Association analysis of HTR6 and HTR2A polymorphisms in sporadic Alzheimer's disease

Short Communication


1 Laboratory of Biochemistry, Central Institute of Mental Health, Mannheim, and
2 Department of Psychiatry and Psychotherapy, Saarland University, Homburg/Saar, Federal Republic of Germany
3 Institute of Neurological and Gerontological Sciences, International University of Catalonia, Barcelona, Spain

Received March 1, 2001; accepted June 27, 2001

Summary. In order to identify gene variants related to the serotonergic neurotransmitter system that possibly represent a hereditary risk factor for sporadic Alzheimer's disease (AD), patients suffering from AD and non-demented psychiatric inpatients without symptoms of dementia were genotyped for polymorphisms of HTR6 (267C/T) and HTR2A (−1438G/A). Although there was a tendency toward an increased number of the genotype TT of the 5-HT₆ receptor polymorphism in AD patients when compared to controls (2.8% vs. 1.3%), neither this nor the 5-HT₂A promoter polymorphism showed significant differences in their genotypic or allelic distribution among patients and controls. These polymorphisms probably do not represent major genetic risk factors of AD. However, further studies including other genetic variants of the serotonergic neurotransmitter system are needed in order to elucidate their role in AD.

Keywords: Alzheimer's disease, association, genetics, polymorphism, risk factor, serotonin.

Introduction

The risk of sporadic Alzheimer’s disease (AD) is in part determined genetically. Apart from the well known apolipoprotein E allele ε4 (Saunders et al., 1993; Steffens et al., 1997), further gene polymorphisms probably contribute to this devastating disease.

The role of the serotonergic neurotransmitter system in the pathophysiology of AD has been recognised for many years (Cross et al., 1984; Volicer...
et al., 1985; Whitford et al., 1986; Nitsch et al., 1996; Meltzer et al., 1998). However, there are relatively few genetic studies investigating the association between AD and variants of genes involved in the serotonergic system.

Recently, an association between the 5-HT₆ receptor polymorphism (267C/T) and AD has been reported (Tsai et al., 1999). Additionally, associations between genetic variants of the 5-HT₂A and 5-HT₂C receptors and psychotic symptoms in AD (Holmes et al., 1998) have been described, as well as between a polymorphism of the 5-HT-transporter promoter and late onset AD (Li et al., 1997; Oliveira et al., 1998).

In order to further elucidate possible associations between genes relevant for the serotonergic system and AD, the present study focused on the 5-HT₆ receptor polymorphism (267C/T) and the 5-HT₂A promoter polymorphism (−1438G/A). The former consists of a single nucleotide polymorphism in position 267 of the coding region of the 5-HT₆ receptor gene (Monsma et al., 1993), the latter is characterised by a single nucleotide polymorphism in position −1438 of the regulatory region of the 5-HT₂A receptor gene (Ohara et al., 1998; Enoch et al., 1999). Both polymorphisms have been investigated for their association with mood disorders in previous studies, with negative results for the 5-HT₆ receptor variant (Hong et al., 1999) and inconclusive results for the 5-HT₂A promoter polymorphism (Ohara et al., 1998; Enoch et al., 1999).

In order to evaluate the specificity of possible genetic markers and risk factors for AD, we compared the results of genotyping of AD patients with the data obtained from patients suffering from other psychiatric disorders without symptoms of dementia. Most control individuals were suffering from depressive symptoms. In contrast to other studies comparing AD patients with healthy controls, we chose this approach in order to evaluate whether the genetic markers investigated represent specific risk factors for AD and not for depression. This is important because the clinical picture of AD and depression can be very similar, especially at the beginning. Furthermore, it cannot be excluded that AD and depression possess similarities in their hereditary background (Forsell et al., 1997; Wetherell et al., 1999).

The present investigation was part of an ongoing study with this aim (Thome et al., 1999).

Methods

71 AD patients diagnosed according to ICD-10, DSM-IV and NINCDS-ADRDA criteria, were included in the study. 156 psychiatric inpatients without dementia served as controls. Both case and control groups were recruited from the same inpatient psychiatric facility. There were no statistical differences in age and gender distribution between both groups. This investigation was part of a larger ongoing study. DNA was extracted from venous blood of each individual using standard procedures. Genotypes were determined using polymerase chain reaction (PCR). For the determination of the 5-HT₆ receptor polymorphism (267C/T), a 200bp fragment was amplified by PCR using primers (5′- AACCTTTCCTGGTGTGCTCTTC-3′, 5′-ATGACGGTGACGGTCCAGGCG-3′) flanking the region containing the gene variation (Tsai et al., 1999). The PCR conditions consisted of a 5min denaturation step at 94°C, 30 cycles of 60s denaturation at 94°C, 30s annealing at 68°C and 45s extension at 72°C and a final 10min extension step.