSV-pseudotyped lentiviral vectors which has been found to efficiently transduce the neurons of the CNS of rodents. In addition, Expression was observed without severe side effects. However, VSV pseudotyped lentiviral vectors are still being tested in human cells and so far, it was found that the vectors become inactivated, so it needs to be put in some sort of envelope to become effective.