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HISTORICAL NOTE

Rett syndrome: the Brazilian contribution to the gene discovery

Síndrome de Rett: a contribuição brasileira para a descoberta do gene

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ABSTRACT

A brief history of the syndrome discovered by Andreas Rett is reported in this paper. Although having been described in 1966, the syndrome was only recognized by the international community after a report by Hagberg et al. in 1983. Soon, its importance was evident as a relatively frequent cause of severe encephalopathy among girls. From the beginning it was difficult to explain the absence of male patients and the almost total predominance of sporadic cases (99%), with very few familial cases. For these reasons, it was particularly difficult to investigate this condition until 1997, when a particular Brazilian family greatly helped in the final discovery of the gene, and in the clarification of its genetic mechanism. Brief references are made to the importance of the *MECP2* gene, 18 years later, as well as to its role in synaptogenesis and future prospects.

Keywords: Rett syndrome; brain diseases; genes.

RESUMO

Uma breve história de uma síndrome neurológica descoberta por Andreas Rett é relatada neste artigo. Embora tenha ocorrido em 1966, a síndrome só foi reconhecida pela comunidade internacional após um relato de Hagberget al, em 1983. Logo, sua importância ficou evidente como causa relativamente frequente de encefalopatia grave entre as crianças do sexo feminino. Desde o início, foi difícil explicar a ausência de envolvimento de pacientes do sexo masculino e a quase absoluta preponderância de casos esporádicos (99%), com muitos poucos casos familiares. Por essas razões, foi difícil investigar essa condição até 1997, quando uma família brasileira em particular ajudou muito na descoberta final do gene e no esclarecimento de seu mecanismo genético. São feitas referências sucintas à importância do gene MECP2, dezoito anos depois, bem como ao seu papel na sinaptogênese e nas perspectivas futuras.

Palavras-chave: Síndrome de Rett; encefalopatias; genes.

Rett syndrome, which was described 52 years ago in Vienna, Austria, by Andreas Rett, a pediatrician, is caused by a heterozygous mutation of the *MECP2* gene located in the distal region of the X chromosome, which encodes a MECP2 protein, or methyl-CpG 2 binding repressor protein, which binds to methylated DNA[1,2]. This is a protein with two isoforms, preferentially expressed in the brain, regulating the synaptogenesis process. Approximately 80% of the time this mutation is found with the classic phenotypes, but mutation of the gene can also occur in 50% of the cases of atypical phenotypes or mild forms of the syndrome; X-linked non-random inactivation might explain most of this clinical variability. The *MECP2* is a small gene, with only four exons, two of them being coding exons (3 and 4).[1,2] Hundreds of mutations have been identified, 54% of them are related to causing Rett syndrome. This gene has the function of silencing others, regulating the synaptogenesis process in the infant brain, which peaks in the first two years of life – when the classic syndrome is expressed clinically as stagnation and even regression of neurological or psychomotor development. Rett syndrome is

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a sexually-dominant disease, much more common in females and extremely rare in males[1,2]. In this historical review we discuss the Brazilian contribution to the discovery of the gene of Rett syndrome.

ANDREAS RETT – A SHORT BIOGRAPHY

A medical aphorism teaches students and professionals that in the act of diagnosing and treating, more than the examination or technological resources, the clinic diagnosis is paramount. Andreas Rett (Figure 1), working at the Boltzman Institute in Vienna, based on isolated clinical patients, described what appeared to be a disease seen exclusively in females. His reasoning was initially based on only 22 young women[3,4]. We now know that Rett syndrome has also been described in male patients, but they are very rare and present with a more severe phenotype. Andreas Rett was born in Furth, Bavaria, on January 2, 1924 and studied medicine at the University of Innsbruck (Austria) and Bonn (Germany). After receiving his medical degree, he specialized in developmental pediatrics and began to practice in Vienna, where he worked until the end of his life[3,4]. In the clinic, he mostly focused on examining and treating children who had developmental delay or special educational needs. He was a great clinician, whose considerable capacity for observation allowed him to identify a new neurological entity, later coined Rett syndrome. Nowadays, this has been recognized as a cause of physical and mental impairment in girls (1/10,000 female births). The syndrome was named Rett syndrome by Bengt Hagberg (Figure 2) in a seminal article, in 1983[5].

RETT SYNDROME – THE DEFINITION OF THE SYNDROME

In this syndrome, girls, as described by Rett, had a very typical condition and progression: a normally-born child with no history of gestational or obstetric events, families with no histories of other cases, or even those with other genetic disorders, who presented with developmental delay between six months and two years of age; this occurs mainly because *de novo* pathogenic variants occur much more frequently in male gametogenesis[1,2,3,4]. In the original description, patients also presented with peculiar and typical involuntary movements with their hands: the Rett-type manual stereotypic movement disorders. Nowadays, it is known that this phenotype occurs in other disorders, such as *FOXG1*- and *CDKL5*-associated encephalopathy, and many others[6,7]. In 1966, Rett described this clinical condition in German[3], in a periodical of limited circulation, presenting an English version only in 1977[4]. However, it took a long

Figure extracted from http://www.aeiou.at/aeiou.encyclop.data.image.r/r539792a.jpg, accessed March 4th, 2019.
Figure 1. Andreas Rett (1924–1997).

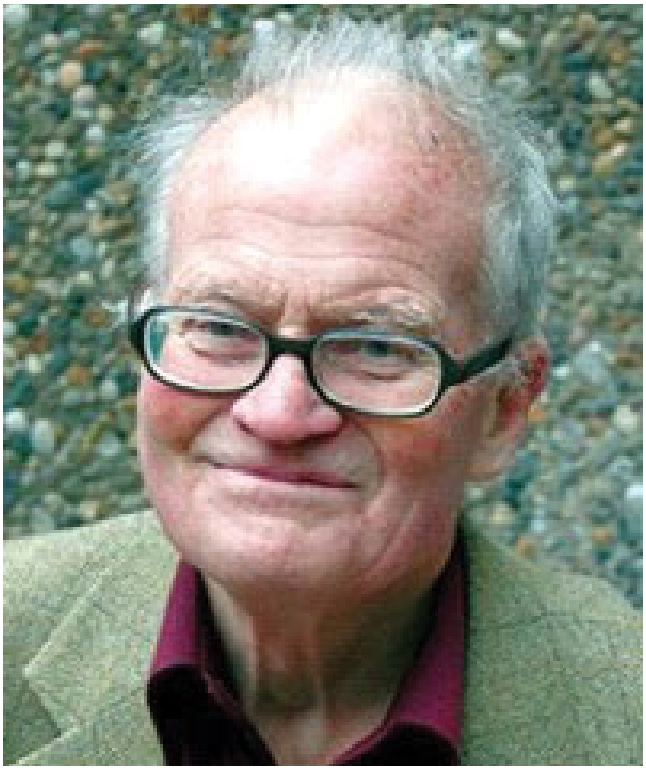

Figure extracted from https://tidsskriftet.no/2015/09/legelivet/minneord-2, accessed March 4th, 2019.
Figure 2. Bengt Hagberg (1923–2015).

Figure 3. Dr. SakkuBai Naidu and Dr. Pereira (JLPP, personal archive, with permission).

Figure 4. Three Brazilian sisters with classical Rett syndrome, who participated in the study that enabled the description of the *MECP2* gene as the genetic cause of the disease (1997, JLPP, personal archive, with permission of the author and the patient's family).

time for this content to circulate among peers in the community of child neurologists and neurologists in Europe[1,3,4]. In 1983, Hagberg et al.[5] published a report on 35 patients. From then on the neurological community of Europe and the USA gradually recognized the syndrome. Although Rett syndrome typically occurs in females, pathogenic mutation in *MECP2* in males usually does not have the Rett syndrome-like phenotype but instead presents with a severe epileptic encephalopathy, with hypotonia and apnea. The exception to the previous statement is males with Klinefelter syndrome (47, XXY), which also has a Brazilian contribution[8,9].

Rett syndrome, genetic studies, and the Brazilian contribution

SakkuBai Naidu (Figure 3) and Hugo Moser, from the Kennedy Institute, promoted the first American conference on Rett syndrome in 1986, where they reported on the natural history of 70 patients[10,11]. In Brazil, in 1987, Sergio Rosemberg et al. reported on the analysis of the first five Brazilian patients[12]. In 1991, linked to the International Rett Syndrome Association, the Paraná region of the Brazilian Rett Syndrome Association was founded in Curitiba, when the diagnoses of some patients were recognized. Subsequently, a monograph on 12 Brazilian patients was written[13]. One family had three affected siblings (Figure 4). It was known that, in international literature, no more than a dozen familial cases (full-sisters or half-sisters) had been reported, among more than 3,000 sporadic cases[1,2,5]. The case histories of the three patients were presented at a medical conference on the syndrome in Gothenburg, Sweden, in 1996[14]. On this occasion, DNA samples of the three Brazilian girls and their parents were also forwarded by Dr. José Luiz Pinto Pereira (Figure 3) to other groups of geneticists in London and Stockholm. SakkuBai Naidu, a neurogeneticist at the Kennedy Institute, had been studying the syndrome at Johns Hopkins Hospital for more than a decade and was interested in this family with three affected sisters, a unique case now known worldwide. In order to make further research possible, in October 1997 the patients were moved to Baltimore. Initially, Naidu et al. published the chromosome mapping of Rett syndrome and a candidate region on the telomere of Xq[10] in collaboration with geneticists from Stockholm and London. Soon after, the confirmation of the genetic locus in Xq2.8[15] was also published by Sirianni et al.[16], including Dr. Pereira (a neuropediatrician) and Professor Pilotto (a geneticist and professor at the Federal University of Paraná). In this manner, not only could the gene locus be confirmed, but it was also possible to demonstrate that the DNA sequences were inherited by the affected children from the mother and were not shared in the same chromosomal subregion by their normal sisters[16]. Finally, in the same year, another group of geneticists led by Dr. Hudha Zoghbi, with Dr. Uta Francke as a collaborator, both from the Howard Hughes Medical Institute, Baylor College of Medicine, made the final discovery of the gene, leading to further publications[17,18]. In these publications, the participation of the Brazilian family, with three affected sisters, was highly relevant to the discovery of the Rett syndrome gene. In conclusion, these three Brazilian sisters made an enormous contribution to the genetic description of the *MECP2* as the cause of Rett syndrome.

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