The relationship of Rett syndrome and MECP2 *disorders to autism*

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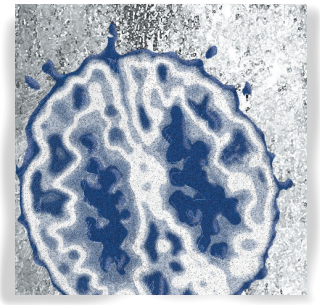

Rett syndrome (RTT, MIM#312750) is a neurodevelopmental disorder that is classified as an autism spectrum disorder. Clinically, RTT is characterized by psychomotor regression with loss of volitional hand use and spoken language, the development of repetitive hand stereotypies, and gait impairment. The majority of people with RTT have mutations in Methyl-CpG-binding Protein 2 *(*MECP2*), a transcriptional regulator. Interestingly, alterations in the function of the protein product produced by* MECP2*, MeCP2, have been identified in a number of other clinical conditions. The many clinical features found in RTT and the various clinical problems that result from alteration in MeCP2 function have led to the belief that understanding RTT will provide insight into a number of other neurological disorders. Excitingly, RTT is reversible in a mouse model, providing inspiration and hope that such a goal may be achieved for RTT and potentially for many neurodevelopmental disorders.*

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Introduction

Rett syndrome (RTT, MIM#312750) is a neurodevelopmental disorder (NDD) that is classified as an autism spectrum disorder (ASD) in the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)*[1] and occurs in approximately 1 in 10 000 female births.[2] RTT is mostly found in girls, although a small number of boys have been identified with RTT. Although autistic features are present in some people with RTT, especially during the regressive stage, many unique clinical features differentiate RTT from idiopathic autism.

Wide interest in RTT exists because, in 1999, RTT became the first ASD with a defined genetic cause.[3] Although the majority of people with RTT have mutations in the X-linked transcriptional regulator *Methyl-CpG-binding Protein 2* (*MECP2*),[4] up to 5% of people with RTT do not have mutations in *MECP2*. In some cases, people with RTT or RTT-like features have mutations in other genes. Furthermore, mutations in *MECP2* have been identified in people who do not have the distinctive clinical features of RTT, but rather have other neural developmental disorders (NDDs).[5] For this rea-

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son, RTT remains a clinical diagnosis defined by a consensus of clinical criteria.[5] In addition to the loss of function mutations in *MECP2* that cause RTT, duplication of *MECP2* causes a distinct NDD,[6] indicating that the nervous system is very sensitive to *MECP2* dose, and any disruption in the function of the protein product, MeCP2, can lead to neurological and psychiatric problems.

The identification of the genetic cause of the majority of cases of RTT has led to the development of a number of mouse models of the disease.[7-12] These models have provided valuable insight into the pathophysiology of the disorder and point towards possible therapeutic interventions. Importantly, the animal model has demonstrated that the disease is reversible,[13] providing hope for the development of therapies that will ameliorate or completely rescue the disease.

The many clinical features found in RTT and the various clinical problems that arise from disrupting MeCP2 function has lead the concept that RTT is a "prototypical NDD"[14] that can act as a Rosetta stone to provide understanding and insight into a vast array of genetically defined and genetically undefined clinical conditions such as idiopathic autism.[15] To provide general information about RTT and *MECP2*-related disorders, this review will describe the clinical features of these disorders, with a focus on the autistic features present and the unique clinical features that define these disorders. Finally, a brief overview of the animal models of these diseases will be presented and will show how work with these models has led to the conceptualization and initiation of clinical trials in RTT.

Clinical features of RTT

RTT is a disease that primarily affects girls because the gene responsible for the majority of the cases, *MECP2*, is located on the X chromosome.[3] Disruption of one copy of *MECP2* leads to, in most cases, RTT. The disease is characterized by regression with a loss of hand skills and spoken language after a period of normal development and the onset of distinctive repetitive hand movements, which was originally described in the 1960s by a pediatrician, Dr Andreas Rett,[16] and widely recognized after the description in the 1980s by Hagberg and colleagues.[17] Individuals with all the features of RTT are considered to have "classic" or typical RTT. It has been recognized that certain individuals have some, but not all, of the features of classic RTT or have distinct clinical features that distinguish them from classic RTT. These cases have been defined as "atypical" RTT. Typical and atypical RTT will be described below.

Clinical criteria for typical RTT

The diagnosis of RTT is based exclusively on a set of clinical criteria derived from expert consensus.[5] For the diagnosis of typical RTT, the affected individual must have had a period of relatively normal development after birth, followed by a regression of skills including volitional hand use and spoken language. Hand use is replaced by distinctive, purposeless hand movements (stereotypies) and gait is impaired. The disease has a typical disease course with stabilization after the regression, which distinguishes RTT from neurodegenerative conditions such as Batten disease.

Stages of RTT

As mentioned above, typical RTT has a characteristic disease progression, which has been subdivided into distinct clinical stages. Affected children are born after an unremarkable pregnancy and appear to have relatively normal initial psychomotor development, although they may be regarded as somewhat hypotonic. Between 6 and 18 months, the children enter Stage 1, the stagnation stage.[18] In this stage, a failure to meet developmental milestones at the appropriate age occurs. This developmental delay may be significant enough to warrant parental and physician concern or only be recognized in hindsight.

After this period of developmental stagnation, a period of active regression, or Stage 2, ensues. This typically occurs at 1 to 4 years old, although in some cases the regression may occur earlier or later.[18] The regression can be sudden and dramatic, or can occur gradually over an extended period of time. During this stage, volitional hand use and language are lost. The loss of these skills may be total, or may be a reduction of previously acquired skills. In addition to the loss of motor skills and language, some affected individuals become socially withdrawn during the regression: disliking physical contact, avoiding eye gaze, and being indifferent to visual and aural stimulation. Without the development of more distinctive manifestations of RTT, such as the repetitive hand stereotypies, the diagnosis of autism may be entertained at this stage.

Although the regression can occur over a variable period, eventually this loss of skills stops and Stage 3, the plateau or pseudo-stationary period, begins.[18] Skills are stabilized and may improve slightly over time, although spoken language and volitional hand skills remain markedly impaired throughout life. The gait impairment is typically noted at this time, if not already apparent. Affected people have a particular gait which is considered to be markedly dyspraxic and ataxic. Additionally, the distinctive repetitive hand stereotypies, which are classically described as hand wringing or washing, but may be hand tapping/clapping or clasping, typically manifest during this stage. This stage usually persists until the teens or early twenties.

The final stage, Stage 4 or the late motor decline, is classically defined as the complete loss of the ability to walk.[18] Using this definition, some individuals who never learned to walk directly enter Stage 4 from Stage 2. In contrast, other people never lose the ability to walk and thus would be considered to remain in Stage 3 throughout their lives. This definition has been recognized to be inadequate, as nearly all individuals with RTT show motor changes in their teens and twenties, regardless of their ability to walk. The motor changes reflect a change from relatively low tone (hypotonia) to increased tone (dystonia and rigidity). Parkinsonism becomes common, with hypomimia and bradykinesia.[19,20]

Additional clinical features

Movement abnormalities

In addition to the characteristic movement abnormalities present in RTT—hand stereotypies and gait dyspraxia—a wide variety of movement problems are present in affected individuals. Most affected individuals are initially hypotonic at birth and early in life, but develop dystonia especially in the ankles and lower extremities. Choreiform movements of the limbs and oromotor dyskinesias with tongue thrusting can be present. Some individuals have truncal rocking, titubation, and/or tremor. Teeth grinding (bruxism) is a common problem.

Growth failure

A notable feature in RTT is the fact that the majority of affected people are short, underweight, and microcephalic. All of these features are acquired, as birth weight, length, and head size are normal. The growth failure can be serious enough to warrant gastrostomy placement. Head growth is one of the first features to fail to proceed with a normal velocity, and careful measurements can identify this as early as 2 months of life.[21] A combination of decreased head growth velocity and developmental delay in girls is currently the most likely way that affected individuals are identified prior to regression.

Gastrointestinal problems

Nearly all affected individuals have significant gastrointestinal problems. Motility and coordination are disrupted throughout the entire gastrointestinal tract, leading to chewing and swallowing problems, gastroesophageal reflux, delayed stomach emptying,[22] bloating, and constipation.[17] These gastrointestinal issues can have a significant impact on quality of life in affected people.

Seizures and nonepileptic spells

The majority of affected people have seizures during their lives; however a significant percentage (up to 40%) of people do not have seizures.[23] This is somewhat surprising given the markedly abnormal electroencephalogram (EEG) present in all affected people.[24] The EEG abnormalities include frequent multifocal epileptiform discharges, which can become nearly continuous during sleep, and slow background activity.[24] A wide variety of antiseizure medications have been used to control seizures in RTT, and no clinical trials have been performed to indicate improved efficacy with any particular agent. Some people have medically intractable epilepsy requiring either vagal nerve stimulator placement[25] or ketogenic diet,[26] both of which have some efficacy in RTT.

In addition to epileptic seizures, people with RTT also commonly have nonepileptic paroxysmal events. The events are often associated with breathing abnormalities and can clinically appear to be seizures, even to trained clinical observers. During these events, the patient may have tonic extension of limbs with a vacant look, often with breath-holding. Occasionally the nonepileptic paroxysms can include high-amplitude irregular movement of limbs more akin to a paroxysmal dyskinesia. The events are more common at sleep/wake transitions. Because the semiology of these events can be consistent

with true epileptic events, it is important to consider evaluation with video EEG to confirm the epileptic nature of paroxysmal events in RTT. Unfortunately, no medical therapy has proven beneficial for treatment of these nonepileptic events in RTT.

Breathing abnormalities

Nearly all people with RTT have some degree of breathing abnormalities. Commonly there is some degree of hyperventilation and/or apnea.[27-29] The hyperventilation can be significant enough to cause hypocapnea, and some investigators have proposed treatment with gas mixtures containing increased concentrations of carbon dioxide.[30] The apneic events can cause a decrease in blood oxygen and occasionally are prolonged to the point of loss of consciousness. The breathing abnormalities are significantly increased during wakefulness and may be exaggerated by anxiety,[31] but can be observed during sleep.[28] Furthermore, there appears to be a lack of coordination between breathing and heart rate, suggesting a failure within the medullary network that integrates these physiological systems.[27,28,32]

Cardiac abnormalities

Approximately 20% of people with RTT have prolonged QTc intervals.[33] Importantly, approximately a quarter of deaths in RTT are sudden and unexpected,[34] and the prolonged QTc interval is suspected to underlie these sudden deaths. In addition to the cardiac electrical abnormalities, people with RTT have decreased beat-to-beat variation,[35] periods of tachycardia,[29] and periods of bradycardia.[32]

Autistic features and other behavioral problems

Autistic features such as social withdrawal and avoidance of eye gaze occurs in some people with RTT, often during the period of active regression (Stage 2).[18] In fact, a large proportion of people with RTT meet *DSM-IV* criteria for pervasive developmental disorder not otherwise specified (PDD-NOS),[36-38] and some people eventually diagnosed with RTT are initially diagnosed with autism.[39] Leonard and colleagues found that the initial diagnosis of autism is more likely in less severely affected individuals.[39] This is consistent with the recognition that autistic features are more common in a milder atypical variant of RTT, the preserved speech variant (PSV).[40] In general, the autistic features present during the regression stage of RTT seem to improve during Stage 3 with increased and even intense eye gaze and interest in social interactions. Nonetheless, a variety of studies have found distinct features of autism in RTT that may persist after regression.[41] In the only study that systematically applied a measure specific to autistic features, Mount and colleagues found that people with RTT showed increased autistic features compared with individuals with severe intellectual disability[42] using the Autism Behavior Checklist.[43] Using broader behavior screening measures, Wulfaett and colleagues found that autistic features are present in approximately 50% of people with RTT, but these features decrease with time so that 19% no longer met criteria for an ASD.[44] Recent work using computer-based eye-tracking devices indicates that people with RTT have a preference to look at human faces, especially eyes, which is in contrast to gaze preference in autism.[45] Thus, the exact nature of autistic features in RTT and their change over the course of the disease remains an extremely important research question that needs to be systematically assessed using appropriate measures.

In addition to the autistic features mentioned above, a number of behavioral abnormalities have been observed in RTT. One of the most prominent is anxiety, which often presents as fearful expression and increased breathing abnormalities and hand stereotypies when in a novel and stimulating environment.[46,47] Additionally, some people with RTT have self-injurious behaviors such as head banging, chewing on hands and fingers, and hitting themselves.[46,48] It has been noted that people with RTT have increased pain tolerance.[49] Sometimes people with RTT will have outbursts of unexplained screaming or laughing.[47] Finally, sleep is markedly disrupted in RTT, with increased incidence of difficulty falling asleep, frequent late-night/early morning arousals, and increased daytime napping.[31,50] A recent study using polysomnography compared RTT subjects with controls and found that RTT subjects had increased numbers of awakenings per hour of sleep and spent a larger percentage of time awake after falling asleep.[51]

Atypical forms of RTT

A number of people present with regression and many but not all of the required clinical features for the diag-

nosis of typical RTT; thus, a provision has been made for the clinical diagnosis of atypical RTT.[5] It has been recognized that there is clustering of people with similar features to define distinct forms of atypical RTT. These atypical forms have distinctive clinical and genetic aspects that differentiate them from typical forms of RTT.

Preserved speech variant

The PSV is the most commonly identified atypical form of RTT, and characterized by milder severity and more regained spoken language after regression.[52] Speech is greatly improved compared with typical RTT, with affected individuals potentially speaking in sentences.[52,53] The speech produced is not completely normal, and many people with PSV have speech perseveration, pronoun reversal, and echolalia.[52,53] In addition to improved language, many people with PSV have better preserved hand function, better ability to walk, and potentially less significant hand stereotypies. Growth failure is also often not as severe, and some people with PSV are overweight and even macrocephalic.[54] Autistic and aggressive features are also more prominent in PSV compared with typical RTT, and the disease might be confused with autism if the hand stereotypies are mild.[40] Nearly all people identified with PSV have mutations in *MECP2*.

Early seizure variant

Seizures in the first year of life are uncommon in typical RTT,[55] so individuals who present with early seizures have long been recognized as being distinct.[56] The seizures in people with the early seizure variant can present as a very severe epileptic disorder, infantile spasms.[57] Regression occurs in the context of severe seizures, making it very different from regression in typical RTT and more akin to loss of skills often seen in other epileptic encephalopathies. Information about the features of this variant is less than in typical RTT or the PSV, but in general affected people seem to have persistent eye gaze avoidance.[58] In general, autistic features are more predominant in the early seizure variant compared with typical RTT.[59] Many people with the early seizure variant do have breathing abnormalities very similar to that seen in typical RTT.[58] Importantly, very few people with early seizure variant have been found to have mutations in *MECP2*,[60] instead of mutations in a different gene, *Cyclin-dependent kinase like-5* (*CDKL5*) mutations have been found in most early seizure variants. As more people are identified with *CDKL5* mutations, it is becoming apparent that mutations in this gene may cause a distinct clinical entity with some clinical features similar to RTT, but others very different. This argues that it may be beneficial to consider this as a distinct clinical entity rather than a variant of RTT.

Congenital variant

Some people with RTT-like features never have a period of normal development and may have microcephaly from birth.[57,61] A major challenge in the diagnosis of people in this group with an atypical form of RTT is establishing clear psychomotor regression as opposed to a lack of skill acquisition. Recent work has identified mutation in *FOXG1* in some people with the congenital variant,[62] and very few people with this variant have been found that have mutations in *MECP2*.[63] Most people with *FOXG1* mutations have a structural brain abnormality, partial agenesis of the corpus callosum,[62] which is not found in typical RTT. Similar to people with *CDKL5* mutations, as more individuals are identified with *FOXG1* mutations it is becoming apparent that this represents a distinct clinical entity with unique features different from RTT.[64]

Other clinical conditions in girls with *MECP2* mutations

Girls with *MECP2* mutations

Girls with MECP2 mutations have been found with clinical conditions distinct from RTT. Some are conditions that have distinct similarities to RTT but are clinically distinct, such as Angelman syndrome.[65-67] In other cases, the affected girls have clear neurodevelopmental problems of a less severe nature than RTT, such as learning disability and uncontrolled aggression,[68] or electrical status epilepticus during sleep.[69] Finally, although it has not been identified as a common cause of autism,[70-74] some cases of autism have been found to have clearly pathogenic mutations in *MECP2*.[75] Interestingly, there is evidence that non-coding mutations in the 3'UTR of *MECP2* may cause autism[76,77] or other neurodevelopmental disorders such as attention deficit/hyperactivity

disorder.[77] Although animal work has determined that alteration to the 3'UTR can have clear detrimental effects on *MECP2* function and behavior, the exact pathological basis of these 3'UTR mutations has not been established, and is an important area for further research. Although the number of cases of neurodevelopmental disorders other that RTT with clear pathogenic mutation in *MECP2* is somewhat limited, this may reflect an observational bias both in terms of what clinical features cause physicians to perform testing and the exact molecular nature of genetic testing that is performed on a clinical basis, which primarily targets the coding region of *MECP2*. Until we have a clearer idea of the full phenotypic spectrum that can be caused by *MECP2* mutations and a better way to establish the functional significance of non-coding mutations in *MECP2*, we will not overcome this observational bias. As it stands now, these rare cases provide evidence that alterations in MeCP2 function can cause a variety of neurological and psychiatric features and understanding RTT and MeCP2 function will help in the broader understanding of neurodevelopmental disorders in general.

Boys with *MECP2* mutations

Some boys have been identified with clinically defined RTT and RTT-disease causing mutations in *MECP2*, but the majority of these individuals have additional genetic features such as an extra X-chromosome (47 XXY, Kleinfelter syndrome)[78,79] or somatic mosaicism.[80,81] Usually, boys with a normal complement of chromosomes and a mutation in *MECP2* present with a distinct clinical condition, congenital encephalopathy, and often die within the first years of life due to autonomic dysfunction.[82] Since the discovery of the association of mutations in *MECP2* and RTT, effort has been made to determine if mutations in *MECP2* might cause X-linked mental retardation (XLMR). Clear pathogenic mutations have been identified, but also a number of sequence changes of uncertain significance. One of the most interesting mutations identified from XLMR families, and the only recurrent clearly pathogenic mutation identified in these boys, is p.A140V. This change has been identified in multiple members from three families[83-85] and in three sporadic cases.[86,87] All of the affected boys have at least moderate intellectual disability (ID) and additional interesting clinical features including movement abnormalities such as tremor and spasticity and psychiatric features such as mania and psychosis. Interestingly, many of the mothers who have the p.A140V mutation have learning disability or mild ID. A mouse expressing p.A140V has been generated which has neuronal abnormalities and behavior problems, indicating that this missense mutation changes MeCP2 function and causes the clinical condition in people.

***MECP2* duplication syndrome**

The mutations identified in *MECP2* which cause RTT are all believed to be loss of function mutations because deletion of the coding sequence causes RTT.[4] An interesting concept developed when a mouse which overexpressed MeCP2 was found to have seizures, behavioral problems, and a shortened lifespan,[88] indicating that gain of function of *MECP2* is also detrimental to nervous system functioning. Subsequently, a large number of boys with a duplication of Xq28, which contains *MECP2*, have been identified, and it appears that duplications of this region account for approximately 1% of XLMR cases[89] and is a large cause of sporadic ID in boys.[90] Affected boys have moderate to severe ID and have additional distinct features. Most have severely impaired spoken language abilities, movement problems such as choreiform movements and tremor, seizures,[6] and progressive spasticity.[89] Immunological dysfunction has been observed[91] and recurrent infections can be problematic,[6,90,92,93] potentially contributing to the shortened lifespan observed.

Autistic features are common in boys with *MECP2* duplications.[6] Seven of eight boys evaluated with the Autism Diagnostic Observational Schedule met criteria for ASD.[6] Interestingly, detailed neuropsychological characterization of apparently unaffected carrier mothers identified an increased frequency of anxiety, depressive symptoms, and behavioral rigidity.[6] Interestingly, some of the carrier mothers met criteria for the broad autism phenotype when assessed with the Broad Autism Phenotype Questionnaire,[6] suggesting that subtle increases in MeCP2 function can contribute to behavioral changes.

Reversibility in animal models

A number of mouse models of RTT have been generated[7,8] which reproduce many features of the disease[33,94] and show remarkable face and construct validity.[95] These

have provided insight into the pathophysiology of disease in RTT and are a useful substrate to perform preclinical testing. The most important experiment performed using these mouse models was the demonstration that restoring MeCP2 function in animals lacking the gene, even after symptoms have developed.[13] This was the first demonstration of reversibility of a neurodevelopmental disorder after symptom development which has provided great hope not only for RTT but for neurodevelopmental disorders in general. It will be very informative to the field to determine whether restoring gene function in disease such as Fragile X and Angelman syndrome also can rescue problems after disease onset in animal models.

Current approaches to treatment

Currently, treatment for RTT is based entirely on treating symptoms, such as treating epilepsy with anti-seizure drugs or treating constipation with laxatives. The discovery of reversibility in the mouse model of RTT has developed a strong impetus to explore treatment options directed to modify or even reverse the disease. One major focus of disease modifying treatments is based on genetic experiments demonstrating that increasing levels of brain-derived neurotrophic factor (BDNF) improves symptoms and longevity in mice.[96] This led to successful treatment of Rett mice with drugs that increase BDNF levels[97] or activate a BDNF receptor.[98] Either of these approaches may be useful in RTT. In alternative approach, Rett animals were treated with a tripeptide derived from insulin-like growth factor 1 (IGF1), which improved cardiorespiratory function and lifespan.[99] This has led to the initiation of a clinical treatment trial using full-length recombinant human IGF1 in people with Rett syndrome (NCT01253317).

Conclusions

RTT is a disease with a number of interesting clinical features, many of which overlap with other neurological, neurodevelopmental, and neuropsychiatric disorders. Additionally, alterations in the function of the protein product of the gene mutated in most cases of RTT, *MECP2*, can cause neurodevelopmental disorders distinct from RTT, including many that have autistic features. Combined with the availability of excellent animal models this makes RTT and *MECP2*-related disorders not only a fascinating and tractable subject for study, but the understanding that comes from such studies will likely provide insight into a wide spectrum of neurodevelopmental, neurological, and psychiatric diseases. The promise provided by the reversibility of disease in the mouse model of RTT has become and inspiration for the entire neurodevelopmental field and great hope exists that therapeutic options developed for RTT will prove useful for other neurodevelopmental disorders. ❑

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 1994.
2. Laurvick CL, de Klerk N, Bower C, et al. Rett syndrome in Australia: a review of the epidemiology. *J Pediatr*. 2006;148:347-352.
3. Amir RE, Van den Veyver IB, Wan M, Tran CQ, Francke U, Zoghbi HY. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. *Nat Genet*. 1999;23:185-188.
4. Neul JL, Fang P, Barrish J, et al. Specific mutations in methyl-CpG-binding protein 2 confer different severity in Rett syndrome. *Neurology*. 2008;70:1313-1321.
5. Neul JL, Kaufmann WE, Glaze DG, et al. Rett syndrome: revised diagnostic criteria and nomenclature. *Ann Neurol*. 2010;68:944-950.
6. Ramocki M, Peters SU, Tavyev YJ, et al. High penetrance of autism and other neuropsychiatric symptoms in individuals with MECP2 duplications. *Ann Neurol*. 2009;66:771-782.
7. Guy J, Hendrich B, Holmes M, Martin JE, Bird A. A mouse Mecp2-null mutation causes neurological symptoms that mimic Rett syndrome. *Nat Genet*. 2001;27:322-326.
8. Chen RZ, Akbarian S, Tudor M, Jaenisch R. Deficiency of methyl-CpG binding protein-2 in CNS neurons results in a Rett-like phenotype in mice. *Nat Genet*. 2001;27:327-331.
9. Samaco RC, Fryer JD, Ren J, et al. A partial loss of function allele of methyl-CpG-binding protein 2 predicts a human neurodevelopmental syndrome. *Hum Mol Genet*. 2008;17:1718-1727.
10. Shahbazian M, Young J, Yuva-Paylor L, et al. Mice with truncated MeCP2 recapitulate many Rett syndrome features and display hyperacetylation of histone H3. *Neuron*. 2002;35:243-254.
11. Lawson-Yuen A, Liu D, Han L, et al. Ube3a mRNA and protein expression are not decreased in Mecp2R168X mutant mice. *Brain Res*. 2007;1180:1-6.
12. Goffin D, Allen M, Zhang L, et al. Rett syndrome mutation MeCP2 T158A disrupts DNA binding, protein stability and ERP responses. *Nat Neurosci*. 2012;15:274-283.
13. Guy J, Gan J, Selfridge J, Cobb S, Bird A. Reversal of neurological defects in a mouse model of Rett syndrome. *Science*. 2007;8:8.
14. Neul JL, Zoghbi HY. Rett syndrome: a prototypical neurodevelopmental disorder. *Neuroscientist*. 2004;10:118-128.
15. LaSalle JM, Hogart A, Thatcher KN. Rett syndrome: a Rosetta stone for understanding the molecular pathogenesis of autism. *Int Rev Neurobiol*. 2005;71:131-165.
16. Rett A. [On a unusual brain atrophy syndrome in hyperammonemia in childhood]. *Wien Med Wochenschr*. 1966;116:723-726.
17. Hagberg B, Aicardi J, Dias K, Ramos O. A progressive syndrome of autism, dementia, ataxia, and loss of purposeful hand use in girls: Rett's syndrome: report of 35 cases. *Ann Neurol*. 1983;14:471-479.

La relación entre el síndrome de Rett, los trastornos MECP2, y el autismo

El síndrome de Rett (RTT, MIM#312750) es un trastorno del neurodesarrollo que se clasifica dentro del espectro autista. El RTT clínicamente se caracteriza por una regresión psicomotora con pérdida del uso de la mano con un propósito y del lenguaje verbal, el desarrollo de reiteradas estereotipias de las manos y el deterioro de la marcha. La mayoría de las personas con RTT tienen mutaciones en la proteína 2 de unión a metil-CpG (MECP2), un regulador de la transcripción. Resulta interesante saber que se han identificado alteraciones en la función del MeCP2, producto proteico producido por la MECP2, en otras situaciones clínicas. Las diversas características clínicas que se han encontrado en el RTT y los varios problemas clínicos producidos por la alteración en la función del MeCP2 han llevado a plantear que la comprensión del RTT proporcionará información sobre numerosos trastornos neurológicos. El RTT es reversible en un modelo de ratón, lo que resulta provocador para proporcionar inspiración y esperanza para que dicho objetivo sea alcanzado para el RTT y potencialmente para muchos otros trastornos del neurodesarrollo.

Les relations entre le syndrome de Rett, les troubles de la MECP2 *et l'autisme*

Le syndrome de Rett (RTT, MIM#312750) est un trouble du développement neurologique classé dans les troubles autistiques. Cliniquement, le syndrome de Rett est caractérisé par une régression psychomotrice avec perte de l'utilisation volontaire de la main et du langage parlé, par le développement de stéréotypies répétitives de la main et par une démarche détériorée. La plupart des personnes atteintes du RTT ont des mutations de la protéine MECP2 *(*Methyl-CpG-binding Protein 2*), un régulateur transcriptionnel. Or, des altérations fonctionnelles de la protéine produite par* MECP2*, MeCP2, ont été retrouvées dans d'autres pathologies. La coexistence de ces altérations et des problèmes cliniques différents qui en découlent avec les nombreux tableaux cliniques du RTT laissent penser que comprendre le RTT permettra d'approfondir un certain nombre de troubles neurologiques. Il existe, de manière particulièrement intéressante, une forme réversible de RTT dans un modèle murin ; c'est une source d'inspiration et d'espoir qu'il le soit dans le modèle humain ainsi que pour de nombreux troubles du développement neurologique.*

18. Hagberg B. Clinical manifestations and stages of Rett syndrome. *Ment Retard Dev Disabil Res Rev*. 2002;8:61-65.
19. FitzGerald PM, Jankovic J, Glaze DG, Schultz R, Percy AK. Extrapyramidal involvement in Rett's syndrome. *Neurology*. 1990;40:293-295.
20. FitzGerald PM, Jankovic J, Percy AK. Rett syndrome and associated movement disorders. *Mov Disord*. 1990;5:195-202.
21. Hagberg G, Stenbom Y, Engerstrom IW. Head growth in Rett syndrome. *Brain Dev*. 2001;23:S227-S229.
22. Motil KJ, Schultz RJ, Browning K, Trautwein L, Glaze DG. Oropharyngeal dysfunction and gastroesophageal dysmotility are present in girls and women with Rett syndrome. *J Pediatr Gastroenterol Nutr.* 1999;29:31-37.
23. Glaze DG, Percy AK, Skinner S, et al. Epilepsy and the natural history of Rett syndrome. *Neurology*. 2010;74:909-912.
24. Glaze DG. Neurophysiology of Rett syndrome. *Ment Retard Dev Disabil Res Rev*. 2002;8:66-71.
25. Wilfong AA, Schultz RJ. Vagus nerve stimulation for treatment of epilepsy in Rett syndrome. *Dev Med Child Neurol*. 2006;48:683-686.
26. Liebhaber GM, Riemann E, Baumeister FA. Ketogenic diet in Rett syndrome. *J Child Neurol*. 2003;18:74-75.
27. Julu PO, Kerr AM, Apartopoulos F, et al. Characterisation of breathing and associated central autonomic dysfunction in the Rett disorder. *Arch Dis Child*. 2001;85:29-37.
28. Weese-Mayer DE, Lieske SP, Boothby CM, Kenny AS, Bennett HL, Ramirez JM. Autonomic dysregulation in young girls with Rett Syndrome during nighttime in-home recordings. *Pediatr Pulmonol*. 2008;43:1045-1060.
29. Weese-Mayer DE, Lieske SP, Boothby CM, et al. Autonomic nervous system dysregulation: breathing and heart rate perturbation during wakefulness in young girls with Rett syndrome. *Pediatr Res*. 2006;60:443-449.
30. Julu PO, Witt Engerstrom I. Assessment of the maturity-related brainstem functions reveals the heterogeneous phenotypes and facilitates clinical management of Rett syndrome. *Brain Dev*. 2005;27(suppl 1):S43-S53.
31. Glaze DG, Frost JD Jr, Zoghbi HY, Percy AK. Rett's syndrome: characterization of respiratory patterns and sleep. *Ann Neurol*. 1987;21:377-382.
32. Rohdin M, Fernell E, Eriksson M, Albage M, Lagercrantz H, Katz-Salamon M. Disturbances in cardiorespiratory function during day and night in Rett syndrome. *Pediatr Neurol*. 2007;37:338-344.
33. McCauley MD, Wang T, Mike E, et al. Pathogenesis of lethal cardiac arrhythmias in mecp2 mutant mice: implication for therapy in Rett syndrome. *Sci Transl Med*. 2011;3:113ra125.
34. Kerr AM, Armstrong DD, Prescott RJ, Doyle D, Kearney DL. Rett syndrome: analysis of deaths in the British survey. *Eur Child Adolesc Psychiatry*. 1997;6:71-74.
35. Guideri F, Acampa M, Hayek G, Zappella M, Di Perri T. Reduced heart rate variability in patients affected with Rett syndrome. A possible explanation for sudden death. *Neuropediatrics*. 1999;30:146-148.
36. Gillberg C. Autism and Rett syndrome: some notes on differential diagnosis. *Am J Med Genet Suppl*. 1986;1:127-131.
37. Gillberg C. Autistic symptoms in Rett syndrome: the first two years according to mother reports. *Brain Dev*. 1987;9:499-501.
38. Tsai LY. Is Rett syndrome a subtype of pervasive developmental disorders? *J Autism Dev Disord*. 1992;22:551-561.
39. Young DJ, Bebbington A, Anderson A, et al. The diagnosis of autism in a female: could it be Rett syndrome? *Eur J Pediatr*. 2008;167:661-669.
40. Zappella M, Meloni I, Longo I, et al. Study of MECP2 gene in Rett syndrome variants and autistic girls. *Am J Med Genet B Neuropsychiatr Genet*. 2003;119:102-107.
41. Kaufmann WE, Tierney E, Rohde CA, et al. Social impairments in Rett syndrome: characteristics and relationship with clinical severity. *J Intellect Disabil Res*. 2011;56:233-247.
42. Mount R, Charman T, Hastings R, Reilly S, Cass H. Features of autism in Rett syndrome and severe mental retardation. *J Autism Dev Disord.* 2003;33:435-442.

43. Krug DA, Arick JR, Almond PJ. *Autism Screening Instrument for Educational Planning*. Austin, TX: Pro Ed, 1993.
44. Wulffaert J, Van Berckelaer-Onnes IA, Scholte EM. Autistic disorder symptoms in Rett syndrome. *Autism*. 2009;13:567-581.
45. Djukic A, McDermott MV. Social preferences in Rett syndrome. *Pediatr Neurol*. 2012;46:240-242.
46. Sansom D, Krishnan VH, Corbett J, Kerr A. Emotional and behavioural aspects of Rett syndrome. *Dev Med Child Neurol*. 1993;35:340-345.
47. Mount RH, Hastings RP, Reilly S, Cass H, Charman T. Behavioural and emotional features in Rett syndrome. *Disabil Rehabil*. 2001;23:129-138.
48. Coleman M, Brubaker J, Hunter K, Smith G. Rett syndrome: a survey of North American patients. *J Ment Defic Res*. 1988;32:117-124.
49. Downs J, Geranton SM, Bebbington A, et al. Linking MECP2 and pain sensitivity: the example of Rett syndrome. *Am J Med Genet A*. 2010;152A:1197-1205.
50. Young D, Nagarajan L, de Klerk N, Jacoby P, Ellaway C, Leonard H. Sleep problems in Rett syndrome. *Brain Dev*. 2007;29:609-616.
51. Carotenuto M, Esposito M, D'Aniello A, et al. Polysomnographic findings in Rett syndrome: a case-control study. *Sleep Breath*. In press.
52. Zappella M, Gillberg C, Ehlers S. The preserved speech variant: a subgroup of the Rett complex: a clinical report of 30 cases. *J Autism Dev Disord*. 1998;28:519-526.
53. Zappella M, Meloni I, Longo I, Hayek G, Renieri A. Preserved speech variants of the Rett syndrome: molecular and clinical analysis. *Am J Med Genet*. 2001;104:14-22.
54. Renieri A, Mari F, Mencarelli MA, et al. Diagnostic criteria for the Zappella variant of Rett syndrome (the preserved speech variant). *Brain Dev*. 2008.
55. Steffenburg U, Hagberg G, Hagberg B. Epilepsy in a representative series of Rett syndrome. *Acta Paediatr*. 2001;90:34-39.
56. Hanefeld F. The clinical pattern of the Rett syndrome. *Brain Dev*. 1985;7:320-325.
57. Goutieres F, Aicardi J. Atypical forms of Rett syndrome. *Am J Med Genet Suppl*. 1986;1:183-194.
58. Pini G, Bigoni S, Engerstrom IW, et al. Variant of Rett syndrome and CDKL5 gene: clinical and autonomic description of 10 cases. *Neuropediatrics*. 2012;43:37-43.
59. Bahi-Buisson N, Kaminska A, Boddaert N, et al. The three stages of epilepsy in patients with CDKL5 mutations. *Epilepsia*. 2008;49:1027-1037.
60. Archer HL, Evans J, Edwards S, et al. CDKL5 mutations cause infantile spasms, early onset seizures, and severe mental retardation in female patients. *J Med Genet*. 2006;43:729-734.
61. Rolando S. Rett syndrome: report of eight cases. *Brain Dev*. 1985;7:290-296.
62. Ariani F, Hayek G, Rondinella D, et al. FOXG1 is responsible for the congenital variant of Rett syndrome. *Am J Hum Genet*. 2008;83:89-93.
63. Huppke P, Laccone F, Kramer N, Engel W, Hanefeld F. Rett syndrome: analysis of MECP2 and clinical characterization of 31 patients. *Hum Mol Genet*. 2000;9:1369-1375.
64. Kortum F, Das S, Flindt M, et al. The core FOXG1 syndrome phenotype consists of postnatal microcephaly, severe mental retardation, absent language, dyskinesia, and corpus callosum hypogenesis. *J Med Genet*. 2011;48:396-406.
65. Watson P, Black G, Ramsden S, et al. Angelman syndrome phenotype associated with mutations in MECP2, a gene encoding a methyl CpG binding protein. *J Med Genet*. 2001;38:224-228.
66. Turner H, MacDonald F, Warburton S, Latif F, Webb T. Developmental delay and the methyl binding genes. *J Med Genet*. 2003;40:E13.
67. Milani D, Pantaleoni C, D'Arrigo S, Selicorni A, Riva D. Another patient with MECP2 mutation without classic Rett syndrome phenotype. *Pediatr Neurol*. 2005;32:355-357.
68. Huppke P, Maier EM, Warnke A, Brendel C, Laccone F, Gartner J. Very mild cases of Rett syndrome with skewed X inactivation. *J Med Genet*. 2006;43:814-816.
69. Huppke P, Held M, Laccone F, Hanefeld F. The spectrum of phenotypes in females with Rett Syndrome. *Brain Dev*. 2003;25:346-351.
70. Beyer KS, Blasi F, Bacchelli E, Klauck SM, Maestrini E, Poustka A. Mutation analysis of the coding sequence of the MECP2 gene in infantile autism. *Hum Genet*. 2002;111:305-309.
71. Harvey CG, Menon SD, Stachowiak B, et al. Sequence variants within exon 1 of MECP2 occur in females with mental retardation. *Am J Med Genet B Neuropsychiatr Genet*. 2007;144B:355-360.
72. Li H, Yamagata T, Mori M, Yasuhara A, Momoi MY. Mutation analysis of methyl-CpG binding protein family genes in autistic patients. *Brain Dev*. 2005;27:321-325.
73. Lobo-Menendez F, Sossey-Alaoui K, Bell JM, et al. Absence of MeCP2 mutations in patients from the South Carolina autism project. *Am J Med Genet B Neuropsychiatr Genet*. 2003;117:97-101.
74. Vourc'h P, Bienvenu T, Beldjord C, et al. No mutations in the coding region of the Rett syndrome gene MECP2 in 59 autistic patients. *Eur J Hum Genet*. 2001;9:556-558.
75. Carney RM, Wolpert CM, Ravan SA, et al. Identification of MeCP2 mutations in a series of females with autistic disorder. *Pediatr Neurol*. 2003;28:205-211.
76. Coutinho AM, Oliveira G, Katz C, et al. MECP2 coding sequence and 3'UTR variation in 172 unrelated autistic patients. *Am J Med Genet B Neuropsychiatr Genet*. 2007;144B:475-483.
77. Shibayama A, Cook EH, Jr, Feng J, et al. MECP2 structural and 3'-UTR variants in schizophrenia, autism and other psychiatric diseases: a possible association with autism. *Am J Med Genet B Neuropsychiatr Genet.* 2004;128:50-53.
78. Hoffbuhr K, Devaney JM, LaFleur B, et al. MeCP2 mutations in children with and without the phenotype of Rett syndrome. *Neurology*. 2001;56:1486-1495.
79. Schwartzman JS, Bernardino A, Nishimura A, Gomes RR, Zatz M. Rett syndrome in a boy with a 47,XXY karyotype confirmed by a rare mutation in the MECP2 gene. *Neuropediatrics*. 2001;32:162-164.
80. Armstrong J, Pineda M, Aibar E, Gean E, Monros E. Classic Rett syndrome in a boy as a result of somatic mosaicism for a MECP2 mutation. *Ann Neurol*. 2001;50:692.
81. Clayton-Smith J, Watson P, Ramsden S, Black GC. Somatic mutation in MECP2 as a non-fatal neurodevelopmental disorder in males. *Lancet*. 2000;356:830-832.
82. Kankirawatana P, Leonard H, Ellaway C, et al. Early progressive encephalopathy in boys and MECP2 mutations. *Neurology*. 2006;67:164-166.
83. Klauck SM, Lindsay S, Beyer KS, Splitt M, Burn J, Poustka A. A mutation hot spot for nonspecific X-linked mental retardation in the MECP2 gene causes the PPM-X syndrome. *Am J Hum Genet*. 2002;70:1034-1037.
84. Orrico A, Lam C, Galli L, et al. MECP2 mutation in male patients with non-specific X-linked mental retardation. *FEBS Lett*. 2000;481:285-288.
85. Winnepenninckx B, Errijgers V, Hayez-Delatte F, Reyniers E, Frank Kooy R. Identification of a family with nonspecific mental retardation (MRX79) with the A140V mutation in the MECP2 gene: Is there a need for routine screening? *Hum Mutat*. 2002;20:249-252.
86. Cohen D, Lazar G, Couvert P, et al. MECP2 mutation in a boy with language disorder and schizophrenia. *Am J Psychiatry*. 2002;159:148-149.
87. Couvert P, Bienvenu T, Aquaviva C, Poirier K, Moraine C, Gendrot C et al. MECP2 is highly mutated in X-linked mental retardation. *Hum Mol Genet*. 2001;10:941-946.
88. Collins AL, Levenson JM, Vilaythong AP, et al. Mild overexpression of MeCP2 causes a progressive neurological disorder in mice. *Hum Mol Genet*. 2004;13:2679-2689.
89. Lugtenberg D, Kleefstra T, Oudakker AR, et al. Structural variation in Xq28: MECP2 duplications in 1% of patients with unexplained XLMR and in 2% of male patients with severe encephalopathy. *Eur J Hum Genet*. 2009;17:444-453.
90. del Gaudio D, Fang P, Scaglia F, et al. Increased MECP2 gene copy number as the result of genomic duplication in neurodevelopmentally delayed males. *Genet Med*. 2006;8:784-792.
91. Friez MJ, Jones JR, Clarkson K, et al. Recurrent infections, hypotonia, and mental retardation caused by duplication of MECP2 and adjacent region in Xq28. *Pediatrics*. 2006;118:e1687-1695.
92. Van Esch H, Bauters M, Ignatius J, et al. Duplication of the MECP2 region is a frequent cause of severe mental retardation and progressive neurological symptoms in males. *Am J Hum Genet*. 2005;77:442-453.
93. Smyk M, Obersztyn E, Nowakowska B, et al. Different-sized duplications of Xq28, including MECP2, in three males with mental retardation, absent or delayed speech, and recurrent infections. *Am J Med Genet B Neuropsychiatr Genet*. 2008;147B:799-806.

94. Ward CS, Arvide EM, Huang TW, Yoo J, Noebels JL, Neul JL. MeCP2 is critical within HoxB1-derived tissues of mice for normal lifespan. *J Neurosci*. 2011;31:10359-10370.
95. Samaco RC, Mandel-Brehm C, Chao HT, et al. Loss of MeCP2 in aminergic neurons causes cell-autonomous defects in neurotransmitter synthesis and specific behavioral abnormalities. *Proc Natl Acad Sci U S A*. 2009;106:21966-21971.
96. Chang Q, Khare G, Dani V, Nelson S, Jaenisch R. The disease progression of Mecp2 mutant mice is affected by the level of BDNF expression. *Neuron*. 2006;49:341-348.
97. Ogier M, Wang H, Hong E, Wang Q, Greenberg ME, Katz DM. Brain-derived neurotrophic factor expression and respiratory function improve after ampakine treatment in a mouse model of Rett syndrome. *J Neurosci*. 2007;27:10912-10917.
98. Schmid DA, Yang T, Ogier M, et al. A TrkB small molecule partial agonist rescues TrkB phosphorylation deficits and improves respiratory function in a mouse model of Rett syndrome. *J Neurosci*. 2012;32:1803-1810.
99. Tropea D, Giacometti E, Wilson NR, et al. Partial reversal of Rett Syndrome-like symptoms in MeCP2 mutant mice. *Proc Natl Acad Sci U S A*. 2009;106:2029-2034.