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# The history behind ALS type 8: from the first phenotype description to the discovery of VAPB mutation

## A história por detrás da ELA tipo 8: da primeira descrição do fenótipo à descoberta da mutação VAPB

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**ABSTRACT**

Over the past 68 years, the Finkel type late-onset adult autosomal dominant spinal muscular atrophy (SMA) that is allelic with amyotrophic lateral sclerosis-8 (ALS8) gained a genotype-phenotype correlation among the motor neuron diseases through the work of groups led by Zatz and Marques Jr.

**Keywords:** Spinal muscular atrophy, amyotrophic lateral sclerosis, ALS8, VAPB gene.

**RESUMO**

Nos últimos 68 anos, a atrofia muscular espinhal (AME), autossômica dominante, de início tardio, em adultos, conhecida como doença de Finkel, que é alélica com esclerose lateral amiotrófica tipo 8 (ELA8), ganhou uma correlação fenotípica e genotípica dentre as doenças do neurônio motor, a partir da colaboração dos grupos de Zatz e Marques Jr.

**Palavras-chave:** Atrofia muscular espinhal, esclerose lateral amiotrófica, ELA8, gene VAPB.

## INTRODUCTION

Motor neuron diseases (MND) encompass several neurological disorders characterized by progressive degeneration of the corticospinal tract, anterior horn cells of the spinal cord, and motor neurons of brainstem[1]. The main progressive and neurodegenerative disease in this group with adult onset is amyotrophic lateral sclerosis (ALS), which results in progressive loss of function of the upper and lower motor neurons of the brain, brainstem, and spinal cord, leading to atrophy and fatal motor paralysis[1,2]. Survival rate in most patients is two to five years[2,3]. Jean-Martin Charcot first described this disease in 1874, after correlating a series of cases that occurred from 1865 to 1869[4]. After 146 years of description, knowledge on ALS has expanded greatly with the discovery of biomarkers, genes, and new phenotypes[2,3]. Approximately 10% of ALS cases are hereditary[2,3]. More than 20 genes associated with ALS have been identified so far, starting with mutation of the Cu/Zn superoxide dismutase gene (SOD1) in 1993[2,3,5,6]. The most recent gene discovery - KIF5A/ALS 25 (kinesin family member 5A) - in 2018 also has an autosomal dominant inheritance pattern[5]. Along with the SOD1 mutation, mutations in the C9orf72, FUS, and TARDBP genes are most frequently associated with ALS[2,3,5,6]. Meanwhile, spinal muscular atrophy (SMA) is the most common group of inherited motor neuronopathies, and also the second most common autosomal recessive disorder in clinical practice[7]. Today, late adult-onset SMA represents an important group of inherited neurodegenerative disorders with different genetic causes, including SMN1-related proximal SMA, Kennedy's disease and Finkel type SMA, an autosomal dominant adult-onset SMA linked to a specific heterozygous pathogenic mutation (p.Pro56Ser) in the VAPB (vesicle-trafficking protein B) gene in chromosome 20q13.32, coding the VAMP-associated membrane protein type B[7].

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## FINKEL'S CONTRIBUTION TO DESCRIBING A LATE-ONSET NEURODEGENERATIVE LOWER MND

In 1962, Nunjo Finkel (Figure 1), a renowned Brazilian neurologist, described a series of four cases of patients in the same family with an atypical manifestation of MND, which he classified as a "late pseudomyopathic form of heredo--familial progressive muscle atrophy"[8]. The cases originated in the southeastern Brazilian town of Guarani, in the state of Minas Gerais. All patients presented with slowly progressive atrophy and proximal weakness associated with low back lordosis, abdominal bulge, and postural tremor[8] (Figure 2). Finkel insightfully noticed that the atrophy of these cases was neurogenic in origin rather than myogenic, due to the significant fasciculation that was present, and initially attributed an autosomal recessive inheritance pattern[8]. (Figure 3) Later, in 1982, Richieri-Costa et. al.[9] described two other families with 80 individuals affected with the same atrophy phenotype described by Finkel. Although this could not be confirmed, an ancestral correlation was suggested considering that the disease was extremely rare outside Brazil, the phenotypes were identical, and the two families came from the same rural area in Brazil[9]. The paper also refuted the possibility that inheritance was autosomal recessive. It stated that, in fact, it was autosomal dominant.[9] In addition, Richieri-Costa described other less common symptoms, such as cramps and myotonic phenomena[9]. From this work, the disease Finkel described in 1962 became known as Finkel type late-onset autosomal dominant spinal muscular atrophy (MIM #18980), considered a familial motor neuron disease with an absolutely higher frequency in the southeastern region of Brazil.[6,8,10]

## DISCOVERY OF THE VAPB MUTATION IN BRAZILIAN PATIENTS – THE CONTRIBUTION FROM THE UNIVERSITY OF SÃO PAULO (USP)

Almost 40 years after Finkel's description, Nishimura et al. (of the group led by Dr Mayana Zatz) described the P56S mutation in a highly conservative domain of the VAPB (vesicle-trafficking protein B) gene in 24 individuals from seven families affected by motor neuron disease[11] (Figure 4). Of these individuals, three families (eight patients) had the phenotype described by Finkel (late-onset SMA). The other families had distinct phenotypes, such as atypical ALS (with the presence of essential tremor) and typical ALS (clinically severe, with rapid progression)[11]. This type of genetically determined ALS was later defined as ALS8, a rare autosomal dominant subtype of familial ALS (FALS) originally identified in Brazilian families. Zatz's group found wide phenotypic heterogeneity related to the mutation, including within the families, broadening the clinical spectrum of the disease and expanding knowledge on the pathophysiological aspects of and potential treatments for this disease[11]. In 2005, Nishimura et al. evaluated eight

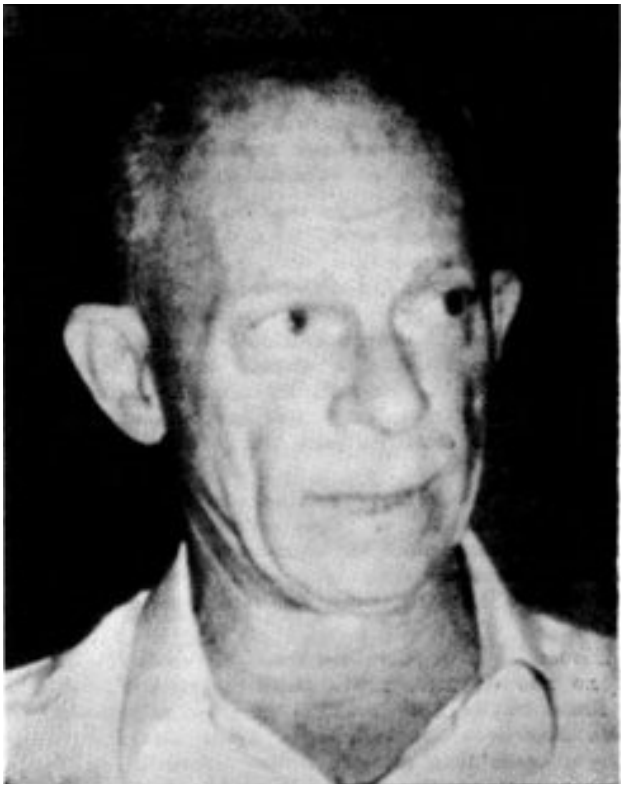

Figure 1. Nunjo Finkel (1926-1992). (Extracted from In Memoriam. Arq. Neuropsiquiatr. 1992 Set;50(3))

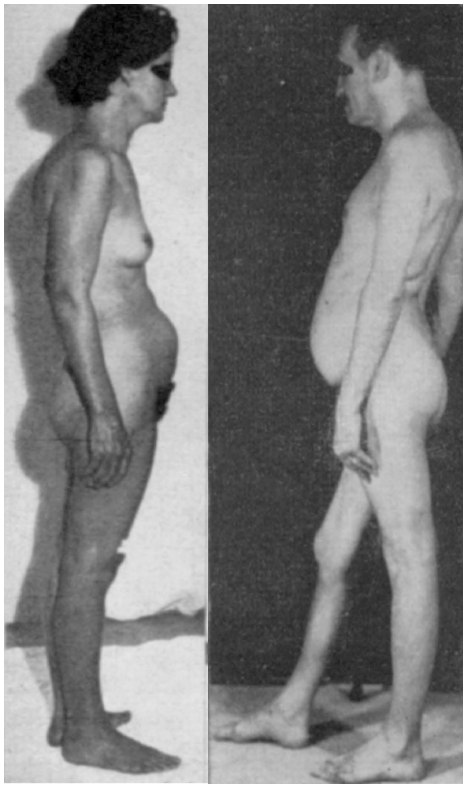

Figure 2. Finkel´s patients with SMA, with abdominal protusion and low back lordosis. (Extracted from reference 8)

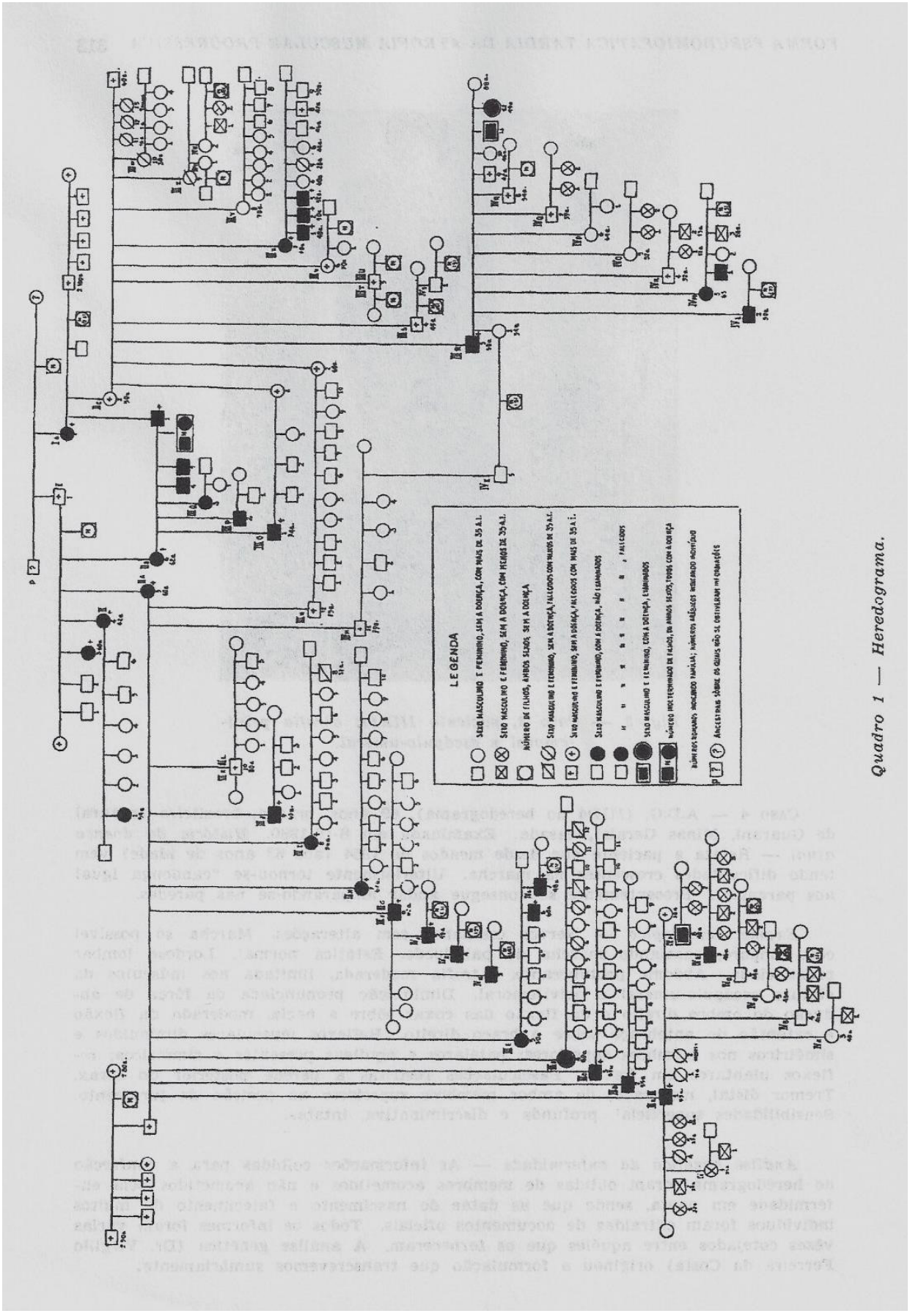


Figure 3. Heredogram of Finkel's family with SMA. (Extracted from reference 8)

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# A Mutation in the Vesicle-Trafficking Protein VAPB Causes Late-Onset Spinal Muscular Atrophy and Amyotrophic Lateral Sclerosis

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**Motor neuron diseases (MNDs) are a group of neurodegenerative disorders with involvement of upper and/or lower motor neurons, such as amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), progressive bulbar palsy, and primary lateral sclerosis. Recently, we have mapped a new locus for an atypical form of ALS/MND (atypical amyotrophic lateral sclerosis [ALS8]) at 20q13.3 in a large white Brazilian family. Here, we report the finding of a novel missense mutation in the vesicle-associated membrane protein/synaptobrevin-associated membrane protein B (VAPB) gene in patients from this family. Subsequently, the same mutation was identified in patients from six additional kindreds but with different clinical courses, such as ALS8, late-onset SMA, and typical severe ALS with rapid progression. Although it was not possible to link all these families, haplotype analysis suggests a founder effect. Members of the vesicle-associated proteins are intracellular membrane proteins that can associate with microtubules and that have been shown to have a function in membrane transport. These data suggest that clinically variable MNDs may be caused by a dysfunction in intracellular membrane trafficking.**

Figure 4: Zatz´s group contribution: The discovery of the VAPB gene that causes SMA and ALS8.[11]

families (over 1,500 individuals) in whom 220 members were affected, and confirmed the presence of the P56S mutation in the VAPB gene[10]. Most of the families were of Portuguese-Brazilian ancestry, and one of African-Brazilian descent. The authors used haplotype analysis to confirm a common founder effect 23 generations ago, consistent with the Portuguese colonization of Brazil[10].

## CONTRIBUTIONS BY THE DEPARTMENT OF NEUROLOGY AT THE RIBEIRÃO PRETO MEDICAL SCHOOL (USP- RP)

In 2004, Marques Jr. et al. described a large Brazilian family with late-onset, autosomal dominant, proximal and progressive SMA associated with dysautonomic symptoms and severe weakness of the abdominal muscles that resulted in a prominent abdomen[12]. The authors identified the localization of this disorder with chromosome 20q13.2-13.3 and called it hereditary motor and autonomic neuropathy 1[12]. In the same year, Nishimura et al. defined that a mutation in the vesicle-trafficking protein VAPB causes late-onset spinal muscular atrophy and amyotrophic lateral sclerosis.[11] In 2006, Marques et al. ( from the Marques Jr. group) assessed 16 members of a Brazilian family affected by a late-onset, autosomal dominant, progressive, motor and autonomic disorder associated with the presence of a VAPB (Pro56Ser) mutation with a different phenotype of MND[13]. The patients exhibited proximal and axial muscle weakness and atrophy, fasciculations, and cramps associated with abdominal protrusion defined the motor phenotype. These patients also presented with distal tremor as well as autonomic abnormalities, including choking, chronic intestinal constipation, sexual and sudomotor dysfunction[13]. Furthermore, in 2008, the same group described neurophysiological findings for six members of this same family, detailing late-onset, dominant, proximal spinal muscular atrophy with dysautonomia related to the VAPB Prof56Ser mutation[14]. The electroneuromyographic findings were consistent with the II motor neuron disorder, and the abdominal muscles were severely affected from a topographical standpoint, which is considered the most frequent clinical tool when the disease initially emerges[14].

## CONCLUSION

Contributions from the groups led by Zatz and Marques Jr. on Finkel type late-onset adult autosomal dominant SMA allelic with ALS8 broadened our understanding of motor neuron disease[8,9,10,11,12,13,14]. More recently, different brazilian

neurological groups have published studies about ALS8 emphasizing different clinical aspects.[15–19] With each new discovery, ALS and SMA prove to be more complex than previously imagined. Remarkable advances in neurogenetics are transforming the knowledge generated by these distinguished researchers into hope for disease-modifying treatments in the near future.

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