# Rett Syndrome

Richard H. Haas M.B., B.Chir.

Professor of Neurosciences and Pediatrics


UNIVERSITY *of* CALIFORNIA, SAN DIEGO

MEDICAL CENTER

Rady Children's Hospital San Diego

# Faculty Disclosure Information

- UCSD Clinical Trial Investigator in Rett Syndrome with Acadia Pharmaceuticals

- No other Relevant Information to Disclose

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Andreas Rett

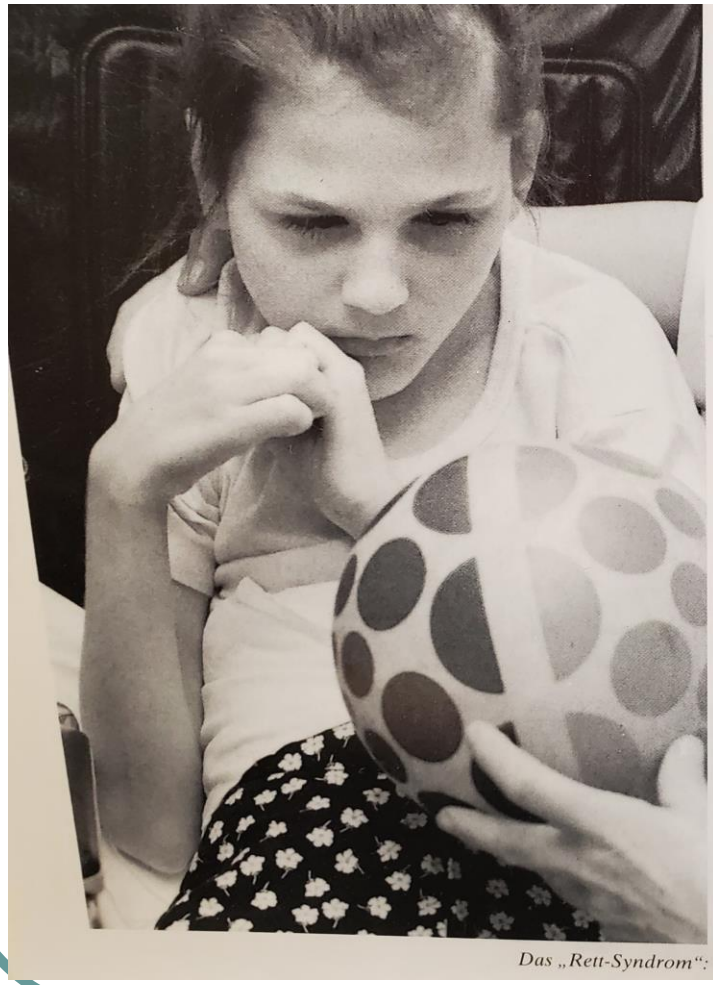
Children in our hands
A life with disabled people

1990

# How it started

- In 1965 in Vienna Austria Dr. Rett ‘sat in the waiting room of our cramped, poor clinic - there were two girls I have known for a long time on their mothers’ lap. By a fortunate coincidence, both mothers let go of their girls' arms at the same time ……..’

# ‘Washing Movements’



Das „Rett-Syndrom“:

Stereotypien der Handbewegungen, die nur bei Mädchen auftreten.

# Andreas Rett

Uber ein zerebral-atrophisches Syndrom bei Hyperammoniamie

Vienna, Bruder Hollinek, 1966

IRSA


# A Progressive Syndrome of Autism, Dementia, Ataxia, and Loss of Purposeful Hand Use in Girls: Rett's Syndrome: Report of 35 Cases

Bengt Hagberg, MD,* Jean Aicardi, MD,† Karin Dias, MD,‡ and Ovidio Ramos, MD†

Thirty-five patients, exclusively girls, from three countries had a uniform and striking progressive encephalopathy. After normal general and psychomotor development up to the age of 7 to 18 months, developmental stagnation occurred, followed by rapid deterioration of higher brain functions. Within one-and-a-half years this deterioration led to severe dementia, autism, loss of purposeful use of the hands, jerky truncal ataxia, and acquired microcephaly. The destructive stage was followed by apparent stability lasting through decades. Additional insidious neurological abnormalities supervened, mainly spastic parapareses, vasomotor disturbances of the lower limbs, and epilepsy. Prior extensive laboratory investigations have not revealed the cause. The condition is similar to a virtually overlooked syndrome described by Rett in the German literature. The exclusive involvement of females, correlated with findings in family data analyses, suggests a dominant mutation on one X chromosome that results in affected girls and nonviable male hemizygous conceptuses.

Hagberg B, Aicardi J, Dias K, Ramos O: A progressive syndrome of autism, dementia, ataxia, and loss of purposeful hand use in girls: Rett's syndrome: report of 35 cases. Ann Neurol 14:471–479, 1983

Rett's syndrome: report of 35 cases. Ann Neurol 14:471–479, 1983

In 1966 Rett [5, 6a], in Vienna, described a syndrome of "cerebral atrophy and hyperammonemia" observed only in girls and characterized by autistic behavior and dementia, apraxia of gait, loss of facial expression, and stereotyped use of the hands. The syndrome had its onset toward the end of the first year of life or during the first half of the second year and had a slowly progressive course. The same author in greater detail reported on 21 cases of the same syndrome in 1974 [6].

# Rett Syndrome

- Affects girls almost exclusively
- Normal birth history and early development
- Slowing of development age 8 -18 mths *Stage 1*
- Regression 18 mths- 3 years: loss of purposeful hand use, acquired language, autistic features, seizures *Stage 2*
- Limited improvement in sociability and motor function age 3 -10 years *Stage 3*
- Late motor deterioration in the teens *Stage 4*

# RS: Characteristic Features

- Motor
  - Stereotypic Hand Movements
  - Bruxism
  - Dystonia, Rigidity later
  - Apraxia
- CNS/Cognitive
  - Intellectual Disability/ No Language
  - Seizures
  - Respiratory Pattern
  - Sleep Disturbance

# Typical Rett Syndrome

# RS: Characteristic Features

- Somatic
  - Growth
  - Cardiac conduction
  - Scoliosis
  - Osteopenia
  - Nutrition/ Swallowing & Dysmotility

# Bone Abnormalities in RS

- Dysmorphic Features
  - Short 4th Toes (28/137, 20% Kerr 1995)
- Scoliosis/ Kyphosis
  - Complications of  Motor Disability, Contractures,  Hip sublaxation
- Osteopenia

# The Motor System in RS: A Summary

- Clinical extrapyramidal disease
  - Hypotonia → dystonia → ridgidity
  - Hand movement steriotypies
- Progressive impairment
- Neuropathological evidence of substantia nigra involvement, cerebellar and spinocerebellar atrophy, mild neuropathy
- Evidence of degeneration; substantia nigra
- Low brain and CSF monoamines and ACh -
  - ? cause or effect

# Classification of Rett Syndrome

- US
  - TYPICAL 80%
  - ATYPICAL 20%
- High Functioning
- Low Functioning

- SWEDISH
  - CLASSICAL
  - ATYPICAL
    - Forme Fruste
    - Late Childhood Regression
    - Preserved Speech
    - Congenital
    - Other
  - MALE RS

*Ann Neurol.* 2010 December ; 68(6): 944–950. doi:10.1002/ana.22124.

# Rett Syndrome: Revised Diagnostic Criteria and Nomenclature

**Jeffrey L. Neul, MD, PhD[1], Walter E. Kaufmann, MD[2], Daniel G. Glaze, MD[1], John Christodoulou, MBBS, PhD, FRACP, FRCPA[3], Angus J. Clarke, FRCP, FRCPCH[4], Nadia Bahi-Buisson, MD, PhD[5], Helen Leonard, MBChB[6], Mark E. S. Bailey, PhD[7], N. Carolyn Schanen, MD, PhD[8], Michele Zappella, MD[9], Alessandra Renieri, MD, PhD[10], Peter Huppke, MD[11], and Alan K. Percy, MD[12] for the RettSearch Consortium[*]**

**Main Criteria**

| | |
|---|---|
| **1** | Partial or complete loss of acquired purposeful hand skills. |
| **2** | Partial or complete loss of acquired spoken language** |
| **3** | Gait abnormalities: Impaired (dyspraxic) or absence of ability. |
| **4** | Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms |

**Exclusion Criteria for typical RTT**

| | |
|---|---|
| **1** | Brain injury secondary to trauma (peri- or postnatally), neurometabolic disease, or severe infection that causes neurological problems*** |
| **2** | Grossly abnormal psychomotor development in first 6 months of life# |

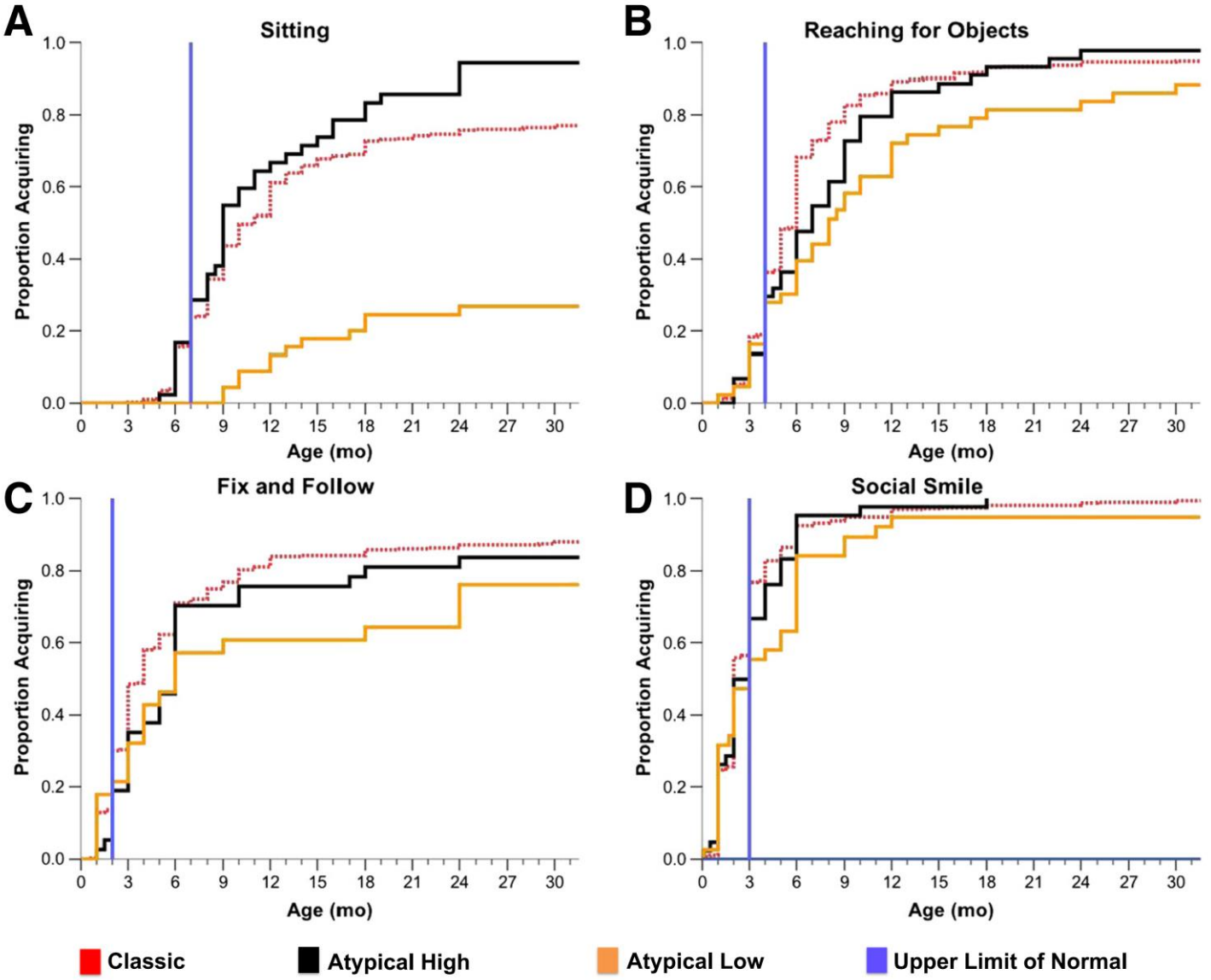
**Supportive Criteria for atypical RTT##**

| | |
|---|---|
| **1** | Breathing disturbances when awake |
| **2** | Bruxism when awake |
| **3** | Impaired sleep pattern |
| **4** | Abnormal muscle tone |
| **5** | Peripheral vasomotor disturbances |
| **6** | Scoliosis/kyphosis |
| **7** | Growth retardation |
| **8** | Small cold hands and feet |
| **9** | Inappropriate laughing/screaming spells |
| **10** | Diminished response to pain |
| **11** | Intense eye communication - “eye pointing” |

*Ann Neurol.* 2010 December ; 68(6): 944–950.

# Early Development in Rett Syndrome

Neul *et al. Journal of Neurodevelopmental Disorders* 2014, **6**:20



# Differential Diagnosis of Rett Syndrome

- Autism Spectrum
  - Early Regression
  - Lack of Language
- Global Developmental Delay
  - Genetic/ Metabolic
- Epileptic Encephalopathy
  - Early seizure onset – EEG findings

**Genetic Testing**

# Epidemiology in Rett Syndrome

- Females only (?)
- 1/10,000- 1/23,000
- All Races
- Familial Cases
- Swedish Clusters

# Etiology

- ? Genetic
- ? Acquired
  - Why only girls?

# Rett Syndrome: Statistics on Kindred Cases. Other Familial Cases (IRSA March 1996)

| | |
|---|---|
| Full Sisters | 8 Cases |
| Half-Sisters | 2 Cases |
| Full Cousins | 1 Case |
| Second Cousins | 2 Cases |
| Second Half-Cousins | 1 Case |
| Aunt/Niece | 2 Cases |
| Great-Grand Aunt/Niece | 1 Case |
| Sister & Half-Brother with RS Children Suspected | 1 Case |
| Rett Mother/Rett Daughter | 1 Case |
| Male Variants | 22 Cases |

# Rett Syndrome: Statistics on Kindred Cases. Twins (IRSA March 1996)

- Monozygotic Twins, Concordant 11
- Monozygotic Twins, Discordant 1
- Dizygotic Twins, Concordant 2
- Dizygotic Twins, Discordant 13
  - Female/Female (5 Cases)
  - Female/Male (8 Cases, 1 Provisional)

# Genetics of Rett Syndrome

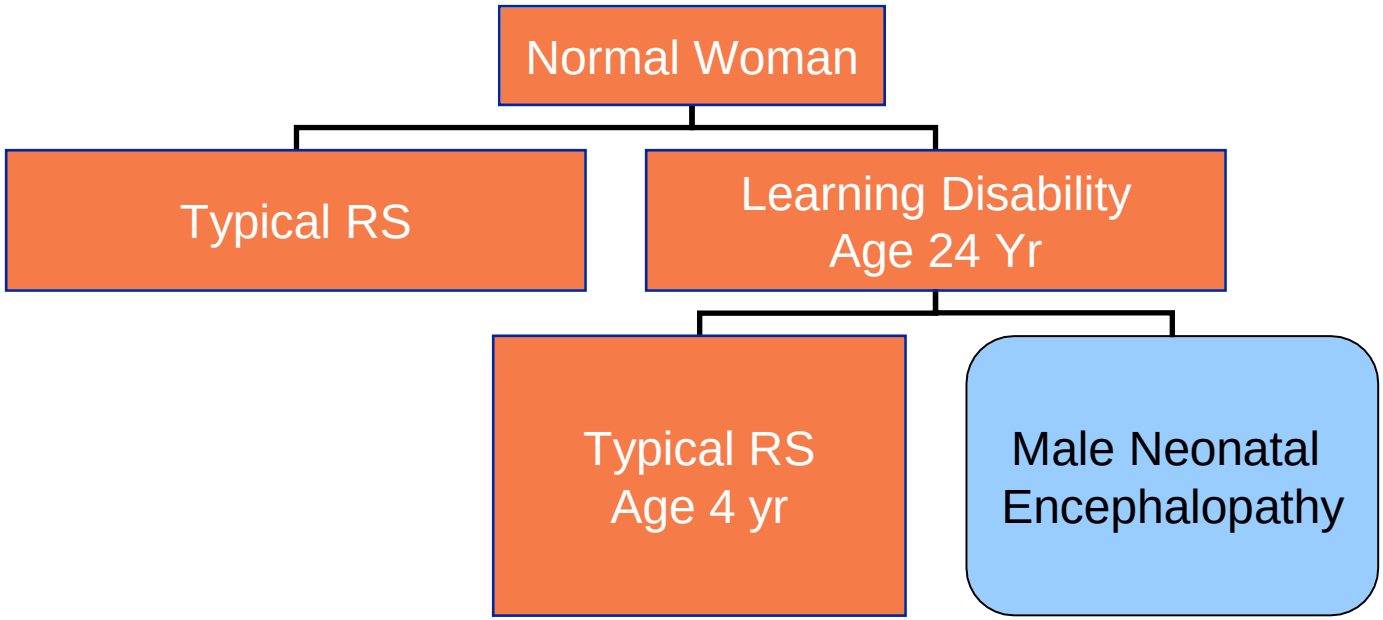
- CONFUSING
  - STRONG EVIDENCE OF A GENETIC BASIS
    - Mother/ Daughter Transmission
    - Twins
    - Other Familial Cases
    - Clustering in Swedish Cases

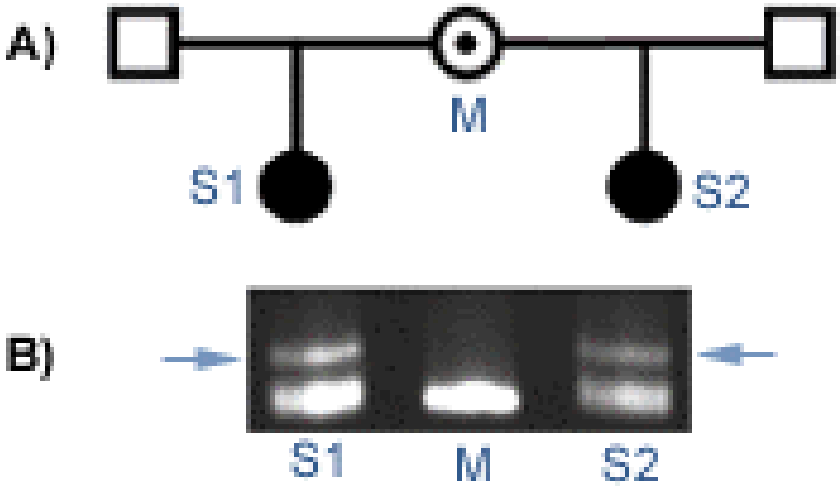
# Rett Syndrome

Probably a New Genetic Mechanism

Haas 1995

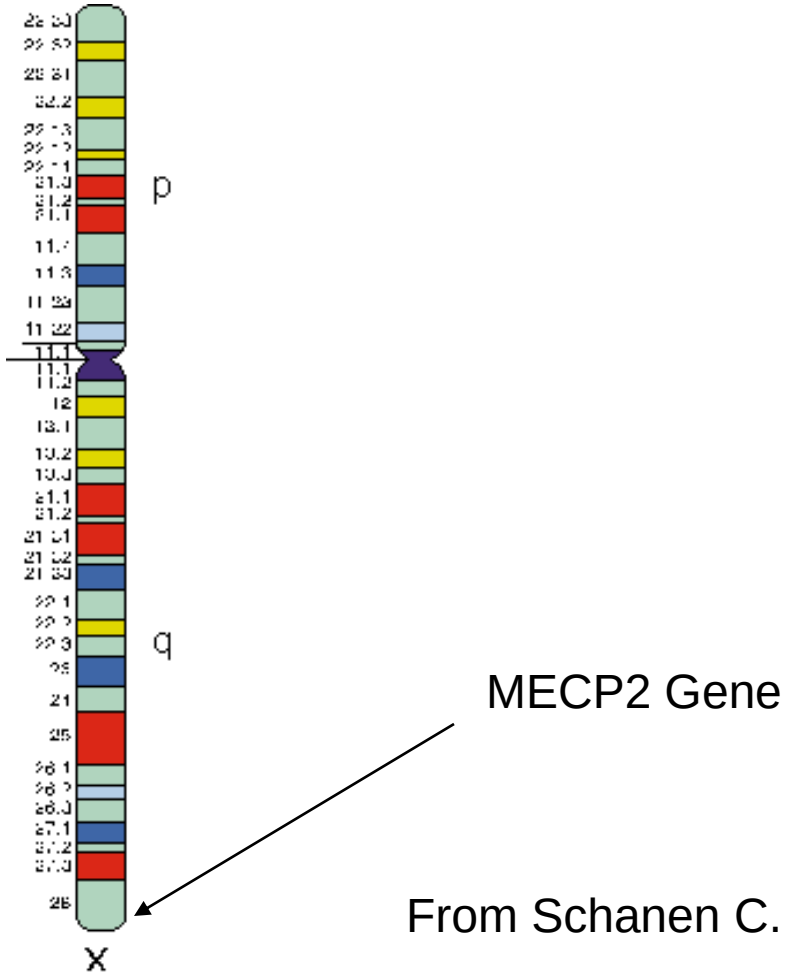
# Familial RS


Normal Woman
Typical RS
Learning Disability
Age 24 Yr
Typical RS
Age 4 yr
Male Neonatal
Encephalopathy




**A)** Pedigree of half-sisters (S1 and S2) with Rett syndrome and their carrier mother (M). **B)** Conformation-sensitive gel electrophoresis (CSGE) showing the same extra band (arrows) in the DNA of both half-sisters, not present in their mother (M). It is likely that the mother, who is normal, transmitted the disease to her daughters through a germline mutation present in her ovum, but not in the other cells of her body. [Adapted from Amir, R.E. et al. (1999) *Nature Genetics* 23, 185 –188., with permission.]

# MECP2 is on the distal end of the long arm of X



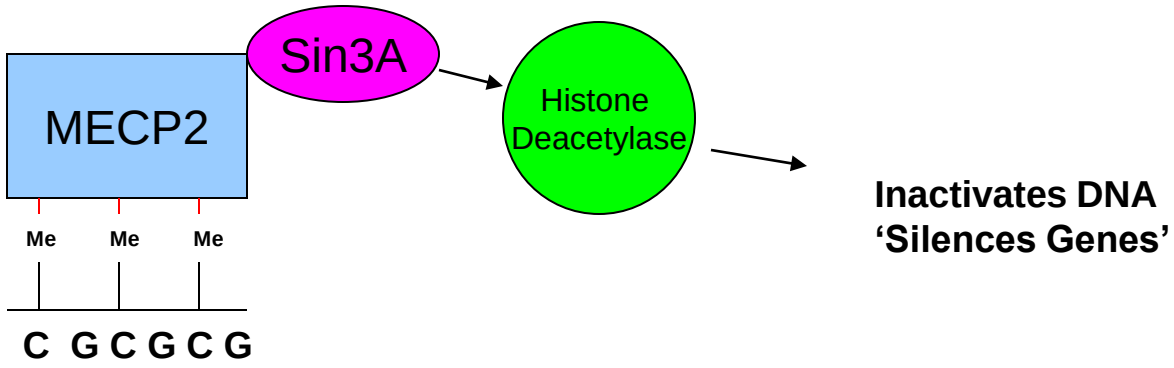
# Methyl-CpG Binding Protein 2 (MeCP2)

- The MeCP2 gene (GeneCard) (OMIM 300005) is located on Human Xq28 chromosome.
- It encodes for Methyl-CpG Binding Protein 2, a chromosomal protein, 486 amino acids long, that binds to methylated DNA.
- Involved in the regulation of transcription and alteration of chromatin structure.

  A gene suppressor.

# MECP2

- Methyl-CpG-binding protein 2
  - Silences and modulates genes



# Rett Phenotype Gene Panel

- FOXG1 (14q12)
- IQSEC2 (Xp11.22)
- MECP2 (Xq28)
- MEF2C (5q14.3)
- SCN8A (12q13.13)
- CDKL5 (Xp22.13)
- STXBP1 (9q34.11)
- ALDH5A1 (6p22.3)
- GABBR2 (9q22.33)