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The study of genetic polymorphisms related to serotonin in Alzheimer's disease: a new perspective in a heterogenic disorder

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Abstract

Genetic and environmental factors have been implicated in the development of Alzheimer's disease (AD), the most common form of dementia in the elderly. Mutations in 3 genes mapped on chromosomes 21, 14 and 1 are related to the rare early onset forms of AD while the ε4 allele of the apolipoprotein E (APOE) gene (on chromosome 19) is the major susceptibility locus for the most common late onset AD (LOAD). Serotonin (5-hydroxytryptamine or 5-HT) is a key neurotransmitter implicated in the control of mood, sleep, appetite and a variety of traits and behaviors. Recently, a polymorphism in the transcriptional control region upstream of the 5-HT transporter (5-HTT) gene has been studied in several psychiatric diseases and personality traits. It has been demonstrated that the short variant(s) of this 5-HTT gene-linked polymorphic region (5-HTTLPR) is associated with a different transcriptional efficiency of the 5-HTT gene promoter resulting in decreased 5-HTT expression and 5-HT uptake in lymphocytes. An increased frequency of this 5-HTTLPR short variant polymorphism in LOAD was recently reported. In addition, another common polymorphic variation in the 5-HT_{2A} and 5-HT_{2C} serotonin receptor genes previously analyzed in schizophrenic patients was associated with auditory and visual hallucinations in AD. These observations suggest that the involvement of the serotonin pathway might provide an explanation for some aspects of the affective symptoms commonly observed in AD patients. In summary, research on genetic polymorphisms related to AD and involved in receptors, transporter proteins and the enzymatic machinery of serotonin might enhance our understanding of this devastating neurodegenerative disorder.

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Key words
- Alzheimer's disease
- Allelic association
- Serotonin polymorphisms

Alzheimer's disease (AD), the most common form of dementia in the elderly, is a complex disorder characterized by a progressive deterioration of memory, language and other cognitive functions. In addition to a genetic contribution, environmental factors such as educational level or the occurrence of head injuries have also been implicated in the development of late onset AD (LOAD; first symptoms after 60/65 years of age) (1).

Mutations in three relatively rare genes, associated with early onset AD (EOAD; first symptoms before 60/65 years of age) have been reported in the recent years: the amyloid precursor protein gene (APP), the presenilin 1 gene (PS1) and the presenilin 2 gene (PS2), respectively on chromosomes 21, 14 and 1 (2-5).

A new susceptibility locus for familial LOAD has been also identified on chromosome 12 (6). On the other hand, the ε4 allele of the apolipoprotein E (APOE) gene, mapped on chromosome 19, has been reported in numerous studies worldwide as a risk factor associated mainly with the LOAD form (7), which was also confirmed in the Brazilian population (8). More recently, some association studies have shown that the allelic variant (-427C) and the haplotype [-491A-427C] of the APOE promoter are associated with an increased risk for AD (9,10).

Several hypotheses have been proposed to address the biological mechanisms by which APOE affects the relative risk (and age at onset) to develop AD, including the possibility that APOE somehow contributes to deposition of the amyloid ß peptide (7).

This year, Leuween et al. (11) found frameshift mutants of ß amyloid precursor protein and ubiquitin-B in Alzheimer and Down patients and suggested that transcript mutations could be an important factor in non-familial AD.

Serotonin (5-hydroxytryptamine or 5-HT) is a key neurotransmitter in the central and peripheral nervous systems that is implicated in the control of mood, sleep, appetite and a variety of traits and behaviors. Its potential role in psychiatric conditions such as depression, obsessive-compulsive disorder, schizophrenia and AD has been the subject of considerable study (12). The 5-HT transporter (5-HTT) acts by regulating the magnitude and duration of serotoninergic neurotransmission and of the peripheral actions of 5-HT (13). 5-HTT may therefore be involved in the pathogenesis of several psychiatric disorders (14-17). 5-HTT is encoded by a gene at 17q11.1-q12 with 14 exons which spans approximately 35 kb (18-22).

Polymorphism in the transcriptional control region upstream of the 5-HTT gene has been reported. The long and short variants of this 5-HTT gene-linked polymorphic region (5-HTTLPR) have different transcriptional efficiency of the 5-HTT gene promoter resulting in decreased 5-HTT expression and 5-HT uptake in lymphocytes. This polymorphism has been studied in several psychiatric diseases, and personality traits with some contradictory findings (16,17,23-30).

In a European study, Collier et al. (17) found that the frequency of the low-activity short variant(s) of the 5-HTTLPR was higher among patients with affective disorders than in normal controls. However, in a study of 86 unrelated patients (47 with bipolar disorder and 39 with schizophrenia) and 98 normal controls from the Brazilian population we observed no statistically significant differences among the three groups (31).

An increased frequency of the 5-HTTLPR short variant polymorphism and LOAD was recently reported by Li et al. (32) and confirmed by us in a Brazilian sample of AD patients (33). Subsequently we demonstrated that the association of the short variant in the APOE ε4 allele does not increase the risk for LOAD (34).

On the other hand, common polymorphic variations in the 5-HT_{2A} and 5-HT_{2C} seroto-

nin receptor genes (102-T/C and Cys 23 Ser polymorphism, respectively) have been analyzed in patients with schizophrenia and with different responses to the drug clozapine (35-37).

Another recent study has shown that the 5-HT_{2A} and 5-HT_{2C} serotonin receptor genes were respectively associated with auditory and visual hallucinations in AD. Interestingly, these polymorphisms are clinically silent until the onset of the neurodegenerative process (38).

The mechanisms by which these polymorphisms may alter the action of serotonin on the synaptic gap are not known since the T102C variant does not change the amino acid sequence of this serotonin receptor. According to Arranz et al. (37), the secondary protein structure or the mRNA stability might be altered by this variant although Burnett and Harrison (39) found no relation between the T102C genotype and receptor abundance. An alternative hypothesis would be that this polymorphism may be in linkage disequilibrium with another causative mutation in close proximity to this marker.

In any case, the involvement of the serotonin pathway might provide an explanation for some aspects of the affective symptoms commonly observed in AD patients. It is possible that the depressive symptoms associated with AD might be related to these or other still unknown biological factors rather than representing only the patient reaction to the diagnosis and to the limitations imposed by the disease (40). Relevant to this hypothesis is the fact that the medication currently used to circumvent the mood alterations in AD is supposed to inhibit serotonin uptake.

In summary, research on genetic polymorphisms related to AD and involved in receptors, transporter proteins and the enzymatic machinery of serotonin might enhance our understanding of the pathological mechanisms involved in this devastating neurodegenerative disorder.

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