International Journal of Science and Research Methodology (IJSRM)
Volume 29, Issue 3, March 2026 ijsrm.humanjournals.com ISSN: 2454-2008

A Review on Rett Syndrome

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Received: 20 January 2026 Revised: 30 January 2026 Accepted: 20 February 2026

ABSTRACT :

Rett Syndrome (RTT) is a rare neurodevelopmental disorder primarily affecting girls, characterized by regression of acquired skills and development of distinctive hand movements. Since its first description by Andreas Rett in 1966, significant advances have been made in understanding the genetic and molecular basis of RTT. This review provides an overview of RTT, focusing on clinical features, genetic mechanisms, and current therapeutic approaches. We reviewed clinical and genetic data from a cohort of patients with classical and atypical RTT, diagnosed based on established clinical criteria. Genotype analysis involved review of clinical genetic testing, Exmore sequencing, and analysis of mosaicism. Pathway analysis was performed to understand the molecular mechanisms underlying RTT. Patients with classical and atypical RTT presented with a range of symptoms, including motor dysfunction, seizures, gastrointestinal issues, sleep disorders, and behavioural abnormalities. Therapeutic approaches include various therapies (physical, occupational, speech), management of gastrointestinal symptoms, seizure control, and behavioural interventions. RTT is a complex disorder with a clear genetic basis, primarily caused by MECP2 mutations. Understanding the molecular pathways involved has led to promising therapeutic strategies, though further research is needed to improve outcomes for patients with RTT.

Keywords : Exmore sequencing, Rett syndrome, MECP2, CDKL5, FOXG1, SCN8A, Genotyping;, Pathogenicity.

INTRODUCTION :

It's been over five decades since Andreas Rett first described the distinctive clinical feature that is now known as Rett Syndrome and more than 20 years have passed since it was discovered that Rett Syndrome is caused by a mutation in the MECP2 X-linked gene. Intensive research across the molecular, cellular, and clinical domains--ranging from studies of MeCP2-DNA interactions to studies that define a growing spectrum of MECP2-related disorders, including MECP2-bloat, has revealed the remarkable complexity of the function of MeCP2.[1]

As its name suggests, MCP2 binds to methylated DNA and is central to regulating and coordinating the expression of thousands of genes. Although MeCP2 is ubiquitously expressed, it is particularly abundant in the brain, where it is estimated that there is almost one molecule of MeCP2 for every two nucleosomes in mature neurons. This extraordinary abundance combined with the inherently non structured nature of MeCP2 and its ability to adopt multiple functional conformations have made it difficult to define its exact molecular role.[2] Current evidence suggests that MeCP2 is involved in both transcriptional repression and activation, interacts with RNA splicing and microRNA-mediated mechanisms, and plays a critical role in maintaining synapse formation in the nervous system. The precise molecular function of MeCP2 is therefore still under discussion.

This review examines the clinical manifestations of MECP2 related disorders and their underlying neural mechanisms, and highlights key studies that may guide the development of viable therapeutic strategies. We are also considering the feasibility of gene therapy as a therapeutic strategy and discussing existing treatments that can benefit affected people while therapies to modify diseases are still being developed.[3]

HISTORY:

A period of seemingly normal growth and development precedes a continuous regression of motor and communication skills in Rett syndrome, a neurodevelopmental condition. Since RETT is diagnosed clinically, it is crucial to identify its distinctive characteristics early on in the clinical evaluation process.[4] Delays in brain and head growth, irregularities in locomotion, seizures, cognitive impairment, lack of purposeful hand usage with characteristic repetitive hand movements, and developmental slowness are among the core signs. Additional symptoms could include gastrointestinal issues, abnormal breathing patterns, and apraxia that affects eye

and speech motions. Individual differences in clinical severity and illness progression are common, and some patients have unusual or variant forms of RETT.[5]

METHODS:

Cohort selection and phenotypic analysis:-

An RETT specialist used the Boston Children's Hospital Repository Core for Neurological Diseases to find eleven children with clinical characteristics suggestive of Rett syndrome (RTT) who had negative results from initial clinical testing for MECP2 mutations. The Boston Children's Hospital Institutional Review Board gave their approval to the study protocol. The evaluation of epilepsy, electroencephalography (EEG) results, magnetic resonance imaging (MRI) results, non-epileptic events, developmental history, physical examination findings, and previous genetic and metabolic assessments were all part of the thorough clinical phenotyping and review of medical records[6]. Every original EEG and MRI data set that was accessible was examined separately. The 2010 RTT Neal et al. diagnostic criteria were used to examine each of the 11 cases.

Review of clinical genetic testing: [7]

Every clinical genetic test result, including repeat MECP2 gene analyses that were made available after enrolment, was thoroughly examined.

Exmore sequencing:[8]

After potentially harmful variants were identified, DNA from propends and, if available, their parents was subjected to polymerase chain reaction (PCR) to confirm the variants and evaluate inheritance patterns. Variants were categorised as evidently de novo when both parents were sequenced and determined to be negative for the variant, and as suspected de novo when parental DNA was not available for sequencing. The human genome reference construct hg19 is used to describe genomic coordinates for Exmore sequencing results. Variants previously described as disease-associated and those discovered as de novo were thought to have a higher probability of being pathogenic. Furthermore, recognised genotype-phenotype correlations and in silicon prediction techniques were assessed to assess pathogenicity, especially when full parental sequencing data were not available.

Mosaicism:[9]

In order to evaluate parental mosaicism, TOPO TA cloning (Invitrogen, Carlsbad, CA) was carried out in one family where a possibly harmful inherited variation was found.

Pathway analysis:[10]

To investigate the biological pathways and functional gene networks connected to the detected variations, pathway analysis was carried out using Gene MANIA.To find possible molecular connections related to disease mechanisms, the study used co-expression data, route information, and known genetic interactions.

RESULTS:[11]

Six of the 11 patients in our sample who presented with clinical symptoms indicative of Rett syndrome (RTT) had predicted pathogenic genetic variations, and one patient had a plausible genetic explanation.Every patient underwent a thorough phenotypic characterisation, which included evaluation of their developmental history, non-epileptic occurrences, epilepsy, physical examination findings, and magnetic resonance imaging (MRI) data.[12]cases were categorised as having RTT-like characteristics that did not fit formal diagnostic criteria, atypical RTT (one patient), or classical RTT (three cases) based on predetermined diagnostic criteria.The genetic and phenotypic variability seen in RTT-associated presentations is highlighted by this thorough investigation.[13,14]

Patients with classical RTT

It was discovered that two of the three patients with classical Rett syndrome had pathogenic mutations in MECP2.Both previous single-gene sequencing and Exmore sequencing carried out in this study identified a presumed de novo mutation, which was discovered by repeat MECP2 sequencing in a research setting in Patient. This mutation was later recorded in the clinical record but was unknown at the time of enrolment.Exmore analysis revealed a hitherto undiscovered, seemingly de novo frameshift loss in MECP2, in Patient. Despite previous clinical MECP2 sequencing, deletion/duplication analysis in 2008, and later research-based Exmore sequencing, no genetic aetiology was found in the third patient with typical RTT.

Patient with atypical RTT[15]

Patient 10, diagnosed with atypical Rett syndrome has a suspected de novo, probably harmful frameshift mutation in STXBP1, Despite the commencement of neonatal seizures, this patient showed seemingly normal early development. Any how, around 6 to 7 months of age, the patient experienced developmental regression in the context of infantile spasms with hyper arrhythmia.Spasm movements were seen during focal seizures as early one month of birth, and early electroencephalograms (EEGs) showed shifting asymmetry of epileptiform activity.Bi frontal epileptiform discharges, intermittent bifrontal slowing, and poorly established sleep architecture were among the EEG results at three years of age. The patient had generalised hypotonia at first, but later developed spasticity, acquired microcephaly, and short stature. Cooing, saying "hi," and using two signals were the only way an 8 year old can able to express themselves. By the age of four, the child was able to walk independently.[15,16] Peripheral vasomotor abnormalities, self-harming and repetitive behaviours, sleep difficulties, and unprovoked laughing and screaming episodes were further characteristics linked to Rett syndrome. There was intentional hand use, but no pincer grasp; instead of wringing, hand automatisms included mouthing and clasping. At first, the brain MRI showed delayed myelination, but further imaging showed that it had normalised.

Patients with features of RTT that do not meet formal diagnostic criteria for RTT

Four of the seven patients with clinical characteristics suggestive of Rett syndrome (RTT) who did not fit the official diagnostic criteria had potentially harmful mutations involving MECP2, FOXG1, SCN8A, and IQSEC2. Insufficient supportive clinical features led to the exclusion of one patient. The phenotypic and genetic variability seen in RTT-like presentations is highlighted by these studies.[17]Three patients had significantly aberrant development during the first six months of life, which led to their exclusion from the RTT categorisation.Because there was no indication of developmental setback followed by stabilisation or recovery, three more patients did not meet diagnostic criteria.

It was discovered that Patient 9 had a pathogenic mutation, She had hand dyskinesia's, widespread hypertonia, and microcephaly in addition to a severe global developmental delay without any signs of relapse. Serial electroencephalograms showed generalised slowing without epileptiform discharges and no epilepsy. [18]On cranial magnetic resonance imaging, a small corpus callosum and mild hypo myelination were seen. At the age of four and a half, expressive language was restricted to a few words.Her uneven walk, sleep difficulties, unprovoked shrieking episodes, and a temporary partial lack of purposeful hand usage associated to dyskinesia's and an intense urge to touch were all evident.[19]

PATHOPHYSIOLOGY :

About 95% of instances of Rett syndrome , a neurodevelopmental condition, are brought on by mutations in the MECP2 gene. Endothelial cells linked to the cerebral vasculature are among the neuronal and non-neural cell groups in the brain that are impacted by the malfunction of MeCP2, a DNA-binding protein that is widely distributed.[20]

The pathophysiology of neurodegenerative diseases are progressively linked to the breaking down of vascular integrity, which is main thing for preserving brain homeostasis. According to recent research, Rett syndrome has a disease-specific microvascular network with noticeably higher permeability than isogenic controls. This suggests that MECP2 mutations have reduced barrier function. Furthermore, micro RNA profiling and RNA sequencing analysis have shown that hyper permeability in RTT is linked to the overexpression of in patient-derived endothelial cells.[19,21] Notably, the illness phenotype is successfully saved when expression returns to baseline, restoring the integrity of the endothelium barrier. These results show that vascular dysfunction in RTT is mediated and emphasise its possible significance for translational and therapeutic uses.

According to recent research, MECP2 can both activate and repress transcription. Nevertheless, it is still unknown exactly how MECP2 mutations cause Rett syndrome. According to one theory, a lack of MECP2 prevents the cerebral cortex's synapses from properly maturing. Another theory contends that aberrant neural development results from disruptions in the metabolism of brain cholesterol caused by loss of MECP2. Further data suggests that MECP2 is a positive cofactor for RNA polymerase IImediated transcription of several neuronal genes with CpG is lands in promoter-proximal areas, and that decreased expression of these genes in neurones may contribute to RTT disease.[22]

The p75 neurotrophic receptor (p75NTR) is involved in the control of oxidative stress and inflammation. Recent research has shown that the clinical signs of Rett syndrome are linked to disturbed redox homeostasis and increased inflammatory responses. Research shows that LM11A-31's regulation of p75NTR decreases the expression of the pro-oxidant enzyme NOX4 and restores protein glutathionylation. Moreover, LM11A-31 significantly reduces the expression of pro-inflammatory mediators such as interleukin-6 and interleukin-8 and alters the activity of transcription factors that control inflammatory signalling and antioxidant defences.[23]

In Rett syndrome, studies show that defective dendritic arborisation in the cortex causes aberrant neuronal signalling and disturbed autonomic, motor, and cortical system maturation. Additionally, new data indicates that glial cells express MECP2, and that DNA methylation-driven glial dysfunction plays a role in the pathophysiology of illness.[24] MECP2 mutations in astrocytes cause disruptions to metabolic and mitochondrial pathways, which lead to smaller mitochondria, decreased respiratory capacity, and changed proteins in the electron transport chain and tricarboxylic acid cycle. Neuronal function may be negatively impacted by RTT astrocytes' higher cytosolic amino acids and increased mitochondrial reactive oxygen species.[25]

CLINICAL FEATURES OF RTT

Early growth of the symptoms that appears to be normal is followed by a period of developmental and regression in people with Rett syndrome. Early infancy may reveal subtle anomalies such as hypotonia, jerky limb movements, and lack of social involvement. An early sign of neurological involvement is the slowing of head growth between the ages of two to four months, which repeatedly results in acquired microcephaly. Core clinical symptoms include loss of acquired speech, stereotyped repetitive movements in place of intentional hand usage, and stoppage of cognitive and motor development. These symptoms usually appear between 12 and 18 months. By adolescence, progressive motor impairment, which is often linked to ataxia, may cause the loss of independent ambulation. Autonomic dysfunction, respiratory problems, seizures, anxiety, orthopaedic issues, and, in certain cases, diminished visually evoked cortical responses due to poor visual processing are other prevalent symptoms.

The course of Rett syndrome usually plateaus and stabilises after the regression phase.People who are affected usually live into maturity and need lifetime, all-encompassing care.People with RTT may briefly exhibit autistic-like behaviours during the regression phase, such as social disengagement and decreased eye contact, but these traits usually go away as people age, and social engagement may eventually improve. Crucially, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, no longer lists RTT as an autistic spectrum condition.However, those with RTT who display traits similar to autism may be classified as having ASD linked to RTT.

Numerous studies have examined genotype phenotype similarities in classic Rett syndrome; however, X chromosome inactivation makes interpretation challenging.While balanced inactivation in afflicted daughters can result in Rett syndrome, favourable XCI skewing in moms with a MECP2 mutation may provide a normal phenotype.According to certain research, early truncations are more severe than later ones, and truncating mutations produce more severe clinical characteristics than missense mutations.Other studies, however, have not consistently linked the kind of mutation to the severity of the disease, indicating that other genetic or epigenetic factors might have an impact on the clinical diversity seen in Rett syndrome patients.

Numerous investigations have found no conclusive link between the kind of mutation and the clinical severity of Rett syndrome.Additionally, there was no discernible relationship between the type of mutation and the total clinical severity score in studies including girls with peripheral balanced X chromosomal inactivation.Certain clinical characteristics, however, seemed to change depending on the type of mutation.Elevated amounts of homovanillic acid in the cerebrospinal fluid and a greater frequency of respiratory problems were linked to truncating mutations.Conversely, missense mutations were more frequently associated with the onset of scoliosis, indicating that although the overall severity may not vary, the underlying genetic mutation may have an impact on specific symptoms. [26]

Recent studies have demonstrated a strong correlation between the location of mutations in regard to the nuclear localization signal and clinical characteristics.Four important correlations between mutation type, location, and phenotype were found in a study examining the clinical characteristics and types of MECP2 mutations in patients with Rett syndrome at age five. The NLS was shown to be more severely affected by mutations than by those that preserved it.Compared to other alterations, deletions in the carboxy -terminal area were less severe.Missense mutations in the MBD had a similar effect to those in the TRD, however truncating mutations, with the exception of those at the carboxyterminus, were more severe than missense mutations. The authors propose that the inclusion of carboxy-terminal deletions and other truncating mutations in the analysis could account for discrepancies found in previous research.Carboxy-terminal deletions were already handled as outliers in earlier studies, which also showed that early truncating mutations were linked to more severe clinical symptoms.These results corroborate subsequent discoveries that truncating mutations that interfere with the nuclear localization signal (NLS) typically result in more severe abnormalities than those that do not.This suggests that the clinical severity of Rett syndrome is significantly influenced by the location and functional impact of truncating mutations, especially with regard to the NLS.[27,28]

SYMPTOMS : [29]

The first sign for Rett syndrome are delay in development. These start when your child doesn’t reach required milestones for certain age. As your child gets older, symptoms of developmental problem become more visible.

This affects child’s muscles, movement and behaviour include:

- Balancing and coordination problems.
- Difficulty in speaking.
- Difficulty in chewing or swallowing.
- Muscle weakness.
- Problems during performing familiar movements.
- Repeated hand movements like clapping, squeezing, wringing.

Other symptoms of Rett syndrome include:

- Seizures
- Irritability
- Difficulty sleeping
- Gastrointestinal problems
- Brain not fully developed
- Slow growth

Life-threatening symptoms may include:

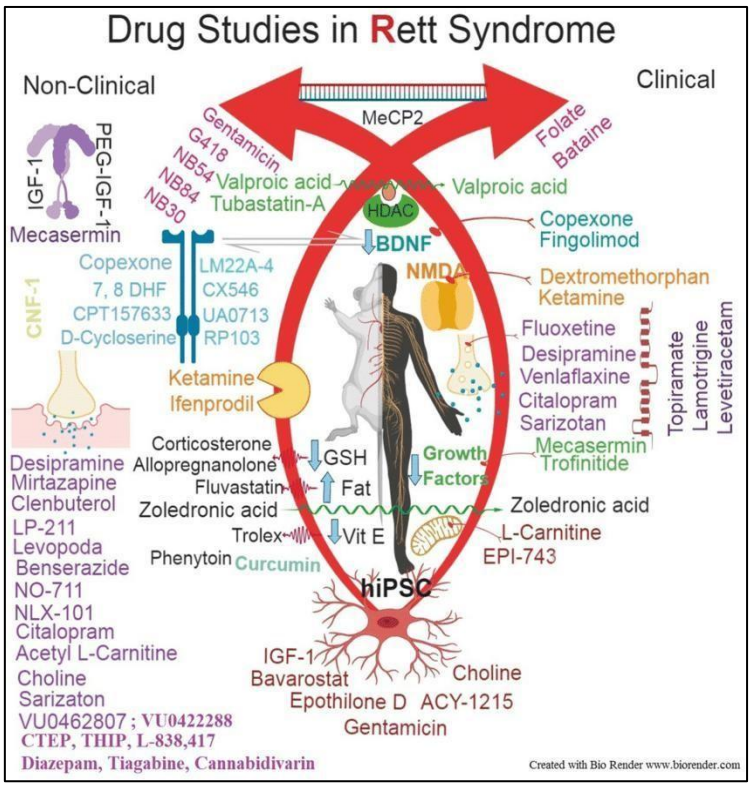
- Difficulty in breathing
- Irregular Heartbeats

CAUSES :

A genetic variant of the MECP2 gene causes most cases of Rett syndrome. Not all cases of Rett syndrome affect the MECP2 gene. This gene provides instructions to make the MECP2 protein. This protein holds the connection between nerve cells and helps your child's brain function as expected. Some genetic variants to other genes, like CDJK5 and FOXG1, can lead to atypical types. Some unidentified genes can also cause symptoms. The genetic change occurs randomly. It's not usually inherited. [30]

TREATMENT AND MANAGEMENT

The US Food and Drug Administration has approved trofinetide as the first and main pharmacologic treatment the Rett syndrome in patients two years of age and older. The tripeptide glycine-prolineglutamate, which is produced when insulin like growth factor-1 is broken down, has a synthetic analogue in this one. It is hypothesised that trofinetide, which contains glutamate and glycine residues, modulates N methyl-D aspartate receptor activity, which helps in supporting of neuronal survival and neuronal signalling.



(Fig- 1A)[30]

Trofinetide treatment at a dose of 200mg for 40 weeks has been shown in recent clinical studies to produce long-lasting improvement in Rett syndrome clinical symptoms. These results imply that trofinetide is a potentially useful and well-tolerated therapeutic alternative for people with RTT, a condition for which there are currently few available therapy options. Furthermore, trofinetide has been shown to be safe and effective over the long term by the outcomes of the LAVENDER and LILAC clinical studies. [30]

Most treatment discontinuations due to treatment-emergent adverse events are caused by mild to moderate diarrhoea, which is common but usually self-limiting and goes away quickly after stopping the medication. One bottle may only last approximately three days, depending on the patient's weight. Other restrictions include the relatively high cost per bottle and the limited length of drug delivery. Weight loss may result from the gastrointestinal side effects of trofinetide, which are frequently linked to vomiting and diarrhoea, according to reviews. Despite these disadvantages, there are presently no direct therapeutic rivals for trofinetide because current RTT treatments only target certain symptoms, including seizures or violent behaviours, and they use drugs that were first created for people without Rett disease.

Supportive Therapies:

There is currently no cure for Rett syndrome, only supportive care with an emphasis on symptom control through an all encompassing interprofessional care. Seizure disorders, sleep disturbances, behavioural abnormalities, respiratory irregularities, cardiac dysfunction, gastrointestinal complications, and an increased risk of bone fractures are important medical issues that need to be continuously assessed and managed in people with RTT.

Gastrointestinal symptoms:

People with Rett syndrome often struggle with gastrointestinal issues, and researchers have been looking into how probiotics can help. One study found that Lactobacillus plant arum was very effective, it stuck around in the gut 100% of the time with zero dropouts, which is awesome. Not only that, but it also improved dystonia symptoms with minimal side effects, like some loose stools. These digestive issues, like constipation and acid reflux, are pretty common in Rett syndrome patients.

Thankfully, there are ways to manage them, such as taking calcium carbonate, histamine H_2 blockers, or bumping up fibre intake. It's all about finding what works best for each individual. The probiotic was well-tolerated, making it a practicable option. The study showed promising results, offering hope for improved gut health in Rett syndrome patients. Gastrointestinal problems can be

challenging, but there's potential for relief. Lactobacillus plant arum could be a game-changer for some. Managing symptoms is key to improving quality of life. The link between gut health and overall well-being is clear. Probiotics might be a useful tool in this journey. Rett syndrome requires a comprehensive approach to care. Gut health is an important aspect of overall health. Finding effective treatments can be a relief for families.

Seizure disorders :

About 60% of people with Rett syndrome have a seizure problem of some kind. Anti seizure drugs including valproate, lamotrigine, levetiracetam, carbamazepine, and other antiepileptic drugs (AEDs) are frequently used to treat seizures. The most popular and successful of them are clobazam, lamotrigine, levetiracetam, and valproate. According to a multicentre research, the most common seizure types in RTT are generalised tonic-clonic and myoclonic seizures, with absence and focal seizures occurring less frequently. It has been demonstrated that anti seizure medications greatly alter the severity and frequency of seizures. The ketogenic diet, vagal nerve stimulation, and steroid therapy are examples of non pharmacologic treatments that have also been linked to improvements in cognitive function and a decrease in the burden of seizures.

There was just one instance of temporary drooling and somnolence during the start of CBD therapy, and no other serious side effects or worsening of symptoms were noted. Additional advantages were improvements in spasticity and decreases in anxiety and agitation. In people with epilepsy and Rett syndrome, a long-term observational study assessed the effectiveness and acceptability of cannabidiol as an adjuvant treatment. The majority of patients had fewer seizures, according to the statistics. All things considered, the study found that CBD is generally well tolerated, has potential therapeutic utility for treating drug-resistant epilepsy in RTT, and may improve the efficacy of clobazam when used in combination therapy.

Behavioural and sleep disorders:

In Rett syndrome, selective serotonin reuptake inhibitors are the most effective treatment for behavioural abnormalities, especially anxiety. Positive clinical responses to cariprazine emphasise how dopamine system failure contributes to the intricate mental symptoms linked to RTT.

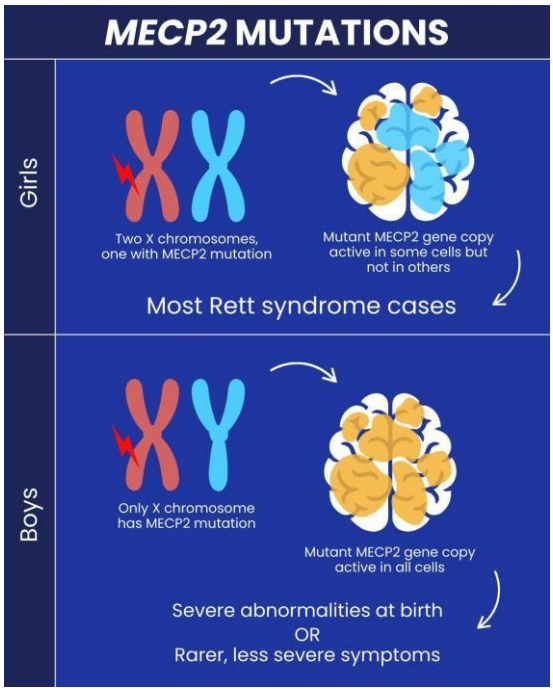
The inability to fall asleep and numerous night time awakenings are among the common sleep difficulties experienced by people with Rett syndrome. Since one of the main characteristics of RTT is autonomic nervous system dysfunction, heart rate variability has been utilised extensively to evaluate autonomic regulation during waking Following the exclusion of airway obstruction and other secondary causes, these issues can frequently be treated with trazodone and proper sleep hygiene practices. Additionally prevalent are respiratory irregularities, which can show up as breath-holding episodes, hyperventilation, or apnoea. Even when overall cardiac autonomic regulation seems to be maintained throughout sleep, recent research has demonstrated that people with RTT exhibit a shift in sympathovagal balance toward sympathetic dominance with decreased vagal activity during both awake and sleep.

Musculoskeletal disorders: [31]

The risk of bone fractures is around four times higher in people with Rett syndrome than in the general population, which emphasises the importance of closely monitoring vitamin D levels and taking the right supplements when necessary. Over the past 19 years, there has been a rise in the utilisation of surgical intervention for scoliosis linked with RTT, despite its relative rarity. According to reports, people with RTT undergoing surgery have higher healthcare costs, longer hospital stays, more complications and a higher chance of no routine discharge outcomes when compared to other patients with neuromuscular scoliosis.

A 12-week course of once-weekly, low-dose extracorporeal shock wave therapy (ESWT) was found to be helpful for children with Rett syndrome, resulting in improvements in lower limb gross motor performance and a decrease in spasticity. Analyses employing acoustic radiation force impulse sonoelastography showed alterations that were in line with less rigid muscles. Individuals with RTT may have MECP2 mutations, which variably and constantly affect the underlying pathophysiology of the condition and may be the cause of the variation in therapeutic response to ESWT.

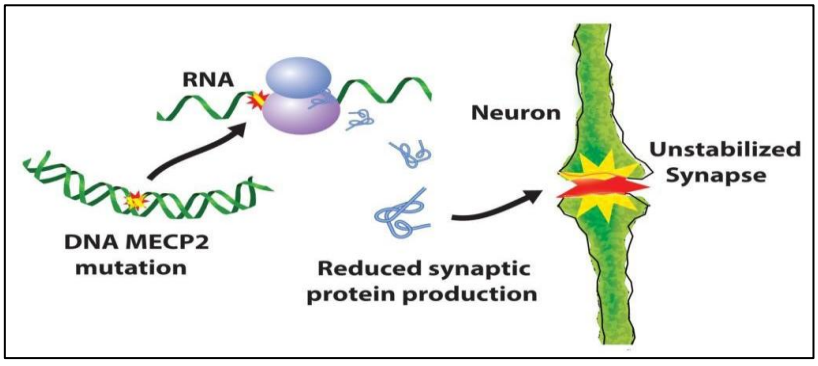
MECP2 Mutations in PSVs:



(Fig-1B)[32]

Research on Rett syndrome variations offers important information about the relationships between genetics and phenotype. In contrast to the conventional variety of Rett syndrome, the preserved speech variant (PSV) is a milder form in which language skills are mostly preserved. MECP2 mutations have been found in 29 PSV cases to date. Classic Rett syndrome has also mutations in PSV instances are evenly distributed throughout functional domains, with and have these mutations, suggesting that PSV and the illness have a similar molecular base. Occurring in the MBD,38%31% in the carboxy-terminal area. Although the range of specific mutation types is still 28% in the TRD, been shown to restricted, MECP2 In cases with preserved speech variant (PSV), milder mutations like R133C, carboxy-terminal deletions, and truncations that occur after the nuclear localization signal (NLS) are generally more common. Threonine 158 (T158), which is frequently changed to methionine (T158M) in classic Rett syndrome, is mutated in a small percentage of people. It's interesting to have symptoms thatare less severe than those of traditional Rett syndrome.The X chromosomal inactivation in each of these cases is significantly skewed (92:8), indicating favourable inactivation that could lead to a milder phenotype.Although XCI data was not accessible, certain early truncations that disrupted the NLS were also recorded.

Phenotypes of Males with MECP2 Mutations:



(Fig-1C)[33]

Although it was once thought that Rett syndrome only affected females, a number of case reports have shown that it can also affect guys. It was thought that Rett syndrome would hardly ever occur in men because early familial research suggested that the condition might be connected to an X-linked dominant gene with male lethality. Several groups of afflicted boys with mutations in the MECP2

gene have been identified since the gene was discovered and cloned. These cases are typically divided into three groups: boys who have lesser neuropsychiatric symptoms, boys who have severe neonatal encephalopathy that causes early infant death, and boys who present with classic Rett syndrome. Although some genetic differences allow males to survive, boys with classic Rett syndrome sometimes have the same MECP2 gene abnormalities as in affected girls. Some people have a 46, XXY karyotype, which is associated with Klinefelter's syndrome. In this condition, an extra X chromosome produces a normal copy of the MECP2 gene, allowing for survival.[32]

These people have a masculine phenotype. Similar to the random X chromosome inactivation seen in females, somatic mosaicism occurs in other circumstances, when boys have a mixture of normal and mutant MECP2 cells. Rarely, a guy having 46 chromosomes, XX karyotype is produced by translocation of Y chromosome's SRY region onto an X chromosome. In one well-known instance, a youngster with classic Rett syndrome had a mutation in the MECP2 gene but no symptoms of Klinefelter's disease or somatic mosaicism. The transcriptional repression domain contains the discovered mutation, It is expected that similarly to mutations mostly seen in females with Rett syndrome. Severe new born brain dysfunction is frequently linked to similar mutations in boys. The difference in clinical characteristics between boys with this mutation, however, suggests that other genetic or epigenetic factors might affect and alter the severity and manifestation of the Rett syndrome phenotype in males who are afflicted.

These boys had the identical mutations in the MECP2 gene as in their sisters who were diagnosed with Rett syndrome, according to genetic study. According to this research, males without a normal wildtype copy of the MECP2 gene exhibit more severe neurological abnormalities, whereas females with Rett syndrome appear to have a lesser clinical manifestation of similar mutations. The majority of MECP2 mutations linked to severe encephalopathy in boys and Rett syndrome in girls affect the function of the MeCP2 protein by disrupting the nuclear occurring in the methyl-CpG-binding domain. Boys with mild, non-Rett clinical characteristics with mutations in the MECP2 gene have found in recent enquiries. These people were identified either from unrelated boys exhibiting developmental delay, traits similar to Angel man syndrome, or neuropsychiatric disorders including psychosis, or from families with inherited X-linked intellectual disability. Although mild intellectual disability is a common finding, the observed phenotypes are varied. Tremors, hypotonia, mood swings, obesity, and gynecomastia are possible further symptoms. When found in heterozygous female carriers, the MECP2 mutations observed in these boys are thought to have less severe effects than those usually found in girls with Rett syndrome. About 1% to 2% of cases of intellectual disability in males may be caused by mutations in the MECP2 gene, according to Covert and colleagues (2001). Other scientists, however, contend that a number of these documented changes might be innocuous polymorphisms that have little bearing on clinical symptoms. A Dutch study that found MECP2 mutations in just 0.2% of males with intellectual disabilities lends credence to this theory. These results emphasize the necessity of thorough sequencing of the MECP2 gene in phenotypically normal and in-depth pedigree research in order to reliably difference benign genetic variations from disease causing mutations, the exception of three mutations found inside the binding domain, milder symptoms in boys with mutations are generally linked to alterations in the C-terminal sector of the protein. The most common reported mutation in males was not been linked to classic Rett syndrome. Another mutation, R406X, which is also brought by C to T transition, manifests in males with progressive stiffness and intellectual dysfunction but not in cases with classic Rett syndrome. [32,33]As many mutations observed in Rett syndrome, this mutation is mostly caused by C to T transition at a CpG hotspot.

Research process has shown that controlling the expression of particular target genes, the MeCP2 protein considerably contributes to gene silence.MeCP2 has been demonstrated to down the retrotransposons in transfection tests, although retrotransposons are unaffected.Further, MeCP2 inhibits the leukosialin gene when methylation occurs in its promoter region, there is no verified in - vivo proof that attaches itself directly to the leukosialin promoter.Even while MeCP2 is known to have a part in experimental research has not yet been able to point out the precise targeted genes that are involved in the pathophysiology of Rett syndrome.

Studies have demonstrated that the MeCP2 protein plays a important role in gene silence by regulating the expression of specific targeted genes. Moreover, when methylation takes place in the promoter region of leukosialin, MeCP2 suppresses it. Any how, there is no confirmation for in vivo evidence that binds to the leukosialin promoter. Despite the fact that MeCP2 is known to play a role in transcriptional control, the specific target genes implicated in the pathophysiology of Rett syndrome have not been identified by experimental investigation. Distal-less home box 5, which is thought to control enzymes involved in the synthesis of gamma-amino butyric acid, it is another possibly targeted gene of the MeCP2 protein. Since DLX5 contains a methylation promoter through mRNA synthesis which is not active, it has been regarded as imprinted gene. DLX5 transcription levels were almost twice as high in mice as in wild-type mice, indicating that MeCP2 is malfunctioning and is not able to inhibit the imprinted allele. Neurological diseases have been associated with this loss of gene repression. GABAergic neuronal activity in Rett syndrome may be impacted by modified imprinting of maternally expressed DLX5.[34]

Researchers discovered a new method that MeCP2 regulates genes: by creating a quiet chromatin loop. Mecp2 helps control the expression of the DLX5 gene in wild-type mice by forming a loop of methylated chromatin close to the DLX5 and DLX6 genes. Mecp2 mutant animals, on the other hand, exhibit acetylated and transcriptionally active chromatin in this area, which results in altered chromatin interactions and markedly elevated expression of DLX5. Recent research, however, revealed that DLX5 and DLX6 are not imprinted and are not impacted by MeCP2 lack. Their results showed that Dlx5, Dlx6, and Peg3 have varied

expression, indicating that these genes are not plausible targets of MeCP2 in humans. researching mice with a truncation mutation and associates discovered corticotrophin releasing hormone as a putative MeCP2 target gene in 2006. They found elevated expression of Crh in the terminalis bed nucleus, central amygdala, and hypothalamic paraventricular nucleus. It was discovered that whereas the shortened form of Mecp2 was unable to attach to the methylation CpG-rich Crh promoter, the wild-type form was able to. A different target gene, which encodes the protein phospholemman, which controls the activity of Na+/K+-ATPase, which was later discovered by Deng and his associates.[34,35] In the frontal part of the brain of null mice and Rett syndrome patients, elevated expression was found, suggesting that MeCP2 shows transcription.

FUTURE DIRECTIONS :

Deep brain stimulation, gene therapy, antisense oligonucleotides, and pharmaceutical methods to alter neurotrophic pathways or improve the stability of MeCP2 proteins are among the many therapeutic techniques that the area is actively exploring. Clinical studies have already been conducted on a number of basic scientific improvements, with small but encouraging results .Even with these advancements, there are still a lot of unmet needs that need to be filled in order to successfully convert them into safe and effective treatment choices.[36] Sensitive, specific, and non-invasive biomarkers are desperately needed to evaluate therapy efficacy and safety.Since both an excessive decrease in MECP2 duplication syndrome and an excessive increase in Rett syndrome are harmful, strict control of MeCP2 levels is necessary.Therefore, to bring MeCP2 activity back to wild-type levels, indicators that allow for customised dose prediction are needed.Gaining a better knowledge of how mutations affect MeCP2 function and stability will be necessary to achieve this accuracy.Remarkably, some mutations mainly cause the protein to become unstable; for instance, the mutation only results in a 16% decrease in MeCP2 levels, but it is enough to produce Rett syndrome. [37]

CONCLUSION AND PERSPECTIVES

Research has demonstrated the complex function of MeCP2 over the course of more than 20 years. Crucially, Rett syndrome's (RTT) mutation spectrum offers a useful framework for assessing suggested functional models and comprehending the pathophysiology of the condition. RTT mutations fit nicely with two models. First, MeCP2 might serve as a biochemical connection between the NCOR–SMRT co-repressor complex and chromatin. Second, the MBD, AT-hook, and basic cluster domains may enable DNA binding that allows MeCP2 to control chromatin layout. These models direct future research along with possible unknown roles of the MBD and NID. The downstream pathways that depend on the crucial molecular interactions of MeCP2 represent another significant unresolved problem. Despite the fact that MeCP2 has long been linked to transcriptional regulation, the concept that extensive alterations in gene expression are the main cause of Rett syndrome pathophysiology is not supported by the available data. Instead, it is yet unknown how disturbed MeCP2 interactions cause neural dysfunction.

Therefore, it is essential to determine whether particular cellular pathways and functions are impacted by MeCP2 depletion or mutation. Answering this question will be essential to comprehending the pathophysiology of the disease and could lead to the discovery of more accurate molecular targets for upcoming therapeutic interventions. Long genes enriched in methylated CpA dinucleotides are preferentially upregulated in particular brain regions of Mecp2-null mice, according to a recent model that suggests MeCP2 regulates transcription in a gene-length-dependent manner. It is conceivable that MeCP2 affects transcription worldwide rather than regulating specific target genes due to its large abundance and extensive binding throughout the genome. As a result, methods that concentrate on finding common traits among deregulated genes in MeCP2 mutants-such as gene length, methylation patterns, and baseline expression levels—may offer important new information on the mechanisms underlying MeCP2-mediated transcriptional regulation. MeCP2 depletion has been shown to have several downstream nuclear effects, especially in neurones from Rett syndrome patients as well as in animal and cellular models.

These include decreased synaptogenesis, compromised protein synthesis, and aberrant mitochondrial activity. It is still challenging to distinguish whether these deficiencies are subsequent outcomes of more widespread neuronal dysfunction or fundamental effects of MeCP2 loss, even though each of them is a likely contributor to RTT pathology. Future studies should concentrate on finding the cellular abnormalities most closely associated with disease pathology and improving models of MeCP2 molecular function in light of the RTT mutation spectrum. Developments in genetic, cellular, and biochemical methods have a great deal of promise to advance science and guide the creation of new treatments.

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How to cite this article:
Kollu Trinath et al. Ijsrm.Human, 2026; Vol. 29 (3): 11-22

Conflict of Interest Statement: All authors have nothing else to disclose.