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X-Chromosome Linked Rett Syndrome

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Abstract

Rett Syndrome (RTT) is a genetic brain disorder which typically becomes apparent after 6 to 18 months of age in females synonymized as "Cerebroatrophic hyperammonemia". It is due to genetic mutation of the MECP2 gene present on the X-chromosome. Develops as a new mutation with <1% of cases being inherited from a person's parents, mainly among girls. Boys with similar mutation typically die shortly after birth. Characterized by less eye contact, delays in gross motor skills, decreasing head growth, and lasts for a few months to years. It is extremely rare and if occurs nutritional support can be beneficial. Supportive treatment includes laxative, sedative, vitamin, anticonvulsant, etc. There are fewer than 5000 cases per year (India). Speech, occupational and physical therapy can be helpful to prevent this syndrome. Nomy is a surgical option which can be used to treat RTT.

Keywords: Genetic disorder, majorly in girls, nomy, physiotherapy, speech

INTRODUCTION

Etiology and Pathophysiology

Most cases of Rett syndrome (RTT) are caused by mutation in a single gene. Most classic cases are caused by mutation within methylcytosine-binding protein 2 (*MECP2*) gene. Figure 1(a) and (b) depicts mutation. *MECP2* gene is located on X-chromosome. Between 90 to 95% of girls with RTT have a mutation on *MECP2* gene [1–3]. In families with a child affected by RTT, probability of having a second child with the syndrome is very low [4]. 8 mutations in the *MECP2* gene represent most prevalent causes of RTT. Development and severity depend on the location and type of the mutation on the *MECP2* gene [5].

Protein made by MECP2 is necessary for nervous system development especially brain. Mutation causes gene to either make insufficient amount of protein or to make a damaged protein that body can't use. In either case, if working protein is not enough, brain doesn't develop normally and leads to Rett syndrome.

Researches are still going on that how the brain utilizes MECP2 protein and how is protein utilization cause RTT. Males affected by these mutations can survive infancy and those who have duplication of normal *MECP2* gene and survive, are severely affected. MECP2 protein either little or more is always harmful.

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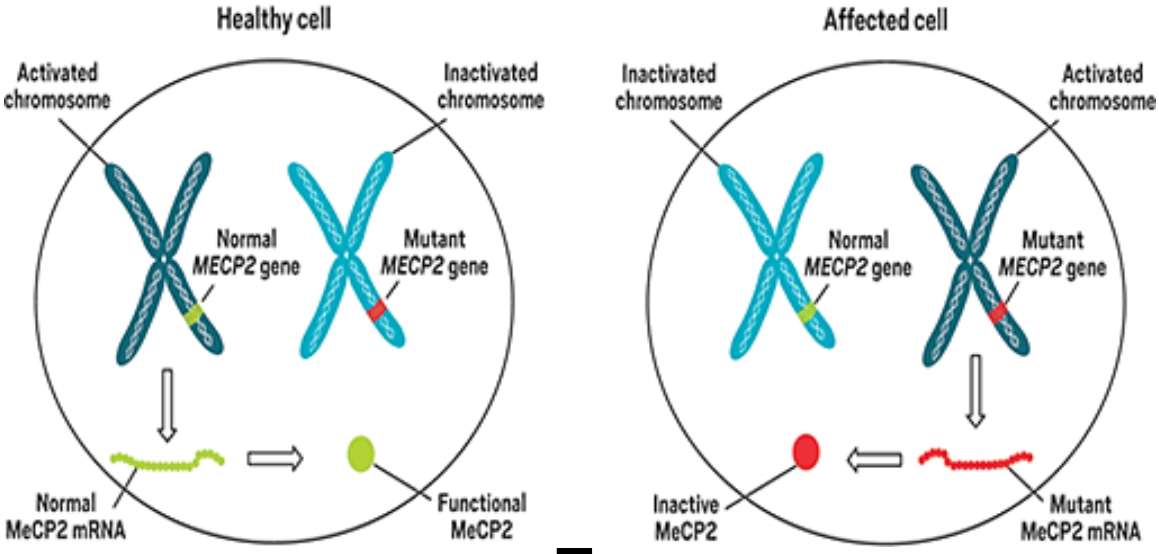
These mutations are very random usually not inherited or passed from one generation to the next. In a very small % of families, RTT mutations are inherited and passed on by female carriers [2, 6]. Females are more prone to RTT cause: 2 types of chromosomes determine sex of an embryo: X and Y chromosomes. Girls have 2 X chromosomes, and boys have 1 X and 1 Y chromosome.

Mutated gene that causes RTT is located on X chromosome, females have twice the opportunity to

develop a mutation due to the presence of two X chromosomes. Females with RTT have one mutated X chromosome and one normal X chromosome so only 1 X chromosome in given cell remains active throughout life which will be determined by cell itself. If mutated gene is more active than normal gene, symptoms will be more severe in this case. Due to this, most females survive infancy only.



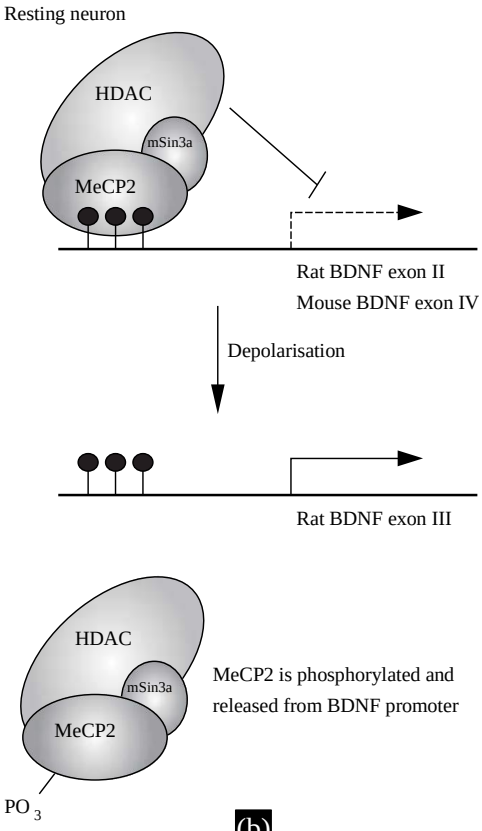


Figure 1. (a) MECP2 mutation and linked activity; (b) Proposed model for MeCP2 regulated expression of BDNF. In the resting neuron, MeCP2 binds the BDNF promoter, repressing its activity. Following neuronal depolarisation, MeCP2 is phosphorylated, perhaps by CDKL5, leading to its displacement from the BDNF promoter, and thus allowing BDNF activation.

Boys have only one X chromosome so mutation of gene will take place on that single X chromosome because of this RTT's detrimental effects are not softened. As a result, many males with RTT are stillborn or don't live past infancy [7, 8].

Some boys with Rett syndrome, however, do live past infancy, likely for one of three reasons:

- Mosaicism: A condition in which individual cells within a person have different genetic makeup i.e some of X chromosome genes in boy's body have Rett mutation, and some genes don't. When a lower % of genes have the Rett syndrome mutation, the symptoms are not as severe.
- Klinefelter syndrome i.e. a boy with 2 X chromosome and 1 Y chromosome. Out of which, one X chromosome will be active, so if one X carries a mutation in *MECP2 protein*, the severity of symptoms depend on the number of cells that have the mutant X active in the body.
- The genetic mutation is less severe than other forms of RTT mutation [9].

Duplication of the *MECP2* gene can occur in boys and affects intellectual and physical functions.

Types

Two main types of Rett syndrome are: classic/typical, and atypical [10]. Types differ by their symptoms or by the specific gene mutation.

The majority of Rett syndrome patients have the classic form i.e. **typical** form which develops in four phases:

1. **Early Onset Phase**: Development continues/stops completely. Sometime, it takes hold at such a subtle pace that parents and doctors do not notice it at first. It is believed that this phase begin at the age of around 6 months. The infants show problems with very early development [11, 12]. Another 42% [12] show stereotyped hand movements during this time period.
2. **Rapid Destructive Phase**: Child loses skills quickly. First loses voluntary hand movement and speech ability. Breathing problems and stereotypical hand movements like wringing, washing, and clapping/tapping also start randomly during this stage.
3. **Plateau Phase**: Child's further development of disease slows and other problems may seem to lessen or improvement may be seen. Seizures and movement problems are common. Most sufferers spend all their life at this stage.
4. **Late Motor Deterioration Phase**: Individuals may become stiff or lose muscle tone; some even loose mobility. Scoliosis (Figure 2) may be present and even can turn severe enough to require bracing or surgery. Stereotypic hand movements and breathing problems seem to become less.

There are currently five known variants of atypical Rett syndrome, defined by characteristic symptoms, age at which the symptoms present, or genetic makeup.

Forms of atypical Rett syndrome that have been identified to date include:

1. **Congenital Rett Syndrome** (Rolando Variant) [7]: associated with mutations of FOXG1 gene.
2. **Early-Onset Rett Syndrome** (Hanefeld Variant) [7]: associated with CDKL5 gene mutation.
3. **Late-Childhood Rett Syndrome**
4. **Forme Fruste Rett Syndrome**
5. **Preserved-Speech Variant of Rett Syndrome** (Zappella Variant) [13]

SYMPTOMS

Loss of muscle tone i.e. hypotonia [14], an infant's arms and legs will appear "floppy" [15].
Symptoms may vary among patients and range from mild to severe [16].

Typical Symptoms: (Symptoms are shown in Figure 3)

1. Loss of ability to grasp and intentionally touch things
2. Loss of ability to speak

3. Severe problems of balance or coordination leading to loss of the ability to walk. Although a majority [17] of patients can walk after medication.
4. Mechanical and repetitive hand movements, like hand wringing, hand washing, or grasping
5. Breathing complication like hyperventilation
6. Anxiety
7. Social-behavioral problems
8. Intellectual disability

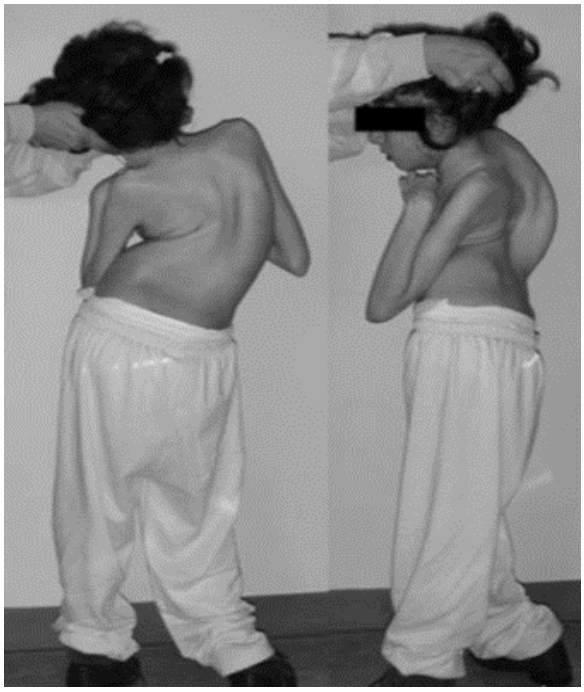


Figure 2. Scoliosis.

Figure 3. Abnormalities—symptoms faced.

Additional Associated Problems

1. Scoliosis or curvature of the spine from side to side is a major [17] problem of girls with Rett syndrome. The curving of the spine sometimes becomes so severe that girls require surgery. Braces can relieve the problem to certain limit.
2. Seizures occur at some moment.
3. Constipation and gastroesophageal reflux—Gastrointestinal tract related problems
4. Discomfort in the abdomen
5. Gallbladder problems such as gallstones [18]
6. Cardiac or heart problems, [19, 20]: irregular heart rhythm, types of arrhythmia (rarely)
7. Trouble feeding oneself, swallowing and chewing food, and have to rely on feeding tubes.
8. Disturbed sleep patterns at night (during childhood) and increased sleep (after age 5) [21, 22]. May lead to death during sleep.
9. Excessive saliva and drooling [15]
10. Poor circulation in hands and legs [15]
11. Walking on toes or the balls of feet [23]
12. Walking with a wide gait (ataxia) [23]
13. Grinding the teeth (bruxism) [23]

Symptoms can vary from person to person and from one stage to the next. Symptoms may also improve in the "Plateau phase".

DIAGNOSIS

Blood Evaluation

Genetic evaluation of blood sample can identify the presence of mutations that cause RTT in child.[1] Mutation of *MECP2* gene may occur even in other conditions, symptoms of syndrome may not always be present, so health care providers also need to evaluate the child's symptoms to confirm a diagnosis [24].

Clinical Symptoms/Diagnostic Criteria

A child must meet the following five necessary criteria to be diagnosed with classic Rett syndrome [25, 26]:

- A pattern of development: regression, then recovery or stabilization
- Partial or complete loss of voluntary hand movements like grasping with fingers, reaching for things, etc.
- Partial or complete loss of spoken language
- Repetitive hand movements like wringing hands, washing, squeezing, clapping
- Gait abnormalities

A slowing of head growth in patients between 3 months and 4 years of age, leading to acquired microcephaly, is also characteristic of RTT [26, 27].

ATypical RTTs

After blood test to confirm child's genetic makeup, doctor may diagnose the child with atypical RTT if child demonstrates development, followed by regression and then recovery or stabilization. Doctor will confirm at least 2/4 main criteria, and 5/11 supportive criteria before making a diagnosis [25].

Other Possible Diagnosis

Sometimes misdiagnosed as regressive autism, cerebral palsy, or nonspecific developmental delays. [24]. For some males, features of RTT'S occur with another genetic condition called Klinefelter syndrome. Effects are reduced in this case because one X chromosome is mutated while the other is normal.

TREATMENTS

Most people with RTT benefit from well-designed IV independent of age, it's better in the early stage. With therapy and assistance, it may help patients to live better life [28]. Treatments aim to slow loss of abilities and improve or preserve voluntary movement. Need for these treatments depends on the severity of different symptoms [29–32].

Hydrotropy/Physical Therapy

- Improves/maintains mobility and balance
- Reduces misshapen back and limbs
- Provides weight-bearing training for patients with scoliosis [32]

Occupational Therapy

- Improves or maintains use of hands
- Reduces stereotypic hand movements such as wringing, washing, clapping, rubbing, or tapping
- Teaches self-directed activities like dressing and feeding

Speech-Language Therapy

- Teaches non-verbal communication
- Improves social communication

Feeding Assistance

- To strengthen bones and slow scoliosis, supplements of calcium and minerals are helpful.
- High-calorie, high-fat diet to increase height and weight [32]

Physical Assistance

- Braces/surgery to correct scoliosis and splints to adjust hand movements

Medication

- Reduce breathing problems
- Eliminate problems with abnormal heart rhythm
- Relieve indigestion and constipation
- Control seizures

Nomy (Surgeries)

- Scoliosis surgery: It has multiple complications.
- Spinal infusion surgery: Carried out during the early onset of the severity of disorder to avoid further complications.

Drugs

Still, no medications are available for the treatment.

Antiepileptic drugs (AEDs)	seizure.
Antireflux agents	gastroesophageal reflux (GER).
Sedative-hypnotic agents	sleep disturbances.

Levocarnitine may also be effective.

Caution is taken if propranolol used to reduce autonomic tone as paradoxical hypertension is possible.

CONCLUSION

Recent advances in our knowledge of MECP2 splicing, its specific targets, and the phenotypes and expression in mutant mice have greatly contributed to our understanding of the etiology of RTTs. Studies in cell lines and mouse models have confirmed the contribution of skewing of X inactivation

to phenotypic variability. Have given glimpses of the mechanisms by which MECP2 mutations lead to RTTs, and have enhanced the understanding of the functions of MeCP2, which no longer appears to be the global transcriptional repressor it was once assumed to be. Rather, it may function to regulate the dynamic expression of neuronal genes and the formation of new synaptic connections in response to electrical signaling, thereby explaining the specifical neuronal phenotype associated with MECP2 mutations. Moreover, some of the phenotypic variability observed in RTTs has been confirmed to result from genetic heterogeneity. Several reports have identified mutations in CDKL5 in specific atypical RTTs variants associated with early-onset seizures. To fully explain the RTTs, disease phenotype will require the identification of further gene targets for MeCP2 and CDKL5, particularly those predominantly active in the central nervous system (Figure 4).

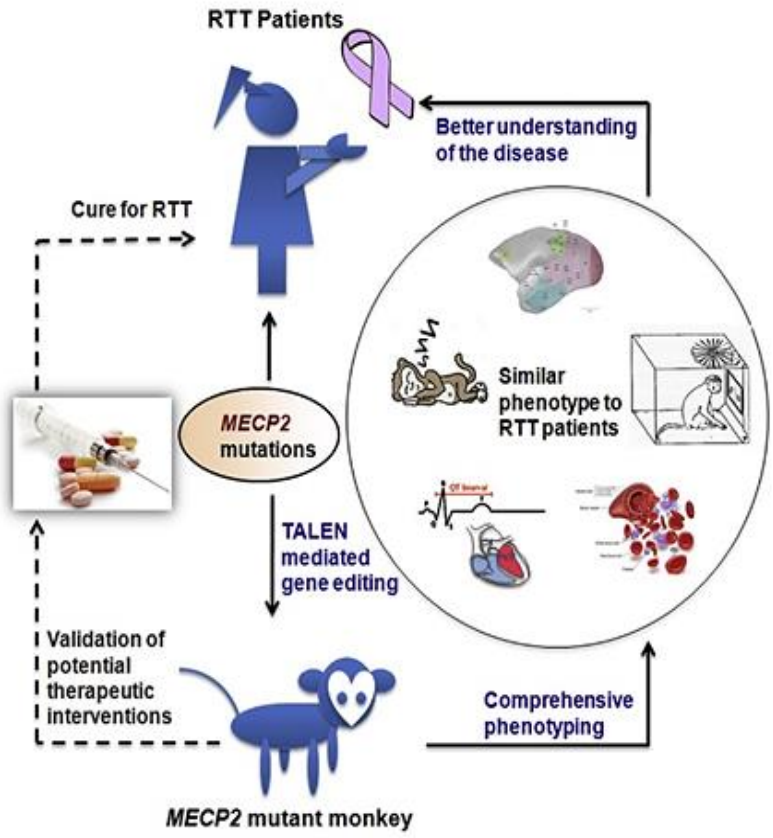


Figure 4. Summarized RTT.

Further studies may enhance discovery and treatment in the pre-symptomatic stage or early in the evolution of the disorder.

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