

Prion protein gene in Alzheimer's disease

O gene da proteína priônica na doença de Alzheimer

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Alzheimer's disease (AD) is a complex disorder, including sporadic (representing the majority of cases) and familial forms, the latter being usually linked to a genetic etiology. Three major genes have been already described as the cause of AD: amyloid precursor protein (APP) gene, presenilin 1 gene (PSEN1), and presenilin 2 gene (PSEN2), typically presenting with an early onset (before 60 years). However, these genetic forms are responsible for less than 5% of all AD cases¹. Conversely, more common gene polymorphisms, such as the presence of the $\epsilon 4$ allele of the apolipoprotein E (APOE) gene, are associated with an increased risk of developing late-onset AD^{2,3}. Numerous other candidate genes have been identified, especially through genome-wide association studies, and are currently the topic of intensive research^{1,2}.

Among the polymorphisms that have been explored in relation to AD, homozygosis for methionine at codon 129 of the prion protein gene (PRNP) has been associated with a 1.3-fold increased risk of developing the disease in populations of Caucasian origin, in comparison with heterozygosis (i.e., methionine/valine), according to a meta-analysis⁴. However, these findings have not been confirmed by other investigators, particularly in a study including patients with definite AD⁵.

Human prion diseases, although very rare, share some neuropathological features with AD, especially the accumulation of misfolded proteins [prion protein (PrP^C) and β -amyloid] in the brain tissue. Moreover, PrP^C seems to function as a receptor for the β -amyloid oligomers, and this interaction could mediate the characteristic neurotoxicity of AD pathology, leading to synaptic failure and cognitive decline^{6,7}.

Within this context, the paper published in this issue of *Arquivos de Neuro-Psiquiatria* by Smid et al.⁸ adds another piece of information to this intriguing and interesting puzzle. The authors conducted a case-control study comparing PRNP polymorphisms in AD patients and matched controls, and they also explored associations between the genotypes and cognitive performance. No genotype differences were found between AD and controls in relation to PRNP, even when APOE genotype was taken into account in the analysis. Moreover, cognitive performance was not influenced by PRNP polymorphisms.

Hence, the overall results of the study are essentially negative. This could be explained by sample size limitations or by the ethnic background of the population, possibilities that were already acknowledged by the authors. On the other hand, the findings are in agreement with those of previous reports, particularly with the sole neuropathological investigation published on this topic⁵. No similar data from other Brazilian populations are available for comparison, as this is the first study to have explored PRNP polymorphisms in AD in the country. This latter feature brings special relevance to the present study. We need more and better information about the genetics of dementia in Brazil and in other developing countries, either to confirm or to refute current candidate genes, as well as to identify new ones, which may ultimately contribute to improve our understanding about the pathogenesis of these devastating conditions.

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