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Evidence of association of KIBRA genotype with episodic memory in families of psychotic patients and controls

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ABSTRACT

The first genome-wide association study of human memory identified an association between a common T/C polymorphism of the KIBRA gene (rs17070145) and episodic memory performance in normal individuals; subsequent studies have implicated the same polymorphism in Alzheimer's disease. Since impaired neurocognitive performance, including memory, may be both a core feature of schizophrenia and a candidate endophenotype, we attempted to replicate this association in a total sample of 544 subjects (including patients with psychosis, their unaffected relatives as well as normal individuals). In the combined sample there was a significant association between the KIBRA T allele and better performance in the single principle component of the memory measures, which included immediate and delayed logical and visual memory from the Wechsler Memory Scale ($p = 0.019$). In the unaffected individuals (patients' relatives and healthy controls) we observed an association of KIBRA with immediate and delayed logical memory ($p = 0.020$ and 0.025, respectively), while in patients with psychosis with delayed visual memory ($p = 0.05$). This study replicates the association between the KIBRA gene and episodic memory and suggests a possibly differential effect of the polymorphism in psychotic and non-psychotic individuals.

1. Introduction

Human memory is a heritable, polygenic trait. Twin studies have estimated that between 30% and 50% of the variance in performance in memory tasks can be attributed to genetic factors (McClearn et al., 1997; Thapar et al., 1994). In the first genome-wide association study of memory, Papassotiropoulos et al. identified an association between a common single nucleotide polymorphism (SNP) in the intron 9 of the KIBRA gene (rs17070145) and human episodic memory performance (Papassotiropoulos et al., 2006). The initial findings in a cohort of 351 healthy young Swiss adults were replicated in two independent cognitively normal cohorts, ($n = 256$ and 424) of European ancestry. Gene expression experiments showed that KIBRA is expressed in the hippocampus and other memory-related brain structures while an fMRI study demonstrated significant KIBRA allele-dependent differences in hippocampal activation, further supporting the role of KIBRA in human memory. The same group recently extended their findings, presenting evidence for association of the same SNP with late-onset Alzheimer's disease (AD) in two large samples (Corneveaux et al., 2008). These findings, if confirmed, may have important clinical implications as recent evidence in animal models suggests that the KIBRA gene and the RhoA/ROCK pathway is a possible pharmacological target to treat memory deficits (Huentelman et al., 2009).

The findings of Papassotiropoulos et al. (2006) were replicated in a German sample of 64 healthy elderly subjects, with greater effect sizes (Schaper et al., 2008) and in an Australian sample of 312 adults over the age of 50, attending a memory clinic (Almeida et al., 2008). However, a large study using two different European ancestry cohorts ($n = 319$ and 365) failed to replicate these findings (Need et al., 2008), while a recent study from Scotland demonstrated an association of KIBRA specifically with delayed recall of semantically unrelated items (Bates et al., 2009). Another study that examined a sample of Italian older adults with subjective memory complaints ($n = 70$) detected a significant association between KIBRA genotype and long-term verbal memory tests, but with the opposite alleles (Nacmias et al., 2008), while a study of

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391 Spanish patients with Alzheimer's disease (AD) and 428 normal controls again revealed an association with late-onset AD in the opposite direction from the original study (Rodriguez-Rodriguez et al., 2009). In view of the inconsistency of these findings, further studies are needed to clarify the role of KIBRA polymorphism in the variation of human memory ability.

Quite apart from improving our understanding of the biological basis of normal cognition, by identifying the genes that determine cognitive performance, we may also gain valuable insight into disease pathophysiology. Since dementia primarily affects human memory, genes associated with normal memory variation have been examined as risk factors for dementia *per se*. Furthermore deficits in executive function, learning, and memory may represent candidate endophenotypes for schizophrenia. Studies showing intermediate deficits in attention and memory in patients' unaffected relatives (Gur et al., 2007) support their use as potential neurocognitive indices of the genetic liability for schizophrenia. In a recent twin study with structural equation modeling Toulopoulou and colleagues demonstrated that selected neurocognitive measures correlated significantly with schizophrenia and that shared genetic variability explained the majority of the phenotypic correlation between intelligence and schizophrenia (Toulopoulou et al., 2007). Thus, identifying quantitative trait loci for memory or intelligence may also prove useful in the detection of schizophrenia susceptibility genes. Therefore, we attempted to replicate the association between KIBRA and episodic memory in a sample of healthy individuals, patients with psychosis, and their unaffected relatives.

2. Materials and methods

2.1. Participants

Five hundred and forty-four individuals were successfully genotyped for the KIBRA polymorphism rs17070145, after extensive clinical and neurocognitive evaluation. These individuals were drawn from the Maudsley Family Study (171 males and 186 females from 162 families, mean age: 44.28, sd: 15) and from the Maudsley Twin Study of Schizophrenia (58 males and 129 females from 103 families, mean age: 41.16, sd: 11.4). Recruitment processes for both studies have been described in detail previously (McDonald et al., 2004; Picchioni et al., 2006).

From the total sample, 166 probands met life-time diagnostic criteria for a psychotic illness (schizophrenia or bipolar disorder), 201 were unaffected relatives of psychotic probands and 177 were healthy controls (no personal or family history of psychosis). Clinical diagnoses were established by a trained psychiatrist using the Schedule for Affective Disorders and Schizophrenia (Endicott and Spitzer, 1978) and supplemented with additional clinical information to enable DSM-IV diagnoses to be made. All subjects were Caucasian and provided written informed consent after local and multi centre research ethics committee approval.

2.2. Neuropsychological examination and genotyping

At the time of the neuropsychological examination all of the patients were clinically stable with no recent changes in their medication. The neuropsychological assessment included the Wechsler Memory Scale, revised version (WMS-R) (Wechsler, 1987). The battery used and detailed screening procedures have been described previously (Toulopoulou et al., 2003a,b). In line with the original report (Papassotiropoulos et al., 2006), we restricted our analysis only to measures of episodic memory; more specifically immediate and delayed logical memory and immediate and delayed visual reproduction. The SNP rs17070145 genotyping was performed on an ABI 7900 HT Real Time PCR system (Applied Biosystems, 850 Lincoln Centre Drive, Foster City, California 94404, USA) with standard Taqman genotyping assays.

2.3. Statistical analysis

In preliminary analyses, memory tests were found to correlate strongly with educational achievement, age and clinical status (patients with psychosis performed worse). Thus, we first regressed out the effects of age, gender and years of education and used the standardized residuals in all further analyses. Since between the two samples (Family and Twin studies) there were some procedural changes in the memory scoring and some demographic differences, this process was conducted separately in each study sample and the standardized residuals (z-scores) were subsequently combined.

As the four cognitive tests (immediate and delayed logical memory and visual reproduction) were highly correlated (all correlation coefficients >0.43), in order to summarize the memory data and reduce the number of tests, we performed a principle component analysis (PCA) of the standardized residuals of the four tests adjusted for age, sex and education. This method has been extensively used previously to identify cognitive dimensions in schizophrenia (for a review see Nuechterlein et al., 2004). The PCA solution was restricted to extract one component.

As the total sample included monozygotic (MZ) twin pairs with identical genotype, we randomly included one twin from each MZ pair. The dizygotic twins were treated as regular siblings for the analyses. Since the sample contained related individuals, tests of quantitative association in pedigree data were conducted with the George–Elston regression method, which allows for multigenic and familial (residual) association (George and Elston, 1987). For this analysis we utilized the ASSOC routine in the Statistical Analysis for Genetic Epidemiology package (S.A.G.E., 2007).

In the primary analysis was examined the association of KIBRA with the single principle memory component in the total sample, with two covariates (personal and family history of psychosis). In line with the findings of the original study (Papassotiropoulos et al., 2006), analyses were performed employing the recessive mode of inheritance (TT and CT carriers were combined). To explore the data further, we performed *post-hoc* analyses for each memory test separately in the whole sample and subsequently after dividing the sample into unaffected individuals (including healthy controls and relatives) and cases with psychosis. In light of the exploratory nature of these analyses, we considered nominal p-values <0.05 as evidence of potential association.

3. Results

The genotype distribution in the entire sample (59 TT, 237 CT, and 248 CC carriers) was in Hardy–Weinberg equilibrium ($\chi^2 = 0.045$, $p = 0.83$). After excluding 60 MZ twins and 10 cases with missing data, 474 subjects entered the analysis. The mean standardized residuals for memory performance by genotype in each group (patients, relatives, and controls) are illustrated in Fig. 1. In general, healthy controls performed better than unaffected relatives, who performed better than patients with psychosis, while T allele carriers performed better than CC homozygotes in 11 out of 12 comparisons (Fig. 1).

A single principal component was sufficient to describe the four memory tests, explaining over 65% of the total variance. Quantitative analyses using the SAGE ASSOC suite of the combined sample after adjustment for multigenic, family and sibling effects revealed a significant association between genotype and the principle component ($b = 0.205$, SE = 0.09, $p = 0.019$), in the same direction as the