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Chapter 9

# Rett Syndrome

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## 1. Introduction

Defects in epigenetic mechanisms can give rise to several neurological and behavioral phenotypes. Rett syndrome (MIM 312750) is a pervasive neurodevelopmental disorder that is primarily caused by mutations in a gene encoding methyl-CpG-binding protein 2. The functions of the protein are related to DNA methylation, a key epigenetic mechanism that plays a critical role in gene silencing through chromatin remodeling. Rett syndrome was the first human disorder in which a link between epigenetic modification and neuronal dysfunction was discovered. In this chapter, the clinical features and the molecular pathology of Rett syndrome will be discussed.

### 1.1. History

Rett syndrome was first recognized by the Viennese pediatrician Andreas Rett. In 1965, he observed two girls sitting on their mothers' laps in his waiting room. Both girls were profoundly intellectually disabled and were continually wringing their hands in the same unusual manner. Dr. Rett recollected seeing such behavior in previous patients and searched for their files with his secretary. They found several girls with a similar developmental history and clinical features. He realized that these symptoms constituted something other than cerebral palsy, which was the usual designation at the time. In 1966, Dr. Rett published the first description of the disorder that now bears his name [1]. His paper, however, remained unnoticed by the medical community until the 1980s, when Swedish child neurologist Bengt Hagberg with colleagues published the same clinical findings and named the disorder Rett syndrome [2]. Later, diagnostic criteria were proposed [3], and Rett syndrome became recognized worldwide by pediatricians, neurologists, geneticists, and neuroscientists. Despite great effort, the genetic cause of the disorder was not determined until more than 30 years after the first clinical account. In 1999, mutations within the methyl-CpG-binding protein 2 gene (*MECP2*) were identified in patients with Rett syndrome [4], which became a turning point in

Rett syndrome research. This discovery allowed the molecular confirmation of clinical cases and contributed to amendments of the diagnostic criteria [5]. Most importantly, this finding started an extensive investigation into the molecular mechanisms that underlie the pathology of Rett syndrome.

### 1.2. Occurence

The estimated prevalence of Rett syndrome is 1:10,000 females by the age of 12 years old [6] with no specific ethnic or geographical preference. Rett syndrome is one of the leading genetic causes of profound mental retardation in females, second only to Down syndrome [7]. Male cases are very rare, and their phenotypic manifestations are different from those observed in girls with Rett syndrome.

## 2. Clinical aspects of Rett syndrome

### 2.1. Symptoms and stages

Rett syndrome, in its classic form, begins to manifest in early childhood and is characterized by neurodevelopmental regression that severely affects motor, cognitive, and communications skills.

Prenatal and perinatal periods are usually normal. Affected girls appear to develop normally during the first 6 to 18 months of life and seem to achieve appropriate developmental milestones. Nevertheless, retrospective analyses of home videos often show that, even during this period, affected female infants display some suboptimal development. This underdevelopment may include subtle motor and behavioral abnormalities, as well as hypotonia and feeding problems. General mobility and eye-hand coordination may be inadequate, and an excess of repetitive hand patting can be observed even during the first year of life. However, the overall developmental pattern is not obviously disturbed. The child is usually quiet and placid, and the parents often describe the child as “very good” [1, 8-11]. The characteristic clinical features appear successively over several stages, forming a distinctive disease progression pattern (Figure 1).

**Stage I: Early onset stagnation** (age of onset: 6-18 months). Psychomotor development begins to slow, but the general developmental pattern is not significantly abnormal. The deceleration of head growth (which eventually leads to microcephaly), growth retardation, and weight loss occur in most patients. The child is delayed or ceases in the acquisition of skills. Although babbling and new words may appear, language skills usually remain poor. A girl with Rett syndrome may become irritable and restless, and she may begin to display some autistic features, such as emotional withdrawal and indifference to the surrounding environment [11, 13, 14]

**Stage II: Developmental regression** (age of onset: 1-4 years). This stage may occur over a period of days to weeks and is characterized by a rapid reduction or loss of acquired skills, especially purposeful hand use, speech, and interpersonal contact [15]. In some patients, the

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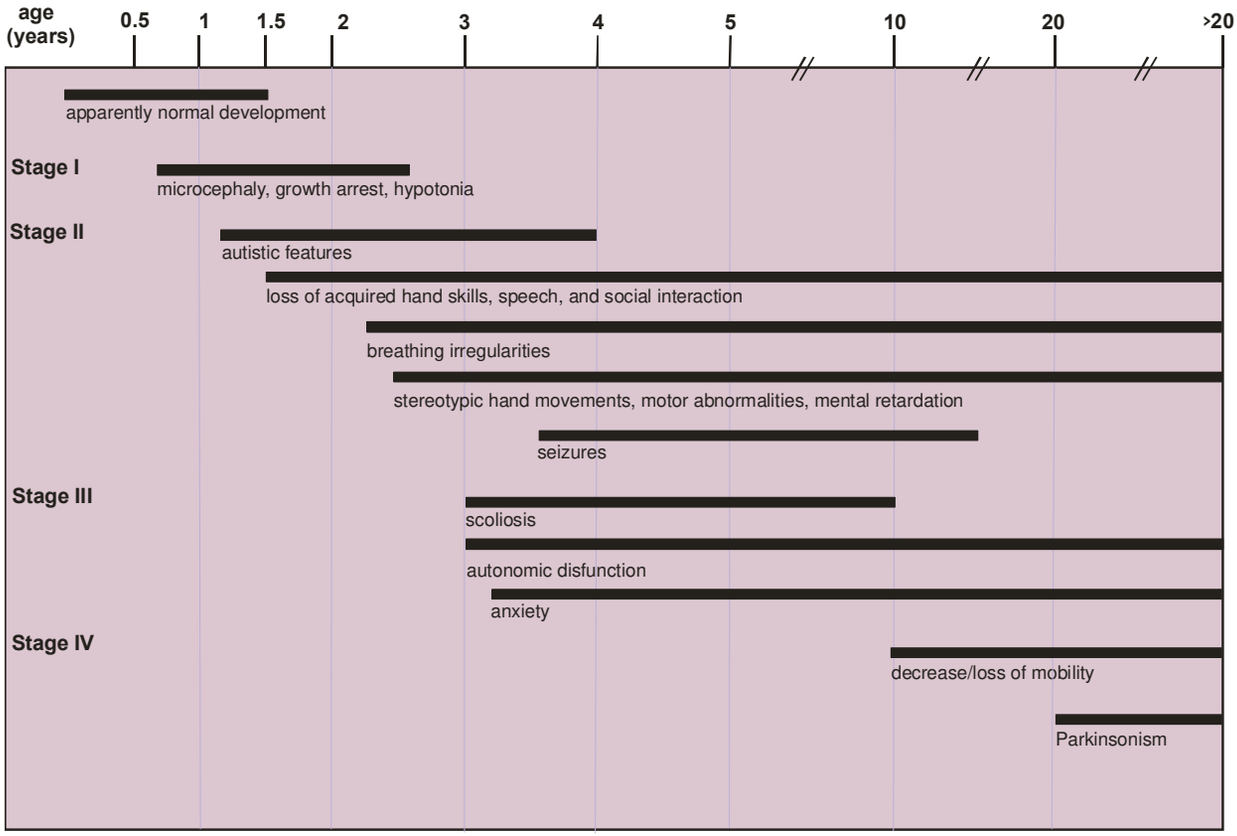


**Figure 1.** Onset and progression of Rett syndrome [12]

decline of motor and communicative performances is more gradual. Interest in people and objects is diminished, but eye contact may be preserved [11]. Voluntary hand use, such as grasping and reaching out for toys, is replaced with repetitive stereotypic hand movements, the hallmark of Rett syndrome. Patterns consisting of wringing, hand washing, mouthing, clapping, rubbing, squeezing, and other hand automatisms occur during waking hours [1, 16, 17]. Febrile seizures are often present, and epileptic paroxysms occur in most patients [18, 19]. The severity of seizures can vary, ranging from relatively mild or easily controlled by medication to severe drug-resistant episodes [20]. Irregular breathing patterns, such as episodes of hyperventilation, breath holding, and aerophagia, usually develop toward the end of the regression period. Panting, spitting, and hypersalivation are also frequent symptoms [8, 21].

**Stage III: Pseudostationary period** (age of onset: 4-7 years, after stage II). This stage can last for years or decades and is characterized by a relative stabilization of the disorder course. Patients may recover some skills, which were lost during the regression stage. Patients can become more joyful and sociable, and they may use eye pointing as a typical way to communicate and to express their needs. Some patients may even learn new words and use simple phrases in a meaningful way. Nevertheless, they continue to suffer from gross cognitive impairments [14]. Despite improved eye contact and non-verbal communication ability, the loss of motor functions further progresses in this stage. Stereotypic hand movements become prominent, as do breathing irregularities. Many patients develop scoliosis, which is often

rapidly progressive and eventually requires surgical treatment. Cold feet and lower limbs, with or without color and atrophic changes, are also common. These conditions occur due to poor perfusion, which is a consequence of altered autonomic control. Sleeping patterns are often disturbed and are characterized by frequent nighttime waking and daytime sleeping. Unexplained night laughing, sudden agitation and crying spells may also be present [11].

**Stage IV: Late motor deterioration** (age of onset: 5-15 years, after stage III). Non-verbal communication and social skills continue to improve gradually. Despite persistent serious cognitive impairment, older patients with Rett syndrome are usually, in contrast to patients with childhood autism, sociable and pleasant with others [22]. Seizures become less frequent and less severe, and stereotypic hand movements become less intense. However, motor deterioration continues with age. Most patients, who previously could walk, become nonambulatory and wheelchair-dependent. Decreased mobility leads to pronounced muscle wasting and rigidity, and, at older ages, the patients often develop Parkinsonian features [11, 23, 24].

Females with Rett syndrome often survive into adulthood and older age, but their life expectancy is less than that of the healthy population. The estimated annual death rate from Rett syndrome is 1.2%. Approximately 25% of these deaths are sudden and they may occur due to autonomic nervous system disturbances or cardiac abnormalities [25-27].

Many other features are associated with Rett syndrome, but they are not considered diagnostic. The patients are generally small for their age [28], which may be due to poor self-feeding abilities and problems with chewing and swallowing. They often suffer from gastroesophageal reflux and bloating. Decreased intestinal motility often results in severe constipation. Electroencephalogram results tend to be abnormal but without any clear diagnostic pattern. A prolonged $QT_c$ interval is observed in many patients and presents a risk for cardiac arrhythmia [26].

### 2.2. Rett syndrome variants

At least five atypical variants have been delineated in addition to classic Rett syndrome. These variants do not have all of the diagnostic features, and they are either milder or more severe than the classic form.

The most common atypical variant of Rett syndrome is “forme fruste”. This mild variant is characterized by a protracted clinical course with partially preserved communication skills and gross motor functions. Other neurological abnormalities that are typical for Rett syndrome are more subtle and can be easily overlooked in this variant [30]. The mild forms of Rett syndrome also include the late regression variant, which manifests in patients of preschool or early school age [30], and the preserved speech variant (also called the Zappella variant) in which patients have preserved language skills and normal head sizes [31].

Severe variants include the early-onset seizure variant (the Hanefeld variant) with the onset of seizures before the age of 6 months [32] and the congenital variant, which is rare and lacks the early period of normal psychomotor development [33]. The Hanefeld variant is often caused by mutations in the *CDKL5* gene [34], and most cases of the congenital variant are related to mutations in the *FOXG1* gene [35]. These genetic abnormalities raise the question of

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| Consider Rett syndrome diagnosis when postnatal deceleration of head growth is observed |
|---|
| **Required for classic Rett syndrome**<br>1. A period of regression followed by recovery or stabilization<br>2. All main and all exclusive criteria<br>3. Supportive criteria are not required, although often present in classic Rett syndrome |
| **Required for atypical or variant Rett syndrome**<br>1. A period of regression followed by recovery or stabilization<br>2. At least 2 of 4 main criteria<br>3. 5 out 11 supportive criteria |
| **Main criteria**<br>1. Partial or complete loss of acquired purposeful hand skills<br>2. Partial of complete loss of acquired spoken language<br>3. Gait abnormalities: impaired ability (dyspraxia) or absence of ability (apraxia)<br>4. Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms<br>**Exclusion criteria for classic Rett syndrome**<br>1. Brain injury secondary to trauma (perinatally or postnatally), neurometabolic disease or severe infection that cause neurological problems<br>2. Grossly abnormal psychomotor development in the first 6 months of life<br>**Supportive criteria for atypical or variant Rett syndrome**<br>1. Breathing disturbances when awake (hyperventilation, breath-holding, forced expulsion of air or saliva, air swallowing)<br>2. Bruxism when awake (grinding or clenching of the teeth)<br>3. Impaired sleep pattern<br>4. Abnormal muscle tone<br>5. Peripheral vasomotor disturbances<br>6. Scoliosis/kyphosis<br>7. Growth retardation<br>8. Small cold hands and feet<br>9. Inappropriate laughing/screaming spells<br>10. Diminished sensitivity to pain<br>11. Intense eye communication and eye-pointing behavior |

**Table 1.** Diagnostic criteria for Rett syndrome [29]

whether these variants are separate clinical entities, different from *MECP2*-related Rett syndrome [11].

### 2.3. Diagnostic criteria

Despite a known genetic cause, Rett syndrome remains a clinical diagnosis. Its diagnosis is based on several well-defined criteria (Table 1), which were revised several times over the past few decades, most recently in 2010 [29].

## 3. The genetics of Rett syndrome

### 3.1. Mapping of the causative gene

The mode of inheritance of Rett syndrome was difficult to identify because more than 99% of the cases are sporadic, and the patients rarely reproduce. Therefore, the traditional genome-wide linkage analysis was not an applicable method for mapping the disease locus. The lack of males manifesting the classic Rett syndrome phenotype together with the occurrence of families with affected half-sisters suggested an X-linked dominant inheritance with lethality in hemizygous males [2, 36]. Focused exclusion mapping of the X chromosome in available familial cases was used to narrow down the candidate region, and the subsequent analysis of candidate genes in the patients finally revealed disease-causing mutations in the *MECP2* gene [4].

### 3.2. *MECP2* gene

The *MECP2* gene (MIM 300005) is located on Xq28 and undergoes X chromosome inactivation (XCI) in females [37, 38]. The gene spans approximately 76 kb and consists of four exons, which encode methyl-CpG-binding protein 2 (MeCP2). Alternative splicing of exon 2 and several polyadenylation signals in a conserved and unusually long 3′ untranslated region (3′UTR) give rise to eight different transcripts regulated in a tissue-specific and developmental stage-specific manner [39-42]. For example, the shortest transcript (1.8 kb) is predominant in adult muscles, heart, blood, and liver. The longest transcript (10.2 kb) occurs at the highest levels in the brain [41, 42]. The unique expression patterns of each transcript suggest a specific biological significance, such as a role in mRNA stability, nuclear export, folding, and sub-cellular localization, thus affecting the levels of the resulting protein [39]. The longest transcript also has one of the longest 3′ UTR tails in the human genome (8.5 kb), with several blocks of highly conserved residues between the human and mouse genomes. These findings argue in favor of a potential regulatory role of the 3′ UTR of the *MECP2* gene [43].

### 3.3. *MECP2* mutations

Mutations in the *MECP2* gene are identified in 90-95% of classic Rett syndrome patients [4, 44]. Because only the coding region and the adjacent non-coding parts of the gene are routinely analyzed, it is highly probable that mutations in more remote regulatory elements are responsible for the rest of the cases. The frequency of *MECP2* mutations in patients with atypical Rett syndrome variants varies considerably between studies. However, the frequency is generally lower (only 20-70% of patients have *MECP2* mutations) than in the classic form [44-46], suggesting that mutations of regulatory elements or other genes are involved more often in atypical Rett syndrome than in the classic Rett syndrome. The identification of *CDKL5* mutations in the Hanefeld variant and *FOXG1* mutations in the congenital variant strongly support the latter idea.

According to the Human Gene Mutation Database [47], more than 550 mutations have been identified in the *MECP2* gene in patients with Rett syndrome. The spectrum of mutations is

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heterogeneous, including missense and nonsense mutations, deletions, insertions, duplications, splice-site mutations, and large deletions of several exons or the entire *MECP2* gene. More than 99% of the mutations occur *de novo* and mostly originate on the paternal X chromosome, which explains the high occurrence of Rett syndrome in the female gender [4, 48, 49]. Familial cases of Rett syndrome (mostly affected sisters or maternal half-sisters) are very rare. *MECP2* mutations in these patients are inherited from an asymptomatic or very mildly affected mother, who carries a somatic mutation, but does not manifest the full pathogenic phenotype due to favorable XCI pattern [50, 51]. Another explanation for transmission of a *MECP2* mutation to the next generation is a germline mosaicism for a mutation. It is suggested when the *MECP2* mutation identified in several affected children is not present in somatic cells of their parents [51, 52].

The majority of point mutations in the *MECP2* gene are C>T transitions, presumably resulting from the spontaneous deamination of methylated cytosines [53]. The mutations are scattered throughout the coding sequence and splice sites, with the exception of exon 2. The eight most common mutations, which are also C>T transitions, account for approximately 70% of the Rett syndrome cases. Approximately 10% of cases are due to deletions, which are mostly clustered in the terminal segment of the coding region [12].

### 3.4. *MECP2* mutations in males and other disorders

Mutations in the *MECP2* gene have long been considered lethal in hemizygous males, and Rett syndrome has been assumed to be exclusively a female disorder. More recently, *MECP2* mutations were not only identified in males but also in females with phenotypes different from Rett syndrome. *MECP2*-related disorders thus represent a broad spectrum of phenotypes in both genders.

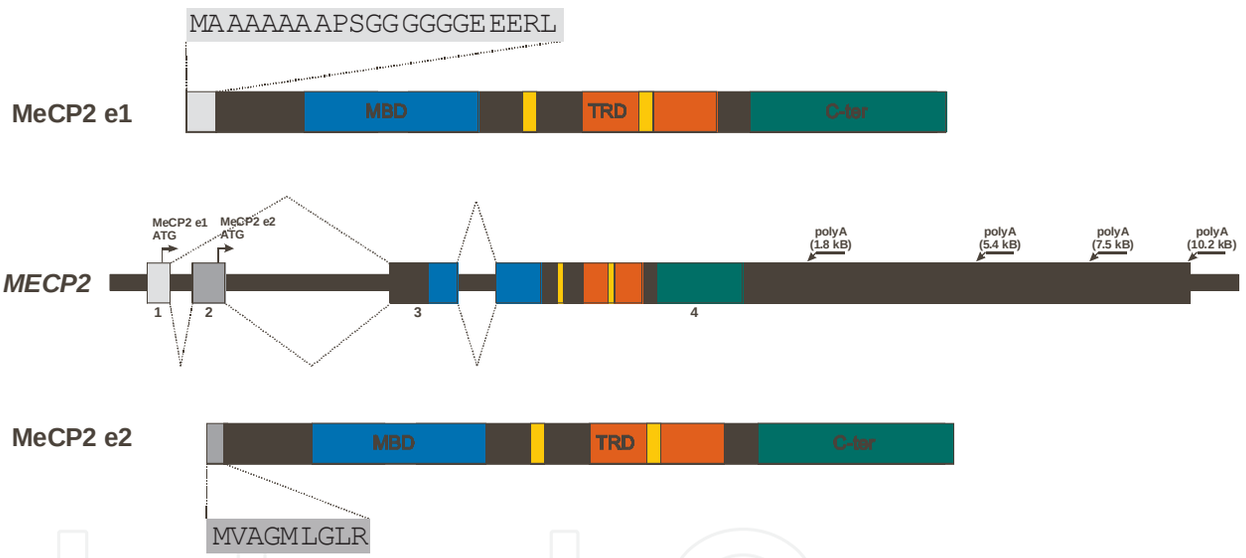
The estimated frequency of *MECP2* mutations in boys with mental retardation is 1.3-1.7% [54]. Typical Rett syndrome features have been observed almost exclusively in boys with Klinefelter syndrome (47,XXY) [55] or somatic mosaicism for a *MECP2* mutation [56, 57]. Other phenotypes include severe congenital encephalopathy with death in the first years of life [58-60] and mild to severe intellectual disability with or without various neurological and psychiatric symptoms [54, 61]. The most common *MECP2* mutations detected in males are duplications of the whole *MECP2* gene (and usually genes in its vicinity). This finding indicates that, besides the lack, an overabundance of fully functional MeCP2 protein is also harmful to the CNS. *MECP2* duplication syndrome is usually very mild or does not manifest in females. In boys, this syndrome is characterized by infantile hypotonia, severe mental retardation, loss of speech, recurrent respiratory infections, seizures, and spasticity [62-64].

In females, *MECP2* mutations have been detected in patients with mild mental retardation, learning disabilities or autism [65, 66]. More severe cases include severe mental retardation with seizures and Angelman-like syndrome [67, 68].

### 3.5. MeCP2 protein

The MeCP2 protein is ubiquitously expressed, but it is particularly abundant in the brain [41, 69]. The protein levels are low during embryogenesis, but they progressively increase during postnatal neuronal maturation and synaptogenesis [70-75]. High expression of MeCP2 in mature neurons implies its involvement in postmitotic neuronal functions, such as the modulation of neuronal activity and plasticity [12].

MeCP2 occurs in two isoforms that arise from alternative splicing of exon 2, and they differ only by their N-termini (Figure 2). MeCP2 e1 (498 amino acids), generated by exons 1, 3, and 4, is the dominant MeCP2 isoform in the brain [76-78]. The MeCP2 e2 isoform (486 amino acids) is encoded by exons 2, 3, and 4. Both isoforms were initially assumed to be functionally equivalent, but recent observations imply that additional isoform-specific functions may exist. This idea is strongly supported by the fact that no mutations in exon 2 have been found in Rett syndrome patients, which contrasts with the finding of identified mutations in exon 1. Thus, defects in MeCP2 e2 may lead to non-Rett phenotypes or fatally affect embryo viability [79, 80].




MBD: methyl-CpG-binding domain, TRD: transcriptional repression domain, C-ter: C-terminal domain, yellow boxes: nuclear localization signals.

**Figure 2.** *MECP2* gene structure and the isoforms MeCP2 e1 and MeCP2 e2 with different N-termini due to alternative splicing of exon 2 and different translation start sites.

Apart from different N-terminal regions, both isoforms share the same amino acid sequence, including at least three functional domains and two nuclear localization signals (Figure 2). The methyl-CpG-binding domain (MBD) (amino acids 78-162) mediates binding to symmetrically methylated CpG dinucleotides [81, 82], with a preference for CpGs with adjacent A/T-rich motifs [83]. The MBD also binds to unmethylated four-way DNA junctions, which suggests the role of MeCP2 in higher-order chromatin interactions [84]. The transcriptional repression domain (TRD) (amino acids 207-310) interacts with numerous proteins, such as co-repressor factors and histone deacetylases, HDAC1 and HDAC2. The nuclear localization signals (NLS)

(amino acids 173-193 and 255-271) mediate transportation of the protein into the nucleus [85]. The C-terminal domain (amino acids 325-486) facilitates binding to DNA [86] and it most likely increases protein stability [87]. This domain also contains conserved poly-proline motifs that can bind to group II WW domain splicing factors [88].

### 3.6. MeCP2 function

The original model suggested that MeCP2 is a global transcriptional repressor [89], and it was based on *in vitro* experiments in which MeCP2 inhibited transcription from methylated promoters. Briefly, the protein binds to the promoters of target genes via its MBD, and the TRD then recruits the co-repressor Sin3A and HDACs [90, 91]. These interactions lead to the deacetylation of histones, resulting in chromatin condensation and the repression of downstream genes. In addition to Sin3A, other co-repressors, such as c-Ski and N-CoR, may interact with MeCP2 [92]. The compaction of chromatin can also be promoted through direct interaction with the C-terminal domain [93], which is an example of HDAC-independent MeCP2-mediated transcriptional repression. The TRD may also directly interact with transcription factor IIB; therefore, MeCP2 may silence transcription by interfering with the assembly of the transcriptional preinitiation complex [94]. Additional factors interacting with the TRD include Brahma, which is a catalytic component of the SWI/SNF-related chromatin-remodeling complex (at least in NIH 3T3 cells) [95], DNA methyltransferase 1 [96], and ATRX, a SWI2/SNF2 DNA helicase/ATPase [97].

Surprisingly, transcriptional profiling studies did not reveal major gene expression changes caused by the lack of functional MeCP2 protein [98, 99]. These observations, together with additional evidence, implied that MeCP2 regulates the transcription of tissue-specific genes in specific brain regions during certain developmental stages instead of acting as a global repressor [98, 100-102]. However, recent studies suggest that MeCP2 reduces genome-wide transcriptional noise, potentially by repressing spurious transcription of repetitive elements [103, 104]. Surprisingly, MeCP2 also interacts with the transcriptional activator CREB, and its genomic distribution is often associated with actively transcribed genes [105, 106]. MeCP2 apparently has dual roles in transcriptional regulation as a repressor and as an activator, and it performs different downstream responses depending on the context.

MeCP2 additionally acts as an architectural chromatin protein that is involved in chromatin remodeling and nucleosome clustering, which is consistent with the fact that the majority of MeCP2-binding sites are located outside of genes [105, 107]. MeCP2 can bind *in vitro* to chromatin fibers and compact them into higher order structures [93, 108, 109].

For further complexity, MeCP2 may also be involved in RNA splicing. Its interaction with the RNA-binding protein Y box-binding protein 1 (YB-1) has been observed, and MeCP2-deficient mice showed aberrant alternative splicing patterns [110].

MeCP2 functions are undeniably much more complex than initially anticipated (Figure 3), although the precise mechanisms of their regulation remain unknown.

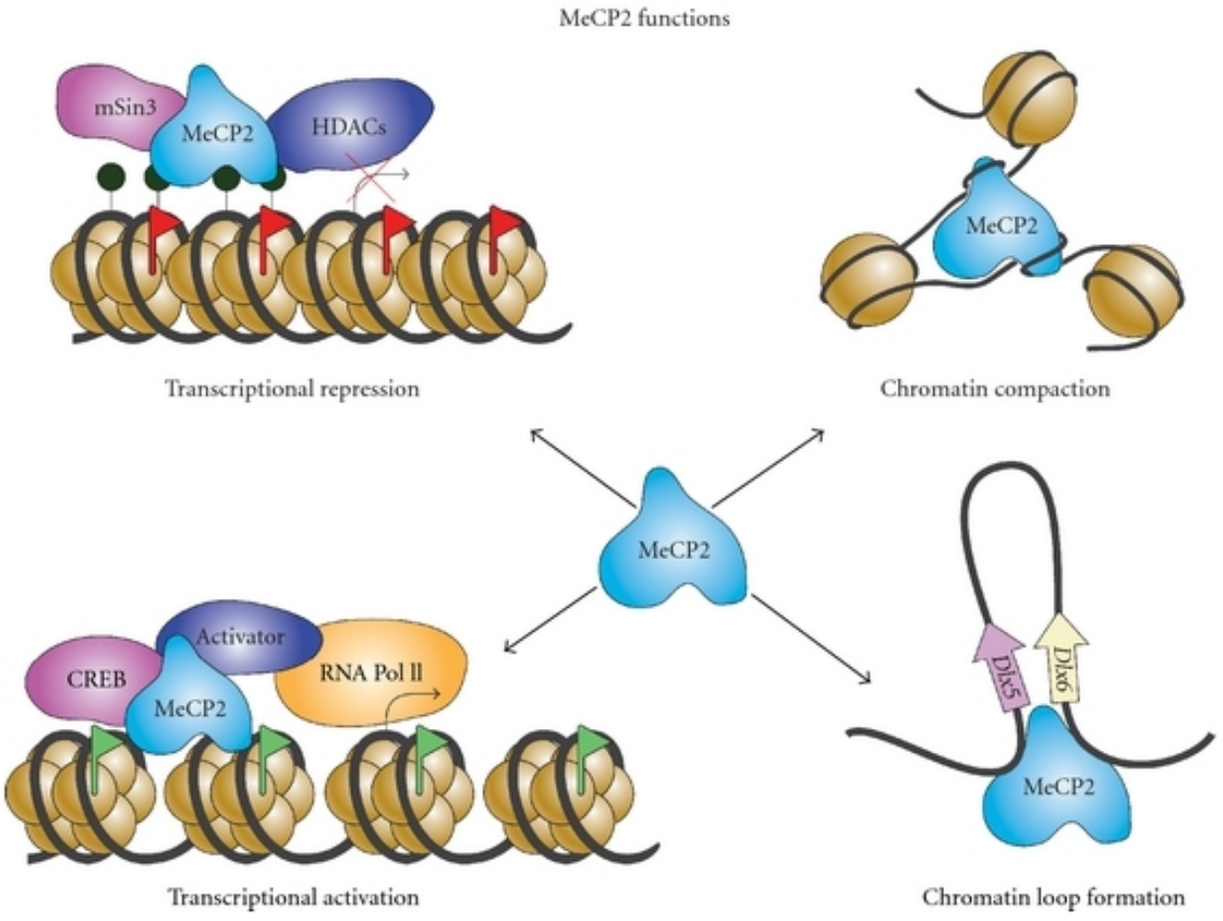



**Figure 3.** Representation of multiple MeCP2 roles [111].

### 3.7. MeCP2 target genes

A comprehensive knowledge of the target genes that are controlled by MeCP2 is essential for understanding the pathomechanisms of Rett syndrome and subsequently developing effective therapeutic strategies. Multiple studies have attempted to identify genes with altered expression in neuronal and nonneuronal tissues from Rett syndrome patients and mouse models, but these studies have often yielded conflicting results [102, 106, 112, 113]. Nevertheless, several candidate target genes have been proposed (Table 2). One of the most extensively studied target genes is the brain-derived neurotrophic factor gene (*Bdnf*), which has been shown to be up and down regulated in an activity-dependent manner through MeCP2 phosphorylation in mice [113-115]. Other targets, such as the imprinted genes *Dlx5* and *Dlx6*, also revealed a novel mode of gene repression mediated by MeCP2 through the formation of a silent chromatin loop (Figure 3) [116, 117].

| Gene | Function | Reference |
|---|---|---|
| *UBE3A* | member of ubiquitin proteasome pathway, transcriptional co-activator | [118] |
| *GABRB3* | neurotransmission (GABA-A receptor) | [118] |
| *PCDHB1* | cell adhesion | [119] |
| *PCDH7* | cell adhesion | [119] |
| *Bdnf* | neuronal development and survival, neuronal plasticity, learning and memory (brain derived neurotropic factor) | [113, 114] |
| *Dlx5* | neuronal transcription factor (probably involved in control of GABAergic differentiation) | [116] |
| *Sgk1* | hormone signaling (regulation of renal functions and blood pressure) | [120] |
| *Fkbp5* | hormone signaling (regulation of glucocorticoid receptor sensitivity) | [120] |
| *Uqcrc1* | member of mitochondrial respiratory chain | [121] |
| *ID1, ID2, ID3, ID4* | transcription factors (involved in cell differentiation and neural development) | [122] |
| *FXYD1* | ion channel regulator | [123] |
| *IGFBP3* | hormone signaling (regulation of cell proliferation and apoptosis) | [124] |
| *GDI1* | regulation of GDP/GTP exchange | [112] |
| *APLP1* | enhancer of neuronal apoptosis | [112] |
| *CLU* | Extracellular molecular chaperone | [112] |
| *Crh* | neuropeptide (regulation of neuroendocrine stress response) | [125] |

**Table 2.** Some of MeCP2 target genes.

### 3.8. The effect of *MECP2* mutations on MeCP2 function

Mutations in the *MECP2* gene are not likely to act in a dominant-negative mechanism because only one allele is active in each female cell due to XCI. The functional consequences of missense mutations on the function of the MeCP2 protein are sometimes especially difficult to predict. This difficulty is because testing the protein's various functions can be problematic because there are still many MeCP2 roles that are as yet unknown or not fully understood. Generally, mutations in the NLS prevent the transportation of the protein to the nucleus. Mutations located within the MBD reduce the affinity of the protein for methylated DNA [87, 126]. However, several mutant proteins with mutations in the MBD have been shown to bind to heterochromatin [127]. Proteins with an intact MBD but with a mutated TRD retain their ability to bind to methylated DNA, but they have impaired repressing activity [87]. Other mutations may affect the stability or the structure (secondary or tertiary) of the protein, and they may interfere with other functions of the protein.

### 3.9. Genotype-phenotype correlation

The severity of the clinical manifestations in Rett syndrome patients is widely variable and is relevant beyond the context of classic vs. atypical variants. Therefore, much effort has been devoted to uncovering the relationships between various *MECP2* mutations and the variability of clinical features. Such knowledge may provide information on the likely clinical profile of new cases with specific *MECP2* mutations and may be useful in designing specific preventive therapeutic interventions.

The general genotype-phenotype correlations were confirmed by numerous studies. As expected, patients with early truncating mutations (specifically p.R168X, p.R270X, p.R255X), large deletions of several exons, or the entire *MECP2* gene usually have the most severe clinical presentations. A milder phenotype is often associated with late truncating mutations that do not affect the MBD or the TRD, such as p.R294X. Interestingly, late truncating mutations together with the missense mutation p.R133C, which is located in the MBD, are frequently detected in patients with a preserved speech variant of Rett syndrome [128-133].

Despite some overall trends, considerable variability in clinical severity is often observed among patients with the same *MECP2* mutation [128, 130, 134]. Such variations may be caused by a different XCI pattern. Favorable skewing of XCI has been observed in some patients with milder phenotypes [135-137] and in asymptomatic carrier mothers [58, 135, 138]. However, XCI cannot be used as the single predictor because, according to several studies, it has limitations in explaining all of the differences of Rett syndrome severity [139-141]. Other modulation factors have been considered, such as *BDNF* [142, 143] and *APOE* [144].

### 3.10. Genetic counseling

A negative result from the *MECP2* analysis (usually including analysis of the entire coding region and copy number analysis of large deletions/duplications) does not rule out the diagnosis of Rett syndrome because regulatory and non-coding regions are not routinely analyzed. The recurrence risk in a family with a single Rett syndrome case and an otherwise negative family history is very low (less than 0.5%) because the majority of *MECP2* mutations arise *de novo*. Mothers of the patients, however, should be tested for *MECP2* mutations found in their daughters to rule out the possibility of being asymptomatic carriers. In such case, the recurrence risk is 50%. Prenatal diagnosis may be performed even in pregnancies of non-carrier mothers due to the likelihood of germline mosaicism.

## 4. Management of Rett syndrome

Currently, there is no effective cure for Rett syndrome. However, hopes for developing a targeted therapy have risen following the announcement of a study that rescued the pathological phenotype in a mouse model after postnatal reactivation of *Mecp2* [145, 146]. Treatment strategies are currently symptomatic and preventive. These strategies are aimed at ameliorating specific symptoms, such as seizures, mood disturbances, sleeping and feeding problems, as well as maintaining and improving motor and communication functions.

Rehabilitation programs and physical therapy help to control and improve balance and movement, maintain flexibility and strengthen muscles. These programs should be adapted to the patient's individual state and needs. Proper physical therapy is also important for preventing joint contractures and other deformities, such as scoliosis. Occupational therapy is recommended for improving purposeful hand use and to attenuate stereotypic hand movements. Particular care should be taken to preserve and maintain alternative communication (eye contact, eye pointing, facial expressions, signs, etc.) and thereby improving social interactions. Receiving necessary nutrients and maintaining an adequate weight may result in improved growth. To ensure appropriate caloric and nutritional intake, a high-fat, high-calorie diet or gastrostomy feeding may be required. Sufficient intake of fluid and high-fiber food is necessary to prevent constipation. The patients with cardiac conduction defects (such as prolonged $QT_c$ intervals) should avoid certain medications, which may worsen the condition. These medications include several antipsychotics (thioridazine, tricyclic antidepressants), certain antiarrhythmics (quinidine, sotalol, amiodarone), and antibiotics (erythromycin) [147].

Early diagnosis and intervention, together with life-long management focused on each patient's specific needs, can significantly improve the health, quality of life, and longevity of patients with Rett syndrome.

## 5. Conclusion

Much progress has been made in the identification of the multiple roles of the MeCP2 protein in the brain since its discovery. Nevertheless, many mysteries still remain in understanding the precise mechanisms of how *MECP2* mutations affect protein function and subsequently contribute to the pathogenesis of Rett syndrome. A significant phenotypic overlap between Rett syndrome and several neurodevelopmental disorders implies that a common pathogenic process may induce or at least contribute to these conditions. The identification of pathogenic *MECP2* mutations in a portion of patients without the classic Rett syndrome phenotype strengthens this theory. Understanding the molecular pathology underlying Rett syndrome will therefore shed more light on the role of epigenetic modifications in neuronal development and function, and it may provide insight into the pathogenesis of other neurodevelopmental disorders.

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