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Association of common *KIBRA* variants with episodic memory and AD risk

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Abstract

KIBRA single nucleotide polymorphism (SNP) rs17070145 was identified in a genome-wide association study (GWAS) of memory performance, with some but not all follow-up studies confirming association of its T allele with enhanced memory. This allele was associated with reduced Alzheimer's disease (AD) risk in 1 study, which also found overexpression of *KIBRA* in memory-related brain regions of AD. We genotyped rs17070145 and 14 additional SNPs in 2571 late onset Alzheimer's disease (LOAD) patients vs. 2842 controls, including African-Americans. We found significantly reduced risk for rs17070145 T allele in the older African-American subjects ($p = 0.007$) and a suggestive effect in the older Caucasian series. Meta-analysis of this allele in > 8000 subjects from our and published series showed a suggestive protective effect ($p = 0.07$). Analysis of episodic memory in control subjects did not identify associations with rs17070145, though other SNPs showed significant associations in 1 series. *KIBRA* showed evidence of overexpression in the AD temporal cortex ($p = 0.06$) but not cerebellum. These results suggest a modest role for *KIBRA* as a cognition and AD risk gene, and also highlight the multifactorial complexity of its genetic associations.

Keywords: Alzheimer's disease; KIBRA; Association studies in genetics; Case control studies; Episodic memory; Gene expression

1. Introduction

Papassotiropoulos and colleagues (Papassotiropoulos et al., 2006) identified an association between human episodic memory and a common *KIBRA* (kidney and brain expressed protein) single nucleotide polymorphism (SNP) (rs17070145) among 341 healthy, young Swiss adults (median age = 22), with replication in 2 additional healthy cohorts from Switzerland ($n = 424$, median age = 21) and USA ($n = 256$, median age = 55). Compared with noncarriers, subjects with the rs17070145 T allele showed better delayed recall across a variety of episodic memory tasks and less hippocampal activation on functional magnetic resonance imaging during an episodic memory task. Follow-up studies have replicated the original association with delayed recall (Almeida et al., 2008; Schaper et al., 2008; Preuschhof et al., 2010; Vassos et al., 2010), found significant association but in the opposite direction (Nacmias et al., 2008), found significant association but only when controlling for initial learning (Bates et al., 2009), or

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found no significant association (Need et al., 2008). Thus, although some of these studies suggest a plausible association between *KIBRA* and episodic memory, the aggregate results remain difficult to interpret given the differences in sample size, country of origin, age at evaluation, and cognitive tests examined (Schneider et al., 2010).

In addition, 2 studies have assessed the role of rs17070145 variant in Alzheimer's disease (AD) risk. Corneveaux and colleagues compared 1629 AD cases to 936 controls from 6 different sources in the USA, Germany, Norway, and Netherlands and found significantly decreased AD risk in rs17070145 T allele carriers (Corneveaux et al., 2008). In contrast, Rodriguez-Rodriguez and colleagues did not find evidence of AD risk association in their 391 AD versus 428 control subjects from Northern Spain (Rodriguez-Rodriguez et al., 2007). When stratified by age, the authors found a significantly risky association among adults older than 86 years, but in the opposite direction (i.e., rs17070145 T allele associated with increased risk of AD).

KIBRA interacts with a multitude of proteins involved in synaptic function, cell polarity, vesicular transport, and neuronal plasticity (Schneider et al., 2010). *KIBRA* is expressed in memory-related structures of the brain (Johannsen et al., 2008) and has increased expression in laser-capture microdissected neurons from the hippocampus, middle temporal gyrus, and posterior cingulate (but not the pathologically spared primary visual cortex) of AD cases in comparison with controls (Corneveaux et al., 2010). Thus far, the available genetic and functional evidence supports *KIBRA* as an interesting candidate gene for cognition and late onset Alzheimer's disease (LOAD) risk, but given the conflicting reports further evidence from independent studies appears warranted.

To investigate the role of *KIBRA* in LOAD risk, we genotyped rs17070145 along with 14 additional SNPs in >5400 subjects (2571 LOAD vs. 2842 elderly controls), including 371 African-American subjects (119 LOAD vs. 252 controls). We also evaluated rs17070145 in a meta-analysis combining our data and all published series, collectively composed of >8000 subjects. Furthermore, we evaluated the role of *KIBRA* variants and episodic memory in >2000 of our elderly control subjects. Finally, we measured *KIBRA* messenger RNA (mRNA) expression levels in the temporal cortex and cerebellum from postmortem AD and non-AD brains. To our knowledge this represents the largest case-control study to date assessing *KIBRA* variants for their role in LOAD risk and cognition. Our results provide additional support for *KIBRA*'s role in cognition and AD risk, but also highlight the multifactorial complexity of these genetic associations.

2. Methods

2.1. Patient samples

We collectively analyzed 2571 LOAD subjects and 2842 elderly controls, where 119 LOAD subjects and 252 controls were African-American and the remaining subjects were Caucasian-Americans. The Caucasian-American series were as follows: clinically diagnosed series from Mayo Clinic, Jacksonville (JS_OLD and JS_YOUNG), Mayo Clinic Rochester (RS_OLD and RS_YOUNG), National Cell Repository for AD (NCRAD_OLD and NCRAD_YOUNG), and autopsy-confirmed series maintained at the Brain Bank at Mayo Clinic Jacksonville (AUT_OLD and AUT_YOUNG). The African-American (AA_OLD and AA_YOUNG) series were collected at Mayo Clinic, Jacksonville. All Caucasian-American series were grouped using age of diagnosis (for clinical LOAD), or age at evaluation (for clinical controls) or death (for autopsy LOAD and controls) of 60–80 years (_YOUNG) and >80 years (_OLD). Because African-American subjects were younger at the time of diagnosis/evaluation than their Caucasian-American counterparts, their median age at the time of diagnosis/evaluation was chosen to designate the AA_OLD (age >74) and AA_YOUNG (60–74) series. The details of these series are available in Supplementary Table 1.

All subjects from the AA, JS, and RS series were diagnosed by a Mayo Clinic neurologist. The neurologist confirmed a Clinical Dementia Rating (CDR) score of 0 for all subjects enrolled as controls; cases had diagnoses of possible or probable AD made according to National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann et al., 1984). In the autopsy-confirmed series all brains were evaluated by the neuropathologist (DWD), where diagnosis of definite AD was also made according to NINCDS-ADRDA-criteria. None of the AUT control subjects had diagnosis of AD, but many had brain pathology unrelated to AD and pathological diagnoses that included vascular dementia, frontotemporal dementia, dementia with Lewy bodies, multisystem atrophy, amyotrophic lateral sclerosis, and progressive supranuclear palsy. The NCRAD LOAD and control subjects were also diagnosed by NINCDS-ADRDA and Clinical Dementia Rating (CDR) of 0, respectively. One AD case from each of the 715 late-onset NCRAD families and unrelated NCRAD controls was analyzed, as previously described (Zou et al., 2010).

This study was approved by the appropriate institutional review board and appropriate informed consent was obtained from all participants.

2.2. SNP genotyping and data quality control (QC)

Fifteen SNPs within or flanking *KIBRA* (also known as *WWC1*) were genotyped. These SNPs were chosen because they were HapMap tagging SNPs (Frazer et al., 2007), were within regions that have >70% interspecies conservation (human and mouse) in 100 bp sliding windows, were previously published variants (Papassotiropoulos et al., 2006), or a combination of these factors (Supplementary Table 2). All SNPs were genotyped using the Sequenom platform (Sequenom Inc., San Diego, CA, USA) (Oeth et al., 2006). All genotype data were assessed for