

Vitamin D receptor and Alzheimer's disease: a genetic and functional study

Liyong Wang^{a,#}, Kenju Hara^{a,d,#}, Jessica M. Van Baaren^a, Justin C. Price^a, Gary W. Beecham^a, Paul J. Gallins^a, Patrice L. Whitehead^a, Gaofeng Wang^a, Chunrong Lu^a, Michael A. Slifer^a, Stephan Züchner^a, Eden R. Martin^a, Deborah Mash^b, Jonathan L. Haines^c, Margaret A. Pericak-Vance^a, John R. Gilbert^{a,*}

^a *Hussman Institute for Human Genomics, University of Miami Miller School of Medicine (1501) NW 10 Ave, Miami, Florida, USA*

^b *Department of Neurology, Brain Endowment Bank, University of Miami Miller School of Medicine, 3049 Parkinson Building, Miami, Florida, USA*

^c *Center for Human Genetics Research, Vanderbilt University Medical Center, 519 Light Hall, Nashville, Tennessee, USA*

^d *Current address: Department of Neurology, Akita Red Cross Hospital, 222-1 Kamikitate Saruda Nawashiro-sawa Akita City, Japan 010-1495*

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Abstract

Genetic studies on late-onset Alzheimer's disease (AD) have repeatedly mapped susceptibility loci onto chromosome 12q13, encompassing the vitamin D receptor (VDR) gene. Epidemiology studies have indicated vitamin D insufficiency as a risk factor for AD. Given that VDR is the major mediator for vitamin D's actions, we sought to clarify the role of VDR in late-onset AD. We conducted an association study in 492 late-onset AD cases and 496 controls with 80 tagging single nucleotide polymorphisms (SNPs). The strongest association was found at a promoter SNP rs11568820 ($P = 9.1 \times 10^{-6}$, odds ratio (OR) = 1.69), which resides within the transcription factor Cdx-2 binding site and the SNP has been also known as CDX2. The risk-allele at rs11568820 is associated with lower VDR promoter activity ($p < 10^{-11}$). The overexpression of VDR or vitamin D treatment suppressed amyloid precursor protein (APP) transcription in neuroblastoma cells ($p < 0.001$). We provide both statistical evidence and functional data suggesting VDR confers genetic risk for AD. Our findings are consistent with epidemiology studies suggesting that vitamin D insufficiency increases the risk of developing AD.

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1. Introduction

Late-onset Alzheimer's disease (Alzheimer's disease (AD) [MIM 104300]) is a progressive neurodegenerative disorder with environmental and genetic components. For familial, early-onset AD, amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) have been identified as causal genes. For late-onset AD, apolipoprotein E (APOE) gene has been universally established as a susceptibility gene (Corder et al., 1993; Farrer et al., 1997;

Saunders et al., 1993). However, 50% of late-onset AD patients do not carry the APOE ϵ 4 allele, indicating the existence of additional genetic factors for late-onset AD (Daw et al., 2000; Slioter et al., 1998).

In searching for additional genetic risk factors for late-onset AD, our group first reported strong evidence for linkage on chromosome 12q13 (Pericak-Vance et al., 1997), which was replicated by multiple independent studies (Kehoe et al., 1999; Rogaeva et al., 1998; Wu et al., 1998). The vitamin D receptor (VDR) gene, located within the critical interval on 12q13, is a plausible candidate to confer susceptibility for late-onset AD. As the receptor for 1,25-dihydroxy vitamin D₃ (1,25-(OH)₂ D₃, the active metabolite of vitamin D), VDR mediates biological actions of vitamin D.

* **Corresponding author.** Tel: +1-305 243 2282.

E-mail address: jgilbert@med.miami.edu (J.R. Gilbert).

Liyong Wang and Kenju Hara contributed equally to the manuscript.

It has been increasingly recognized that vitamin D is involved in not only Ca^{2+} homeostasis in bone but also plays an active role in the nervous system (Garcion et al., 2002). First, enzymes involved in $1,25\text{-(OH)}_2\text{D}_3$ biosynthesis and degradation have been found in the brain (Neveu et al., 1994; Zehnder et al., 2001). The VDR is expressed in the human brain, with the highest expression in the hypothalamus and in the large neurons of the substantia nigra (Eyles et al., 2005; Sutherland et al., 1992). Second, cross-sectional studies have reported higher prevalence of vitamin D deficiency in AD patients and individuals with vitamin D insufficiency (25 dihydroxy vitamin D3 ≤ 20 ng/mL) had double the risk of having AD comparing to individuals with sufficient vitamin D status (Buell et al., 2010; Sato et al., 1998). Furthermore, vitamin D deficiency has been found to be associated with cognitive impairment in both AD patients and general population (Annweiler et al., 2010; Oudshoorn et al., 2008; Przybelski and Binkley, 2007; Wilkins et al., 2006). Recently, in a prospective study of more than 1000 elderly men, a lower serum vitamin D level at baseline predicates cognitive decline during the 4.6 years follow-up (Slinin et al., 2010). Interestingly, our recent genome-wide association study (GWAS) on late-onset AD detected evidence for association in VDR ($p = 0.0006\text{--}0.0001$) (Beecham et al., 2009).

Alzheimer's disease is characterized by the presence of cerebral senile plaques composed of aggregated amyloid- β (A β) peptides produced from proteolytic cleavage of the APP. It is generally thought that APP plays a key role in the pathogenesis of AD (Hardy and Selkoe, 2002). Missense mutations in the APP gene were the first genetic factor identified for familial early-onset AD (Chartier-Harlin et al., 1991; Tanzi et al., 1992). The gene dosage of APP is known to be crucial for AD pathogenesis. Down syndrome or trisomy 21 caused by the presence of all or part of an extra chromosome 21 shows AD brain pathology (Wisniewski et al., 1985). Recently, it has been reported that APP duplication causes autosomal dominant early-onset AD (Rovelet-Lecrux et al., 2006). As a transcription factor, VDR interacts with SMAD3 (Yanagisawa et al., 1999) which is known to regulate APP transcription through TGF beta signaling (Lesné et al., 2003). It is intuitive to postulate that VDR confers genetic susceptibility to AD via modulating APP transcription.

2. Methods

2.1. Samples

All sample sets are derived from the Collaborative Alzheimer Project (CAP: the Hussman Institute for Human Genomics at the University of Miami Medical Center and the Center for Human Genetics Research at Vanderbilt University Medical Center). The CAP sample sets used for association analysis in this report are independent from previously published genetic linkage screen datasets (Liang

et al., 2006). Written informed consent was obtained from participants in agreement with protocols approved by the institutional review board at each contributing center. Inclusion criteria have been described in detail previously (Beecham et al., 2009). Briefly, each late-onset AD affected individual meets the NINCDS/ADRDA criteria for probable or definite AD and had an age at onset (AAO) greater than 60 years of age (McKhann et al., 1984). Cognitive controls were biologically unrelated individuals who were age and gender matched to the cases, and from within the same clinical catchment areas. All cognitive controls were examined and none showed signs of dementia by history and upon interview. The discovery sample set contains a total of 988 individuals of European descent. There are 492 late-onset AD cases with mean age of 72.9 ± 6.6 years and 496 cognitive controls with mean age of 74.3 ± 6.5 years. Cases are 61% female and controls are 63% female.

2.2. Genotyping and resequencing

We searched for additional polymorphisms in all exons and the promoter region (-5829 to $+4437$ bp) in the VDR gene by direct resequencing. The Applied Biosystems 3730 XL sequencer was used for resequencing in conjunction with manufacturer-recommended sequencing protocols. Primers were designed to completely incorporate the exons, intron boundaries, and the promoter region using Primer3 software. Primer sequences are available upon request.

The SNP browser software (Applied Biosystems) (De La Vega, 2007) was used to select additional tagSNPs and coding single nucleotide polymorphisms (SNPs) with minor allele frequency > 0.05 . The SNPs were selected to cover the entire region of the VDR gene and its flanking region. TaqMan allelic discrimination[®] assay was used for genotyping and data were analyzed with SDS software (Applied Biosystems). Each experimental sample is genotyped once in 384-well plates. For the purpose of quality control, 12 quality control samples in addition to the experimental samples were duplicated in each 384-well plate and the genotypes of duplicated samples were compared to evaluate genotyping calling consistency. The SNPs that showed mismatches on quality control samples were reviewed by an independent genotyping supervisor to evaluate potential genotyping errors. All SNPs included in the final analysis have passed quality control. In addition, SNPs with call rate less than 95% were dropped from further analysis.

2.3. Statistical analysis

Association tests were performed using the Armitage trend test (Armitage, 1955). All quality control, association analyses, and test for deviations from Hardy-Weinberg equilibrium (HWE) were conducted using PLINK (Purcell et al., 2007). Linkage disequilibrium (LD) between SNPs was calculated using Haploview software (Barrett et al., 2005). Both analysis of variance (ANOVA) and t -test

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