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MECP2-Related Disorders

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Summary

Disease characteristics. *MECP2*-related disorders include classic Rett syndrome, variant or atypical Rett syndrome, and mild learning disabilities in females and neonatal encephalopathy and mental retardation syndromes in males. Classic Rett syndrome is a progressive neurologic disorder in girls characterized by normal birth and apparently normal psychomotor development during the first six to 18 months of life. The girls then enter a short period of developmental stagnation followed by rapid regression in language and motor skills. The hallmark of the disease is the loss of purposeful hand use and its replacement with repetitive stereotyped hand movements. Screaming fits and inconsolable crying are common by age 18-24 months. Additional characteristics include autistic features, panic-like attacks, bruxism, episodic apnea and/or hyperpnea, gait ataxia and apraxia, tremors, and acquired microcephaly. After this period of rapid deterioration, the disease becomes relatively stable, though girls will likely develop dystonia and foot and hand deformities as they grow older. Seizures occur in up to 90% of affected females; generalized tonic-clonic seizures and partial complex seizures are the most common. Females with classic Rett syndrome typically survive into adulthood, but the incidence of sudden, unexplained death (which may be caused by cardiac arrhythmias) is significantly higher than in controls of similar age. Atypical Rett syndrome is increasingly observed as *MECP2* mutations have been identified in individuals previously diagnosed with autism, mild learning disability, clinically suspected but molecularly unconfirmed Angelman syndrome, or mental retardation with spasticity or tremor. Males meeting the clinical criteria for Rett syndrome have been identified in association with a 47,XXY karyotype and post-zygotic *MECP2* mutations resulting in somatic mosaicism. Males with a 46,XY karyotype and a *MECP2* mutation may have such severe neonatal encephalopathy that they die before their second year.

Diagnosis/testing. The diagnosis of Rett syndrome rests on clinical diagnostic criteria established for the classic syndrome and/or molecular testing of the *MECP2* gene. Molecular genetic testing identifies *MECP2* mutations in approximately 80% of females with classic Rett syndrome. Such testing is available clinically.

Management. Treatment is mainly symptomatic and multidisciplinary and may include psychosocial support for family members.

Genetic counseling. Rett syndrome is inherited in an X-linked dominant manner. Approximately 99.5% of cases are single occurences in a family, resulting either from a *de novo* mutation in the child with Rett syndrome or from inheritance of the disease-causing mutation from one parent who has somatic or germline mosaicism. A mother who is a carrier may have favorably skewed X-chromosome inactivation that results in her being unaffected

or only slightly affected. When the mother of an affected individual is found to have the *MECP2* mutation identified in her affected child, the risk to sibs of the proband of inheriting the mutant *MECP2* allele at conception is 50%. If a mutation is not identified in the parent, the risk to sibs of the proband is low; however, germline mosaicism in either parent cannot be excluded. Prenatal testing is available in pregnancies at risk if the *MECP2* mutation has been identified in a family member. Of note, because germline mosaicism cannot be excluded, it is appropriate to offer prenatal diagnosis to couples who have had a child with Rett syndrome or mental retardation as a result of a *MECP2* mutation regardless of whether the disease-causing mutation has been identified in a parent.

Diagnosis

Clinical Diagnosis

The spectrum of phenotypes in *MECP2*-related disorders includes: classic Rett syndrome, variant Rett syndrome, and very mild learning disabilities in females and neonatal encephalopathy and syndromic or nonsyndromic mental retardation syndromes in males.

Classic Rett syndrome. In 1988, well before the discovery of the genetic basis of Rett syndrome, clinical diagnostic criteria were developed [Rett Syndrome Diagnostic Criteria Work Group 1988]. The following are limitations to clinical diagnosis using these criteria:

- Clinical diagnosis may be considered tentative until the affected individual reaches age two to five years, by which point she has likely gone through several stages of the disease.
- Atypical forms may be either milder or more severe than classic Rett syndrome [Hagberg 1995]:
  - In the more severe variant, no period of grossly normal development occurs, and early manifestations include congenital hypotonia and infantile spasms.
  - In the milder variant, girls have less dramatic regression and milder mental retardation [Hagberg 1989].
  - Other children experience an even more gradual regression that begins after the third year, lose purposeful hand use, and develop seizures; however, they retain some speech and the ability to walk [Zappella et al 1998].

More recently, the diagnostic criteria have been modified to resolve inconsistencies and ambiguities in the categorization of affected individuals into classic Rett syndrome (Table 1) or variant Rett syndrome (Table 2) [Hagberg et al 2002].

Table 1. Classic Rett Syndrome: Revised Diagnostic Criteria

	Criteria
Necessary	• Normal prenatal and perinatal history • Normal psychomotor development for the first six months • Normal head circumference at birth • Postnatal deceleration of head growth in most individuals • Loss of purposeful hand skills between age six months and 2.5 years • Hand stereotypies • Evolving social withdrawal, communication dysfunction, loss of acquired speech, and cognitive impairment • Impairment or deterioration of locomotion
Supportive	• Breathing disturbances during waking hours • Bruxism • Impairment of sleeping pattern from early infancy • Abnormal muscle tone associated with muscle wasting and dystonia • Peripheral vasomotor disturbances • Progressive kyphosis or scoliosis • Growth retardation • Hypotrophic, small, and cold feet and/or hands
Exclusion	• Evidence of a storage disorder including organomegaly • Cataract, retinopathy, or optic atrophy • History of perinatal or postnatal brain damage • Confirmed inborn error of metabolism or neurodegenerative disorder • Acquired neurologic disorder caused by severe head trauma or infection

Table 2. Variant Rett Syndrome: Suggested Diagnostic Criteria

	Criteria
Inclusion	• At least three of the six main criteria • At least five of the 11 supportive criteria
Main	• Reduction or absence of hand skills • Loss or reduction of speech (including babble) • Hand stereotypies • Loss or reduction of communication skills • Deceleration of head growth from early childhood • Regression followed by recovery of interaction
Supportive	• Breathing irregularities • Abdominal bloating or air swallowing • Bruxism • Abnormal locomotion • Kyphosis or scoliosis • Lower limb amyotrophy • Cold, discolored, and usually hypotrophic feet • Night-time screaming and other sleep disturbances • Inexplicable episodes of screaming or laughing • Apparently diminished sensitivity to pain • Intense eye contact and/or eye pointing

Hagberg et al 2002

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Gene. *MECP2* is the only gene known to be associated with *MECP2*-related disorders.

Clinical uses

- Diagnostic testing in selected individuals with Angelman syndrome or with nonsyndromic or syndromic X-linked intellectual disability and in males with a neonatal encephalopathy phenotype
- Confirmatory diagnostic testing in individuals with classic Rett syndrome or one of its variants
- Prenatal diagnosis

Clinical testing

- **Sequence analysis.** Bidirectional sequencing of the entire *MECP2* coding region detects disease-causing mutations in approximately 80% of individuals with classic Rett syndrome.

- **Mutation scanning.** *MECP2* mutation scanning (DHPLC followed by sequence analysis) identifies mutations in approximately 80% of individuals with classic Rett syndrome.
- **Deletion testing.** Quantitative PCR or multiplex ligation-dependent probe amplification (MLPA) identifies large deletions (spanning kilobases) of *MECP2* in some affected individuals previously considered to be mutation negative. These large deletions are more common in individuals with classic Rett syndrome (36%) than atypical (3%) Rett syndrome [Schollen et al 2003; Ariani et al 2004; Laccone et al 2004; Archer et al 2006; Huppke et al 2005; Ravn, Nielsen, Skjeldal et al 2005; Shi et al 2005].

Table 3 summarizes molecular genetic testing for this disorder.

Table 3. Molecular Genetic Testing Used in *MECP2*-Related Disorders

Test Methods	Mutations Detected	Mutation Detection Frequency by Test Method	Test Availability
Sequence analysis/mutation scanning	*MECP2* sequence variants	70%-90% [1]	Clinical Testing
Deletion testing (quantitative PCR or MLPA)	Deletions in *MECP2*	Up to 16% [2]	

1. In individuals with classic Rett syndrome [Dragich et al 2000, Shahbazian & Zoghbi 2001]
2. In individuals with classic or variant Rett syndrome

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Genetically Related (Allelic) Disorders

MECP2 duplication syndrome, characterized by infantile hypotonia, severe mental retardation, absence of speech, progressive spasticity, recurrent respiratory infections, and seizures, results from duplications of the *MECP2* gene ranging in size from 0.3 to 2.3 Mb [Van Esch et al 2005, Friez et al 2006].

Clinical Description

Natural History

Females. The phenotypes in females range from classic Rett syndrome, defined by strict clinical criteria, to variant Rett syndrome. Rarely, *MECP2* mutations have been identified in adult women with mild learning disabilities.

- **Classic Rett syndrome.** Affected girls usually have a normal birth and neonatal course followed by apparently normal psychomotor development during the first six to 18 months of life, although analysis of retrospective data shows that the majority of these children have subtle behavioral abnormalities. They are described as very placid, with poor suck or a weak cry [Burford 2005, Einspieler et al 2005]. Head growth may begin decelerating as early as age three months and brain size may eventually be smaller than normal by 30% or more.

  Affected girls then enter a short period of developmental stagnation followed by rapid regression in language and motor skills. The hallmark of the disease is the loss of purposeful hand use and its replacement with repetitive stereotyped hand movements. Most parents describe screaming fits and inconsolable crying by age 18-24 months [Coleman et al 1988]. Additional characteristics include autistic features, panic-like attacks, bruxism, episodic apnea and/or hyperpnea, seizures, gait ataxia and apraxia, tremors, and acquired microcephaly. Intermittent esotropia is common, and

vasomotor changes are often noted, especially in the lower limbs. After this period of rapid deterioration, the disease becomes relatively stable, although girls will likely develop dystonia and foot and hand deformities as they grow older.

Girls with classic Rett syndrome tend to be small; 85%-90% have growth failure and wasting that worsen with age [Motil et al 1998], perhaps in part caused by oropharyngeal and gastroesophageal incoordination that results in poor food intake [Motil et al 1999]. Bowel dysmotility, constipation, and functional megacolon are common; in extreme cases, fecal impaction, volvulus, and intussusception occur [Budden 1997]. The International Rett Syndrome Association has noted that gallbladder dysfunction, including gallstones, is a significant problem. The frequency seems far greater than that in the general population of children [Percy & Lane 2005].

Seizures are reported in up to 90% of females with Rett syndrome; generalized tonic-clonic seizures and partial complex seizures are the most common [Witt-Engerstrom 1992, Steffenburg et al 2001]. Additional manifestations of seizure activity include focal clonic activity, head or eye deviation, and/or apnea [Glaze et al 1998]. Seizures occur more frequently when the disease stabilizes and often decrease during the late motor deterioration stage. Activity described as seizures may not be associated with epileptiform activity on EEG, and clinical events accompanying EEG epileptiform activities are not always recognized as seizures by the parents [Glaze 2005].

Certain EEG findings common to the disorder are not unique to Rett syndrome and thus are not diagnostic. Nonetheless, it may be helpful to know that the EEG shows slowing of the occipital dominant rhythm and background activity with spike or sharp wave discharges during sleep early in the course of the syndrome. During the regression stage, the EEG shows loss of occipital dominant rhythm, further slowing of background activity, and loss of non-rapid eye movement sleep characteristics. Theta and delta activity is markedly slowed, with multifocal spike and wave discharges. Video/EEG monitoring reveals frequent episodes of apnea and hyperventilation, laughing, screaming, and vacant staring spells. Focal electrographic seizures are usually associated with focal clonic activity, head or eye deviation, and sometimes apnea. Generalized electrographic seizures are frequently accompanied by absence episodes or flexor spasms.

Osteoporosis occurs frequently in females with Rett syndrome and has been reported in very young girls, perhaps as a result of poor bone formation. This increases the risk for fractures [Budden & Gunness 2001]. Individuals with Rett syndrome have decreased bone mineral density compared to controls. Ambulatory individuals have better bone mineral density than non-ambulatory individuals [Cepollaro et al 2001]. Over 80% of individuals develop some degree of scoliosis by the age of 25 years [Kerr et al 2003].

Females with Rett syndrome typically survive into adulthood, but the incidence of sudden, unexplained death is significantly higher than in controls of similar age [Kerr & Julu 1999]. This sudden death may in part be caused by the higher incidence of longer corrected QT intervals, T-wave abnormalities, and reduced heart rate variability in Rett syndrome [Sekul et al 1994, Guideri et al 1999].

- **Other.** *MECP2* mutations have been identified in females with a Rett syndrome variant, mild learning disability, and even in a few women with no apparent symptoms who demonstrate highly skewed X-chromosome inactivation [Wan et al 1999, Amir et al 2000].

Microcephaly is not an invariant feature of Rett syndrome: Oexle et al (2005) reported an adult woman with a *MECP2* mutation mental retardation, seizures, and macrocephaly.

In addition, *MECP2* mutations may be found in females with mild learning disability [Orrico et al 2000] and clinically suspected but molecularly unconfirmed Angelman syndrome [Watson et al 2001].

Males. Males with a 46,XY karyotype can have mutations in *MECP2* [Villard et al 2000, Orrico et al 2000, Masuyama et al 2005].

Males with *MECP2* mutations may have a severe neonatal-onset encephalopathy with microcephaly, a relentless clinical course that follows a metabolic-degenerative type of pattern, abnormal tone, involuntary movements, severe seizures, and prominent breathing abnormalities (including central hypoventilation or respiratory insufficiency) [Wan et al 1999, Villard et al 2000, Zeev et al 2002, Kankirawatana et al 2006]. Often, males with *MECP2* mutations have such a severe neonatal encephalopathy that they die before their second year [Schanen et al 1998, Wan et al 1999].

MECP2 mutations have been identified in some individuals with Angelman syndrome [Watson et al 2001, Kleefstra et al 2004].

Males meeting the clinical criteria for classic Rett syndrome have been identified in association with a 47,XXY karyotype [Hoffbuhr et al 2001, Leonard et al 2001, Schwartzman et al 2001] and post-zygotic *MECP2* mutations resulting in somatic mosaicism [Clayton-Smith et al 2000, Topcu et al 2002].

X-linked mental retardation. *MECP2* mutations may also be found in families exhibiting X-linked mental retardation, which may range from mild non-progressive mental retardation in females to severe mental retardation in males associated with manic-depressive psychosis, pyramidal signs, parkinsonian features, and macro-orchidism (the so-called PPM-X syndrome) [Dotti et al 2002, Klauck et al 2002, Gomot et al 2003].

Pathogenesis of Rett syndrome. The principal characteristics of Rett syndrome and their developmental pattern indicate that abnormal development of the cortex in late infancy may result from dysregulation of subcortical regulator systems, brain stem, basal forebrain nuclei, and basal ganglia. Brain stem involvement is apparent based on many of the functional disturbances in Rett syndrome: breathing, cardiac rate, swallowing, peripheral vasomotor disturbances, sleep, bowel motility, salivation, and pain discrimination. These findings suggest dysregulation of autonomic tone with failure to regulate vagal (parasympathetic) tone and respiratory rhythm, suggesting immaturity of the respiratory regulator.

Neuropathology of Rett syndrome. The brains are small and closely packed with neurons. Decreased dendritic spines and arbors have been noted in brain neuropathology [Armstrong 2005].

Genotype-Phenotype Correlations

Genotype-phenotype correlation studies have so far yielded inconsistent results. It is necessary to gain a far better understanding of *MECP2* function and to conduct more controlled studies before valid conclusions can be drawn about the effect of mutation type on the phenotype.

Amir et al (2000) found a positive correlation between truncating mutations and breathing abnormalities, whereas scoliosis was more common in individuals with missense mutations.

Neither the overall severity score nor other parameters (age of onset, mortality, seizures, and somatic growth failure) correlated with the type of mutation.

Cheadle et al (2000) found significantly milder disease in individuals with missense mutations than in those with truncating mutations; they also found that late truncating mutations produced milder phenotypes than early truncating mutations.

Cheadle et al (2000) and Huppke et al (2000) both reported several individuals with the same mutation but different phenotypes, findings suggesting that factors other than mutation type influence disease severity. One such factor is the pattern of X-chromosome inactivation (XCI); females who have a mutation but have favorably skewed XCI may have mild symptoms or none at all [Wan et al 1999, Amir et al 2000].

Several of the *MECP2* mutations found in males with mental retardation are typically missense or late truncating mutations that have not been identified in girls with Rett syndrome. Because some of the missense mutations such as A140V do not totally inactivate the protein, they cause mental retardation in males but very mild cognitive impairment in females [Dotti et al 2002, Klauck et al 2002, Gomot et al 2003].

Weaving et al (2003) showed that clinical severity can in part be predicted based on the type of mutation (missense versus truncation), its location, particularly when positioned within a functional domain, and the presence of skewed X-chromosome inactivation (XCI) [Weaving et al 2003]; similar conclusions were reached by Schanen et al (2004), Chae et al (2004), and Charman et al (2005).

Leonard et al (2003) determined that the phenotype of individuals with the p.R133C mutation is less severe than the usual phenotype, which is consistent with in vitro functional studies demonstrating that R133C does not impair binding to DNA.

Penetrance

Occasionally, rare obligate heterozygotes for a pathogenic *MECP2* mutation may have no clinical evidence of Rett syndrome — the result of protective highly skewed X-chromosome inactivation.

Nomenclature

Females who fulfill all of the diagnostic criteria for Rett syndrome are classified as having typical or classic Rett syndrome. With increasing experience it has become clear that females with Rett syndrome present with a much broader phenotype than originally described. The majority of Rett syndrome variants are milder than classic Rett syndrome, particularly with regard to gross motor disability and degree of fine motor dysfunction.

Hagberg described five possible Rett syndrome variant, or atypical forms [Hagberg et al 1993]:

- A form seen in females with apparently classic Rett syndrome in whom the presentation is dominated by seizures and onset is before age six months
- Congenital or precocious Rett syndrome, in which regression is never clearly identified but the clinical picture is otherwise classic
- A form in which regression develops later and more gradually than in classic Rett syndrome
- 'Forme fruste' Rett syndrome, with a milder, incomplete, and protracted clinical course. Regression occurs later (age 1-3 years) and is not as severe as that in classic

Rett syndrome, as hand use may be preserved and stereotypic hand movements may be minimal or atypical.

- 'Preserved speech' variant

Prevalence

The prevalence of Rett syndrome in females is estimated to be 1:8,000 by age 15 years [Laurvick et al 2005].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Angelman syndrome (AS) is characterized by mental retardation, severe speech impairment, gait ataxia and/or tremulousness of the limbs, and a unique behavior with an inappropriate happy demeanor. Microcephaly and seizures are common. Developmental delay is first noted at around age six months; however, the unique clinical features of AS do not become manifest until after age one year. Developmental regression should help distinguish Rett syndrome from Angelman syndrome clinically, and seizures tend to be much more difficult to manage in Angelman syndrome. Analysis of parent-specific DNA methylation imprints in the 15q11.2-q13 chromosome region detects approximately 78% of individuals with AS, including those with a deletion, uniparental disomy, or an imprinting defect; *UBE3A* sequence analysis detects mutations in an additional approximately 11% of individuals. The remaining 10% of individuals with classic phenotypic features of AS have a presently unidentified genetic mechanism. Watson et al (2001) found *MECP2* mutations in four of 25 females and one of 22 males who had a clinical diagnosis of AS, but no molecular abnormality involving 15q11.2-13. Three of the five subsequently demonstrated progressive clinical features more typical of Rett syndrome than AS.

Individuals with Rett syndrome — especially those who do not have microcephaly, seizures, or kyphoscoliosis — are commonly diagnosed with autism; however, *MECP2* mutations are not a significant cause of autism [Lobo-Menendez et al 2003]. See Autism Overview.

Cerebral palsy is often suspected in older individuals with Rett syndrome or males with spasticity, severe wasting, and mental retardation. A detailed history of early childhood development in the light of the revised diagnostic criteria [Hagberg et al 2002] and molecular genetic testing of *MECP2* should reveal the proper diagnosis.

Mutations in *CDKL5*, the gene encoding cyclin dependent-like kinase 5, have been identified in individuals with a Rett syndrome-like phenotype. Virtually all individuals with *CDKL5* mutations reported to date have had an early-onset seizure variant of Rett syndrome, the so-called Hanefield variant [Tao et al 2004; Weaving et al 2004; Evans, Archer, Colley et al 2005; Scala et al 2005]; however, it seems that mutations in this gene account for only a small subset of individuals with a Rett syndrome-like phenotype.

MECP2-related disorders should be considered in male infants with neonatal encephalopathy, or severe hypotonia or in families with a history of X-linked mental retardation.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with a *MECP2*-related disorder, the following evaluations are recommended:

- Formal developmental assessment
- Assessment of feeding/eating, digestive problems (including constipation and gastro-esophageal reflux), and nutrition using history, growth measurements and, if needed, gastrointestinal investigations
- History of sleep and/or breathing problems
- Video/EEG monitoring to obtain definitive information about the occurrence of seizures and the need for antiepileptic drugs
- ECG to screen for prolonged QTc
- Assessment of brain stem autonomic dysfunction to identify appropriate therapies [Julu et al 2001, Julu & Witt-Engerstrom 2005]
- Examination for scoliosis

Treatment of Manifestations

Management is mainly symptomatic and focuses on optimizing the individual's abilities using a dynamic multidisciplinary approach, with specialist input from dietitians, physiotherapists, and occupational, speech, and music therapists [Lotan et al 2004, Weaving et al 2005]. Psychosocial support for families is an integral part of management.

Therapeutic horseback riding, swimming, and music therapy are often beneficial [Budden 1997].

Effective communication strategies, including the use of augmentative communication techniques, need to be explored for these severely disabled individuals [Ryan et al 2004].

Treatment for seizures needs to be individualized with input from a pediatric neurologist. Topiramate may improve seizure control and/or respiratory abnormalities [Goyal et al 2004].

Risperidone (low dose) or selective serotonin uptake inhibitors have been somewhat successful in treating agitation. Melatonin can ameliorate sleep disturbances [Budden 1997, McArthur & Budden 1998]. Chloral hydrate, hydroxyzine, or diphenhydramine may be used along with melatonin.

Ample fluid intake and a high fiber diet can help prevent acute intestinal blockage. When diet is ineffective, Miralax (polyethylene glycol) and other stool softeners may be used to control constipation; they are tolerated better than milk of magnesia.

Anti-reflux agents, smaller and thickened feedings, and positioning can decrease gastroesophageal reflux.

Scoliosis [Kerr et al 2003] and spasticity [Budden 1997] need to be treated to maintain mobility.

Surveillance

- Examination at regular intervals by a multidisciplinary team with particular attention to growth, nutritional intake, dentition, gastrointestinal function, mobility and communication skills, hand function, and orthopedic and neurologic complications
- Periodic ECG to screen for prolonged QTc
- Examination at regular intervals for the progression of scoliosis

Agents/Circumstances to Avoid

Because individuals with Rett syndrome have an increased risk of life-threatening arrhythmias associated with a prolonged QT interval [Sekul et al 1994], avoidance of drugs known to prolong the QT interval, including the following, is recommended:

- Prokinetic agents (e.g., cisapride)
- Antipsychotics (e.g., thioridazine), tricyclic antidepressants (e.g., imipramine)
- Antiarrhythmics (e.g., quinidine, sotolol, amiodarone)
- Anesthetic agents (e.g., thiopental, succinylcholine)
- Antibiotics (e.g., erythromycin, ketoconazole)

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

L-carnitine was tested in a double-blind trial. Although parents and caregivers reported improvements in the general well-being of affected individuals [Ellaway et al 1999], significant functional improvements were not observed.

Carbidopa/levodopa may be tried for rigidity, but its benefit is unsubstantiated.

Following the report of reduced CSF folate concentration in four females with Rett syndrome [Ramaekers et al 2003], Neul analyzed CSF from an additional 76 individuals with Rett syndrome, but could not reproduce earlier findings, and found that supplementation with folinic acid did not lead to any noticeable clinical improvements [Neul et al 2005]. It therefore remains to be established whether cerebral folate deficiency contributes to the pathophysiology of Rett syndrome.

Because elevated opioids had been observed in the CSF of individuals with Rett syndrome, the oral opiate antagonist, naltrexone, was investigated. Although it decreased breathing dysrhythmias and had some sedating properties, the efficacy of naltrexone is controversial [Percy et al 1994].

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

MECP2-related disorders are inherited in an X-linked dominant manner.

Risk to Family Members

Parents of a female proband

- Approximately 99.5% of cases are single occurrences in a family, resulting either from a *de novo* mutation in the child with a *MECP2*-related disorder or from inheritance of the disease-causing mutation from one parent who has germline mosaicism. If the disease-causing *MECP2* mutation has been identified in the proband, it is appropriate to offer molecular genetic testing to both parents.
- A mother who has a *MECP2* mutation may have favorably skewed X-chromosome inactivation that results in her being unaffected or mildly affected.

Parents of a male proband

- The father of an affected male will not have the disease or be a carrier of the mutation.
- If the disease-causing *MECP2* mutation has been identified in the proband, it is appropriate to offer molecular genetic testing to the mother.
- A mother who has a *MECP2* mutation may have favorably skewed X-chromosome inactivation that results in her being unaffected or mildly affected.

Sibs of a proband

- The risk to sibs depends upon the genetic status of the parents.
- When the mother of an affected individual is found to have the *MECP2* mutation identified in her affected child, the risk to sibs of inheriting the mutant *MECP2* allele at conception is 50%.
- If a mutation is not identified in a parent, the risk to sibs is low. However, germline mosaicism in either parent cannot be excluded even if the disease-causing *MECP2* mutation present in the proband has not been identified in DNA extracted from the leukocytes of either parent. Germline mosaicism has been reported [Amir et al 1999, Zeev et al 2002, Mari et al 2005].

Offspring of a female proband

- Each child of an individual with a *MECP2*-related disorder has a 50% chance of inheriting the mutation. One woman with classic Rett syndrome gave birth to a girl who developed classic Rett syndrome. Mildly affected females have reproduced.
- Females who inherit the mutation are at high risk of developing classic Rett syndrome, although skewed X-chromosome inactivation may result in a milder phenotype.
- Males who inherit the mutation may have a severe neonatal encephalopathy, or, if they survive the first year, will have a severe mental retardation syndrome.

Offspring of a male proband. No male with a *MECP2* mutation has been known to reproduce.

Other family members of a proband. The risk to other family members depends upon the genetic status of the proband's mother. If the mother is found to be affected or to have a *MECP2* mutation, her family members may be at risk.

Related Genetic Counseling Issues

- As with many other genetic conditions, the diagnosis of a *MECP2*-related disorder in a family member may result in evaluation and diagnosis of the mother and other family members who were previously unaware of the presence of a genetic disorder in the family. This discovery can be difficult for the family because of its implications for their own health and because of a sense of "responsibility" for illness in their children. Efforts should be made to anticipate these issues.
- Apparently unaffected sisters of a girl with classic Rett syndrome could have the *MECP2* mutation that is present in their sister but have few to no symptoms because of skewed X-chromosome inactivation. Genetic counseling needs to address this possibility, as the unaffected sisters may be at risk of transmitting the disease-causing *MECP2* mutation to their children.

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Pregnancies of women with a known *MECP2* mutation. Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Male fetuses with a *MECP2* mutation who survive infancy will most likely have severe mental retardation. The phenotype in a female with a *MECP2* mutation is difficult to predict; it can range from apparently normal to severely affected.

Pregnancies of a couple who have a child with a *MECP2*-related disorder. Germline mosaicism cannot be excluded in either parent even when the disease-causing *MECP2* mutation present in the proband is not identified in DNA extracted from parental leukocytes; thus, it is appropriate to offer prenatal diagnosis to such couples whether or not the disease-causing mutation has been identified in a parent [Armstrong et al 2002]. One of nine pregnancies of women who did not have evidence of the *MECP2* mutation identified in their daughters with classic Rett syndrome resulted in the birth of a daughter with the same *MECP2* mutation as the proband [Mari et al 2005].

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified in an affected family member. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of MECP2-Related Disorders

Gene Symbol	Chromosomal Locus	Protein Name
MECP2	Xq28	Methyl-CpG-binding protein 2

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for MECP2-Related Disorders

300005	METHYL-CpG-BINDING PROTEIN 2; MECP2
300673	ENCEPHALOPATHY, NEONATAL SEVERE, DUE TO MECP2 MUTATIONS
312750	RETT SYNDROME; RTT

Table C. Genomic Databases for MECP2-Related Disorders

Gene Symbol	Locus Specific	Entrez Gene	HGMD
MECP2	MECP2	4204 (MIM No. 300005)	MECP2

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

The abundantly expressed nuclear protein MeCP2 is thought to mediate transcriptional silencing and epigenetic regulation of methylated DNA through its association with 5-methylcytosine (5-mC)-rich heterochromatin [Nan et al 1998, Tate et al 1996]. The methyl CpG-binding domain (MBD) of MeCP2 binds to symmetrically methylated CpG dinucleotides; the transcriptional repression domain (TRD) interacts with the co-repressor Sin3A, and together they recruit histone deacetylases [Jones et al 1998, Nan et al 1998, Ng & Bird 1999]. When lysine residues of the core histones H3 and H4 become deacetylated, the chromatin structure changes and renders the DNA inaccessible to the transcriptional machinery. DNA methylation-dependent repression is important for X-chromosome inactivation (XCI) and genomic imprinting. MeCP2 is expressed in all tissues and is hypothesized to act as a global transcriptional repressor [D'Esposito et al 1996, Nan et al 1998, Coy et al 1999].

Most *MECP2* mutations occur *de novo*. The leading hypothesis holds that MeCP2 dysfunction resulting from mutations in the TRD or MBD disrupts the delicate precision of gene expression during development. Some mutations affect residues that are important for DNA binding, whereas others may disrupt the native structure of the protein and/or its interactions with other proteins. The documented nonsense, frameshift, and splicing mutations, most of which are distal to the MBD, likely result in premature termination of the protein. Truncated proteins may still bind methylated DNA but be unable to interact with the corepressor Sin3A; it is also possible that mutations in the carboxy terminus of the protein disable DNA binding [Chandler et al 1999]. In either case, the silencing complex would not be properly assembled, and the target genes could not be properly silenced.

It is puzzling that a ubiquitously expressed gene should give rise to a predominantly neurologic phenotype. Brain tissues may be more vulnerable to compromises in MeCP2 function, or tissue-specific differences in MeCP2 expression levels may occur. (There are, in fact, alternate

transcripts that are differentially expressed in the brain during development [Kriaucionis & Bird 2004, Mnatzakanian et al 2004].) Alternatively, the post-mitotic nature of neurons may make them more susceptible to the ill effects of MeCP2 dysfunction. To understand the pathogenesis of Rett syndrome, it will first be necessary to identify the genes normally targeted by MeCP2 activity. MeCP2 has been known to silence specific genes, such as brain-derived neurotrophic factor [Chen et al 2003, Martinowich et al 2003], *Hairy2a* [Stancheva et al 2003], *Dlx5* [Horike et al 2005], and *sgk* [Nuber et al 2005]. The constellation and consistency of features among individuals with classic Rett syndrome suggest that the disorder may be attributable to the dysfunction of a select group of genes. Functional studies of the various mutations and analysis of animal models for Rett syndrome should illuminate the pathogenesis of the disorder and establish how DNA methylation-dependent processes are disrupted.

Three groups have generated mice lacking functional MeCP2; male mice that are null are born alive and develop tremors, hypoactivity, and small brains. They typically die between age eight and 12 weeks [Chen et al 2001, Guy et al 2001]. Deletion of the mouse *Mecp2* gene in neurons produces a phenotype very similar to that seen with deletion of *Mecp2* in all cells [Chen et al 2001], indicating that despite its purported role as a global transcriptional repressor, MeCP2 function — or one of its functions — may be most critical in neurons. Male mice carrying a mutation that truncates the protein past amino acid 308 ($Mecp2^{308/y}$) appear normal for six weeks, then develop tremor, seizures, hypoactivity, forepaw, stereotypies, and kyphosis [Shahbazian et al 2002].

A fourth group has generated a targeted deletion of the MBD coding region and disruption of mRNA splicing was introduced in the mouse, resulting in a complete loss of *Mecp2* transcripts and protein [Pelka et al 2006]. Postnatal comparison of XO and XY mutant *Mecp2* allele-containing null mice revealed similar effects on mouse growth and viability, suggesting that phenotypic manifestations are not modulated by the Y chromosome. Further assessment of *Mecp2*-null XY mice highlighted cerebellar and hippocampal/amygdala-based learning deficits in addition to reduced motor dexterity and decreased anxiety levels. Brain tissues containing the hippocampal formation of XY *Mecp2*-null mice also displayed significant changes in genetic activity, related to the severity of the mutant phenotype.

In addition, studies by Horike et al (2005), Kaufmann et al (2005), and Makedonski et al (2005) showing that *Mecp2* deficiency leads to epigenetic aberrations of chromatin suggest that *Mecp2* deficiency could lead to loss of imprinting, thereby contributing to the pathogenesis of Rett syndrome.

Finally, evidence suggests that over expression of MeCP2 protein could have detrimental effects on brain development and function as shown in mouse models [Collins et al 2004] and in the human [Shi et al 2005, Van Esch et al 2005].

Normal allelic variants: The *MECP2* gene contains four exons, transcribed from telomere to centromere. Exons 2, 3, and 4 were thought to contain the coding sequence; the first exon was identified through sequence homology between species and was thought to contain a non-coding 5' untranslated region (UTR) [Reichwald et al 2000]. However, it has been more recently shown that a transcript containing exon 1 is the predominant isoform in the brain [Kriaucionis & Bird 2004, Mnatzakanian et al 2004]. Most of exon 4 encodes the unusually long (8.5-kb) 3'UTR; alternate polyadenylation sites here result in differentially expressed transcripts of various sizes, all encoding for the same size protein. The significance of the mRNA features with regard to stability, regulation, and function is currently not well understood [Coy et al 1999, Reichwald et al 2000], but may point to a potential tissue-specific function of the 3'UTR in the regulation of MeCP2 protein synthesis in response to the age-specific requirement of MeCP2 function, at least in the mouse [Pelka et al 2005]. The C-

terminal domain shares homology with neuronal-specific transcription factors containing forkhead domains, suggesting that the protein may have additional, more complex, possibly neuronal-specific functions [Vacca et al 2001]. This region also contains evolutionarily conserved polyhistidine and polyproline regions that may play a role in the interaction of *MECP2* with the nucleosome core [Chandler et al 1999].

Pathologic allelic variants: To date, over 200 individual nucleotide changes that cause pathogenic mutations have been described [Christodoulou et al 2003]; the eight most commonly occurring missense and nonsense mutations account for almost 50% of all mutations and small deletions associated with a deletion hotspot in the C-terminal region of the MeCP2 protein account for an additional 9% of pathogenic mutations [RettBASE]. Although these deletions tend to affect the same region, completely identical deletions are rare.

Mutations are dispersed throughout the gene; however, a clustering of missense mutations occurs 5' of the transcriptional repression domain (TRD), mostly in the methyl binding domain (MBD); another clustering of nonsense and frameshift mutations appears beyond the MBD. More recently, large deletions (kilobases in size) that delete whole exons have been identified in a proportion of affected individuals who were previously considered to be mutation negative. These large deletions are more commonly found in females with classic Rett syndrome (36%; 46/128) than atypical Rett syndrome (3%; 7/229) [Ariani et al 2004; Laccone et al 2004; Amir et al 2005; Huppke et al 2005; Ravn, Nielsen, Skjeldal et al 2005; Shi et al 2005; Archer et al 2006].

On the other hand, pathogenic mutations involving exon 1 appear to be only rarely associated with Rett syndrome [Amir et al 2005; Evans, Archer, Whatley et al 2005; Poirier et al 2005; Ravn, Nielsen, Skjeldal et al 2005; Saxena et al 2006]. In almost all cases the mutations are *de novo*, and some evidence suggests that in the majority of cases the mutation has arisen on the paternal X chromosome [Girard et al 2001, Trappe et al 2001].

Normal gene product: The proteins resulting from the two *MECP2* isoforms, created by alternative splicing of exon 2 and use of two alternative start codons, are almost identical but have alternative N-termini.

The MeCP2 protein has two major functional domains: the methyl binding domain (MBD), which binds specifically to DNA at methylated CpG's, and a transcription repression domain (TRD) that is responsible for recruiting other proteins that mediate transcription repression [Jones et al 1998, Nan et al 1998, Kokura et al 2001, Stancheva et al 2003, Harikrishnan et al 2005]. In addition, the MeCP2 protein has a WW domain at its C-terminus [Buschdorf & Stratling 2004].

Evidence suggests that MeCP2 may play a role in mediating splicing [Young et al 2005].

Abnormal gene product: Functional studies have shown that *MECP2* mutations affect the methyl binding or transcription repression properties of the mutant protein, depending on the location of the mutation [Kudo et al 2001, Kudo et al 2002, Kudo et al 2003]. MeCP2 binds specifically to certain DNA sequences [Klose et al 2005]. Several studies have identified specific MeCP2 targets, suggesting that downstream alterations in the expression of specific MeCP2 targets may contribute to the neurodevelopmental abnormalities seen in Rett syndrome and other *MECP2*-related disorders [Chen et al 2003, Horike et al 2005, Martinowich et al 2003, Nuber et al 2005, Stancheva et al 2003].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

International Rett Syndrome Association (IRSA)
9121 Piscataway Road
Clinton MD 20735
Phone: 800-818-7388; 301-856-3334
Fax: 301-856-3336
Email: irsa@rettsyndrome.org
www.rettsyndrome.org

National Library of Medicine Genetics Home Reference
Rett syndrome

NCBI Genes and Disease
Rett syndrome

Rett Syndrome Research Foundation
4600 Devitt Drive
Cincinnati OH 45246
Phone: 513-874-3020
Fax: 513-874-2520
Email: mgriffin@rsrf.org
www.rsrf.org

Angelman, Rett & Prader-Willi Syndromes Consortium Registry
Department of Molecular and Human Genetics
Baylor College of Medicine
One Baylor Plaza Rm. T619
Houston TX 77030
Phone: 713-798-4795
Fax: 713-798-7773
Email: sweaver@bcm.tmc.edu
Angelman, Rett & Prader-Willi Syndromes Consortium Registry

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited

Amir RE, Fang P, Yu Z, et al. Mutations in exon 1 of MECP2 are a rare cause of Rett syndrome. J Med Genet. 2005;42:e15. [PubMed: 15689438]

Amir RE, Van den Veyver IB, Schultz R, Malicki DM, Tran CQ, Dahle EJ, Philippi A, Timar L, Percy AK, Motil KJ, Lichtarge O, Smith EO, Glaze DG, Zoghbi HY. Influence of mutation type and X

chromosome inactivation on Rett syndrome phenotypes. Ann Neurol. 2000;47:670–9. [PubMed: 10805343]

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;23:185–8. [PubMed: 10508514]

Archer HL, Whatley SD, Evans JC, Ravine D, Huppke P, Kerr A, Bunyan D, Kerr B, Sweeney E, Davies SJ, Reardon W, Horn J, MacDermot KD, Smith RA, Magee A, Donaldson A, Crow Y, Hermon G, Miedzybrodzka Z, Cooper DN, Lazarou L, Butler R, Sampson J, Pilz DT, Laccone F, Clarke AJ. Gross rearrangements of the MECP2 gene are found in both classical and atypical Rett syndrome patients. J Med Genet. 2006;43:451–6. [PubMed: 16183801]

Ariani F, Mari F, Pescucci C, Longo I, Bruttini M, Meloni I, Hayek G, Rocchi R, Zappella M, Renieri A. Real-time quantitative PCR as a routine method for screening large rearrangements in Rett syndrome: Report of one case of MECP2 deletion and one case of MECP2 duplication. Hum Mutat. 2004;24:172–7. [PubMed: 15241799]

Armstrong DD. Neuropathology of Rett syndrome. J Child Neurol. 2005;20:747–53. [PubMed: 16225830]

Armstrong J, Aibar E, Pineda M, Perez MM, Gean E, Carrera M, Casas C, Martinez F, Monros E. Prenatal diagnosis in Rett syndrome. Fetal Diagn Ther. 2002;17:200–4. [PubMed: 12065946]

Budden SS. Rett syndrome: habilitation and management reviewed. Eur Child Adolesc Psychiatry 6 [Suppl. 1997;1]:103–7. [PubMed: 9452932]

Budden SS, Gunness ME. Bone histomorphometry in three females with Rett syndrome. Brain Dev. 2001;23:S133–7. [PubMed: 11738859]

Burford B. Perturbations in the development of infants with Rett disorder and the implications for early diagnosis. Brain Dev. 2005;27:S3–7. [PubMed: 16182489]

Buschdorf JP, Stratling WH. A WW domain binding region in methyl-CpG-binding protein MeCP2: impact on Rett syndrome. J Mol Med. 2004;82:135–43. [PubMed: 14618241]

Cepollaro C, Gonnelli S, Bruni D, Pacini S, Martini S, Franci MB, Gennari L, Rossi S, Hayek G, Zappella M, Gennari C. Dual X-ray absorptiometry and bone ultrasonography in patients with Rett syndrome. Calcif Tissue Int. 2001;69:259–62. [PubMed: 11768194]

Chae JH, Hwang H, Hwang YS, Cheong HJ, Kim KJ. Influence of MECP2 gene mutation and X-chromosome inactivation on the Rett syndrome phenotype. J Child Neurol. 2004;19:503–8. [PubMed: 15526954]

Chandler SP, Guschin D, Landsberger N, Wolffe AP. The methyl-CpG binding transcriptional repressor MeCP2 stably associates with nucleosomal DNA. Biochemistry. 1999;38:7008–18. [PubMed: 10353812]

Charman T, Neilson TC, Mash V, Archer H, Gardiner MT, Knudsen GP, McDonnell A, Perry J, Whatley SD, Bunyan DJ, Ravn K, Mount RH, Hastings RP, Hulten M, Orstavik KH, Reilly S, Cass H, Clarke A, Kerr AM, Bailey ME. Dimensional phenotypic analysis and functional categorisation of mutations reveal novel genotype-phenotype associations in Rett syndrome. Eur J Hum Genet. 2005;13:1121–30. [PubMed: 16077736]

Cheadle JP, Gill H, Fleming N, Maynard J, Kerr A, Leonard H, Krawczak M, Cooper DN, Lynch S, Thomas N, Hughes H, Hulten M, Ravine D, Sampson JR, Clarke A. Long-read sequence analysis of the MECP2 gene in Rett syndrome patients: correlation of disease severity with mutation type and location. Hum Mol Genet. 2000;9:1119–29. [PubMed: 10767337]

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;27:327–31. [PubMed: 11242118]

Chen WG, Chang Q, Lin Y, Meissner A, West AE, Griffith EC, Jaenisch R, Greenberg ME. Derepression of BDNF transcription involves calcium-dependent phosphorylation of MeCP2. Science. 2003;302:885–9. [PubMed: 14593183]

Christodoulou J, Grimm A, Maher T, Bennetts B. RettBASE: The IRSA MECP2 variation database-a new mutation database in evolution. Hum Mutat. 2003;21:466–72. [PubMed: 12673788]

Clayton-Smith J, Watson P, Ramsden S, Black GC. Somatic mutation in MECP2 as a non-fatal neurodevelopmental disorder in males. Lancet. 2000;356:830–2. [PubMed: 11022934]

Coleman M, Brubaker J, Hunter K, Smith G. Rett syndrome: a survey of North American patients. J Ment Defic Res 32 (Pt. 1988;2):117–24. [PubMed: 3398038]

Collins AL, Levenson JM, Vilaythong AP, Richman R, Armstrong DL, Noebels JL, David Sweatt J, Zoghbi HY. Mild overexpression of MeCP2 causes a progressive neurological disorder in mice. Hum Mol Genet. 2004;13:2679–89. [PubMed: 15351775]

Coy JF, Sedlacek Z, Bachner D, Delius H, Poustka A. A complex pattern of evolutionary conservation and alternative polyadenylation within the long 3'-untranslated region of the methyl-CpG-binding protein 2 gene (MeCP2) suggests a regulatory role in gene expression. Hum Mol Genet. 1999;8:1253–62. [PubMed: 10369871]

D'Esposito M, Quaderi NA, Ciccodicola A, Bruni P, Esposito T, D'Urso M, Brown SD. Isolation, physical mapping, and northern analysis of the X-linked human gene encoding methyl CpG-binding protein, MECP2. Mamm Genome. 1996;7:533–5. [PubMed: 8672133]

Dotti MT, Orrico A, De Stefano N, Battisti C, Sicurelli F, Severi S, Lam CW, Galli L, Sorrentino V, Federico A. A Rett syndrome MECP2 mutation that causes mental retardation in men. Neurology. 2002;58:226–30. [PubMed: 11805248]

Dragich J, Houwink-Manville I, Schanen C. Rett syndrome: a surprising result of mutation in MECP2. Hum Mol Genet. 2000;9:2365–75. [PubMed: 11005791]

Einspieler C, Kerr AM, Prechtl HF. Is the Early Development of Girls with Rett Disorder Really Normal? Pediatr Res. 2005;57:696–700. [PubMed: 15718369]

Ellaway C, Williams K, Leonard H, Higgins G, Wilcken B, Christodoulou J. Rett syndrome: randomized controlled trial of L-carnitine. J Child Neurol. 1999;14:162–7. [PubMed: 10190267]

Evans JC, Archer HL, Colley JP, Ravn K, Nielsen JB, Kerr A, Williams E, Christodoulou J, Gecz J, Jardine PE, Wright MJ, Pilz DT, Lazarou L, Cooper DN, Sampson JR, Butler R, Whatley SD, Clarke AJ. Early onset seizures and Rett-like features associated with mutations in CDKL5. Eur J Hum Genet. 2005;13:1113–20. [PubMed: 16015284]

Evans JC, Archer HL, Whatley SD, Kerr A, Clarke A, Butler R. Variation in exon 1 coding region and promoter of MECP2 in Rett syndrome and controls. Eur J Hum Genet. 2005;13:124–6. [PubMed: 15367913]

Friez MJ, Jones JR, Clarkson K, Lubs H, Abuelo D, Bier JA, Pai S, Simensen R, Williams C, Giampietro PF, Schwartz CE, Stevenson RE. Recurrent infections, hypotonia, and mental retardation caused by duplication of MECP2 and adjacent region in Xq28. Pediatrics. 2006;118:e1687–95. [PubMed: 17088400]

Girard M, Couvert P, Carrie A, Tardieu M, Chelly J, Beldjord C, Bienvenu T. Parental origin of de novo MECP2 mutations in Rett syndrome. Eur J Hum Genet. 2001;9:231–6. [PubMed: 11313764]

Glaze DG. Neurophysiology of Rett syndrome. J Child Neurol. 2005;20:740–6. [PubMed: 16225829]

Glaze DG, Schultz RJ, Frost JD. Rett syndrome: characterization of seizures versus non-seizures. Electroencephalogr Clin Neurophysiol. 1998;106:79–83. [PubMed: 9680167]

Gomot M, Gendrot C, Verloes A, Raynaud M, David A, Yntema HG, Dessay S, Kalscheuer V, Frints S, Couvert P, Briault S, Blesson S, Toutain A, Chelly J, Desportes V, Moraine C. MECP2 gene mutations in non-syndromic X-linked mental retardation: phenotype-genotype correlation. Am J Med Genet A. 2003;123:129–39. [PubMed: 14598336]

Goyal M, O'Riordan MA, Wiznitzer M. Effect of topiramate on seizures and respiratory dysrhythmia in Rett syndrome. J Child Neurol. 2004;19:588–91. [PubMed: 15605467]

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;30:146–8. [PubMed: 10480210]

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;27:322–6. [PubMed: 11242117]

Hagberg B. Clinical delineation of Rett syndrome variants. Neuropediatrics. 1995;26:62. [PubMed: 7566453]

Hagberg B, Gillberg C. Rett variants +/- rettoid phenotypes. In: Hagberg B, Anvret M, Wahlstrom J (eds) Rett Syndrome: Clinical and Biological Aspects. MacKeith Press, London, pp 40-60. 1993

Hagberg B, Hanefeld F, Percy A, Skjeldal O. An update on clinically applicable diagnostic criteria in Rett syndrome: comments to Rett Syndrome Clinical Criteria Consensus Panel Satellite to European

Paediatric Neurology Society Meeting, Baden Baden, Germany, 11 September 2001. Eur J Paediatr Neurol. 2002;6:293–7.

Hagberg BA. Rett syndrome: clinical peculiarities, diagnostic approach, and possible cause. Pediatr Neurol. 1989;5:75–83. [PubMed: 2653342]

Harikrishnan KN, Chow MZ, Baker EK, Pal S, Bassal S, Brasacchio D, Wang L, Craig JM, Jones PL, Sif S, El-Osta A. Brahma links the SWI/SNF chromatin-remodeling complex with MeCP2-dependent transcriptional silencing. Nat Genet. 2005;37:254–64. [PubMed: 15696166]

Hoffbuhr K, Devaney JM, LaFleur B, Sirianni N, Scacheri C, Giron J, Schuette J, Innis J, Marino M, Philippart M, Narayanan V, Umansky R, Kronn D, Hoffman EP, Naidu S. MeCP2 mutations in children with and without the phenotype of Rett syndrome. Neurology. 2001;56:1486–95. [PubMed: 11402105]

Horike S, Cai S, Miyano M, Cheng JF, Kohwi-Shigematsu T. Loss of silent-chromatin looping and impaired imprinting of DLX5 in Rett syndrome. Nat Genet. 2005;37:31–40. [PubMed: 15608638]

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;9:1369–75. [PubMed: 10814718]

Huppke P, Ohlenbusch A, Brendel C, Laccone F, Gartner J. Mutation analysis of the HDAC 1, 2, 8 and CDKL5 genes in Rett syndrome patients without mutations in MECP2. Am J Med Genet A. 2005;137:136–8. [PubMed: 16086395]

Jones PL, Veenstra GJ, Wade PA, Vermaak D, Kass SU, Landsberger N, Strouboulis J, Wolffe AP. Methylated DNA and MeCP2 recruit histone deacetylase to repress transcription. Nat Genet. 1998;19:187–91. [PubMed: 9620779]

Julu PO, Kerr AM, Apartopoulos F, Al-Rawas S, Engerstrom IW, Engerstrom L, Jamal GA, Hansen S. Characterisation of breathing and associated central autonomic dysfunction in the Rett disorder. Arch Dis Child. 2001;85:29–37. [PubMed: 11420195]

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. 2005;1:S43–53. [PubMed: 16182494]

Kankirawatana P, Leonard H, Ellaway C, Scurlock J, Mansour A, Makris CM, Dure LS IV, Friez M, Lane J, Kiraly-Borri C, Fabian V, Davis M, Jackson J, Christodoulou J, Kaufmann WE, Ravine D, Percy AK. Early progressive encephalopathy in boys and MECP2 mutations. Neurology. 2006;67:164–6. [PubMed: 16832102]

Kaufmann WE, Jarrar MH, Wang JS, Lee YJ, Reddy S, Bibat G, Naidu S. Histone modifications in Rett syndrome lymphocytes: a preliminary evaluation. Brain Dev. 2005;27:331–9. [PubMed: 16023547]

Kerr AM, Julu PO. Recent insights into hyperventilation from the study of Rett syndrome. Arch Dis Child. 1999;80:384–7. [PubMed: 10086952]

Kerr AM, Webb P, Prescott RJ, Milne Y. Results of surgery for scoliosis in Rett syndrome. J Child Neurol. 2003;18:703–8. [PubMed: 14649553]

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;70:1034–7. [PubMed: 11885030]

Kleefstra T, Yntema HG, Nillesen WM, Oudakker AR, Mullaart RA, Geerdink N, van Bokhoven H, de Vries BB, Sistermans EA, Hamel BC. MECP2 analysis in mentally retarded patients: implications for routine DNA diagnostics. Eur J Hum Genet. 2004;12:24–8. [PubMed: 14560307]

Klose RJ, Sarraf SA, Schmiedeberg L, McDermott SM, Stancheva I, Bird AP. DNA binding selectivity of MeCP2 due to a requirement for A/T sequences adjacent to methyl-CpG. Mol Cell. 2005;19:667–78. [PubMed: 16137622]

Kokura K, Kaul SC, Wadhwa R, Nomura T, Khan MM, Shinagawa T, Yasukawa T, Colmenares C, Ishii S. The Ski protein family is required for MeCP2-mediated transcriptional repression. J Biol Chem. 2001;276:34115–21. [PubMed: 11441023]

Kriaucionis S, Bird A. The major form of MeCP2 has a novel N-terminus generated by alternative splicing. Nucleic Acids Res. 2004;32:1818–23. [PubMed: 15034150]

Kudo S, Nomura Y, Segawa M, Fujita N, Nakao M, Dragich J, et al. Functional analyses of MeCP2 mutations associated with Rett syndrome using transient expression systems. Brain Dev. 2001;23:S165–73. [PubMed: 11738866]

Kudo S, Nomura Y, Segawa M, Fujita N, Nakao M, Hammer S, Schanen C, Terai I, Tamura M. Functional characterisation of MeCP2 mutations found in male patients with X linked mental retardation. J Med Genet. 2002;39:132–6. [PubMed: 11836365]

Kudo S, Nomura Y, Segawa M, Fujita N, Nakao M, Schanen C, Tamura M. Heterogeneity in residual function of MeCP2 carrying missense mutations in the methyl CpG binding domain. J Med Genet. 2003;40:487–93. [PubMed: 12843318]

Laccone F, Junemann I, Whatley S, Morgan R, Butler R, Huppke P, Ravine D. Large deletions of the MECP2 gene detected by gene dosage analysis in patients with Rett syndrome. Hum Mutat. 2004;23:234–44. [PubMed: 14974082]

Laurvick CL, de Klerk N, Bower C, Christodoulou J, Ravine D, Ellaway C, Williamson S, Leonard H. Rett syndrome in Australia: a review of the epidemiology. J Pediatr. 2006;148:347–52. [PubMed: 16615965]

Leonard H, Colvin L, Christodoulou J, Schiavello T, Williamson S, Davis M, Ravine D, Fyfe S, de Klerk N, Matsuishi T, Kondo I, Clarke A, Hackwell S, Yamashita Y. Patients with the R133C mutation: is their phenotype different from patients with Rett syndrome with other mutations? J Med Genet. 2003;40:e52. [PubMed: 12746406]

Leonard H, Silberstein J, Falk R, Houwink-Manville I, Ellaway C, Raffaele LS, Engerstrom IW, Schanen C. Occurrence of Rett syndrome in boys. J Child Neurol. 2001;16:333–8. [PubMed: 11392517]

Lobo-Menendez F, Sossey-Alaoui K, Bell JM, Copeland-Yates SA, Plank SM, Sanford SO, Skinner C, Simensen RJ, Schroer RJ, Michaelis RC. Absence of MeCP2 mutations in patients from the South Carolina autism project. Am J Med Genet B Neuropsychiatr Genet. 2003;117:97–101. [PubMed: 12555243]

Lotan M, Isakov E, Merrick J. Improving functional skills and physical fitness in children with Rett syndrome. J Intellect Disabil Res. 2004;48:730–5. [PubMed: 15494062]

Makedonski K, Abuhatzira L, Kaufman Y, Razin A, Shemer R. MeCP2 deficiency in Rett syndrome causes epigenetic aberrations at the PWS/AS imprinting center that affects UBE3A expression. Hum Mol Genet. 2005;14:1049–58. [PubMed: 15757975]

Mari F, Caselli R, Russo S, Cogliati F, Ariani F, Longo I, Bruttini M, Meloni I, Pescucci C, Schurfeld K, Toti P, Tassini M, Larizza L, Hayek G, Zappella M, Renieri A. Germline mosaicism in Rett syndrome identified by prenatal diagnosis. Clin Genet. 2005;67:258–60. [PubMed: 15691364]

Martinowich K, Hattori D, Wu H, Fouse S, He F, Hu Y, Fan G, Sun YE. DNA methylation-related chromatin remodeling in activity-dependent BDNF gene regulation. Science. 2003;302:890–3. [PubMed: 14593184]

Masuyama T, Matsuo M, Jing JJ, Tabara Y, Kitsuki K, Yamagata H, Kan Y, Miki T, Ishii K, Kondo I. Classic Rett syndrome in a boy with R133C mutation of MECP2. Brain Dev. 2005;27:439–42. [PubMed: 16122633]

McArthur AJ, Budden SS. Sleep dysfunction in Rett syndrome: a trial of exogenous melatonin treatment. Dev Med Child Neurol. 1998;40:186–92. [PubMed: 9566656]

Mnatzakanian GN, Lohi H, Munteanu I, Alfred SE, Yamada T, MacLeod PJ, Jones JR, Scherer SW, Schanen NC, Friez MJ, Vincent JB, Minassian BA. A previously unidentified MECP2 open reading frame defines a new protein isoform relevant to Rett syndrome. Nat Genet. 2004;36:339–41. [PubMed: 15034579]

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;29:31–7. [PubMed: 10400100]

Motil KJ, Schultz RJ, Wong WW, Glaze DG. Increased energy expenditure associated with repetitive involuntary movement does not contribute to growth failure in girls with Rett syndrome. J Pediatr. 1998;132:228–33. [PubMed: 9506632]

Nan X, Ng HH, Johnson CA, Laherty CD, Turner BM, Eisenman RN, Bird A. Transcriptional repression by the methyl-CpG-binding protein MeCP2 involves a histone deacetylase complex. Nature. 1998;393:386–9. [PubMed: 9620804]

Neul JL, Maricich SM, Islam M, Barrish J, Smith EO, Bottiglieri T, Hyland K, Humphreys P, Percy A, Glaze D. Spinal fluid 5-methyltetrahydrofolate levels are normal in Rett syndrome. Neurology. 2005;64:2151–2. [PubMed: 15985595]

Ng HH, Bird A. DNA methylation and chromatin modification. Curr Opin Genet Dev. 1999;9:158–63. [PubMed: 10322130]

Nuber UA, Kriaucionis S, Roloff TC, Guy J, Selfridge J, Steinhoff C, Schulz R, Lipkowitz B, Ropers HH, Holmes MC, Bird A. Up-regulation of glucocorticoid-regulated genes in a mouse model of Rett syndrome. Hum Mol Genet. 2005;14:2247–56. [PubMed: 16002417]

Oexle K, Thamm-Mucke B, Mayer T, Tinschert S. Macrocephalic mental retardation associated with a novel C-terminal MECP2 frameshift deletion. Eur J Pediatr. 2005;164:154–7. [PubMed: 15558314]

Orrico A, Lam C, Galli L, Dotti MT, Hayek G, Tong SF, Poon PM, Zappella M, Federico A, Sorrentino V. MECP2 mutation in male patients with non-specific X-linked mental retardation. FEBS Lett. 2000;481:285–8. [PubMed: 11007980]

Pelka GJ, Watson CM, Christodoulou J, Tam PP. Distinct expression profiles of Mecp2 transcripts with different lengths of 3'UTR in the brain and visceral organs during mouse development. Genomics. 2005;85:441–52. [PubMed: 15780747]

Pelka GJ, Watson CM, Radziewic T, Hayward M, Lahooti H, Christodoulou J, Tam PP. Mecp2 deficiency is associated with learning and cognitive deficits and altered gene activity in the hippocampal region of mice. Brain. 2006;129:887–98. [PubMed: 16467389]

Percy AK, Glaze DG, Schultz RJ, Zoghbi HY, Williamson D, Frost JD Jr, Jankovic JJ, del Junco D, Skender M, Waring S, et al. Rett syndrome: controlled study of an oral opiate antagonist, naltrexone. Ann Neurol. 1994;35:464–70. [PubMed: 8154874]

Percy AK, Lane JB. Rett syndrome: model of neurodevelopmental disorders. J Child Neurol. 2005;20:718–21. [PubMed: 16225824]

Poirier K, Francis F, Hamel B, Moraine C, Fryns JP, Ropers HH, Chelly J, Bienvenu T. Mutations in exon 1 of MECP2B are not a common cause of X-linked mental retardation in males. Eur J Hum Genet. 2005;13:523–4. [PubMed: 15770224]

Ramaekers VT, Hansen SI, Holm J, Opladen T, Senderek J, Hausler M, Heimann G, Fowler B, Maiwald R, Blau N. Reduced folate transport to the CNS in female Rett patients. Neurology. 2003;61:506–15. [PubMed: 12939425]

Ravn K, Nielsen JB, Skjeldal OH, Kerr A, Hulten M, Schwartz M. Large genomic rearrangements in MECP2. Hum Mutat. 2005;25:324. [PubMed: 15712379]

Reichwald K, Thiesen J, Wiehe T, Weitzel J, Poustka WA, Rosenthal A, Platzer M, Stratling WH, Kioschis P. Comparative sequence analysis of the MECP2-locus in human and mouse reveals new transcribed regions. Mamm Genome. 2000;11:182–90. [PubMed: 10723722]

Rett Syndrome Diagnostic Criteria Work Group. Diagnostic criteria for Rett syndrome. Ann Neurol. 1988;23:425–8. [PubMed: 2454607]

Ryan D, McGregor F, Akermanis M, Southwell K, Ramke M, Woodyatt G. Facilitating communication in children with multiple disabilities: three case studies of girls with Rett syndrome. Disabil Rehabil. 2004;26:1268–77. [PubMed: 15513725]

Saxena A, de Lagarde D, Leonard H, Williamson SL, Vasudevan V, Christodoulou J, Thompson E, MacLeod P, Ravine D. Lost in translation: translational interference from a recurrent mutation in exon 1 of MECP2. J Med Genet. 2006;43:470–7. [PubMed: 16155192]

Scala E, Ariani F, Mari F, Caselli R, Pescucci C, Longo I, Meloni I, Giachino D, Bruttini M, Hayek G, Zappella M, Renieri A. CDKL5/STK9 is mutated in Rett syndrome variant with infantile spasms. J Med Genet. 2005;42:103–7. [PubMed: 15689447]

Schanen C, Houwink EJ, Dorrani N, Lane J, Everett R, Feng A, Cantor RM, Percy A. Phenotypic manifestations of MECP2 mutations in classical and atypical Rett syndrome. Am J Med Genet A. 2004;126:129–40. [PubMed: 15057977]

Schanen NC, Kurczynski TW, Brunelle D, Woodcock MM, Dure LS IV, Percy AK. Neonatal encephalopathy in two boys in families with recurrent Rett syndrome. J Child Neurol. 1998;13:229–31. [PubMed: 9620015]

Schollen E, Smeets E, Deflem E, Fryns JP, Matthijs G. Gross rearrangements in the MECP2 gene in three patients with Rett syndrome: implications for routine diagnosis of Rett syndrome. Hum Mutat. 2003;22:116–20. [PubMed: 12872251]

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;32:162–4. [PubMed: 11521215]

Sekul EA, Moak JP, Schultz RJ, Glaze DG, Dunn JK, Percy AK. Electrocardiographic findings in Rett syndrome: an explanation for sudden death? J Pediatr. 1994;125:80–2. [PubMed: 8021793]

Shahbazian M, Young J, Yuva-Paylor L, Spencer C, Antalffy B, Noebels J, Armstrong D, Paylor R, Zoghbi H. Mice with truncated MeCP2 recapitulate many Rett syndrome features and display hyperacetylation of histone H3. Neuron. 2002;35:243–54. [PubMed: 12160743]

Shahbazian MD, Zoghbi HY. Molecular genetics of Rett syndrome and clinical spectrum of MECP2 mutations. Curr Opin Neurol. 2001;14:171–6. [PubMed: 11262731]

Shi J, Shibayama A, Liu Q, et al. Detection of heterozygous deletions and duplications in the MECP2 gene in Rett syndrome by robust dosage PCR (RD-PCR). Hum Mutat. 2005;25:505. [PubMed: 15841480]

Stancheva I, Collins AL, Van den Veyver IB, Zoghbi H, Meehan RR. A mutant form of MeCP2 protein associated with human Rett syndrome cannot be displaced from methylated DNA by notch in Xenopus embryos. Mol Cell. 2003;12:425–35. [PubMed: 14536082]

Steffenburg U, Hagberg G, Hagberg B. Epilepsy in a representative series of Rett syndrome. Acta Paediatr. 2001;90:34–9. [PubMed: 11227330]

Tao J, Van Esch H, Hagedorn-Greiwe M, Hoffmann K, Moser B, Raynaud M, Sperner J, Fryns JP, Schwinger E, Gecz J, Ropers HH, Kalscheuer VM. Mutations in the X-linked cyclin-dependent kinase-like 5 (CDKL5/STK9) gene are associated with severe neurodevelopmental retardation. Am J Hum Genet. 2004;75:1149–54. [PubMed: 15499549]

Tate P, Skarnes W, Bird A. The methyl-CpG binding protein MeCP2 is essential for embryonic development in the mouse. Nat Genet. 1996;12:205–8. [PubMed: 8563762]

Topcu M, Akyerli C, Sayi A, Toruner GA, Kocoglu SR, Cimbis M, Ozcelik T. Somatic mosaicism for a MECP2 mutation associated with classic Rett syndrome in a boy. Eur J Hum Genet. 2002;10:77–81. [PubMed: 11896459]

Trappe R, Laccone F, Cobilanschi J, Meins M, Huppke P, Hanefeld F, Engel W. MECP2 mutations in sporadic cases of Rett syndrome are almost exclusively of paternal origin. Am J Hum Genet. 2001;68:1093–101. [PubMed: 11309679]

Vacca M, Filippini F, Budillon A, Rossi V, Mercadante G, Manzati E, Gualandi F, Bigoni S, Trabanelli C, Pini G, Calzolari E, Ferlini A, Meloni I, Hayek G, Zappella M, Renieri A, D'Urso M, D'Esposito M, MacDonald F, Kerr A, Dhanjal S, Hulten M. Mutation analysis of MECP2 gene in British and Italian Rett syndrome females. J Mol Med. 2001;78:648. [PubMed: 11269512]

Van Esch H, Bauters M, Ignatius J, Jansen M, Raynaud M, Hollanders K, Lugtenberg D, Bienvenu T, Jensen LR, Gecz J, Moraine C, Marynen P, Fryns JP, Froyen G. Duplication of the MECP2 region is a frequent cause of severe mental retardation and progressive neurological symptoms in males. Am J Hum Genet. 2005;77:442–53. [PubMed: 16080119]

Villard L, Kpebe A, Cardoso C, Chelly PJ, Tardieu PM, Fontes M. Two affected boys in a Rett syndrome family: clinical and molecular findings. Neurology. 2000;55:1188–93. [PubMed: 11071498]

Wan M, Lee SS, Zhang X, Houwink-Manville I, Song HR, Amir RE, Budden S, Naidu S, Pereira JL, Lo IF, Zoghbi HY, Schanen NC, Francke U. Rett syndrome and beyond: recurrent spontaneous and familial MECP2 mutations at CpG hotspots. Am J Hum Genet. 1999;65:1520–9. [PubMed: 10577905]

Watson P, Black G, Ramsden S, Barrow M, Super M, Kerr B, Clayton-Smith J. Angelman syndrome phenotype associated with mutations in MECP2, a gene encoding a methyl CpG binding protein. J Med Genet. 2001;38:224–8. [PubMed: 11283202]

Weaving LS, Christodoulou J, Williamson SL, Friend KL, McKenzie OL, Archer H, Evans J, Clarke A, Pelka GJ, Tam PP, Watson C, Lahooti H, Ellaway CJ, Bennetts B, Leonard H, Gecz J. Mutations of CDKL5 cause a severe neurodevelopmental disorder with infantile spasms and mental retardation. Am J Hum Genet. 2004;75:1079–93. [PubMed: 15492925]

Weaving LS, Ellaway CJ, Gecz J, Christodoulou J. Rett syndrome: clinical review and genetic update. J Med Genet. 2005;42:1–7. [PubMed: 15635068]

Weaving LS, Williamson SL, Bennetts B, Davis M, Ellaway CJ, Leonard H, Thong MK, Delatycki M, Thompson EM, Laing N, Christodoulou J. Effects of MECP2 mutation type, location and X-inactivation in modulating Rett syndrome phenotype. Am J Med Genet A. 2003;118:103–14. [PubMed: 12655490]

Witt-Engerstrom I. Age-related occurrence of signs and symptoms in the Rett syndrome. Brain Dev. 1992;14:S11–20. [PubMed: 1378244]

Young JI, Hong EP, Castle JC, Crespo-Barreto J, Bowman AB, Rose MF, Kang D, Richman R, Johnson JM, Berget S, Zoghbi HY. Regulation of RNA splicing by the methylation-dependent transcriptional repressor methyl-CpG binding protein 2. Proc Natl Acad Sci U S A. 2005;102:17551–8. [PubMed: 16251272]

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;28:519–26. [PubMed: 9932238]

Zeev BB, Yaron Y, Schanen NC, Wolf H, Brandt N, Ginot N, Shomrat R, Orr-Urtreger A. Rett syndrome: clinical manifestations in males with MECP2 mutations. J Child Neurol. 2002;17:20–4. [PubMed: 11913564]

Suggested Readings

Caballero IM, Hendrich B. MeCP2 in neurons: closing in on the causes of Rett syndrome. Hum Mol Genet. 2005;14:19–26. [PubMed: 15809268]

Kerr AM, Ravine D. Review article: breaking new ground with Rett syndrome. J Intellect Disabil Res. 2003;47:580–7. [PubMed: 14641805]

Percy AK, Lane JB. Rett syndrome: clinical and molecular update. Curr Opin Pediatr. 2004;16:670–7. [PubMed: 15548931]

Segawa M, Nomura Y. Rett syndrome. Curr Opin Neurol. 2005;18:97–104. [PubMed: 15791137]

Weaving LS, Ellaway CJ, Gecz J, Christodoulou J. Rett syndrome: clinical review and genetic update. J Med Genet. 2005;42:1–7. [PubMed: 15635068]

Williamson SL, Christodoulou J. Rett syndrome: new clinical and molecular insights. Eur J Hum Genet. 2006;14:896–903. [PubMed: 16865103]

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Revision History

- 25 January 2008 (cd) Revision: *MECP2* duplication syndrome added to Genetically Related Disorders
- 15 August 2006 (me) Comprehensive update posted to live Web site
- 11 February 2004 (me) Comprehensive update posted to live Web site
- 3 October 2001 (me) Review posted to live Web site
- September 2000 (vb) Original submission