Rett syndrome

- Rett syndrome (RTT) is a neurodevelopmental disorder that occurs almost exclusively in females
- Typical development through the first 6 to 18 months of life
- Slowing of development
- Decreased head growth
- Loss of speech and most purposeful hand movement, display of stereotypic hand washing/wringer movements, loss of or problems with ambulation, seizures and breathing dysrhythmias

The prevalence of the Rett syndrome

- Reported to exist on all of the populated continents, within all races and ethnic groups, and in most countries of the world (e.g., Budden, 1986; Gouideres & Aicardi, 1985; Hanaoka, Ishikawa & Kamoshi, 1985; Kerr & Stephenson, 1986; Moodley, 1992)
- Affects approximately 1 in every 10,000 to 12,000 live female births (Hagberg, 1985; Kerr & Stephenson, 1986)
- One of the most common causes of mental retardation in females, second only to Down syndrome (Ellaway & Christodoulou, 1999)
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History of the disorder
- 1966 - The disorder was first described by Andreas Rett, an Austrian physician.
- 1980 - Bengt Hagberg, Swedish researcher, independently described the disorder as ‘infantile dementia and loss of hand use’.
- 1983 - The disorder was named Rett syndrome by Hagberg and his colleagues after their discovery of Rett’s earlier work.
- 1984 - First International Rett Syndrome Conference held in Vienna, Austria.
- 1986 - First North American International Rett Syndrome Conference in Baltimore, MD; International Rett Syndrome Association (IRSA) established.

Dr. Andreas Rett

History (continued)
- 1999 – MECP2 gene found to be related to the display of RTT (Amir, van den Veyver, Wan, Tran, Francke & Zoghbi, 1999)
  - MECP2 mutations have been identified in patients with a variety of clinical syndromes.
- 2002 – Dr. Zoghbi announces the creation of a mouse model for RTT research.
- 2007 - RTT disorder symptoms reversed in mouse model with the reintroduction of MECP2 (Guy, Gan Selfridge, Cobb & Bird, 2007).

Clinical presentation and natural history
Clinical presentation

- Classic Rett syndrome has a unique and characteristic course of development
- A staging system provides average guidelines to facilitate the characterization of the disorder patterns and profiles from infancy through adolescence (Hagberg and Witt-Engerstrom, 1986)

Stage 1 - early onset stagnation
(Onset 6 to 18 months of age)

- Deterioration, or at least a general slowing down (stagnation) of motor development
- Hypotonia (low muscle tone) is typically noted
- Somewhat diminished interest in toys and social interaction
- Stereotypic hand movements may begin
- Head circumference growth slows
- This stage usually lasts for a few months but can persist for more than a year

Stage 2 - rapid destructive
(Onset 1-4 years of age)

- Loss of many previously acquired abilities
- Loss of purposeful hand use and high rate stereotyped movements emerge
- Acquired speech is lost
- Stagnation or loss of acquired cognitive abilities
- Intellectual functioning - severe to profound range of mental retardation
- Aberrant breathing patterns; hyperventilation and apnea
- Rapidly declining social interaction
- Seizure activity in approximately one-fourth of individuals
- Sleep abnormalities including delayed sleep onset and increased night awakenings in more than three-fourths of individuals (Piazza et al., 1990)
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Stage 3 - plateau or pseudo-stationary
(Onset 2-10 years)
- Improved social interaction and diminished autistic symptomatology
- Greater awareness of their surroundings and increased attempts at using residual functional skills
- Communication skills are reported to improve [e.g., eye pointing, babbling, or even word pieces to signal communicative intent (Sekul & Percy, 1992)]
- Seizures occur in up to 80% of the girls with Rett syndrome (Coleman et al., 1988)
- Spasticity or rigidity, and scoliosis tend to progress, and
- "Jerky", truncal ataxia and apraxia becomes prominent
- Gait patterns are unsteady and initiating motor movements can be difficult for ambulatory individuals (ataxia/apraxia)

Stage 4 - late motor deterioration
(Onset 10+ years)
- Decreasing mobility and a number of late stage second neuron abnormalities (e.g. drop foot abnormalities, remarkably plantar-flexed feet) may require the use of a wheelchair
- Progressive muscle wasting
- Scoliosis, spasticity, and rigidity
- Spinal cord dysfunction appears to act in conjunction with extrapyramidal features to lessen mobility (Witt-Engerstrom & Hagberg, 1990)
- Cognitive functioning remains stable
- Social interaction (eye contact) and attentiveness improve
- Seizure activity often becomes less problematic

Diagnosis

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Diagnosis of RTT

- Observation and ongoing evaluations of the child's physical and neurological status
- Blood test, the MECP2 sequencing + deletion analysis, to confirm the MECP2 mutation on the child's X chromosome (not present in approximately 20% of cases)
- A pediatric neurologist or developmental pediatrician should be consulted to confirm the clinical diagnosis of Rett syndrome

IRSA diagnostic criteria – necessary criteria

1) Apparently normal prenatal and perinatal history
2) Psychomotor development largely normal through the first six to 18 months or may be delayed from birth
3) Normal head circumference at birth
4) Postnatal deceleration of head growth in the majority of patients, but not all
5) Loss of achieved purposeful hand skill between ages six months and 2.5 years
6) Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms
7) Emerging social withdrawal, communication dysfunction, loss of learned words, and cognitive impairment
8) Impaired (dyspraxic) or failing locomotion

(Hagberg et al., 2002)

IRSA diagnostic criteria – supportive criteria

- Awake disturbances of breathing (hyperventilation, breath-holding, forced expulsion of air or saliva, air swallowing)
- Teeth grinding (bruxism)
- Impaired sleep pattern from early infancy
- Abnormal muscle tone successively associated with muscle wasting and dystonia
- Peripheral vasomotor disturbances (cold, blue hands and feet)
- Scoliosis/Kyphosis progressing through childhood
- Hypotrophic (small) feet; small, thin hands
- Growth retardation

(Hagberg et al., 2002)
IRSA diagnostic criteria – exclusionary criteria

- Enlarged organs or other signs of storage disease
- Retinopathy, optic atrophy, or cataract
- Existence of identifiable metabolic or other progressive neurological disorder
- Acquired neurological disorder resulting from severe infection or head trauma
- Evidence of brain damage before or after birth

(Hagberg et al., 2002)

Diagnostic criteria (DSM-IV-TR)

A. All of the following:
1. Apparently normal prenatal and perinatal development
2. Apparently normal psychomotor development through the first 5 months after birth
3. Normal head circumference at birth

B. Onset of all of the following after the period of normal development:
1. Deceleration of head growth between ages 5 and 48 months
2. Loss of previously acquired purposeful hand skills between ages 5 and 30 months with the subsequent development of stereotyped hand movements (e.g., hand-wringing or hand washing)
3. Loss of social engagement early in the course (although often social interaction develops later)
4. Appearance of poorly coordinated gait or trunk movements
5. Severely impaired expressive and receptive language development with severe psychomotor retardation

Diagnostic criteria (DSM-IV-TR) associated features and disorders

C. Associated features and disorders
1. Severe or profound mental retardation (Axis II)
2. Increased frequency of EEG abnormalities and seizure disorders
3. Nonspecific brain imaging abnormalities
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IRSA vs. DSM-IV-TR

IRSA diagnostic work group
- ‘Largely normal development through first 6 months or may be delayed from birth’
- ‘Postnatal deceleration of head growth will be evident in the majority of cases, but not all’
- ‘Apparently normal development may appear for up to 18 months’

DSM-IV-TR
- ‘Apparent normal psychomotor development through the first 5 months after birth’
- ‘Deceleration of head growth between 5 and 48 months of age’
- Adopted a 5 month upper age level for normal psychomotor development

The two sources differ with regard to Supportive Criteria

- Failure to identify exclusionary criteria

Atypical Rett syndrome

- Atypical RTT: those who do not meet all of the diagnostic criteria for classical RTT
- The diagnosis of atypical RTT must include
  - At least three of the primary criteria, and
  - Five of the eleven supportive criteria
- Atypical RTT accounts for 15-20 percent of all RTT diagnoses

Types of atypical RTT include:

- Congenital onset RTT: developmental delay noticed shortly after birth with no early normal development; or severe seizures in early infancy impairing early development
- Late onset RTT: signs are delayed beyond the typical 18 month onset, in some cases to age 10 years or more
- Preserved speech RTT: retain or recover some degree of speech and hand use and usually do not show growth failure; progressive scoliosis, epilepsy, and other associated disabilities are rare or displayed far less severely
- Male RTT - Klinefelter (XXY) or somatic mosaicism

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Differential diagnosis

- Rett’s Disorder
  - Mostly females
  - Deterioration in developmental milestones, head circumference, overall growth
  - Loss of purposeful hand movements
  - Stereotypic hand movements (hand-wringing, hand washing, hand-to-mouth)
  - Poor coordination, ataxia, apraxia
  - Loss of verbalization
  - Respiratory irregularity
  - Early seizures
  - Low CSF nerve growth factor

- Autistic Disorder
  - Mostly males
  - Abnormalities present from birth
  - Stereotypic hand movements not always present
  - Little to no loss in gross motor function
  - Aberrant language, but not complete loss
  - No respiratory irregularity
  - Seizures rare; if occur, develop in adolescence
  - Normal CSF nerve growth factor

Etiology of Rett syndrome

Rett syndrome: a genetic etiology

- Approximately 70 to 80% of persons with RTT display a mutation in the MECP2 gene, which is found on the X chromosome
- MeCP2 protein serves to ‘silence’ some genes and to ‘activate’ others
- May function in maintenance of developing and mature neurons and their connections
- Highly expressed in brain

Mutation in MECP2 gene
- Incomplete or poorly functioning MeCP2 protein
- Impaired function in cells missing MeCP2 protein
- Tissue effects
- Behavioral Symptoms
Random inactivation of one X-chromosome in each cell

- For females, each cell contains two X-chromosomes
- Each cell only requires 1 active X-chromosome
- Typically, one X chromosome in each cell becomes inactivated through a random process called lyonization
- RTT can present quite differently across individuals - manifesting mild to severe disabilities
- The course and severity of Rett syndrome is determined by the location, type and severity of the mutation and X-inactivation

Rett syndrome and sporadic mutation

- Over 200 mutations of the MECP2 gene have been linked to RTT
- The majority of MECP2 mutations are sporadic mutations
- Eight sporadic mutations responsible for over 50% of known cases of RTT
- Paternal origin suspected
- No known cause of sporadic mutation in Rett syndrome

Familial RTT

- Approximately 1% of cases involve inherited X-linked dominant disorder
- Mother is positive for carrying MECP2 mutation
- Non-random X chromosome inactivation favoring non-mutated X chromosome
- Mother does not display Rett syndrome, but passes mutated MECP2 gene to children

Familial RTT Phenotype
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Rett syndrome and MECP2

- Rett syndrome:
  - Is a clinical diagnosis
  - Is not synonymous with MECP2 mutations
  - May be seen with MECP2 mutations
  - May be seen without MECP2 mutations

- MECP2 mutations may be seen without Rett syndrome

Other disorders linked to mutations of MECP2 Gene

- Angelman syndrome-like phenotype
  (Watson, Black & Ramsden, 2001)
- Mild learning disability (Hoffbuhr et al., 2001) and
- Infantile autism
  (Beyer, Blasi, Bacchelli, Klauck, Maestrini & Poustka, 2002)
- X-linked mental retardation
  (Molini, Bruttini & Longo, 2000)
- Severe encephalopathy
  (Hoffbuhr et al., 2001, Wan et al., 1999)

Other genes associated with RTT

- CDKL5 (cyclin-dependent kinase-like 5) mutations can cause an atypical form of Rett syndrome called the early-onset seizure variant
  - The CDKL5 gene provides instructions for making a protein that appears to be essential for normal brain development
  - Although the function of this protein is unknown, it may play a role in regulating the activity of other genes
  - These individuals generally test negative for a MECP2 mutation
  - The CDKL5 mutation associated with other disorders including:
    - Infantile spasms
    - West syndrome
    - Early onset seizures
    - Autism

Scala et al., 2005
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Mouse models

- Knock-out mouse
  - Mecp2 Deleted
- Knock-in mouse
  - Human Mecp2 mutation inserted

Mouse model and human display of MECP2 mutation

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Mouse Model</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal early development</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Tremors</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Spasticity</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hypoactivity</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Seizures</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Ataxia</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Paw/hand stereotypies</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Social behavior dysfunction</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Kyphosis/scoliosis</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Symptoms reversed in mouse model

- MECP2 gene silenced in mouse model in a manner that allowed it to be ‘switched back on’
- Restoration of fully functional MECP2 over a four week period:
  - Eradicated tremors
  - Normalized breathing
  - Normalized mobility and gait
- Long-term potentiation (ability of a neuron to respond to stimulation and correlated to learning and development) restored to normal function by the reversal experiments
- Cure or Kill!

(Guy et al., 2007)
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Neuropathology in Rett syndrome
- Brain is smaller (30%) and weighs less than expected for individuals weight and height (Armstrong, Dunn, Schultz, Herbert, Glaze & Motile, 1999)
- Under pigmentation of the substantia nigra (Brucke et al., 1988)
- Increased serotonin receptors in the brainstem (Kerr & Wit-Engerstrom; 2001)
- Reduced axonal and dendritic connections in the frontal cortex and the caudate nucleus of the brain (Jellinger, Armstrong, Zoghbi and Percy, 1988)
- Reduced dendritic arborization (Armstrong et al., 1995)

Neuroanatomy of Rett syndrome
- Decreased cerebral blood flow to the prefrontal and temporal lobes (Nielsen, Friberg, Lou et al., 1990)
- Decreased area of caudate nucleus (Cassanova et al., 1991)
- Smaller cerebral hemispheres, basal ganglia, corpus callosum, cerebellar hemispheres, inferior olive, and anterior vermis (Murakami et al., 1992)
- Medulla (brain stem) immaturity (Poo, 2001)

Neurochemical alterations in Rett syndrome
- Reductions in:
  - Dopamine production (Riederer et al., 1985; Zoghbi et al., 1985)
  - Acetylcholine production (Wenk et al., 1991, 1993)
- Increases in:
  - Glutamate production (Hamberger, Gillberg, Palm & Hagberg, 1992; Lappalainen & Rikonen, 1996; Pan, Lane, Hetherington & Percy, 1999)
  - GD1a and GD1b brain gangliosides (Lekman, Hagberg & Svennerholm, 1991)
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Growth patterns and nutrition
- Deceleration across all growth measurements, following the first six months of life (Schultz et al., 1993)
- Nutritional, rather than chromosomal, neurologic, or hormonal, factors underlie this failure to grow
  - Defects in metabolism
  - Carbohydrate (Clark et al., 1990; Haas et al., 1986; Haas & Rice, 1985)
  - Ascorbic acid and
  - Glutathione (Sofic, Riederer, Killian & Rett, 1987)
- Malabsorption of critical nutrients and failure to benefit from adequate caloric intake
- Feeding Problems
  - GI reflux
  - Calcium deficiency
  - Constipation

Cognitive and adaptive functioning
- Standardized measures of intelligence counter-indicated
- Severe or profound range of mental retardation following the regression in stage 2 (Perry, Sarlo-McGarvey and Haddad, 1991)
- True dementia (Charnov et al., 1989) vs. a cognitive arrest or stagnation at the point of the initial motor and language regression (Fontanesi & Haas, 1988; Kerr et al., 1987; Naidu, Murphy, Moser & Rett, 1986)
- Adaptive behavior - skills not dependent on either language or fine motor function retained at a developmental level equivalent to the age of onset (Fontanesi and Haas, 1988)
- Areas of gross motor activity and daily living skills appear to be more advanced than other adaptive functions
- Capable of some cognitive improvement over time (Woodyatt & Ozanne, 1993)

Communication
- Single spoken words and/or word combinations prior to regression (Budden, Meek & Henighan, 1990; Woodyatt & Ozanne, 1992)
- Language non-existent or limited to non-functional consonant-vowel combinations (Budden, Meek & Henighan, 1990; Skejeldal et al., 1995; Zapella, 1992)
- Function at a pre-symbolic language level (Woodyatt & Ozanne, 1992, 1993)
- Vocalizations, facial expressions, gestures, walking towards a desired item or activity, and eye gaze
- Eye pointing and gross switch activated augmentative communication systems
Orthopedic aspects and intervention

- Multiple orthopedic and motor movement disorders
- Disorders vary significantly across the different syndrome stages
- Therapeutic intervention must be individualized
  (Hanks, 1986)

Ataxia and apraxia

- Earliest manifestations of motor problems in Rett syndrome
- Compensatory increased tone to achieve stability, resulting in abnormal movement patterns
- Tone reduction techniques
  1. Use of the therapy ball
  2. Balance stimulating floor activities
  3. Segmental rolling, and
  4. Rotation and weight shift activities
  5. Vestibular movement activities
  (Hanks, 1986, 1990)

Hand stereotypies

- One of the most distinguishing characteristics of the Rett syndrome
- Loss of purposeful hand function
- Nonvolitional movements resulting from an underlying extrapyramidal disorder
- Use of aversive consequences ill advised
- Operant conditioning techniques of limited value
  (Iwata, Pace, Willis, Gamache & Hyman, 1986)
  - Differential reinforcement of an incompatible response most effective
- Splinting
- Music therapy and switch activated toys
  (Hanks, 1986, 1990)
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Spasticity
- Variable level of severity
- May lead to distal contractures
- Contributes to scoliosis
- Treatments:
  - Hydrotherapy
    - Movement in the water
    - Range of motion, and
    - Basic water skills
  - Tone reduction activities
    - Rotation
    - Weight shift, and
    - Vibration

Ambulation
- Critical skill to develop and/or maintain in RTT
- Spatial disorientation – self-perception of an upright posture resulting in a forward, backward, or lateral leaning
- Treatment:
  - Weight bearing exercises
  - Walking
  - Stair climbing
  - Gait training
  - Activities designed to elicit righting and equilibrium responses
    - Use of the large therapy ball
    - Weight shifting

Scoliosis
- Tone reduction activities
  - Gentle lengthening of the concave side and activation of the convex side through elicitation of equilibrium reactions
  - Side lying with the apex of the curve down
  - Exercises designed to maximize use of the muscles the girl avoids using are in order (e.g. feed and lead the child by the hand on her hypotonic side)
  - Good positioning - strollers, wheelchairs, and high chairs fitted to produce a symmetrical sitting posture and an erect spine

(Hanks, 1986; Kjøerholt & Salthammer, 1989)
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Educational implications
- An appropriate education within the Least Restrictive Environment
  - Placement is driven by the needs of the child as specified in their educational plan (e.g., required curricular modifications and accommodations, instructional and related services needs)
- Involvement with typically developing peers and the general curriculum to the extent appropriate
- Promotion of functional skills in authentic settings and situations
  - Meaningful communication
  - Functional academics
  - Self-help and independence to the extent possible
- Empirically validated practices (Iwata et al., 1986)

Conclusion
- Human and animal studies to further clarify the genetic defects associated with RTT (e.g. MECP2, CDKL5, etc.)
- Downstream genes and pathogenesis
- First human disease caused by defects in a protein involved in the regulation of gene expression through interaction with methylated DNA
- Key to a number of human disorders
- Research avenues:
  - ‘Read through’ agents
  - Modulate X chromosome inactivation
  - Gene replacement
- “If we care today, we can cure tomorrow”

Video segments depicting children with Rett syndrome
- http://www.youtube.com/watch?v=6z91XWD4Zel
- http://www.youtube.com/watch?v=Xz18weetzxm
- http://www.youtube.com/watch?v=7S2k2QTMyq4
- http://www.youtube.com/watch?v=Fu3F3Q9s8g
- http://www.youtube.com/watch?v=L9CfaaRiX4c

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