RETT SYNDROME – A PROBLEMATIC DIAGNOSIS?

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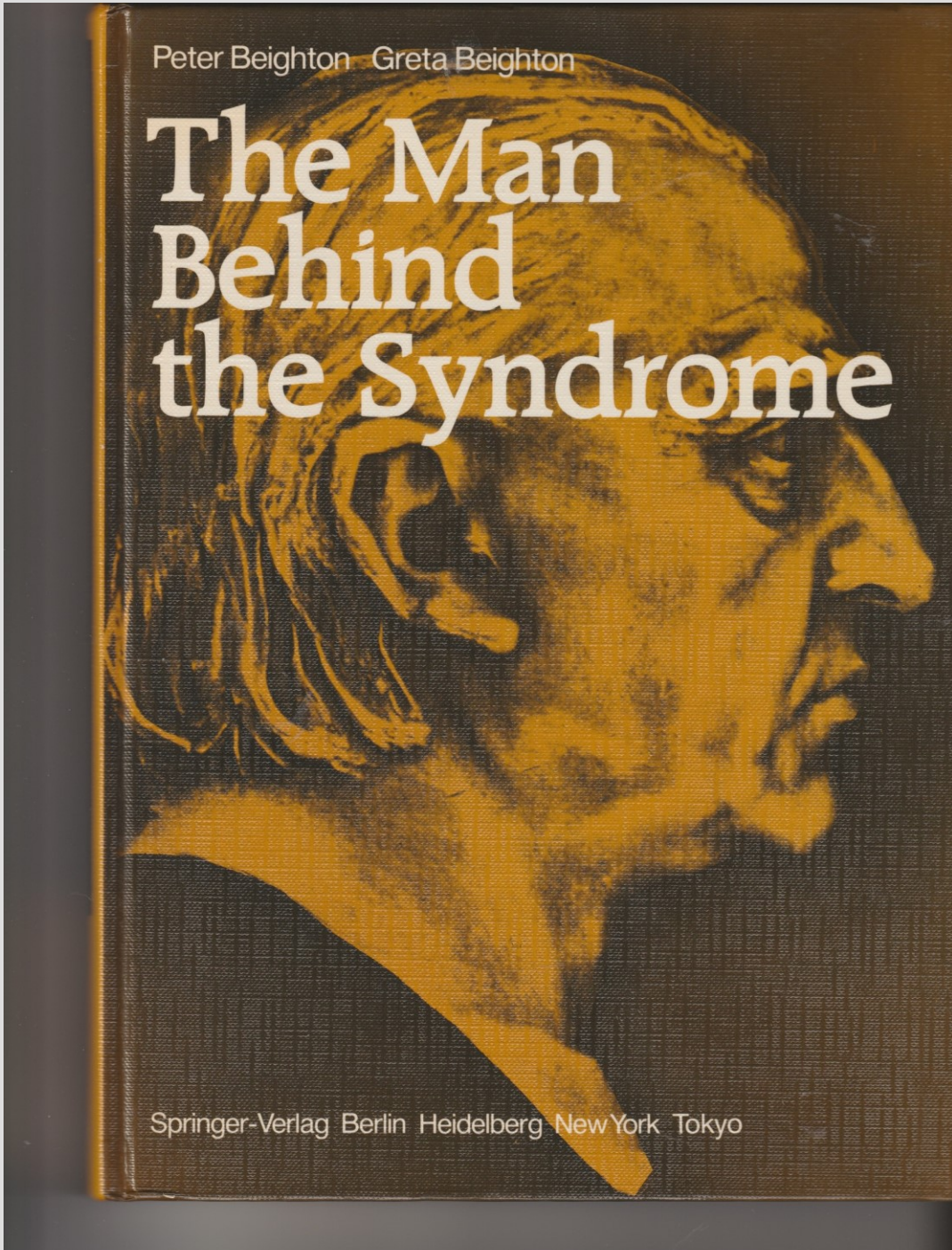
About 1850 and in the forthcoming years – brain disorders were more accurate described and categorised –

Many of them were classified as SYNDROMES



WHAT IS A SYNDROME?

A group of clinical signs and symptoms that occur together and characterize a particular abnormality or condition.

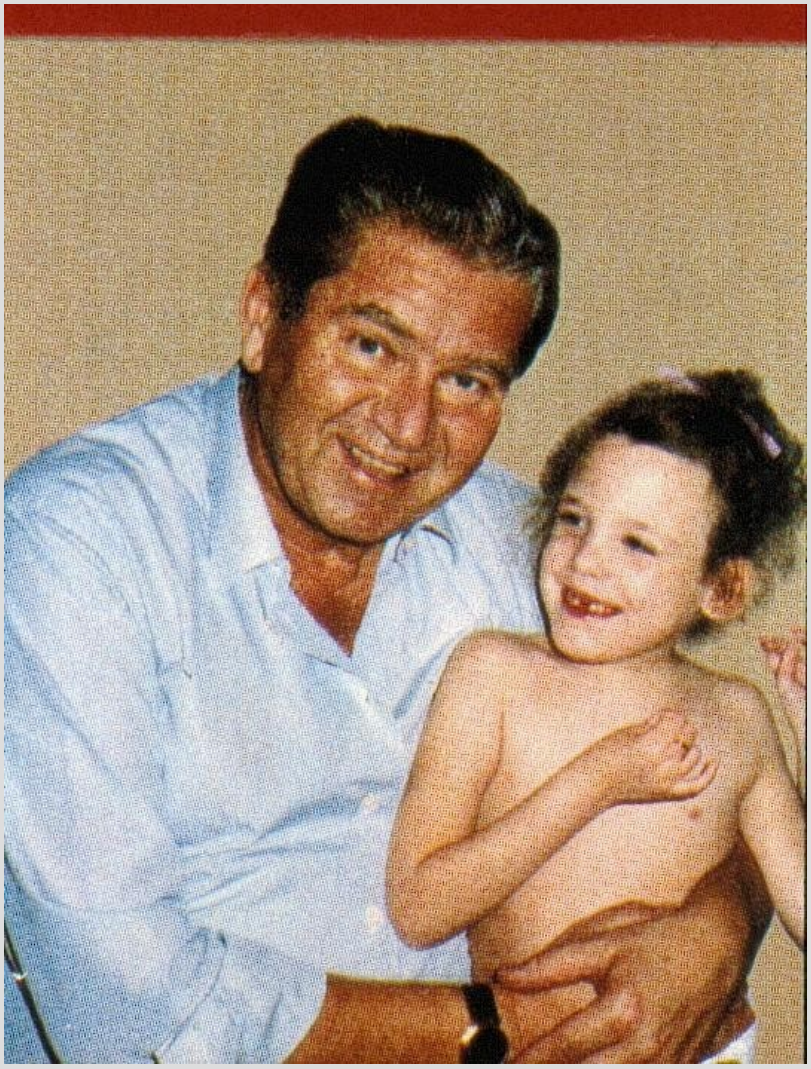
GRETA BOLIN

Mitt barn är annorlunda

ANDREAS RETT

Andreas Rett
Uber ein cerebral-atrophisches syndrome bei hyperammonamie

Vienna: Bruder Hollinek, 1966: 1 - 68



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†

RETT SYNDROME
CLINICAL DIAGNOSTIC CRITERIA

Rett syndrome: Criteria for inclusion and exclusion
Bengt Hagberg MD; Françoise Goutières, MD;
Folker Hanefeld, MD;
Andreas Rett, MD; John Wilson, MD
Brain Dev. 1985, 7(3): 372 - 373

Rett variants: A suggested model for inclusion criteria
Hagberg B and Skjeldal O.

Ped Neurol 1994; 11(1): 5 - 11

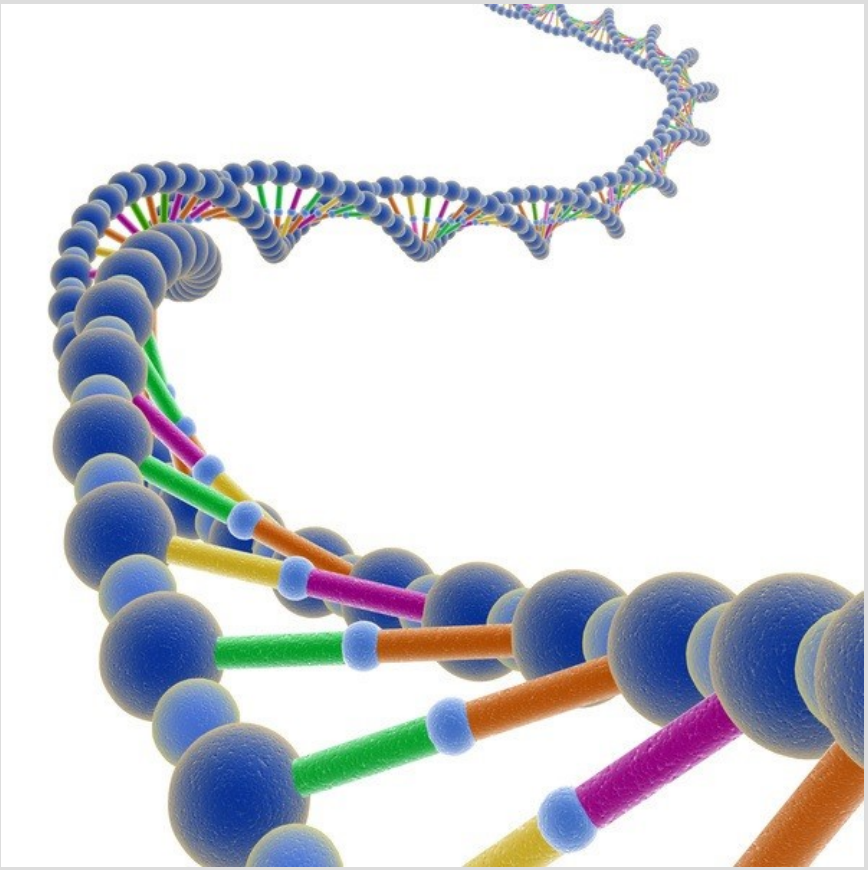
An update on clinically applicable diagnostic criteria.
Hagberg B; Hanefeld F; Percy A. And Skjeldal O.

Eur J Paediatr Neurol 2002, 6: 203 - 297

Rett syndrome: revised diagnostic criteria and nomenclature
Neul JL, Kaufman W; Glaze DG; Christodoulou J;
Clarke AJ; Bahi-Buisson N; Leonard H; Bailey MHS;
Schanen NC, Zapella M; Huppke P and Percy A
Ann Neurol 2010; 68(6): 944 - 950

Discovery of the MECP2 gene

Amir; Zoghbi et al. 1999



MECP2 AND RETT SYNDROME

- MECP2 is involved in many cellular functions
  - Chromatine shaping
  - Regulation of gene expression
  - Synaptic function

- More than 800 different mutations causing Rett syndrome have been mapped
- The majority of the mutations have been found in special areas on the gene, speciial ”hotspots”.
- About 95 % of females with classical Rett syndrome have MECP2 mutations, while about 60 - 70 % of the Rett syndrome variants have mutations.
- About 5 % with classical Rett syndrome are negative for MECP2 mutations. For Rett syndrome variants this number is at least 30 %.

SO – WHAT ABOUT THE REST?

OTHER POSSIBLE RETT SYNDROME GENES

- CDKL 5 and FOXG1 (Weaving LS et al. 2004; Ariani F. et al 2008
- Both these genes cause severe forms of Rett syndromes with early onset of symptoms and early severe epileptic seizures.
- Meghana M. et al. Prevalence and onset of comorbidities in the CDKL5 disorder differ from Rett syndrome
  Orphanet J of Rare diseases (2016) 11:39
- Mitter D. et al. FOXG1 syndrome: genotype-phenotype association in 83 patients with FOXG1 variants.
  Genet Med 2017

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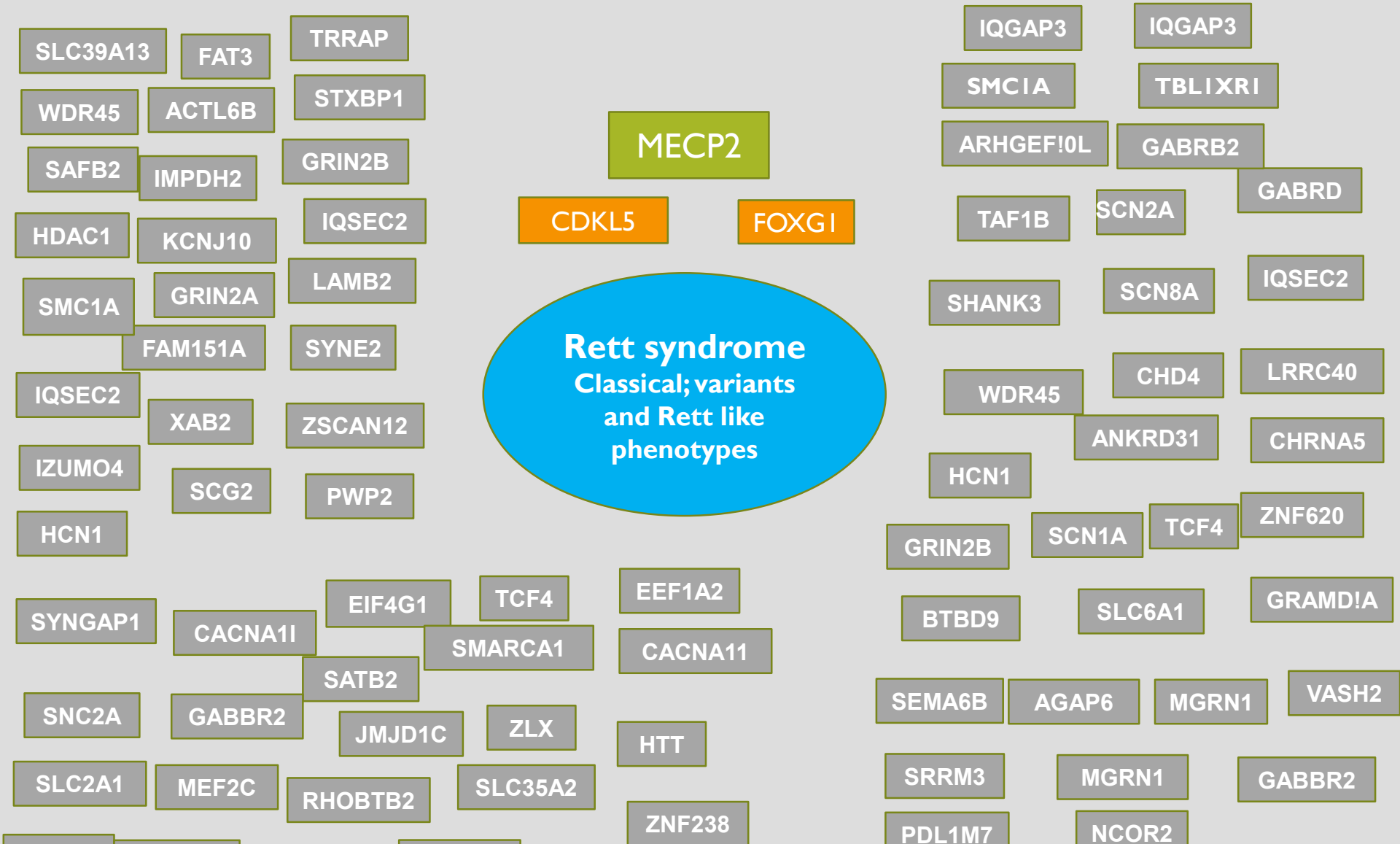
GENES IN CLASSICAL RETT SYNDROME, ATYPICAL RETT AND RETT-LIKE PHENOTYPES



SCN1A

In 80 % of the cases with SCN1A mutations is diagnosed as Dravet syndrome.

Our patients with mutations in this gene fullfilled the diagnostic criteria having a classical Rett syndrome (Neul et al 2010)

No mutations in MECP2, CDKL5 and FOXG1 were found

There is clinical overlap between Dravet and Rett syndrome. However, both our patients fulfill the criteria having classical Rett syndrome

SOME SYNDROMES WHICH OVERLAP WITH RETT SYNDROME

- Pitt-Hopkins syndrome **TCF4**
- Cornelia de Lange syndrome **SMC1A**
- Angelman syndrome **UBE3A**
- Phelan-McDermid syndrome **SHANK3**
- Kleefstra syndrome **EHMT1**
- Christianson type X-linked MR **SLC9A6**
- Glass syndrome **SATB2**

Schönefeld-Greulich et al. Clinical Genetics, 2017

Angelman syndrome and Rett syndrome – Two syndromes with overlapping clinical phenotypes

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IS RETT SYNDROME A PROBLEMATIC DIAGNOSIS TO MAKE?

- FOR MOST OF THE FEMALES IT IS NOT DIFFICULT. Fullfilling the criteria eventually together with MECP mutation)
- IN A FEW CASES IT CAN BE MORE DIFFICULT. Especially in those patients with mutations in the genes associated with other syndromes and especially where different phenotypes overlap
- WE NEED TO BETTER UNDERSTAND THE GENETIC BACKGROUND OF RETT SYNDROME (It could very well be so that other genes could contribute to the Rett phenotype, either alone or by influencing the MECP2 gene Genes are cooperating. .

Many syndromes have overlapping phenotypes

In this situation it is necessary to have strict and robust diagnostic criteria.

Rett syndrome is still a clinical diagnosis based on accepted clinical criteria

THANK YOU VERY MUCH FOR YOUR ATTENTION