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Negative results

No association of Tachykinin receptor 2 (*TACR2*) polymorphisms with Alzheimer's disease

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Abstract

The Tachykinin Receptor 2 (*TACR2*) located at chromosome 10q21.3 belongs to a class of receptors that bind members of the tachykinin neurotransmitter family. The TACR2 binds neurokinin A, also known as substance K, and is expressed in distinct parts of the human brain. Functionally, the TACR2 has been implicated in stress induced hippocampal acetylcholine release and the gene *TACR2* is located within a previously identified linkage region for Alzheimer's disease (AD) on chromosome 10q21. Together, both facts make the *TACR2* a reasonable positional and functional candidate gene for AD. Genotyping of 13 single nucleotide polymorphisms (SNPs) covering the entire gene and haplotypic analysis revealed no association with AD. Thus, we conclude that *TACR2* can be excluded as a major susceptibility gene conferring risk to AD.

Keywords: Alzheimer's disease; Genetics; Tachykinin receptor; TACR2

Alzheimer's disease is a complex neurodegenerative disease that is associated with a variety of genetic and environmental risk factors. However, to date, only one undisputed susceptibility gene has been identified, being the ε4 allele of *APOE* (Saunders et al., 1993). Previously published linkage studies highlighted a linkage region to AD on chromosome 10q21 that includes the Tachykinin Receptor 2 gene (*TACR2* MIM: 162321) (Ertekin-Taner et al., 2000; Myers et al., 2000). Additionally, TACR2 is highly expressed in the medial septum/diagonal band (MSDB), which is known for its cholinergic and GABA-ergic projections to the hippocampus. Atrophy of the septohippocampal cholinergic neurons of the MSDB has been reported in neurodegenerative disorders that are associated with cognitive decline, such as AD (Morozova et al., 2008). Furthermore, it was shown that intraseptal infusions of *TACR2* agonists and antagonists increase or block hippocampal acetylcholine release in rats, respectively (Desvignes et al., 2003). As a consequence the *TACR2* gene represents a reasonable functional and positional susceptibility gene altering the risk for AD.

To comprehensively investigate the genetic role of *TACR2*, we performed a whole gene approach, genotyped 13 SNPs, including 7 tagging SNPs from HapMap, covering the complete genetic region of the *TACR2* gene (see Supplementary material—Table 1) with an intermarker distance of 3.1 kb, determined the linkage disequilibrium (LD) structure, and explored single marker and haplotype associations using Haploview (Barrett et al., 2005) or appropriate regression models. This was undertaken in a thoroughly diagnosed case-control cohort, consisting of individuals clinically diagnosed

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with sporadic AD (n=479; mean age onset, 69.1 ± 9.1 years) and cognitively healthy, age, gender and ethnicity matched population-based controls (n = 322; 66.7 ± 12.0 years). Only marker rs12771121 showed a weak association signal (p = 0.031; dominant model), but this signal did not survive correction for multiple testing. The LD-block structure (see Supplementary material—Figure 1), according to Gabriel et al. (Gabriel et al., 2002), revealed three haplotype blocks at the *TACR2* region, without significant association for any haplotype combination (see Supplementary material—Table 2).

TACR2 represents a reasonable positional and functional candidate gene for AD. The LD-structure of the 13 genotyped SNPs shows high r^2-values except for rs12250793, which is not informative due to a minor allele frequency of 0.002. The marker rs3793853, when compared to the HapMap LD-structure of this region, is located next to a recombination hot spot indicated by low r^2 and D' values. Based on the LD-structure in our collective, similar to that observed in the HapMap collective, the fact that we did not find evidence of a significant association of common *TACR2* variants with AD suggests that it is unlikely that we failed to identify a possible association due to an untyped variant. Likewise with statistical power, as a power analysis revealed that, at a significance level of $\alpha = 0.05$, we had a power of 91% to detect a risk allele of 15% frequency mediating a relative risk of 1.6. However, as the statistical power drops considerably with decreasing minor allele frequencies and in particular for rare variants a possible association of these variants cannot be ruled out. In summary, this study does not provide strong evidence that common genetic variations of *TACR2* are associated with an increased risk to develop AD. Due to the limited sample size, our genetic findings do not rule out a possible genetic association of rare *TACR2* variants and a functional involvement of *TACR2* in the pathogenesis of neurodegeneration in AD.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2009.03.007.

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