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ORIGINAL ARTICLE

KIBRA *T* allele influences memory performance and progression of cognitive decline: a 7-year follow-up study in subjective cognitive decline and mild cognitive impairment

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Abstract

KIBRA is a signal transducer protein, mainly expressed in the kidney and brain. A single-nucleotide polymorphism (SNP rs17070145, *T* → *C* exchange) has been linked to different cognitive function. In 2008, we studied 70 subjects who complained of subjective cognitive decline (SCD) and found that *CT/TT* carriers performed worse than *CC* carriers on a long-term memory test. We followed up the 70 SCD subjects and also 31 subjects affected by mild cognitive impairment (MCI) for a mean follow-up time of 7 years, during which 16 SCD subjects progressed to MCI and 14 MCI subjects progressed to Alzheimer's disease (AD). Carrying the *T* allele was associated with MCI and with a two times-higher risk of developing MCI than *CC* carriers. In the SCD sample, *CT/TT* carriers showed a greater worsening on Rivermead Behavioral Memory Test (RBMT) compared to *CC* carriers. In the MCI sample, *CT/TT* carriers performed worse than *CC* carriers on RBMT. There is a lack of consensus on the effect of KIBRA gene variants on cognitive performances in episodic memory and on the risk of AD. Our results confirm a role of *T* allele on progression of cognitive decline.

Keywords Alzheimer's disease · Subjective cognitive decline · Mild cognitive impairment · KIBRA · ApoE · Neuropsychology

Abbreviations

SCD	Subjective cognitive decline
RBMT	Rivermead Behavioral Memory Test
HDRS	Hamilton Depression Rating Scale

Introduction

KIBRA (also known as WWC1) is a postsynaptic signal transducer protein expressed mainly in the kidney and in memory-related regions of the brain [1, 2]. It has been shown to participate in a number of cellular functions such as cell polarity and migration, vesicle transport, transcriptional regulation, and synaptogenesis. In vitro experiments suggest that, through reduction in postsynaptic levels, it mediates tau-induced memory loss and disruption of synaptic plasticity [3]. In humans, KIBRA was linked to cognition following a genome-wide association study by Papassotiropoulos and colleagues [4]. They found that a common single nucleotide polymorphism (SNP rs17070145, *T* → *C* exchange) within the ninth intron of the KIBRA gene has an effect on episodic memory performance in two Swiss cohorts and one American cohort. In particular *CC* homozygote carriers had significantly worse episodic memory performance compared to *CT/TT* carriers. In an attempt to replicate these findings, several studies have examined the effect of the

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KIBRA polymorphism on episodic memory performance of healthy participants and memory-impaired patients. However, there is a lack of consensus as carrying the *T* allele has been associated both with better performance in episodic memory [5–9], delayed recall [10, 11] and spatial learning [12] and with worse scores at semantic [13] and long-term memory [14], executive function [15], and overall cognitive performance [16]. Other studies were unable to show any association of the SNP with episodic memory [15–18].

Furthermore, a number of case-control studies have been carried out to test the effect of KIBRA SNP rs17070145 on Alzheimer disease (AD) risk with controversial results. A study by Rodríguez-Rodríguez et al. [19] revealed that the *T* allele of *KIBRA* was significantly associated with increased risk for late onset AD, while a later study came to the opposite conclusion [9]. A recent meta-analysis [20] reported that the *C* allele might have a relationship with AD risk, especially among the older population.

In 2008, we presented a study [14] on 70 subjective cognitive decline (SCD) patients in which we showed that SCD with the *CT* or *TT* genotype performed more poorly than those with the *CC* genotype on long-term memory tests. In our opinion, these data suggested that the KIBRA genotype may affect memory performance in a different way in those who complain of memory deficits compared to those who do not.

In the present work, we followed up the 70 SCD subjects (included in the previous study) and 31 MCI subjects (not included in the previous study) in order to evaluate (1) distribution of KIBRA genotypes in SCD and MCI and their effect on the risk of conversion from SCD to MCI and from MCI to AD and (2) association of the *T* allele with measures at baseline and with variations in neuropsychological scores in SCD and MCI during follow-up. To the best of our knowledge, we are aware of only one other prospective study that assesses the effect of KIBRA genotype on the development of MCI and AD [21]. Furthermore, only one other study evaluated the effect of rs17070145 SNP on cognitive performance in MCI [5].

Materials and methods

Participants and clinical assessment

As part of a demographic–genetic–clinical survey on cognitive disorders, we studied 101 consecutive non-demented subjects who self-referred to the Centre for Alzheimer's Disease and Adult Cognitive Disorders of Careggi Hospital in Florence between March 1983 and February 2007.

Inclusion criteria were (1) complaining of cognitive decline with a duration of ≥ 6 months, (2) normal functioning on the activities of daily living and the instrumental activities of daily living scales [22], and (3) unsatisfied criteria for dementia at baseline [23, 24]. Exclusion criteria were history of head injury, current neurological and/or systemic disease, symptoms of psychosis, major depression, alcoholism, or other substance abuse.

All participants underwent a comprehensive familial and clinical history, general and neurological examination, extensive neuropsychological investigation, estimation of premorbid intelligence, assessment of depression, as well as KIBRA and Apolipoprotein E (ApoE) genotype analysis. A positive family history was defined as one or more first-degree relatives with documented cognitive decline. Cognitive complaints were explored during the neurological interview at baseline using a survey based on the Memory Assessment Clinics-Questionnaire [25]. We defined the presence of cognitive complaints if participants perceived decline in cognitive capacity than in the past or if they reported difficulties in carrying out at least four of the following activities: remembering the name of a person just introduced to them; recalling telephone numbers or zip codes used on a daily or weekly basis; recalling where they put objects (such as keys) in their home or office; remembering specific facts from a newspaper or magazine article just read; remembering the item(s) they intend to buy when they arrive at the grocery store or pharmacy. The local ethics committee approved the protocol of the study, and written consent for genetic screening was obtained from all subjects.

In the whole assay, 70 subjects were classified as SCD, according to the terminology proposed by the Subjective Cognitive Decline Initiative (SCD-I) working group [26] (i.e., presence of a self-experienced persistent decline in cognitive capacities with normal performance on standardized cognitive tests); 31 subjects were classified as MCI according to (NIA-AA) criteria for the diagnosis of MCI [27] (i.e., evidence of lower performance in one or more cognitive domains with preserved independence of function in daily life).

All patients underwent clinical and neuropsychological follow-up every 6 or 12 months until March 2017. We defined the progression from SCD to MCI and from MCI to AD according to NIA-AA criteria for the diagnosis of MCI [27] and AD [24], respectively.

Neuropsychological assessment

All subjects were evaluated by means of an extensive neuropsychological battery standardized on a group of 146 normal subjects and described in further detail elsewhere [28]. The battery consisted of global measurements [Mini-Mental State Examination (MMSE), Information-Memory-Concentration Test], tasks exploring verbal and spatial short-term memory (Digit Span; Corsi Tapping Test) and verbal long-term memory (Five Words and Paired Words Acquisition, recall after 10 min and recall after 24; Babcock Short Story immediate and delayed recall), language (Token Test; Category Fluency Task), and visuo-motor functions (copying, drawings). Based on a previous discriminant analysis [28], two composite

memory scores were obtained with positive scores indicating worse performance. Visuospatial abilities were also evaluated by Rey-Osterrieth Complex Figure copy, and visuospatial long-term memory was assessed by means of recall of Rey-Osterrieth Complex Figure test [29]; attention/executive function was explored by means of Dual Task [30], Phonemic Fluency Test [31], and Trail Making Test [32]. Everyday memory was assessed by means of Rivermead Behavioral Memory Test (RBMT) [33]. All raw test scores were adjusted for age, education, and gender according to the correction factor reported in validation studies for the Italian population [28–33]. The presence and severity of depressive symptoms was evaluated by means of the 22-item Hamilton Depression Rating Scale (HDRS) [34].

Apolipoprotein E and KIBRA genotyping

Subjects' DNA was extracted from peripheral blood samples using the phenol–chloroform procedure. We analyzed KIBRA and ApoE gene polymorphisms using standard PCR and RFLP methods, as previously described [14, 35] In particular, for the SNP rs17070145 forward primer was 5′-CCCA CAGAGAAGAGGAAAACC-3′. The reverse primer was 5′-GGTCAAGAGATTCCACAGCC-3′, and the product was digested for 3 h at 37 °C with MnlI restriction enzyme. The frequencies of the ApoE and KIBRA alleles and genotypes were estimated by gene counting. The cases were grouped according to the KIBRA genotype in the *CC* and *CT/TT* carriers in parallel to previous studies.

Statistical analysis

Patient groups were characterized using means and standard deviations (SD). Scores from cognitive tests were reported as *z*-scores (*z*-scores were calculated as the raw score of the patient, minus the mean score of Italian general population, divided by the standard deviation of Italian general population). We tested for the normality distribution of the data using the Kolmogorov-Smirnov test. Depending on the distribution of our data, we used *t* test or non-parametric Mann-Whitney *U* tests for between-groups comparisons and Pearson's correlation coefficient or non-parametric Spearman's ρ (rho) to evaluate correlations between groups' numeric measures. We used chi-square test to compare categorical data. We used binomial logistic regression to ascertain the effect of KIBRA genotype on the risk of developing MCI. Repeated measures ANOVA was used to determine if there was a statistically significant interaction effect between KIBRA genotype and time on neuropsychological score changes. Bonferroni correction was applied to correct for multiple comparisons. All statistical analyses were performed with SPSS software v.13 (SPSS Inc., Chicago, USA). The significance level was set at $p < 0.05$.

Results

Distribution of KIBRA genotypes and risk of MCI

In the whole assay, 40 subjects (40%) were *CC* carriers and 61 subjects (60%) were *CT* (50) or *TT* (11) carriers. The genotypic distribution of the KIBRA gene in this sample was in Hardy-Weinberg equilibrium ($\chi^2 = 3.14$, $p > 0.05$). There were no significant differences between *CC* and *CT/TT* genotypes at baseline with respect to age at onset, age at baseline, disease duration, gender, familiarity, follow-up time, education, MMSE, and HDRS score and carrying the ApoE ε4 allele, neither in the SCD nor MCI group (Table 1).

At baseline, 31 *CC* (78%) and 39 *CT/TT* carriers (63%) were SCD, while 9 *CC* (22%) and 22 *CT/TT* carriers (37%) were MCI (Fig. 1a). The chi-square test did not show any statistically significant association between KIBRA genotype and MCI/SCD status ($\chi^2 = 2.309$, $p < 0.129$). During the follow-up, 16 out of 70 SCD subjects (23%, 5 *CC* and 11 *CT/TT*) progressed to MCI (mean conversion time = 6.77 ± 3.60 years) and 54 (77%, 26 *CC* and 28 *CT/TT*) remained stable (SCD-s, mean follow-up time = 7.49 ± 4.21 years). We reclassified all the subjects of the initial sample according to the follow-up diagnosis in a SCD group of 54 subjects and in a MCI group of 47 subjects. In this setting, 26 *CC* (65%) and 28 *CT/TT* carriers (46%) were SCD, while 14 *CC* (35%) and 33 *CT* (54%) were MCI (Fig. 1b). A statistically significant association between *T* carriage and MCI was found ($\chi^2 = 3.929$, $\varphi = 0.196$, $p = 0.047$). To evaluate the association between KIBRA genotype and MCI and to ascertain if this effect was independent from the longer follow-up time of *CT/TT* carriers, a binomial logistic regression performed including KIBRA genotype and follow-up time as covariates and SCD/MCI status as dependent variable. The logistic regression model was statistically significant ($\chi^2 = 3.976$, $p = 0.046$). *CT/TT* carriers had 2.273 (95% I.C. = 1.002:5.154) times higher odds of developing MCI than *CC* carriers, even if with a slightly statistical significance ($p = 0.049$).

During the follow-up, 14 out of 47 MCI subjects (30%, 4 *CC* and 10 *CT/TT*) developed AD (mean conversion time 4.88 ± 3.69 years) while 29 MCI subjects (62%, 9 *CC* and 20 *CT/TT*) remained stable (MCI-s, mean follow-up time = 7.35 ± 3.29 years). Four MCI subjects developed vascular dementia (8%) and were excluded from the subsequent analysis. No statistically significant associations were found between KIBRA genotypes or alleles and conversion from MCI to AD.

Neuropsychological assessment

Differences in neuropsychological test scores obtained at baseline by *CC* and *CT/TT* carriers in the SCD group were already presented in a previous work [14]. We performed the same analysis only in 54 SCD who remained stable during the

Table 1 Demographic and cognitive data

Demographic	SCD			MCI		
	CC (31)	CT/TT (39)	*p*	CC (9)	CT/TT (22)	*p*
Age at baseline (± SD)	60.87 (± 7.19)	61.74 (± 8.51)	0.652	68.97 (± 6.07)	69.51 (± 6.83)	0.453
Age at onset (± SD)	55.38 (± 7.75)	57.21 (± 8.68)	0.415	55.38 (± 7.75)	57.21 (± 8.68)	0.781
Sex (females/males)	23/9	28/11	0.994	6/3	14/8	0.873
Familiarity (percentage)	65.62%	38.46%	0.023	66.66%	59.09%	0.694
Follow-up (± SD)	5.63 (± 2.13)	7.82 (± 4.14)	0.014	6.47 (± 3.12)	6.54 (± 3.75)	0.962
Disease duration (± SD)	5.34 (± 4.84)	3.82 (± 3.39)	0.081	3.85 (± 2.08)	5.06 (± 4.37)	0.439
Schooling (± SD)	11.34 (± 4.66)	11.00 (± 5.29)	0.792	6.67 (± 4.416)	9.14 (± 4.79)	0.147
MMSE (± SD)	28.48 (± 1.84)	28.33 (± 1.85)	0.808	26.15 (± 1.34)	27.59 (± 1.73)	0.147
ApoE ε4+ (percentage)	19.35%	20.51%	0.904	12.50%	15.00%	0.864
HDRS (± SD)	25.97 (± 4.37)	25.72 (± 3.17)	0.643	27.78 (± 4.52)	25.32 (± 2.99)	0.160

Values quoted in the table are mean (± SD). Age at baseline, age at onset, disease duration, follow-up, and schooling are expressed in years. *p* indicates level of significance for comparison between *CC* and *CT/TT* (statistical significance received a Bonferroni adjustment and being accepted at the $p < 0.005$)

follow-up (SCD-s) and found no differences in neuropsychological test scores at baseline (Fig. 2a, Supplementary Table 1).

We compared neuropsychological scores at baseline also in 29 MCI subjects who remained stable (MCI-s), showing that *CC* carriers performed better than *CT/TT* carriers on RBMT ($p = 0.001$, $\varphi = 0.196$, statistical significance received a Bonferroni adjustment and being accepted at the $p < 0.002$) (Fig. 2b, Supplementary Table 2). This analysis was not performed in MCI subjects who progressed to AD due to the low number in the subsample.

A two-way repeated measures ANOVA was run to determine the effect of KIBRA polymorphism on changes in neuropsychological tests between the baseline visit and the last follow-up neuropsychological evaluation (mean follow-up time = 6.34 ± 2.73 years). In the SCD-s group, a statistically significant interaction between KIBRA genotype and follow-up time on RBMT ($F = 4.95$, $p = 0.031$, partial $\eta^2 = 0.092$) was found (Fig. 3). In particular, while no difference was found at baseline, at the follow-up evaluation, RBMT scores were statistically significantly lower in *CT/TT* than in *CC* carriers ($p = 0.005$). In the MCI-s group, we did not find any statistically significant interactions between KIBRA genotype and follow-up on neuropsychological scores.

Discussion

KIBRA is a postsynaptic signal transducer protein, mainly expressed in the kidney and in memory-related regions of the brain and involved in a number of cellular functions (cell polarity and migration, vesicle transport, transcriptional regulation, and synaptogenesis). A common single-nucleotide polymorphism (SNP rs17070145, $T \rightarrow C$ exchange) within the ninth intron of the KIBRA gene has been linked to different cognitive functions, including episodic memory [5–9],

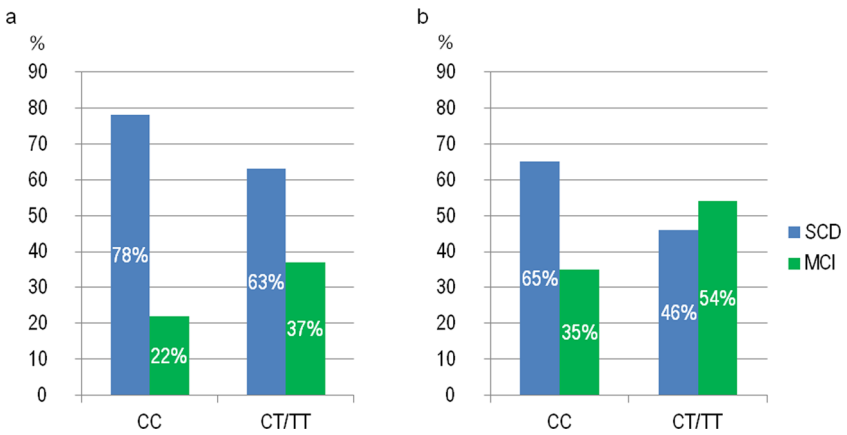

Fig. 1 Relative frequencies of SCD and MCI in *CC* and *CT/TT* groups at baseline (**a**) and at follow-up (**b**). At follow-up, a statistically significant association between *T* carriage and MCI was found

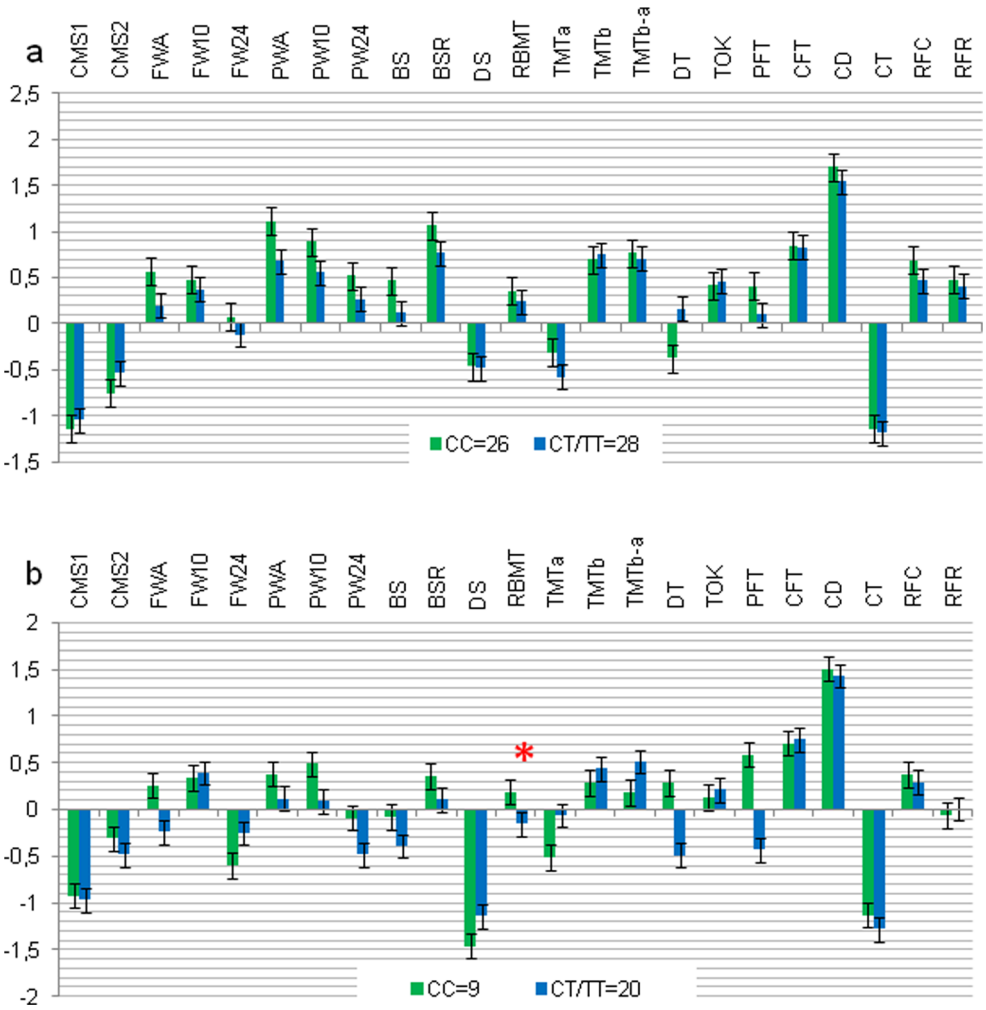

Fig. 2 Neuropsychological tests mean *z*-scores performed at baseline in SCD-s (**a**) and MCI-s (**b**) groups. In the MCI-s group, mean *z*-score of RBMT was significantly higher in *CC* carriers than in *CT/TT* carriers (marked with *). For CMS1, CMS2, TMTa, TMTb, TMTb-a, the higher the score, the worse the performance. CMS, composite memory scores; FWA, PWA, Five Words and paired words acquisition; FWR10, PWR10, recall after 10 min; FWR24, PWR24, recall after 24 h; BS and BSR, Babcock short story immediate and delayed recall; DS, digit span; RBMT, Rivermead Behavioral Memory Test; TMT, Trail Making Test; DT, dual task; TOK, token test; PFT, phonemic fluency test; CFT, category fluency task; CD, copying, drawings; CT, Corsi tapping test; RFC, Rey-Osterrieth Complex Figure copy; RFR, Rey-Osterrieth Complex Figure test

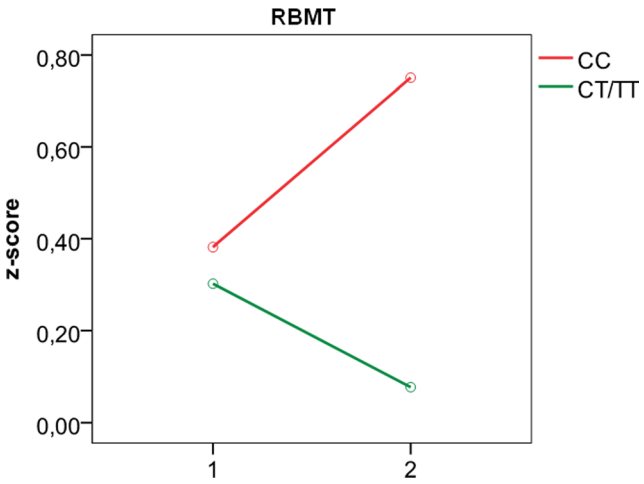

Fig. 3 Profile plot of RBMT scores (expressed as *z*-score) obtained by SCD-s subjects at baseline (**1**) and at last follow-up (**2**). A statistically significant interaction between KIBRA genotype and follow-up time on RBMT is showed. While no difference was found at baseline, at the last follow-up evaluation RBMT scores were statistically significantly lower in *CT/TT* than in *CC* carriers; RBMT Rivermead Behavioral Memory Test

delayed recall [10, 11], spatial learning [12], executive function [15], and overall cognitive performance [16]. For the purpose of the present work, we followed up the 70 SCD subjects and also 31 MCI subjects (not included in the previous study) with clinical and neuropsychological assessment every 6 or 12 months, for a mean time of 7 years.

First of all, we aimed to evaluate the distribution of KIBRA genotypes in SCD and MCI and the possible implication with the risk of progression from SCD to MCI and from MCI to AD.

Considering the diagnosis at baseline, no statistically significant association between KIBRA genotype and SCD or MCI was found. When we reclassified SCD subjects according to the diagnosis of MCI during follow-up, *T* allele resulted to increase the risk of MCI about twofold. We are aware of only two other studies which evaluate the association between MCI and KIBRA genotype. A study by Almeida et al. [5] found no association between KIBRA genotype and MCI. Nevertheless, in this study, follow-up data were not available. A recent work by Porter and colleagues [21] showed that cognitively normal subjects with Aβ-amyloid burden and

ApoE ε4 allele who were KIBRA *CC* carriers had significantly faster rates of decline in verbal episodic memory compared to KIBRA *CT/TT* carriers. Given the discrepancy between these results, we believe that further studies are needed to clarify the relationship between KIBRA and MCI development. As regards progression to AD, we did not find any significant association with KIBRA genotype, as demonstrated also in a previous study [36]. However, as we found a higher risk of MCI in *CT/TT* carriers with respect to *CC* carriers, and as MCI is considered a risk factor for AD, it is not unreasonable to assume a direct relationship also between *T* allele and AD. Literature data show contrasting evidence: Rodríguez-Rodríguez et al. [19] found that the *T* allele was associated with AD in very late-onset-AD while other studies [9, 37, 38] showed an association between *C* allele and the risk of AD. Taken together, this may suggest that the effect of KIBRA on neurodegenerative processes of AD may be more complex than previously thought and influenced by a number of demographic [39, 40], clinical [15], and cognitive conditions.

In the second part of our results, we evaluated the effect of KIBRA polymorphism on neuropsychological performances. In our previous study [14], we found that *CT/TT* carriers among SCD subjects performed worse than *CC* carriers on neuropsychological examination for long-term verbal memory. This result was in contrast with most previous and subsequent literature [5–11]. However, all these studies considered only cognitively healthy subjects. A study on 102 subjects with traumatic brain injury [41] demonstrated that non-carriers of the *T* allele performed better on episodic memory measures than *T* carriers. In only one study [5] were MCI subjects included, with no differences between *T* and *CC* carriers on neuropsychological test scores found. To the best of our knowledge, there are no previous studies on SCD subjects. Therefore, we speculated that the discrepancy between our results and literature data might be due to the different cognitive status of subjects included in our study. Moreover, we should consider that SCD is a patchwork of conditions, including early stages of cognitive decline as well as normal aging and other psychiatric or neurological conditions [42]. For this reason, follow-up is fundamental to distinguish between SCD subjects who are merely "worried well" and subjects in whom SCD is the earliest manifestation of a neurodegenerative process. Thus, we aimed to integrate our previous results and hypothesis in view of follow-up data. In particular, as in our analysis MCI was associated with *T* allele, we speculated that SCD subjects who were *CT/TT* carriers would perform worse on long-term memory test as a larger number of subjects who will develop MCI were included in this group.

So, we replicated the comparison of neuropsychological scores between *CC* and *CT/TT* carriers in SCD subjects who did not progress to MCI. As SCD is defined as a self-experienced decline in cognitive capacity with normal age-, gender-, and education-adjusted performance on standardized cognitive tests [26], SCD subjects who remained stable after a long follow-up time could be considered healthy subjects. In this subsample, no statistically significant differences on neuropsychological scores were found, in line with studies on healthy subjects [15–18].

In the same way, as the MCI definition include subjects who will remain stable, subjects who will develop AD or other dementias and subjects who will regress to normal condition, we compared neuropsychological scores between *CC* and *CT/TT* carriers only on those MCI subjects who remained stable. In this group we found that *CT/TT* carriers performed more poorly than *CC* carriers on RBMT score. Interestingly, in our previous work on SCD [14], a trend to significance was found in this test, with *CT/TT* carriers obtaining lower scores on average. Furthermore, during the follow-up, SCD-s *CT/TT* carriers showed a worsening compared to *CC* carriers precisely on RBMT. RBMT is an ecologically valid memory test battery, and a number of studies [43, 44] showed a role of this test in the prediction of conversion from MCI to AD. In particular, in a recent work by our group [45], RBMT appeared as the most accurate neuropsychological test in predicting conversion from MCI to AD. Lacking clear evidence of association between *T* allele and AD, all these results taken together could indicate a role of *T* allele in the development of AD in SCD and MCI subjects, in line with a previous study [19].

The present study has some limitations. First of all, the small size of the sample and the absence of a control group. Moreover, as it is a single-center study, there may be biases with regard to assessment and diagnosis procedures. Finally, we did not perform a correlation study between KIBRA genotyping and AD biomarkers. Future studies including CSF or neuroimaging data could provide additional information to support our hypothesis. The long follow-up time is the main strength of our study. Indeed, we are aware of only other prospective study on this topic [21] with a comparable follow-up time. Another strength is the presence of MCI subjects, as only one other study evaluated the effect of KIBRA gene on cognitive performance in MCI [5]. Finally, we are aware of only one previous prospective study that assesses the effect of KIBRA genotype on the development of MCI and AD [21].

Conclusion

Our current research supports our previous hypothesis that KIBRA may influence neuropsychological performances in a different way, depending on the cognitive status of the subject. In fact, as most of the studies on this topic have suggested a negative effect of *C* allele in healthy subjects, our results showed that *T* allele negatively influence verbal memory in people with cognitive impairment. Moreover, an association between KIBRA *T* allele and risk of MCI was found. Further

research on a wider sample, considering all the possible variables which could modulate the effect of KIBRA, are needed to better understand the role of KIBRA on human cognition and on neurodegenerative disease predisposition.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards All procedures involving experiments on human subjects have been done in accordance with the ethical standards of the Committee on Human Experimentation of the institution in which the experiments were done or in accordance with the Helsinki Declaration of 1975. Specific national laws have been observed.

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