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Featured Article

Carriers of a common variant in the dopamine transporter gene have greater dementia risk, cognitive decline, and faster ventricular expansion

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Abstract

Introduction: Genetic variants in *DAT1*, the gene encoding the dopamine transporter (DAT) protein, have been implicated in many brain disorders. In a recent case-control study of Alzheimer's disease (AD), a regulatory polymorphism in *DAT1* showed a significant association with the clinical stages of dementia.

Methods: We tested whether this variant was associated with increased AD risk, and with measures of cognitive decline and longitudinal ventricular expansion, in a large sample of elderly participants with genetic, neurocognitive, and neuroimaging data from the Alzheimer's Disease Neuroimaging Initiative.

Results: The minor allele—previously linked with increased DAT expression *in vitro*—was more common in AD patients than in both individuals with mild cognitive impairment and healthy elderly controls. The same allele was also associated with poorer cognitive performance and faster ventricular expansion, independently of diagnosis.

Discussion: These results may be due to reduced dopaminergic transmission in carriers of the *DAT1* mutation.

Keywords: Neuroimaging genetics; Ventricular expansion; Dopamine transporter; Dementia; *DAT1*

1. Introduction

Dopamine (DA) is a powerful regulator of many aspects of brain function, and altered DA transmission can contribute to cognitive impairment [1]. Common variants in DA-related genes have been implicated in cognitive function, age-related cognitive decline, and dementia severity [2,3]. The dopamine transporter (DAT) protein regulates neurotransmission by terminating DA signaling at the synapse through high-affinity reuptake of DA into presynaptic terminals [4]. The DAT protein limits the activation

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of DA receptors [5], and changes in DAT expression directly affect the concentration of synaptic DA and the kinetics of reuptake [6,7]. This protein is encoded by the *DAT1* (or *SLC6A3*) gene [8], and *DAT1* variants may be related to various brain disorders [9].

A recent Taiwanese study reported an association between the major T allele at rs6347 of *DAT1* and moderate dementia [3]. In other words, among demented participants, the minor C allele was significantly more prevalent in patients with severe dementia than in individuals with moderate dementia [3]. Here, we sought to replicate this association in Caucasians, and hypothesized that the minor C allele at this locus would be more common in elderly individuals with Alzheimer's disease (AD) than in both subjects with mild cognitive impairment (MCI) and healthy elderly controls (CON).

The rs6347 single nucleotide polymorphism (SNP) is a common synonymous variant (T>C, Minor Allele Frequency = 0.299) in exon 9 of *DAT1* [10]. It does not affect the amino acid sequence, but may be a regulatory variant [8]. As DA has a crucial role in cognition [1], and age-related cognitive decline [2], we also predicted that the same allele would be associated with poorer cognitive performance, independently of disease status.

DA also regulates the formation of neurotoxic amyloid beta (Aβ) oligomers [11], and lateral ventricular enlargement indicates an accumulation of brain tissue loss [12]. We therefore hypothesized that carriers of the minor allele at rs6347 would show faster expansion of the lateral ventricles, independently of their dementia status. We tested these predictions in a large elderly cohort (N = 738), with genetic, neurocognitive, and neuroimaging data.

2. Methods

2.1. Subjects

Data used in this study were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. Written informed consent was obtained from all participants. To avoid the known effects of population stratification on genetic analysis, we included only non-Hispanic Caucasian subjects [13]. Our final analysis comprised 738 individuals (average age 75.52 ± 6.78 years; 438 men/300 women) including 173 AD, 359 MCI, and 206 CON at baseline.

2.2. Cognitive testing and genotyping

All subjects completed detailed cognitive assessments including the Mini-Mental State Examination (MMSE) [14]. Participants were genotyped using the Illumina 610-Quad BeadChip. Apolipoprotein E (*APOE*) genotyping was performed separately, using an *APOE* genotyping kit, as described in http://www.adni-info.org/Scientists/Pdfs/adniproceduresmanual12.pdf.

2.3. Statistical analyses of allele frequency and associations of rs6347 genotype with MMSE scores

The distributions of allele frequencies for rs6347 were evaluated by χ^2 tests using contingency tables in SPSS 21.0. Statistical analyses of the odds ratio and 95% confidence interval were conducted based on the presence of the minor C allele. We then used the number of minor C alleles at rs6347 to predict baseline MMSE scores, assuming an additive model for allele effects.

2.4. Image acquisition, correction, and preprocessing

Participants were scanned with a standardized magnetic resonance imaging (MRI) protocol developed for this cohort [15,16]. Briefly, high-resolution structural brain MRI scans were acquired at 58 sites across North America, using 1.5 Tesla MRI scanners. A sagittal 3D MP-RAGE sequence was used, and optimized for consistency across sites [16] (TR/TE = 2400/1000 ms; flip angle = 8°; FOV = 24 cm; final reconstructed voxel resolution = 0.9375 × 0.9375 × 1.2 mm^3). Image quality control procedures and postacquisition correction of various image artifacts were performed at a single site (Mayo Clinic) [16].

2.5. Segmentation of the lateral ventricles

Raw MRI scans were preprocessed to reduce signal inhomogeneity and linearly registered to a template (using a nine-parameter registration). Prior methods for ventricular segmentation have used semiautomated, automated [17], and single-atlas or multiatlas methods [18]. Here we segmented the ventricles with our *modified* multiatlas approach described previously [19]. An inverse-consistent fluid registration with a mutual information fidelity term aligned a set of hand-labeled ventricular templates to each scan [20]. The template surfaces were registered into homologous point-to-point correspondence as a group using medial-spherical registration [21]. This approach is very similar to that of [22], except ours is based on surface geometry rather than image voxels. One subject whose meshes deviated by several millimeters from the actual periventricular boundaries was excluded. Our final analysis included 737 ADNI subjects at baseline, 623 at 12-month follow-up, and 481 at 24-month follow-up.

2.6. Statistical associations of rs6347 genotype with ventricular volumes

We first determined if genotype at the rs6347 locus might be associated with baseline ventricular volumes, after adjusting for age, sex, and diagnosis, testing both recessive and additive models of minor C allele effects. As we did not detect an association, we then used generalized linear mixed models to determine if genotype at the rs6347 locus predicted ventricular expansion over a period of two years,