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The Pathogenesis and Treatment Methods for Rett Syndrome

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Abstract:

Rett Syndrome is a neurological condition primarily affecting women. Its symptoms include decreased brain size, inability to speak, and coordination problems. Several gene mutations have been discovered to play a role in this disease, with the *MeCP2* mutation being the most widely known and frequent cause. Scientists are also attempting to create medicines targeting the genetic mutations that may provide a cure. However, the mechanism behind how MeCP2 affects the human brain on a molecular level remains to be discovered. This article summarises the important findings regarding the causes and the treatments of Rett Syndrome. It compares the current methods to treat this disease, including DAYBUE, the newly FDA-approved medicine and the only current medicine that targets Rett Syndrome. Future studies could revolve around the root causes of Rett Syndrome, such as the lack of MeCP2 in neurons, and attempt to solve the problem fundamentally. The findings are significant for humans to advance on finding a cure for this neurological disease.

Keywords: Rett Syndrome; MeCP2; DAYBUE.

1. Introduction

The neurological condition known as Rett Syndrome primarily affects women [1]. Symptoms appear about 6-18 months after typical growth, including problems with movement, coordination, gait, speech, breathing, and slowed development [1]. This disease affects about 1 in 10000 females in the USA at age twelve [2]. Even though RTT is a relatively rare neurological disease, the future of its cure is not promising, which highlights the importance of investigating the fundamental cause and possible treatments of this disease.

Previous researchers have identified the methyl-CpG binding protein-2 (*MeCP2*) gene as a likely cause of RTT, a gene found on the X chromosome's long arm essential for the function of mature neuronal cells [3]. Thus, most of the phenotypes observed from RTT patients have issues with the central nervous system or the brain. Scientists discovered that the most frequent location where mutations occur is exon three, which includes the gene's transcriptional repression and methyl binding domains [4]. According to Bienvenu et al., *MeCP2* most commonly mutates in the CCACC repeats, implying that slippage mispairing is the main cause instead of other types of mutations such as frameshift or nonsense mutations [5]. The *MeCP2*, which is involved in the neurological system and brain by acting as a transcription factor, is encoded by the MeCP2 gene. In addition to *MeCP2,* two other genes cause some of the rarer variants of RTT: the lack of the transcription factor Forkhead box G1 (*FOXG1)* gene and the cyclin-dependent kinase-like 5 (*CDKL5)* gene, which causes (respectively) the Rolando variant as well as the Hanefeld variant [3].

While there isn't a solution for RTT, certain symptoms may be treated with the medication DAYBUE (trofinetide), which the FDA authorized in 2023 for children two years or older [1]. DAYBUE helps to decrease brain edema, raise the quantity of a protective protein there, and prevent certain neurons from becoming overactive [1]. This discovery and others could provide new insights into possible therapies for RTT patients.

Scientists are still attempting to comprehend the mechanisms behind how gene transformations and dysfunctions such as *MeCP2* cause RTT symptoms, especially on a molecular level. This article will focus on analyzing and investigating the genetic factors leading to Rett syndrome and, on this basis, discuss the application prospects of DAYBUE, a new drug for treating Rett syndrome. This article is intended to help raise awareness of this rare disease and provide insights into creating better treatments or medications for Rett Syndrome.

2. Mechanisms and Genetic Causes of RTT

A point mutation in the genome causes most cases of RTT; specifically, according to the Rett Syndrome Vari-

ation Database, five-point mutations have a frequency of 5% or more in RTT patients [6]. This includes the *MeCP2* mutation, a major cause of RTT, and several other rarer mutations.

2.1 *MeCP2 Mutation*

A mutation in the *MeCP2* gene causes most RTT instances. This gene can be found on the Xq28 arm of the X chromosome [4]. It is located between the red opsin gene (responsible for seeing the color of red) and the interlaukin-1-receptor-associated kinase gene [4] and controls the production of the MeCP2 protein. MeCP2 protein can bind to DNA and functions as a cis-stage transcriptional repressor of genes, thereby guiding the transcription process [4]. Simultaneously, the gene could also function as an activator of transcription and utilize CREB1 as a co-activator for genome binding. [4]. This contradictory property of MeCP2 suggests that two isoforms may exist for the gene, created by alternative splicing, which is respectively MeCP2E1 and MeCP2E2 [4]. The former protein's translation starts at exon one. In contrast, the latter protein's translation site is located in exon two, and the two isoforms share exons three and four, where most RTT-related mutations occur [7]. A 2001 study done by Richard Chen, Schahram Akbarian, et al. used mice with abnormal *MeCP2* and discovered that lack of MeCP2 in the nervous system resulted in similar symptoms to RTT patients, revealing the profound influence of the MeCP2 protein in neuronal cells, especially for mature neurons [8]. *MeCP2* also likely plays a role in maintaining synapses between neurons [9]. According to Na et al., the absence of MeCP2 may result in "reduced paired-pulse ratios and faster excitatory postsynaptic response depression," which are both "measures of short-term synaptic plasticity" [10]. In summary, the *MeCP2* gene is an essential component of the human brain and nervous system by acting as both a transcriptional repressor and co-activator, and the deficiency of *MeCP2* is believed to be one of the major causes of RTT.

Since the *MeCP2* gene is located on the X chromosome, there is a statistically higher chance for men to diagnose the disease than women. Men have only one X chromosome, which creates a 50% chance of having RTT, while the number is only 25% in women, who have two X chromosomes (assuming the mutation has a 50% chance of happening). However, typically, males having the disease die prematurely or are stillborn due to exaggerated symptoms, which explains the reason why RTT almost exclusively affects women. However, males with less severe symptoms or mosaicism could live past infancy. Mosaicism refers to the condition where an individual has a different genetic makeup for different cells. Thus, RTT male patients with mosaicism could experience fewer symptoms (as only a part of their cells have the *MeCP2* mutation) [3]. Males with Klinefelter syndrome could also live past infancy, as they have two X chromosomes and one Y chromosome, which also lessens the impact of the mutation on them [3].

Although the exact mechanisms of how *MeCP2* mutations lead to RTT symptoms are not clear, scientists have conducted research attempting to associate the mutation with the severity of RTT. Studies have shown that missense mutations cause milder symptoms than nonsense or frameshift mutations. Still, missense mutations in the transcription repressor and methyl-binding domains produce very similar effects [4]. Therefore, the link between MeCP2 mutations and symptoms must be further confirmed. Furthermore, Fang et al. explained that *MeCP2* mutations most likely result in skewed X-chromosome inactivation in females, leading to more severe symptoms of RTT [11].

Researchers also discovered that the *MeCP2* mutations also stopped the interactions between MeCP2 and "the nuclear receptor corepressor (NCoR) and silencing mediator of retinoic acid and thyroid receptors (SMRT) corepressor complex" [12]. Specifically, the interacting residues disrupt the binding of MeCP2 to the NCoR/SMRT complex, and "The mutated residues in RTT that display the most contact with TBLR1 are associated with intellectual disability" [12]. This indicates that MeCP2 dysfunction would lead to relative intellectual disability in Rett patients, a classic symptom of RTT.

2.2 Other Types of Mutations

Other than MeCP2, several other mutations have also been found to cause RTT. For example, the CDKL5 gene is a likely candidate gene for RTT. This genetic mutation has been associated with the Hanefeld variant of RTT. In this variant, patients experience sudden seizures in the first few months of their lives, followed by the typical RTT symptoms [13]. The CDKL5 gene is a gene that regulates proteins that control "the growth and developments of nerve cells in the brain" [13]. Another variant is the Rolando variant, caused by the FOXG1 gene, which encodes a transcription factor in the brain. The Rolando variant is characterized by relatively severe symptoms and an earlier onset of associated symptoms [13].

3. Solutions and Treatments.

Though there is currently no cure for Rett Syndrome, several treatment methods have been invented that could lessen the symptoms of RTT, though not completely cure it. This includes the recent FDA approval of DAYBUE in patients two years of age or older and other medications.

3.1 DAYBUE

DAYBUE, or trofinetide, was approved by the FDA on March 10, 2023, as a treatment for Rett syndrome for patients two years or older [14]. This drug is believed to be a "glycine-proline-glutamate analog," which means that it is similar to a substance in the brain called "glycine-proline-glutamate" (GPE) [15]. It helps to "reduce inflammation, protects brain cells, and improves signals in the brain" [15]. As a result, certain symptoms of RTT, such as the inability to speak and reduced eye contact, could be reduced. An experiment was conducted to test the effectiveness of DAYBUE on RTT patients; in the LAVENDER study, 187 RTT patients were divided into two groups, one group taking placebo and the other taking DAYBUE. The results were that the patients taking DAYBUE seemed to improve more than those taking a placebo [16]. This proves that DAYBUE may be effective in treating the symptoms of RTT in patients.

However, several side effects could be prevalent for most of those taking DAYBUE; for example, diarrhea, vomiting, and weight loss are especially common, with about 85% of patients experiencing diarrhea [17]. Another very important aspect is the price. The current price of DAYBUE is $21.10 per milliliter, which is about $375,000 annually [18], which many people cannot afford. These statistics show that DAYBUE still has a lot of room for improvement.

3.2 Other Medications

Other than DAYBUE, other treatment methods have been implemented to target specific symptoms of Rett Syndrome or attempt to eradicate the disease as a whole. For example, scientists have used eye gaze technology to solve ataxia problems and reduced eye contact [4].

Furthermore, scientists have also found a way to reactivate the MeCP2 in the inactivated X-chromosomes in neurons by using "pharmacological inhibitors targeting X chromosome inactivation," which promotes the release of "factors to reactivate the X-linked MeCP2" [4]. Specifically, "pharmacological inhibitors that target pharmacological inhibition of factors that promote X-chromosome inactivation" (XCIFs) "in the PI3K/AKT and bone morphogenetic protein signaling pathways" could reactivate the X-linked *MeCP2* in neurons, which amends the notable symptoms of RTT patients such as reduced brain size [19]. Most importantly, the XCIF inhibitors could reactivate MeCP2 in the cerebral cortex of mice [19]. This is an excellent mechanism because it directly provides more MeCP2 and solves the problem fundamentally instead of affecting other body parts.

3.3 Comparison and Analysis

Current methods to treat RTT include DAYBUE, XCIFs, and other treatments for specific symptoms (OTSS). These treatments have very different mechanisms: DAYBUE functions by mimicking GPE, a substance in the human brain, and reducing the damage that RTT does to a patient's brain. XCIFs function by adding in the *MeCP2* by reactivating inactivated X chromosomes in females, thus compensating for the loss of *MeCP2* caused by RTT. OTSSs, on the other hand, usually only attempt to reduce the impact of RTT on the patient's behavior and physical health. XCIF can solve the fundamental problem (a lack of the MeCP2 protein), and DAYBUE reverses RTT's negative impact on the patients' brains and mental health. However, DAYBUE has only recently been approved by the FDA and is not currently widespread, which is also the case for XCIF. Among the three treatment methods, DAYBUE also has very significant side effects, such as diarrhea for about 90% of all patients, and other symptoms, such as vomiting.

4. Conclusion

This article mainly revolves around Rett Syndrome, a rare neurogenetic disease, as well as its causes and treatments. Several genes that may be responsible for this disease have been targeted; for example, the *MeCP2* gene, which is responsible for directing the MeCP2 protein, is affected in most cases of RTT. The lack of MeCP2, an essential protein for the function of adult neurons, would likely cause symptoms related to the disease. Other genes, such as *CDKL5* and the *FOXG1* gene, may also cause special variants of RTT.

Current treatments of RTT include the newly approved DAYBUE, XCIF technology, and other methods. DAYBUE mimics an essential substance in the brain and resists RTT symptoms, while XCIF adds new MeCP2 by reactivating X-chromosomes. These two treatments may provide deep insight into RTT's possible cure(s).

The significance of this article lies in the discussion on medications and the insights they provide on better medicines that could be created. Although scientists are still unsure about many aspects of Rett Syndrome, the research on the basic principles that govern the disease has made great progress, and medicines may be created that could eradicate most of the symptoms or completely cure RTT. This article could also guide future studies and experiments to attempt to solve the root causes instead of merely the symptoms of the disease. However, this article has certain limitations. On the one hand, this article has not expanded very thoroughly on the exact mechanisms of *MeCP2* and other related genes; it also hasn't very

thoroughly explained how numerous techniques to target RTT functions on the molecular level. Therefore, future studies may serve to more systematically understand the algorithms behind Rett Syndrome and hopefully to cure the disease in the future.

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