The Overlapping Spectrum of Rett and Angelman Syndromes: A Clinical Review

Kerry Baldwin Jedele, MD

Rett and Angelman syndromes comprise part of the spectrum of neurologic disorders associated with autism. Their clinical presentations overlap, with both presenting in later infancy with global developmental delays, severe speech and communication impairments, progressive microcephaly, seizures, autistic behaviors, and characteristic albeit different movement disorders and stereotypic hand movements. Although other features can help differentiate these disorders, significant phenotypic overlap and variation in severity sometimes cloud the underlying diagnosis. Rett syndrome is caused by a mutation in the MECP2 gene located on Xq28, whereas Angelman syndrome results from the loss of UBE3A function on chromosomal region 15q11-q13 related to a variety of molecular genetic mechanisms. Recent advances have uncovered interactions between these and other genes that affect the function and structure of neurons in the brain. The reversal of symptoms of Rett syndrome in a mature mouse model suggests the possibility for treatment of these and perhaps other autism-related disorders in the future.

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Rett syndrome (RTT) and Angelman syndrome (AS) both present in infancy or early childhood with global developmental delays, severe speech and communication impairment, progressive microcephaly, movement disorders, seizures, stereotypic hand movements, and autistic behaviors. These syndromes can have significant clinical variation and phenotypic overlap. Only supportive care is presently available for these conditions. Although different genes and mechanisms have been implicated in these 2 syndromes, recent studies have shown intricate interactions linking the underlying defects in RTT and AS. These advances are paving the way to a better understanding and perhaps specific treatment of these and other autistic spectrum disorders.

RTT

RTT is an X-linked dominant disorder predominantly affecting females, caused in over 80% of cases by mutations in the methyl-CpG binding protein 2 (MECP2) gene. The prevalence of RTT in females is 1:10,000 to 1:15,000. Revised diagnostic criteria for classic and variant RTT and AS are shown in Tables 1 and 2, respectively. The only treatments available thus far are supportive.

Classic RTT

Females with classic RTT have an unremarkable pre- and postnatal course, with normal occipital-frontal circumference (OFC) at birth. Although development was originally believed to be normal, a video review of RTT girls in early infancy revealed abnormal movements, postures, and behaviors, especially asymmetric eye opening and closing, bizarre smiling, tongue protrusion, and stereotyped hand and body movements. Infants may have subtle truncal hypotonia with delayed head control, either overly placid or autistic-like behaviors, and sleep disturbance. These observations, although not specific for RTT, may raise clinical suspicion.

Developmental progress stalls in stage I; sitting is delayed in 41.2%, crawling in 63.6%, and walking in 83.3%. This stage may only be recognized in retrospect because development may not yet be clearly abnormal. Within a few weeks to months, stage II starts, with regression in skills. Autistic behaviors appear, often suddenly. Patients lose purposeful hand movements between 12 and 18 months of age followed by stereotyped “hand wringing.” Acquired language is usually lost. Progressive microcephaly is the rule by the first few years of life and correlates with subsequent severity of motor disability and intractable seizures.

Previously acquired major motor skills are slowly lost during stage II. Dysequilibrium, impaired locomotion, and gen-
### Table 1 Revised Diagnostic Criteria for Classic and Variant RTT

#### Revised diagnostic criteria for RTT

**Necessary criteria**

1. Apparently normal prenatal and perinatal history
2. Psychomotor development largely normal from 0 to 6 months, or delay from birth
3. Normal head circumference at birth
4. Postnatal deceleration of head growth in most
5. Loss of purposeful hand skill between 6 and 30 months
6. Stereotypic hand movements: wringing/squeezing, clapping, tapping, mouthing, rubbing
7. Emerging social withdrawal, communication dysfunction, loss of learned words, and cognitive impairment
8. Impaired (dypraxic) or failing locomotion

**Supportive criteria**

1. Awake disturbances of breathing (hyperventilation or forceful expulsion of air or saliva, air swallowing)
2. Bruxism
3. Impaired sleep pattern from early infancy
4. Abnormal muscle tone followed by muscle wasting and dystonia
5. Peripheral vasomotor disturbances
6. Scoliosis/kyphosis progressive through childhood
7. Growth retardation
8. Hypotrophic small and cold feet; small and thin hands

**Exclusion criteria**

1. Organomegaly or other signs of storage disease
2. Retinopathy, optic atrophy, or cataract
3. Evidence of perinatal or postnatal brain damage
4. Existence of identifiable metabolic or other progressive neurologic disorder
5. Acquired neurologic disorders resulting from severe infarctions or head trauma

#### Revised delineation of variant phenotypes

**Inclusion Criteria**

1. Meet at least 3/6 main criteria
2. Meet at least 5/11 supportive criteria

**Six main criteria**

1. Absence or reduction of hand skills
2. Reduction or loss of babble speech
3. Monotonous pattern to hand stereotypes
4. Reduction or loss of communication skills
5. Deceleration of head growth from first years of life
6. RTT disease profile: regression stage followed by recovery of interaction contrasting with slow neuromotor regression

**Eleven supportive criteria**

1. Breathing irregularities
2. Bloating/air swallowing
3. Harsh sounding bruxism
4. Abnormal locomotion
5. Scoliosis/kyphosis
6. Lower limb amyotrophy
7. Cold, purplish feet, usually small
8. Sleep disturbance, including night screaming
9. Laughing/screaming spells
10. Diminished pain response
11. Intense eye contact/eye pointing

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Generalized but asymmetric neuromuscular weakness develops. Hypertonicity, often starting in the legs, appears by early childhood. Despite dystonia, some gross motor functions improve slightly during stage III, in contrast to the continued loss of fine motor skills. By early adulthood, dystonia and hypertonia may result in joint contractures and increasing rigidity. Scoliosis, frequently rapidly progressive, develops in 74%, often accompanied by kyphosis. Osteoporosis with fractures are common, compounded by lack of weight bearing, decreased muscle mass and strength, and joint contractures.

The most striking characteristic in RTT patients is the hands. Subtle stereotypical hand movements may begin in infancy, and, by stage II and particularly stage III, the combination of wringing or “handwashing” movements and hand apraxia is obvious (Fig 1). The loss of purposeful movements and hand skills is the earliest and best clinical indicator of this diagnosis. The hands may become fixed and rigid over time, with a distorted position with wrist flexion. The hands and feet are frequently small, thin, and cold.

Social withdrawal, communication dysfunction, loss of acquired speech, and cognitive impairment are hallmarks of RTT. Screaming, night laughter, and inconsolable crying, sometimes lasting for hours, are frequent in stage III. Apparent high pain threshold and bruxism are common. Patients may have a marked preference for routine and strong attachment to toys and songs. Many classic RTT females have no recognizable communication, with brief gaze shifts as the only communication attempts in others. For others, eye or finger pointing or gestures express basic needs. Eye contact, eye pointing, and socialization often improve after stage II.

Autonomic dysregulation is common in RTT. Hyperventilation, rapid shallow breathing, apnea, breath holding, and Valsalva maneuvers during wakefulness are the rule. Topiramate, used for seizure control, frequently lessens respiratory dysrhythmias. Carbogen decreased seizures and vacant spells caused by severe forceful breathing. The use of naltrexone, an opiate antagonist, improved some respiratory parameters but is controversial because of an association with accelerated progression of RTT symptoms. Cardiac vagal tone and baroreceptor response are abnormal. Progressive loss of physiologic heart rate variability and prolonged corrected QT intervals may explain the increased risk for sudden death, which accounts for a quarter of all deaths in RTT. Medications that prolong the QT interval should be avoided. L-carnitine supplementation improves heart rate variability and might decrease the risk of sudden death.

Oropharyngeal incoordination, gastroesophageal dysmotility, gastroesophageal reflux, impairment of swallowing, constipation, and delayed emptying with gastric distention (the latter also worsened by air gulping) often result in poor nutritional status. Overall physical stature is small, with 85% to 90% of RTT females showing progressive growth failure. RTT females have an increased risk for gallbladder disease.

Abnormalities of sleep/wake patterns include the needs for more sleep than normal persons of the same age, frequent night-time awakenings, (often accompanied by screaming), and delay in sleep onset. Sleep patterns fail to show normal patterns.
maturational decrease in night- and daytime sleep. Behavioral interventions, melatonin, and pipamperone (used in a single case) may lessen sleep disturbances. L-carnitine may improve overall well-being, energy level, communication, and sleep.

Sedation and anesthesia of RTT patients carry a higher rate of complications, particularly prolonged apnea. Drug dosing may have to be adjusted down from the standard for weight and age. The age of death in RTT is highly variable, from infancy to old age; 77.8% in 1 series survived to age 25 years, with pneumonia being the most common single cause of death.

Seizures are a major issue in RTT, occurring in over 80% of individuals. The frequency can be difficult to quantify because patients manifest many paroxysmal nonepileptic motor activities, such as twitching, head jerking, breath holding, tremulousness, hyperventilation, staring, and laughing. Seizures are often misidentified by parents; 42% of nonepileptic activities were erroneously labeled seizures, whereas 15% of seizures went unrecognized. Video encephalographic (EEG) monitoring may be helpful in guiding treatment decisions.

Seizures may be refractory, despite optimal care and multiple medications. The wide spectrum of seizure types in RTT requires a variety of antiepileptic drugs (AEDs). A recent retrospective review of 110 patients found that carbamazepine was the most successful single agent, with sulthiame slightly less effective and valproate significantly less helpful. Note that these were the only drugs given often enough to be statistically analyzed in this group. Topiramate improved seizures in 7 of patients.

EEG abnormalities occur in virtually all RTT patients at some stage of disease, with a peak in stage III (97%) decreasing to 60% in stage IV. Although characteristic patterns of tracings have been identified, these are not specific enough to be diagnostic. Nevertheless, common patterns predominate and correlate with clinical stage, leading to a proposed classification of EEG stages by Glaze. A summary of the seizure activity and EEG abnormalities is presented in Table 3. Magnetic resonance imaging shows no consistent structural abnormalities. On pathologic examination, brain volumes are small but with relatively preserved posterior temporal and posterior occipital regions. No gross malformations, degenerative, or demyelinating processes are seen.

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### Table 2 Clinical Stages and Manifestations of RTT

<table>
<thead>
<tr>
<th>Stage</th>
<th>Descriptor</th>
<th>Age of Onset</th>
<th>Clinical Features</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Early-onset stagnation</td>
<td>5 to 18 months</td>
<td>Delayed developmental progress, Poor postural control “Bottom shufflers”</td>
<td>Weeks to months</td>
</tr>
<tr>
<td>II</td>
<td>Developmental regression</td>
<td>1 to 4 years</td>
<td>Intermittently “in another world” Cognitive impairment apparent Still using eye contact Mild breathing abnormalities Seizures in only 15%</td>
<td>Weeks to months</td>
</tr>
<tr>
<td>III</td>
<td>Pseudostationary phase</td>
<td>Early childhood after stage II</td>
<td>Some communication improvements “Wake-up” period Marked hand apraxia/dyspraxia Slow neuromotor regression Seizures most frequent and severe</td>
<td>Years to decades</td>
</tr>
<tr>
<td>IV</td>
<td>Late motor deterioration</td>
<td>IV A, loss of ambulation after stage III, or IV B, severe debilitation in patients who never walked</td>
<td>Severe wasting and debilitation leading to “frozen stiffness” Complete wheelchair dependency Seizures may lessen or disappear</td>
<td>Decades</td>
</tr>
</tbody>
</table>

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diet decreased seizures, increased social interactions, and helped behavior in small numbers. Vagal nerve stimulation was helpful in 7 of 8 patients refractory to AEDs. Clinicians must consider the type and severity of seizures, along with potential benefits and side effects in choosing appropriate treatment regimens for their patients.

**Variant RTT**

The availability of testing for MECP2 mutations has further expanded our understanding of clinical presentations of RTT and other MECP2-related disorders. MECP2 mutation-positive females with AS-like; infantile hypotonia without initial developmental progress; mild neurologic symptoms with good gross motor, speech and hand skills; autism; and asymptomatic female mutation carrier phenotypes. Skewed X inactivation may account for mild degrees of affection in females.

MECP2-related disorders in males cover a wide range of severity, but may be divided into three main categories. Males with either mosaicism or Klinefelter syndrome (47, XXY) have similar MECP2 mutations and clinical course as classic RTT females. The second group of males with the same mutations as RTT females manifests a severe progressive neuropathy with epilepsy, apnea, and death by age 3 years. Males with different MECP2 mutations may have less severe mental retardation or psychiatric or neurologic problems. MECP2 mutations may be found in 1.3% to 1.7% of nonsyndromic mentally retarded males. Duplication and even triplication of MECP2 has been identified in males with severe and progressive neurodevelopmental abnormalities.

Mutations in the X-linked CDKL5 gene occur rarely in RTT-like patients without MECP2 mutations, most of whom had onset of intractable seizures before 3 months. Myoclonic jerks and infantile spasms are more common in this group. Other CDKL5-positive cases included a female with autism and mild-moderate intellectual disability and a male with profound cognitive impairment and seizures. An RTT-like girl had a chromosomal translocation disrupting the netrin G1 (NTNG1) gene; however, negative mutation testing in 115 MECP2-negative RTT patients suggests that NTNG1 is a rare cause of RTT.

**Inheritance**

Sporadic cases of RTT are the rule, with 99.5% of cases single occurrences within the family. The new mutation almost always occurs on the paternal X chromosome, which may help explain the high preponderance of females with RTT (males do not transmit an X chromosome to their sons). Rare cases of germline mosaicism of MECP2 and CDKL5 and asymptomatic mothers passing on MECP2 mutations account for familial cases. Genetic counseling should be offered to all families regarding recurrence risk and prenatal testing.

**Molecular Genetic Testing**

Initial testing of most of the coding areas (exons) of MECP2 by DNA sequencing and mutation scanning looked for small changes, such as point mutations. This method detects mutations in >80% of cases with classic RTT. After 2003, testing for large gene deletions (not seen using the previous method) detected an additional 10 to 16% of cases. Mutations in exon 1, not included in earlier DNA sequencing, comprise only another 1% of RTT patients. MECP2 testing should be considered for females with features of classic or variant RTT, infants (especially males) with progressive encephalopathy, males with RTT-like features, AS-like children with normal methylation studies, and those with familial X-linked mental retardation without fragile X. Physicians should consider testing for CDKL5 mutations in RTT-like patients with onset of seizures before 3 months but probably not in patients with milder phenotypes who are unlikely to show mutations. NTNG1 testing is presently neither indicated nor available.

**AS**

The main clinical features of AS are severe cognitive impairment, happy affect, ataxia, seizures with a typical EEG pattern, little or no communication abilities, and an unusual
facial appearance. AS has many parallels with RTT, with apparently normal neurologic status and OFC at birth, acquired microcephaly, severe speech impairment, autistic behaviors, seizures, scoliosis, and availability only of supportive care. Unlike RTT, AS affects both sexes equally. There is no developmental regression, and purposeful hand movements are retained. Up to 6% of cases of severe developmental delay and seizures in children may be caused by AS. AS occurs in 1:12,000 to 1:20,000 in the general population. Clinical features revised in 2005 are listed in Table 4. AS is caused by a variety of mechanisms affecting the chromosome segment 15q11-q13, and classification by genetic mechanism correlates well with clinical phenotype (Table 5).

Clinical Course

The pre- and perinatal course and OFC of AS infants is normal. Feeding problems and truncal hypotonia in infancy are frequent but nonspecific findings. By 6 to 12 months, developmental delays without regression are obvious. Severe developmental delays and speech impairment are seen in virtually all patients, and acquired microcephaly affects many, particularly in class I. Most AS patients have an IQ <40, with others functioning at a slightly higher level. Language skills typically range from 0 to 5 words, with a median nine months level equivalent; receptive exceeded expressive language ability. A few patients have some minimal, usually nonfluent, speech; others are able to use some sign language or augmented communication devices at a very basic level. Self-help skills are limited, with daytime urinary continence in about a third; help with dressing and toileting is needed. Most individuals are able to walk independently between 2.5 and 5 years with a characteristic jerky, stiff gait with upraised arms; a smaller percentage, mostly class I, remained nonambulatory.

A unique behavioral pattern characteristic of AS often suggests the diagnosis. Jerky, atactic movements in association with inappropriate laughter, and a happy affect led to the name “Happy Puppet” syndrome, no longer used because of

### Table 3 Correlation of Clinical Stage With Typical Seizure Frequency, Type, and EEG Characteristics in RTT

<table>
<thead>
<tr>
<th>Stage</th>
<th>Seizure Activity</th>
<th>EEG Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Awake</td>
</tr>
<tr>
<td>I</td>
<td>Rare</td>
<td>Normal or slight slowing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slowing of dominant occipital and background activity</td>
</tr>
<tr>
<td>I-II</td>
<td>15%</td>
<td>Further slowing of background activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Loss of occipital dominant rhythm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Later onset focal spike or sharp wave</td>
</tr>
<tr>
<td>III</td>
<td>80%</td>
<td>Moderate-marked slowing of background activity</td>
</tr>
<tr>
<td></td>
<td>Increased severity and frequency, often mixed types</td>
<td>Multifocal spike- and/or sharp-wave discharges</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Generalized slow spike-wave pattern</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Occasional females with only slight background slowing</td>
</tr>
<tr>
<td>Late III</td>
<td></td>
<td>Generalized slow spike-wave pattern</td>
</tr>
<tr>
<td>IV</td>
<td>Fewer seizures, usually partial</td>
<td>Marked slowing of background activity, multifocal spike- and/or sharp-wave discharges or generalized slow spike-wave</td>
</tr>
<tr>
<td></td>
<td>Many patients seizure-free</td>
<td>Some patients with near-normal activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Monorhythmic generalized or frontal-central slow 3 to 6 Hz (theta) activity</td>
</tr>
</tbody>
</table>

Data from Glaze and Moser et al.

Severe developmental delays and speech impairment are seen in virtually all patients, and acquired microcephaly affects many, particularly in class I. Most AS patients have an IQ <40, with others functioning at a slightly higher level. Language skills typically range from 0 to 5 words, with a median nine months level equivalent; receptive exceeded expressive language ability. A few patients have some minimal, usually nonfluent, speech; others are able to use some sign language or augmented communication devices at a very basic level. Self-help skills are limited, with daytime urinary continence in about a third; help with dressing and toileting is needed. Most individuals are able to walk independently between 2.5 and 5 years with a characteristic jerky, stiff gait with upraised arms; a smaller percentage, mostly class I, remained nonambulatory.

A unique behavioral pattern characteristic of AS often suggests the diagnosis. Jerky, atactic movements in association with inappropriate laughter, and a happy affect led to the name “Happy Puppet” syndrome, no longer used because of
its negative connotations. Recent evaluation of the behavioral phenotype indicates abnormal food-related behaviors, hyperactivity, fascination for water, hand flapping, and sleep disturbance to be characteristic. Overall, 42% of children with AS meet criteria for diagnosis of autism. Tremulousness is common but must be differentiated from mild myoclonic epilepsy. AS individuals remain sociable throughout life. Attention span improves in adulthood, although aggressive behaviors may emerge, possibly related to communication difficulties.

Delayed sleep onset, night wakening, lower percentage of REM sleep, and increased breathing disorders and periodic leg movements may worsen the quality of life in both AS individuals and their caretakers. The severity of sleep problems is not related to variables such as AS class, age, epilepsy, or living situation. Melatonin has been shown to be effective in sleep disturbances. The effectiveness of other medications, such as sedatives, has not been documented.

Protracted bradycardia during and slow recovery after anesthetic administration was reported in a single case. The use of anesthetic agents that do not affect GABA, such as propofol and fentanyl derivatives, was suggested.

AS persons have varying degrees of growth failure. Class I patients are smaller with more microcephaly, whereas growth is normal or near normal in classes II-IV. Forty percent to 70% of persons develop scoliosis, often progressive. Contractures may develop in adulthood. Puberty occurs at the normal age in males and females, and pregnancy in an affected female has been reported. Overall health is generally good except for seizures.

Facial dysmorhisms include a wide mouth, deep-set eyes, widely spaced teeth, and prominent chin (Fig 2). These features are often subtle in childhood, becoming more prominent with age. Hypopigmentation occurs primarily in class I patients. Ocular manifestations include iris and choroidal hypopigmentation, retinocochrroidal atrophy, and strabismus.

Seizures are common in AS, occurring in over 80% of patients and frequently starting in late infancy or early childhood. Infantile spasms are rare, and most initial seizures occur (often with fever) by 3 years. Many seizure types occur across all AS classes. Atypical absences, complex partial with eye deviation and vomiting, generalized tonic clonic, unilateral clonic, and myotonic seizures are most common; status epilepticus, either nonconvulsive or myoclonic, occurs in over half of patients. In class I patients, epilepsy is universal, more severe, frequently generalized, often of mixed type, and of earlier onset (average 13 months). Refractory epilepsy and status epilepticus (84% each) and daily seizures (95%) were especially troublesome in this subgroup. Seizure frequency may also increase in adults with AS.

EEG patterns are characteristic in AS and may suggest this diagnosis. The 3 main EEG patterns may occur separately or in combination. These patterns occur in all classes independent of seizure severity but vary by age. Laan and Vein summarized the main EEG patterns as follows: the first and most common EEG pattern in both children and adults consists of rhythmic 2 to 3 Hz delta activity mainly over the frontal regions with superimposed interictal multifocal spikes and sharp waves of moderate amplitude. Slow activity tends to be predominant over the epileptiform activity and is more generalized. A variation on this pattern, seen in half of AS patients before diagnosis, is intermittent or continuous runs of rhythmic triphasic 2- to 3-Hz high-amplitude activity. The second pattern, frequently seen in young children, shows spikes and sharp waves mixed with 3- to 4-Hz high-amplitude components. This pattern is mainly posterior in distribution and seen most readily with eye closure during both wakefulness and sleep. The third pattern is generalized

### Table 4 Clinical Features of AS

<table>
<thead>
<tr>
<th>Class</th>
<th>Associated (20% to 80%)</th>
<th>Consistent (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.</td>
<td>Consistent (100%)</td>
<td></td>
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<tr>
<td></td>
<td>Severe developmental delay</td>
<td>Movement or balance disorder, usually ataxia of gait and/or tremulous movement of limbs. May include forward lurching, unsteadiness, clumsiness or quick, jerky motions</td>
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<tr>
<td></td>
<td>Unique behavioral profile, with any combination of frequent smiling/laughter, happy demeanor, easy excitability, hand-flapping, hypermotoric behavior</td>
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<tr>
<td></td>
<td>Speech impairment with no or minimal use of words; receptive and non-verbal communication better than verbal skills</td>
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<tr>
<td>B.</td>
<td>Frequent (&gt;80%)</td>
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<td></td>
<td>Delayed, disproportionate growth of OFC, usually &lt;2 SD by age 2 years</td>
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<tr>
<td></td>
<td>Seizures with onset &lt;3 years old; seizure disorder lasts through adulthood</td>
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<tr>
<td></td>
<td>Abnormal EEG, with characteristic pattern, often with onset &lt;2 years old and not correlated with clinical seizures</td>
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<tr>
<td>C.</td>
<td>Associated (20% to 80%)</td>
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<tr>
<td></td>
<td>Flat occiput</td>
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<tr>
<td></td>
<td>Protruding tongue</td>
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<tr>
<td></td>
<td>Tongue thrusting; suck/swallowing difficulties</td>
<td></td>
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<tr>
<td></td>
<td>Feeding problems and/or truncal hypotonia during infancy</td>
<td></td>
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<tr>
<td></td>
<td>Prognathia</td>
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<td></td>
<td>Wide mouth, widely spaced teeth</td>
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<tr>
<td></td>
<td>Frequent drooling</td>
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<tr>
<td></td>
<td>Excessive chewing/mouthing behaviors</td>
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<td></td>
<td>Strabismus</td>
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<td></td>
<td>Hypopigmentation compared to family (in deletion cases)</td>
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<tr>
<td></td>
<td>Brisk deep tendon reflexes in lower extremities</td>
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<td></td>
<td>Uplifted flexed arm position, especially during ambulation</td>
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<td></td>
<td>Wide-based gait with pronated ankles</td>
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<td></td>
<td>Increased sensitivity to heat</td>
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<td></td>
<td>Abnormal sleep-wake cycles and diminished need for sleep</td>
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<td></td>
<td>Attraction to/fascination with water</td>
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<td></td>
<td>Abnormal food-related behaviors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Obesity (older children and adults)</td>
<td></td>
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<tr>
<td></td>
<td>Scoliosis</td>
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<td></td>
<td>Constipation</td>
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persistent rhythmic 4- to 6-Hz high-amplitude activity, which does not extinguish on eye closure.93 The delta pattern is the most specific for AS and is extremely unusual in other syndromes.94 Magnetic resonance imaging typically shows no structural abnormalities except for mild cortical atrophy or dysmyelination73; muscle biopsy and electromyography are normal.72

Treatment of seizures varies by seizure type and may require more than one AED, particularly in class I patients. Many patients improve long-term using a combination of valproic acid with other AEDs, including clonazepam, lamotrigine, and benzodiazepines.72,92,95 Topiramate and ethosuximide are effective and well tolerated.96,97 Piracetam is used for myoclonus.81 Carbamazepine, oxcarbazepine,92,98 and vigabatrin92 are associated with deterioration in seizure control and should not be used. In general, GABAergic AEDs tend to be more effective, likely because a cluster of GABA-A receptor genes are deleted in the critical region of 15q11-q13.72 Ketogenic diet is effective in refractory cases.92

Molecular Genetics and Inheritance

The chromosomal region 15q11-q13 contains a number of genes, including ubiquitin-protein ligase E3A gene (UBE3A), shown to cause AS. This region is subject to differential gene silencing via methylation during gametogenesis in the parents. This imprinting is controlled by a nearby imprinting center (IC). Understanding the various mechanisms causing AS is crucial to ordering and interpretation of diagnostic testing.

The loss of function of the UBE3A accounts for over 80% of AS.99 This loss of function can occur by at least 4 mechanisms, summarized in Table 5. The most common, class I, involves deletion of the maternal UBE3A allele and surrounding genes, whose additional deletion is believed to contribute to the more severe phenotype. In class II, both chromosomes 15 are parental in origin, with no maternal copy present. Class III is caused by mutations of the IC, resulting in an improper methylation pattern, with both alleles acting as if they were paternal copies. Classes I to III therefore show only a paternal methylation pattern of this region of 15q. (Interestingly, the opposite pattern with only maternal methylation is seen in Prader-Willi syndrome.) Class IV results from a mutation within the maternal UBE3A gene, silencing its function but leaving both the maternal and paternal methylation patterns intact on testing. Class V patients have no identifiable molecular genetic cause.72 Although there is generally good correlation between genotype and phenotype, patients with identical mutations may have very different phenotypes.100,101

Testing strategies, as outlined in the GeneTests website, are based on the frequencies and mechanisms of the various classes of AS.103 Methylation testing is performed first to detect patients in classes I to III. If positive, further testing is
performed to distinguish between these classes, first FISH to detect deletions followed (if negative) by DNA polymorphism analysis and analysis for IC deletion. This further testing helps predict both phenotype and recurrence risk for future children. For patients with normal methylation, UBE3A sequence analysis is performed. A karyotype to look for rare chromosomal rearrangements should be performed on all affected patients. Recurrence risks for families with 1 affected child can vary from <1% to almost 100% in rare cases, depending on the underlying molecular or chromosomal mechanism. Families should be referred for genetic counseling for discussion of recurrence risks and reproductive options.

Assisted reproductive technologies in subfertile couples, including intracytoplasmic sperm injection and hormonal stimulation, have been associated with an increased risk of an imprinting defect leading to AS. A few AS-like patients have MECP2 mutations; this testing should be considered in class V patients.

**Underlying Mechanisms of Action of RTT and AS and Outlook for Treatment**

The exact roles of MECP2 and UBE3A in brain functioning are not yet entirely understood. MECP2 protein is ubiquitously expressed and binds specifically to methylated DNA. MECP2 acts in concert with other proteins to repress transcription in targeted genes and promote heterochromatin formation. Decreased MECP2 expression is seen in AS and autism brain samples. In addition, MECP2 deficiency reduces the expression of both E6-associated protein (E6AP) (the protein product of UBE3A) and GABRB3 (a subunit of the GABA-A receptor cluster on 15q11-13) in brains from RTT, AS, and autism patients. These findings suggest overlapping gene dysregulation pathways in the AS-critical region as an underlying cause for these 3 conditions.

MECP2 also represses expression of brain-derived neurotrophic factor, crucial for dendritic patterning and thus adult neuronal plasticity, learning, and memory. The repression of this factor is consistent with the reduced dendritic branching and spines seen in ultrastructural studies of RTT and AS brains.

Recent work in RTT mouse models using transgenes to restore MECP2 activity in both immature and mature adult mice showed significant improvements or even normalization of neurologic function. This reversal of symptoms indicates that RTT is not strictly a neurodevelopmental disorder. Rather, MECP2 seems to be crucial in stabilizing and maintaining mature neurons. Although not immediately applicable for human therapies, the prospect of at least partial reversibility of neurologic abnormalities in affected patients is heartening.

UBE3A produces the protein E6AP, which acts by helping target proteins for selective degradation. The mechanism(s) whereby a lack of E6AP produces AS is as yet unclear.

**Conclusion**

The RTT and AS spectra of neurologic disorders are increasingly being recognized as causes of a wide variety of conditions seen by pediatric and adult neurologists. Prompt diagnosis based on clinical suspicion is important for ensuring the initiation of appropriate supportive physical, occupational, speech, behavioral, and medical therapy. Molecular genetic confirmation of these diagnoses is crucial because of significant clinical overlap and to help define recurrence risk for future pregnancies. New advances in research suggest the possibility of treatment of these and other autistic spectrum disorders in the future.

**URL Resources**

The following are web sites with valuable information:

GeneTests: [http://www.genetests.org](http://www.genetests.org) for reviews of RTT and AS and listing of laboratories offering molecular genetic testing.


**References**

Rett and Angelman syndromes


