Interactive effects of *KIBRA* and *CLSTN2* polymorphisms on episodic memory in old-age unipolar depression

Alexandra Pantzar \(^{a,b}\), Erika J. Laukka \(^{a}\), Anna Rita Atti \(^{b}\), Goran Papenberg \(^{a,c}\), Lina Keller \(^{a,d}\), Caroline Graff \(^{d,e}\), Laura Fratiglioni \(^{a,f}\), Lars Bäckman \(^{a,f}\)

\(^{a}\) Aging Research Center, Karolinska Institutet and Stockholm University, Gävlegatan 16, 113 30 Stockholm, Sweden  
\(^{b}\) Bologna University, Bologna, Italy  
\(^{c}\) Max Planck Institute for Human Development, Berlin, Germany  
\(^{d}\) Karolinska Institutet, Department NVS, KI-Alzheimer Disease Research Center, Stockholm, Sweden  
\(^{e}\) Karolinska University Hospital, Department of Geriatric Medicine, Stockholm, Sweden  
\(^{f}\) Stockholm Gerontology Research Center, Stockholm, Sweden

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**A B S T R A C T**

The *KIBRA* (rs17070145) C-allele and the *CLSTN2* (rs6439886) T-allele have both been associated with poorer episodic memory performance. Given that episodic memory is affected in depression, we hypothesized that the combination of these risk alleles would be particularly detrimental to episodic memory performance in depressed persons. In the population-based SNAC-K study, 2170 participants ( \( \geq 60 \) years) without dementia (DSM-IV criteria) and antidepressant pharmacotherapy were clinically examined and diagnosed following ICD-10 criteria for unipolar depression, and genotyped for *KIBRA* and *CLSTN2*. Participants were categorized according to unipolar depression status (yes, no) and genotype combinations (*KIBRA*: CC, any T; *CLSTN2*: TT, any C). Critically, a three-way interaction effect showed that the CC/TT genotype combination was associated with poorer episodic recall and recognition performance only in depressed elderly persons, with depressed CC/TT carriers consistently performing at the lowest level. This finding supports the view that effects of genetic polymorphisms on cognitive functioning may be most easily disclosed at suboptimal levels of cognitive ability, such as in old-age depression.

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1. Introduction

Episodic memory, the conscious recollection of past experiences, is a complex polygenic phenotype (Rasch, Papassotiropoulos, & de Quervain, 2010). Twin and adoption studies have estimated the heritability for episodic memory to 30–60% (Finkel, Pedersen, & McGue, 1995; Johansson et al., 1999; Volk, McDermott, Roediger, & Todd, 2006), and genetic influences on cognitive abilities continue to be high in old age (McClearn, 2006; Plomin, Pedersen, Lichtenstein, & McClearn, 1994; Swan et al., 1999). Gene–gene and gene–environment interactions add to the high heterogeneity of cognitive performance. Thus, a large proportion of cognitive variability will remain unexplained if the study focus is limited to effects of single nucleotide polymorphisms (SNPs; Cirulli et al., 2010; Harris & Deary, 2011; Laukka et al., 2013; Papassotiropoulos & de Quervain, 2011).

Kidney and brain expressed protein (*KIBRA*, rs17070145, a T > C substitution) and Calsyntenin 2 (*CLSTN2*, rs6439886, a T > C substitution) were both identified as episodic memory-related genes in the first genome wide association study on episodic memory (Papassotiropoulos et al., 2006). *KIBRA*, a member of the signal transduction protein family (Büther, Plaas, Barnekow, & Kremerskothen, 2004; Kremerskothen et al., 2003), located at chromosome 5q34-q35.2, encodes a cytoplasmic protein, and is involved in synaptic plasticity and transmission, long-term-potentiation, and signal transduction (Makuch et al., 2011; Schneider et al., 2010). *CLSTN2* encodes the synaptic protein calsyntenin 2, located at chromosome 3q23, and is involved in postsynaptic signaling (Hentsch et al., 2002). Both *KIBRA* and *CLSTN2* are expressed in brain regions critical to episodic memory, such as the hippocampus (Hentsch et al., 2002; Papassotiropoulos et al., 2006; Schneider et al., 2010).

Research on effects of *KIBRA* and *CLSTN2* on episodic memory in healthy populations has yielded mixed results. The *KIBRA* T-allele performance advantage in episodic memory (Papassotiropoulos et al., 2006) has been replicated (Almeida et al., 2008; Bates et al., 2009; Corneveaux et al., 2010; Muse et al., 2013; Schaper, Kolsch, Popp, Wagner, & Jessen, 2008; Vassos et al., 2010; Yasuda et al., 2010), although several studies have not found this association (Burgess et al., 2011; Kauppi, Nilsson, Adolfsson, Eriksson, & Nyberg, 2011; Nacmias et al., 2008; Need et al., 2008, 2009; Todd, 2006), and genetic influences on cognitive abilities continue to

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Wersching et al., 2011). The CLSTN2 C-allele performance advantage (Papassotriopouls et al., 2006) has only been replicated once (Jacobson, Piccotto, Heath, Meقن, & Gelernter, 2009), whereas two other studies have failed to replicate this finding (Need et al., 2009; Zhang, Kranzler, Poling, Grueen, & Gelernter, 2009). Of chief interest for the present study, the positive effect of the KIBRA T-allele on episodic memory has been shown to increase in the presence of the CLSTN2 C-allele (Preuschhof et al., 2010) although other research has failed to confirm this interaction effect (Jacobson et al., 2009; Sédille-Mostafaie et al., 2011).

The KIBRA gene has also been investigated in memory-aﬀected disorders, such as mild cognitive impairment (Almeida et al., 2008), dementia (Burgess et al., 2011; Corneveaux et al., 2010; Hayashi et al., 2010; Rodriguez-Rodriguez et al., 2009), psychotic disorders (Vassos et al., 2010), and depression (Galecki et al., 2010). The main outcome of these studies has been risk of disease and results have been mixed.

Loss of brain resources associated with normal aging and disease may magnify the eﬀects of diﬀerent polymorphisms on cognitive functioning, as postulated by the resource-modulation hypothesis (Lindenberger et al., 2008). This hypothesis rests on the assumption that the function relating brain resources to cognitive performance is nonlinear, so that genetic variability is more likely to result in performance diﬀerences when resources move away from close-to-optimal levels. Evidence in favor of this hypothesis has been obtained in recent work comparing younger and older adults in diﬀerent cognitive functions, including executive functioning and working memory (Nagel et al., 2008; Störmer, Passow, & Li, 2012), episodic memory (Li et al., 2013a, 2013b; Papenbörjör et al., 2013), and inhibitory control (Colzato, Wildenberg, & Hommel, 2013). Further, a recent report examining genetic eﬀects on cognitive performance in patients undergoing chemotherapy found evidence in favor of the resource-modulation hypothesis (Small et al., 2011).

Depression is a highly distressing and prevalent disorder, currently aﬀecting about 350 million people worldwide (World Health Organization, 2012). A number of studies have shown that old-age depression is associated with episodic memory deﬁcits (Bäckman, Hill, & Fostell, 1996; Kindermann & Brown, 1997; Pantzar et al., 2014). A possible mechanism for this is hypercortisolism, which may cause hippocampal volume reduction (e.g., Duman, Heninger, & Nestler, 1997; McEwan, 2003; Sapolsky, 2000). As noted above, the resource modularity hypothesis predicts magniﬁed genetic effects in populations with reduced structural and neurochemical brain resources (Lindenberger et al., 2008). Thus, we hypothesized that the combination of disadvantageous KIBRA and CLSTN2 alleles may be particularly detrimental to episodic memory performance in persons with old-age unipolar depression.

2. Methods

2.1. Participants

The Swedish National Study on Aging and Care in Kungsholmen (SNACK) includes an extensive medical, social, and psychological database. Participants (N = 3363) were randomly selected from elderly persons (≥ 60 years) living in the Kungsholmen municipality in Stockholm, Sweden. At baseline, 2948 participants completed cognitive testing (see Lautkka et al. (2013), for a detailed description of the study sample). Unipolar depression was diagnosed by a psychiatrist according to ICD-10 criteria (World Health Organization, 1992), using speciﬁc depressive symptoms derived from the Comprehensive Psychopathological Rating Scale (CPRS; Åsberg, Montgomery, Perris, Schalling, & Sedvall, 1978) during a clinical interview (see Pantzar et al. (2014), for a detailed description of the diagnostic procedures). SNACK was approved by the ethical committee at Karolinska Institutet, Stockholm, Sweden, and the ethical guidelines from the Helsinki declaration were followed.

The study sample comprised 2170 participants, where 79 (3.6%) were depressed (mild, n = 42; moderate, n = 35; severe, n = 2), after exclusion of participants with dementia (DSM-IV criteria; American Psychiatric Association, 2000); non-depressed (ND), n = 102; depressed (D), n = 20; developmental disorder: ND, n = 1; current antidepressant pharmacotherapy: ND, n = 193, D, n = 21; current or past schizophrenia or other psychosis: ND, n = 8, D, n = 5; and bipolar disorder, ND, n = 11, D, n = 4). In addition, 316 persons were excluded due to missing genetic information (due to refusal or assay failures). Descriptive information for the study sample, stratified by genotypes and depression status, is presented in Table 1.

2.2. Episodic memory tests

Free recall was assessed with a word list including 16 unrelated nouns (e.g., carrot, ring, fork). Words were presented visually and auditorily at a rate of 5 s/word. The performance score was number of correctly recalled words immediately after presentation of the last item in the series. 2 min was allowed for free recall. Immediately following free recall, a recognition test was administered. This test involved the presentation of 32 nouns (16 targets, 16 lures), and participants’ task was to determine whether or not the word had been presented previously (yes–no recognition). The performance score was number of hits minus number of false alarms (see Lautkka et al. (2013), for a detailed description of the testing procedure).

2.3. Genotyping

Genotyping of KIBRA rs17070145 and CLSTN2 rs6439886 was performed on DNA obtained from peripheral blood samples. MALDI-TOF analysis was applied to

<table>
<thead>
<tr>
<th>KIBRA</th>
<th>CC (n=926)</th>
<th>Any C (n=225)</th>
<th>TT (n=701)</th>
<th>66.7</th>
<th>59.9</th>
<th>64.1</th>
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<tr>
<td>Women %</td>
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<td>59.1</td>
<td>72.1</td>
<td>66.7</td>
<td>64.1</td>
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<tr>
<td>Age: M (SD)</td>
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<td>4.18</td>
<td>12.10</td>
<td>66.7</td>
<td>64.1</td>
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<tr>
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<td>28.96</td>
<td>66.7</td>
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<tr>
<td>MMSE: M (SD)</td>
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<td>9.2</td>
<td>72.1</td>
<td>66.7</td>
<td>64.1</td>
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<table>
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<tr>
<th>KIBRA</th>
<th>CC (n=34)</th>
<th>Any C (n=7)</th>
<th>TT (n=27)</th>
<th>85.7</th>
<th>67.7</th>
<th>50.0</th>
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<td>77.75</td>
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<td>75.55</td>
<td>85.7</td>
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<td>10.29</td>
<td>85.7</td>
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<tr>
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<tr>
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<td>10.73</td>
<td>76.07</td>
<td>85.7</td>
<td>50.0</td>
<td></td>
</tr>
</tbody>
</table>

Note: MMSE = Mini-Mental State Examination; M = mean; SD = standard deviation.
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