

# MECP2-Related Disorders in Males

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Methyl CpG binding protein 2 ( *MECP2* ) is an unstructured protein that can adopt local secondary structures when binding to other molecules, which explains its involvement in multiple molecular interactions and thereby, functions. Thus, *MECP2* is a multifunctional gene that acts as a transcriptional regulator (both activating and repressing) and a chromatin remodeler; it also interacts with the RNA splicing machinery and with microRNA processing machinery, among others. Post-translational modifications are also implicated in regulating its activity and interactions with other proteins.

Rett syndrome

encephalopathy

loss-of-function

males

## 1. *MECP2* Gene

Methyl CpG binding protein 2 ( *MECP2* ) (OMIM \*300005) encodes the protein MeCP2 and is located in the Xq28 region which can be inactivated for gene dosage compensation of the X chromosome in females <sup>[1]</sup>. *MECP2* has four exons and undergoes alternative splicing from which two well-characterized isoforms are generated—isoform e1 and isoform e2. Isoform e1 retains exons 1, 3, and 4 whereas isoform e2 retains exons 2, 3, and 4. *MECP2\_e1* is conserved across vertebrates while e2 appeared later in the class Mammalia <sup>[2]</sup>. *MECP2\_e1* is the most abundant isoform in the brain although the ratio between the two isoforms varies across different tissues; for example, *MECP2\_e2* is more abundant in fibroblasts <sup>[2]</sup>. Even though both isoforms share the majority of their sequence and the main functional domains, they are not completely redundant. Each of them has their own properties, spatial expression, function, and interacting partners <sup>[3][4][5]</sup>.

*MECP2* has several structural domains—N-terminal domain (NTD), methyl-binding domain (MBD), intervening domain (ID), transcriptional repression domain (TRD), and C-terminal domain (CTD). MBD and TRD are considered crucial functional domains. MBD enables the binding to methyl CpG dinucleotides and is where most of disease-causing mutations are located. TRD is needed for the binding and posterior recruitment of co-repressor proteins, such as NCoR, SMRT, and HDAC3, in order to repress transcription <sup>[6]</sup>. The protein has a nuclear localization signal (NLS) domain as well. MeCP2 is an unstructured protein that can adopt local secondary structures when binding to other molecules, which explains its involvement in multiple molecular interactions and thereby, functions <sup>[7][8]</sup>. Thus, *MECP2* is a multifunctional gene that acts as a transcriptional regulator (both activating and repressing) and a chromatin remodeler; it also interacts with the RNA splicing machinery and with microRNA processing machinery, among others <sup>[9]</sup>. Post-translational modifications are also implicated in regulating its activity and interactions with other proteins <sup>[10][11]</sup>. The resultant protein MeCP2 is ubiquitously expressed even though it is more abundant in the brain, especially in neuronal cells. It is noteworthy that the level

of expression correlates with the maturation of neurons, indicating the importance of MeCP2 not only in neuronal development but also in neuronal maturation and maintenance [\[12\]\[13\]](#).

Since mutations in the *MECP2* gene were first reported in 1999 in female and male patients with Rett syndrome (RTT) (OMIM #312750) [\[14\]\[15\]](#), genetic alterations ranging from single nucleotide mutations to large deletions have been described and associated with RTT. As the majority of the reported cases described affected females, it was suggested that mutations in *MECP2* lead to embryonic lethality or early postnatal death in males, since no wildtype allele can be partially expressed as in females. However, sporadic reports of boys with mutations in this gene have shown otherwise [\[15\]\[16\]\[17\]\[18\]\[19\]](#).

As can be inferred, *MECP2* is a dosage-sensitive gene because loss-of-function mutations lead to RTT, but whole gene duplication leads to *MECP2* duplication syndrome(MDS). This must be taken into consideration when looking for a treatment.

## 2. Mutations in MECP2

Whenever a mutation in *MECP2* is found in a patient, RTT becomes a possible diagnosis. RTT was first clinically described in 1966 by Andreas Rett in girls. In 1999, Zoghbi's group linked *MECP2* to RTT [\[14\]\[15\]](#). Since then, groups all over the world have reported patients, reaching a few thousands of cases. In fact, *MECP2* mutations cause 97% of classic RTT cases [\[20\]\[21\]](#).

Several specific *MECP2* mutation screenings have been performed in males affected by neurological disorders. In all of them, a low frequency of variants in *MECP2* was found [\[22\]\[23\]\[24\]\[25\]](#). RettBASE is an international curated database, which gathers the genetic variation found in individuals with RTT and related clinical disorders. To date, there have been 3924 female cases with mutations in *MECP2* and 345 male cases. As in females, in males, mutations range from single nucleotide changes to larger deletions involving up to 240 nt [\[26\]\[27\]](#). Small duplications from one to seven nucleotides have also been reported in RettBASE. The disparity of cases for each sex and the difficulties in creating the first male mouse model suggested that mutations in *MECP2* in males were lethal. Fortunately, different groups have reported new patients and, nowadays, it was known that the effects of these mutations range from severe neonatal encephalopathies and premature death (as in the case of c.806delG [\[26\]](#)) to mild intellectual and psychomotor impairment (as in c.608C > T [\[19\]](#)) and that they are not always related to RTT.

In 2003, Ravn et al. compared the first group of 18 male patients with pathogenic variants in *MECP2*. They classified the variants into two groups—mutations causing RTT in girls and mutations that do not affect or cause mild intellectual disability (ID) in females. This genetic classification corresponds with the phenotypes of the boys, which are divided into two groups as well—cases with severe neonatal encephalopathy and cases with non-specific mental retardation. They pointed out that, among the patients harboring RTT mutations, two kinds of patients could be found. Whenever the patient has Klinefelter syndrome (47, XXY) or is a mosaic, the boy develops an RTT phenotype. However, if the chromosomal complement is normal and no mosaicisms are found, the boy usually dies at a very early age [\[26\]](#).

The incorporation of next generation sequencing (NGS), especially of gene panels, has helped reduce the time needed for a molecular diagnosis in patients with rare diseases because of its ability to multiplex genes and patients. NGS has enabled the finding of the molecular cause in patients with either a more recognizable RTT phenotype and for whom traditional techniques were unable to detect a variation, or a more ambiguous phenotype such as X-linked intellectual disability [28][29][30]. The implementation of NGS as a diagnostic tool has found new patients with *MECP2* variations, especially males, who otherwise might never have been redirected for a *MECP2* direct sequencing test [own data]. In addition, NGS-based methods possess a high read coverage for the amplified genes which makes them a technique to take seriously into consideration for mosaicism detection rather than Sanger sequencing [31].

### 3. Duplication of MECP2

In the late 1990s, several groups were trying to link patients with X-linked mental retardation (XLMR) to specific genetic alterations or genes. During this search, several cases with X chromosome distal duplications were reported [32]. In particular, Lubs et al., described a family of five affected boys with an Xq28 duplication inherited from carrier mothers which later were confirmed to be proper cases of MDS [33][34]. Because of that first article, MDS was originally named as Lubs X-linked mental retardation syndrome, a name that still can be found in OMIM (MIM #300260).

Even though MDS is a rare syndrome and most of the articles describe sporadic or small familial cases rather than large cohorts, to date, there are more than 600 cases reported worldwide [32][33][34][35][36][37][38][39][40][41][42][43][44][45][46][47][48][49][50][51][52][53][54][55][56][57][58][59][60][61][62][63][64][65][66][67][68][69][70][71][72][73][74][75][76][77][78][79][80][81][82][83][84][85][86][87][88][89][90][91][92][93][94][95][96][97][98][99][100][101][102][103][104][105][106][107][108][109][110][111][112][113].

As mentioned, some clinical features, such as epilepsy, respiratory tract infections, or constipation, appear or worsen with age. As a result, Peters et al., reported that their older participants have more severe clinical symptoms, specifically regarding motor dysfunction (e.g., dystonia, scoliosis, and/or rigidity) and functional skills (e.g., motor skills, communication skills, chewing, and swallowing) [111]. A longitudinal Japanese study found a similar outcome by comparing the clinical traits of MDS boys at their first medical visit and some years later [112].

The location of the duplications has been studied as well. It was thought that girls with translocations of the duplications to autosomal chromosomes were more severely affected than girls with interstitial duplications, since the former escape XCI [56][88]. However, females with duplications in tandem and a severe phenotype have also been reported [68].

### 4. Modeling RTT and MDS for Future Therapies

The difficulty in accessing target tissue samples from children affected by neurodevelopmental disorders has encouraged researchers to create specific animal and cellular models to gain knowledge of rare diseases as RTT and MDS. In RTT, the most frequently used animal model has been the male *Mecp2* -null mouse (*Mecp2*  $-/-$ ) which manifests the early severe phenotype seen in humans [114]. Despite being the major source of findings

related to mechanisms and pathways in RTT, the translatability of mouse models towards humans is not clear, especially regarding RTT females. Several mouse models for MDS have also been created [115][116]. Alternative models, such as primary cultures of patients' peripheral tissues, human embryonic stem cells (hESCs), or human-induced pluripotent stem cells (hiPSCs) reprogrammed from patients' somatic cells, have proven to be very useful [85][117]. Tang and colleagues found that in hiPSCs of a male RTT patient, elevating KCC2 levels could ameliorate the functional deficits caused by the absence of MeCP2, and showed that IGF1 treatment works in the mentioned tissue [118][119]. Kim et al., also found that in RTT hiPSC knockdown of LIN28 expression partially reversed the synaptic deficits [120]. Recently, 3D aggregates from hiPSCs have been developed in an attempt to mimic the complex architecture and functions of organs such as the brain [121]. Moreover, region-specific brain organoids have been generated. The created organoids have also proven to be mutation-dependent and different initial phenotypic alterations have been found in organoids with different backgrounds [122]. All these in vitro human-derived models seem truly promising, not only because of the molecular and genetic insight they are generating, but also because several drugs are being tested and these could, ultimately, undergo clinical trials.

Even though most of the clinical trials for RTT have female participants, according to the register of the U.S. National Library of Medicine a few clinical trials have incorporated male patients. Such is the case of NCT00593957, NCT01520363 with dextromethorphan, NCT02790034 with sarizotan, and NCT00299312, in which a phase of genetic and physical characterization of RTT patients has been done. On the other hand, there are no clinical trials registered yet for MDS, but some promising results have been obtained in the previous in vitro and animal models. Recently, Ash and so on, found that the hyperactivity seen in ERK the pathway in MDS could, similar to other autism-associated disorders, be reversed with ERK-specific pharmacologic inhibitors [123][124]. Moreover, antisense oligonucleotide (ASO) therapies are showing promising results in mice, especially because of their ability to reduce MeCP2 expression in a dose-dependent manner [116]. It was showed that CNS administration of *MECP2* -ASO is well tolerated and beneficial in a mouse model. Although these first studies do not include the *IRAK1* gene, they provide a translatable approach that could be feasible for treating MDS. The CRISPR-Cas system has been tested in animal models and human primary fibroblasts and has successfully corrected the duplication of *MECP2* including *IRAK1* [117]. However, there is not enough evidence so far to suggest possible approaches to therapy targeted the pathophysiology underlying these two diseases. Further work could bring deep brain stimulation, ASO, and gene therapy into the clinic within the coming decades [8].

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