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Association between Sirtuin 2 gene rs10410544 polymorphism and depression in Alzheimer's disease in two independent European samples

Stefano Porcelli · Raffaele Salfi · Antonis Politis · Anna Rita Atti · Diego Albani · Armando Chierchia · Letizia Polito · Aikaterini Zisaki · Christina Piperi · Ioannis Liappas · Siegfried Alberti · Martina Balestri · Agnese Marsano · Evangelia Stamouli · Antonis Mailis · Gloria Biella · Gianluigi Forloni · Virginia Bernabei · Barbara Ferrari · Loredana Lia · George N. Papadimitriou · Diana De Ronchi · Alessandro Serretti

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Abstract Among the several genes associated with late-onset Alzheimer's disease (LOAD), recently, Sirtuin genes have roused a growing interest because of their involvement in metabolic homeostasis and in brain aging. Particularly SIRT2 gene has been associated with Alzheimer's disease (AD) as well as with mood disorders. The aim of this study is to investigate the possible associations between Sirtuin 2 gene (SIRT2) rs10410544 polymorphism and AD as well as depression in AD. In addition, we performed some exploratory analyses to investigate possible associations between the rs10410544 genotype and clinical features. We investigated these associations in two independent samples: the first one was composed of 275 Greek inhabitants and 117 patients; the second sample counted 181 Italian people and 43 patients. All patients were affected by LOAD. We failed to find any association between rs10410544 genotype and AD in the two samples. On the other hand, we found an association between the single nucleotide polymorphism (SNP) and depressive symptomatology (in the total sample $p = 0.002$), which was modulated by the tumor necrosis factor (TNF) values. Particularly, TT genotype seems to be protective versus depression. Finally, in the exploratory analyses, we found that the TT genotype was associated with earlier AD onset and a longer duration of the illness. In conclusion, we confirmed the association between SIRT2 gene and mood disturbances, although in AD patients. Further, we provided evidence that the TT genotype may be protective versus depressive symptoms, allowing an easier and thus earlier diagnosis of AD. This awareness may lead to a more detailed approach to these patients concerning diagnosis and therapy.

Keywords Alzheimer's disease · Depression · SIRT2 gene · Inflammatory cytokines

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S. Porcelli · R. Salfi · A. R. Atti · S. Alberti · M. Balestri · A. Marsano · V. Bernabei · B. Ferrari · L. Lia · D. De Ronchi · A. Serretti (✉)
Department of Biomedical and NeuroMotor Sciences, University of Bologna, Viale Carlo Pepoli 5, 40123 Bologna, Italy
e-mail: Alessandro.Serretti@unibo.it

A. Politis · I. Liappas · E. Stamouli · A. Mailis · G. N. Papadimitriou
Department of Psychiatry, University of Athens Medical School, Eginition Hospital, Athens, Greece

D. Albani · A. Chierchia · G. Biella · G. Forloni
Department of Neuroscience, Istituto di Ricerche Farmacologiche "Mario Negri", Milan, Italy

L. Polito
Golgi Cenci Foundation, Abbiategrasso, Milan, Italy

A. Zisaki
Laboratory of Pharmacology, University of Athens Medical School, Athens, Greece

C. Piperi
Laboratory of Biological Chemistry, University of Athens Medical School, Athens, Greece

Introduction

Dementias are a growing health problem because of population aging worldwide. Consistently, a doubling of their

prevalence in 20 years from the 24 million affected people at present to about 50 million in 2030 was estimated (Ferri et al. 2005). Among various dementia-causing neurodegenerative disorders, AD is the most prevalent, particularly in subjects aged 75 years or more (Reitz et al. 2011). AD is a particular type of dementia clinically characterized by an initial impairment in memory that evolves to a profound deterioration in learning, episodic memory, working memory, verbal and semantic fluency until death, which usually occurs 8 years after diagnosis (Drago et al. 2011). Nowadays, AD diagnosis is performed on clinical evidence of deterioration in memory and cognition, but for a certain one the *post-mortem* proof is necessary with brain atrophy and the characteristic intracellular neurofibrillary tangles containing hyperphosphorylated tau protein and extracellular amyloid plaques containing deposits of beta amyloid (Avramopoulos 2009).

The role of genetics in etiology of AD was remarked more than 40 years ago with the evidence of an increased incidence of the disease in Down's syndrome affected individuals (Ertekin-Taner 2007). Later, further evidence of a genetic role in AD came from twin studies, which showed a higher prevalence among monozygotic twins compared to dizygotic ones (Ertekin-Taner 2007). These studies allowed also distinguishing AD in two main forms: the early-onset (EOAD) and the late-onset AD (LOAD). The EOAD is a familial pre-senile form of AD, which shows an autosomal dominant mode of inheritance, and the genetic background of this form was quickly detected with the coming of the genetic age in the 1990s. Particularly, linkage analyses and sequence comparisons led to the identification of the three genes accounting for most familial AD cases: amyloid β precursor protein (AβPP) (Goate et al. 1991), presenilin 1 (PSEN1) (Sherrington et al. 1995) and presenilin 2 (PSEN2) (Levy-Lahad et al. 1995). Nonetheless, the majority (95 %) of AD cases are LOAD and do not follow the Mendelian inheritance, although a degree of heritability was found also in this form (Gatz et al. 1997; Olgiati et al. 2011). In LOAD great importance has been attributed to gene coding for apolipoprotein E (ApoE) which seems to be able to regulate the γ-secretase cleavage implicated in AD physiopathology (Serretti et al. 2007). In particular, it has been demonstrated that ApoE ε4 allele induces higher levels of pro-inflammatory cytokines which chronically activate microglial cells, found in AD neuritic plaques (Olgiati et al. 2010). In the last decades, besides ApoE, a number of genes have been investigated, particularly after the development of Genome Wide Association Studies (GWAS), and the most important have been reported in AlzGene online database (http://www.alzgene.org/). Among genes reported in this database there are the SIRT genes, which encode for a family of seven proteins with nicotinamide adenine dinucleotide-dependent deacetylase activity implicated in regulation of cell cycle, DNA transcription, epigenetic modifications and repair, metabolism of glutamate and reactive oxygen species (ROS) production. Until now, studies investigating the associations between these genes and AD showed contrasting results. Particularly, in a previous report SIRT1 and SIRT3 were not associated with AD (Albani et al. 2010), while a study reported an association between the rs10410544 SIRT2 polymorphism and AD (Polito et al. 2012). SIRT2 activity has been recently associated with suppression of tumorigenesis (Kim et al. 2011) and modulation of NF-κB with the consequent influence on transcription of inflammatory genes (Rothgiesser et al. 2010), which are in turn largely related to formation of amyloid plaques in AD. Moreover, low levels of SIRT2 mRNA have been found in mood disorders (Abe et al. 2011), suggesting a role for this gene also in affective disorders. Therefore, the present study aims to investigate the effects of the rs10410544 SIRT2 gene variants on AD, and the effects of this variant on mood symptoms in AD patients. For these aims, we performed a case-control association study using two independent samples recruited in two European centers for a long-lasting project (Greece-Italy Genetic Association Study on LOAD, GIGAS_LOAD).

Methods

Design of study

Two independent samples were investigated in the present study, both recruited within the ongoing GIGAS_LOAD project. The samples were recruited in two independent centers, one in Athens (Greece) and one in Emilia Romagna (Italy). The aim of this project is to identify candidate genes associated with LOAD. Different protocols were implemented for the Greek and Italian arms and approved by local ethical committees. The GIGAS_LOAD group already reported on the IL-1α gene (Serretti et al. 2009) and SORL1 gene (Olgiati et al. 2012). All participants were included after obtaining their informed consent or the consent of their legal wardens.

Greek sample

Patient sample The Greek sample was described elsewhere (Serretti et al. 2009; Olgiati et al. 2010; Olgiati et al. 2012). Briefly, recruitment setting was the Neuropsychiatric Clinic of the Eginition Hospital in Athens, an academic center for neuropsychiatric disorders. The study included 117 patients who met Diagnostic and Statistical Manual for Mental Disorder IV, Text Revised (DSM-IV-TR)

criteria for AD (American Psychiatric Association, Task Force on DSM-IV 2000), which were consecutively referred to the center. The diagnostic evaluation was done by two independent psychiatrists (diagnostic concordance κ 0.80). Their age of illness onset was $\geq$60 years. The assessment procedure was described elsewhere (Olgiati et al. 2010; Politis et al. 2010; Serretti et al. 2009). Briefly, the Greek version of the Mini-Mental State Examination (MMSE) (Folstein et al. 1975) was used to assess the cognitive impairment. Scores were adjusted by age and education years according to the following formula: adjusted MMSE = raw MMSE$-$(0.471 $\times$ [Education-12]) + (0.131 $\times$ [Age-70]) (Mungas et al. 2001). Psychotic symptoms were assessed with the Neuropsychiatric Inventory (NPI) (Cummings et al. 1994) and depressive manifestations were assessed with the Cornell scale for depression in dementia (CDDS) (Alexopoulos et al. 1988). According to literature data, a score of 8 or higher was considered suggestive of significant depressive symptomatology (Barca et al. 2010). In addition each patient underwent a complete examination including physical examination, laboratory testing and brain MRI to exclude causes of dementia other than AD. No anti-inflammatory drug had been administered for >1 month before clinical evaluation and the assessment of cytokine production. The rs10410544 SIRT2 genotype was available for 95 of the initial 117 patients.

Control sample One hundred and fifty-eight unrelated controls were selected from the general population living in Athens, aged $\geq$65 years. Eligible subjects were contacted by phone and, after explaining the objectives of the study, invited for a screening examination. Volunteers gave their written informed consent and were included in the study if they had no history of neurologic disease, normal physical examination and an MMSE score >28. The composite international diagnostic interview (CIDI) was administered to exclude any DSM-IV axis I disorder. A family history method was used to exclude dementia in controls' relatives (Li et al. 1997; Silverman et al. 1992). The rs10410544 SIRT2 genotype was available for 131 of the 158 subjects of the sample.

Italian sample

The Italian sample was already reported and its features and the assessment employed were described elsewhere (De Ronchi et al. 2005). Briefly, the recruitment area was the territory of Faenza and Granarolo (55,000 inhabitants) in Emilia Romagna (Northern Italy) where an epidemiological study with the aim of investigating the cognitive and affective correlates of aging process is ongoing since 1991 (De Ronchi et al. 2005). Details on the study sample have already been provided elsewhere (Forlani et al. 2013). Out of 462 subjects who underwent the clinical re-evaluation, 181 subjects gave also the consensus for performing genetic analysis. For all 181 individuals, 138 healthy subjects and 43 patients affected by dementia, SIRT2 rs10410544 genotype was available. All participants were assessed by the Cambridge Examination for Mental Disorders of Elderly Persons–Revised (CAMDEX-R) (Roth et al. 1986). The CAMDEX-R consists of three main sections: a structured clinical interview with the patient, aimed to obtain systematic information about the present state, past history and family history; a brief neuropsychological battery including all items of the Mini-Mental State Examination (MMSE). Furthermore, the cognitive section (CAMCOG) (Huppert et al. 1995) has been shown to have high sensitivity and specificity, and can highly discriminate mild cognitive deficits from normal cognitive functioning. CAMDEX-R has also been used to detect the prevalence of depression and other mental health conditions in the elderly. Indeed, CAMDEX-R items analysis allows formulating diagnosis of dementia, depression and psychiatric disorders according to DSM-IV and International Classification of Diseases-10 (ICD-10) criteria (Forlani et al. 2013).

Total sample

In order to increase the power of the samples, we finally merged the two samples together. Then, we repeated the analyses also on the total sample obtained, composed of 138 cases and 269 healthy controls.

DNA analysis

Blood samples were collected by standard venipuncture into evacuated tubes with and without EDTA. Plasma and serum were stored at $-80°$ until analysis. Genomic DNA (gDNA) was extracted using standard procedures by a semiautomated vacuum-based nucleic acid extractor (Applied Biosystems, Inc., Foster City, CA). The rs10410544 polymorphism was analyzed by real-time polymerase chain reaction (RT-PCR) allelic discrimination assay on an ABI Prism 7300 HT instrument, using predesigned TaqMan genotyping assays and standard assay conditions (Applied Biosystems Inc., Foster City, CA). Genetic analysis was performed by personnel blind to diagnostic and clinical status of the subjects.

Biochemical parameters

Several metabolic parameters have been evaluated in the Italian sample and in the Greek patient sample with standard procedures (see Supplementary Tables 1 and 2).

Unfortunately, only C-RP measures were available for both samples.

Further, in the Greek sample, a specific evaluation of inflammatory markers at baseline and after direct stimulation has been performed. The methods for performing this evaluation have been previously described (Olgiati et al. 2010).

Statistical analysis

All data analyses were performed using the statistical package, version 7.0 (StatSoft Italia, Vigonza, Padua, Italy) for Windows® (1995). Analysis of variance (ANOVA), analysis of co-variance (ANCOVA) and Chi-square statistical analyses were performed when appropriate. All p values were two-tailed. The power of our total sample to detect significant differences between patients and controls was performed using G*Power software, version 3.1.2. For Chi-square analysis, considering an alpha value of 0.05, the sample had enough power (0.80) to detect small-medium effect sizes ($d = 0.29$).

Results

The clinical features of the two samples were reported in Table 1. The different groups were homogeneous according to these features, both considering patients versus controls and Greek sample versus Italian sample.

Allelic and genotype frequencies were distributed according to the Hardy–Weinberg equilibrium in the total sample (respectively, $p = 0.07$ and $p = 0.625$), as well as in the two samples (data not shown).

Concerning the case-control analyses, we did not find any difference in both genotype and allelic distribution of SIRT2 rs10410544 polymorphism between patients and controls in the total sample, as well as in the two samples split (see Table 2).

When we considered the presence or absence of clinical depression in patient samples (using CDDS cut-off of ≥ 8 in the Greek Sample (Barca et al. 2010) and DSM-IV diagnostic criteria (American Psychiatric Association., American Psychiatric Association. Task Force on DSM-IV 2000) in the Italian one), we found an association between rs10410544 genotype and depressive symptoms (Greek sample $p = 0.02$, Italian sample $p = 0.03$, total sample $p = 0.002$). We performed an exploratory analysis in order to examine in depth our positive match and we found an association comparing T homozygotes versus C carrying subjects (homozygotes and heterozygotes) in both samples (Greek sample $p = 0.01$, Italian sample $p = 0.05$, total sample $p = 0.002$). Taking into account these positive results, we investigated also the relationship between genotype and CDDS score in the Greek sample, finding that CC carriers showed higher scores at CDDS (mean score 7.42 ± 5.05) compared to the other subjects ($p = 0.04$, $F = 3.26$). When we controlled this associations for possible confounding factors, we found an impact on the association between rs10410544 genotype and CDDS scores of TNFα value (baseline value $p = 0.04$; after stimulation $p = 0.04$; ΔTNFα $p = 0.05$) (for details see supplementary tables 1 and 3).

Concerning the presence or absence of psychotic symptoms we did not find any association with SIRT2 genotype. For detailed results see Table 3.

Finally, we performed some exploratory analyses in order to investigate the possible associations among genotype and the other clinical variables and scale scores. The detailed results were reported in the supplementary tables 1, 2, 3 and 4. Unfortunately, for the total sample it was possible only investigate the associations among the genetic variant and C-RP and MMSE scores due to the different clinical data available for the two samples. For these two variables, we failed to find any association with rs10410544 genotype (see supplementary table 5). On the other hand, in the Greek sample we found associations among rs10410544 variant and Onset of disease ($p = 0.03$, $F = 3.54$) and duration of disease ($p = 0.03$, $F = 3.51$) (see supplementary table 1). In particular TT carriers showed a higher risk to develop earlier AD and to have longer disease compared to other subjects. No other associations were detected in this sample. In the Italian Sample, we found only two associations among SIRT2 genotype and percentages of eosinophil and basophil granulocytes,

Table 1 Description of samples

	Greek sample		Italian sample		Total Sample	
	Cases $n = 95$	Controls $n = 131$	Cases $n = 43$	Controls $n = 138$	Cases $n = 138$	Controls $n = 269$
Sex	M = 39 %	M = 46 %	M = 30 %	M = 55 %	M = 36 %	M = 51 %
Age	75.6 ± 6.6	72.6 ± 8.8	88.5 ± 6.4	81.8 ± 5.8	79.6 ± 9.2	77.3 ± 8.7
Onset	73.2 ± 5.7		>65		>65	
MMSE	17.1 ± 6.5	>28	17.3 ± 7.5	>28	17.6 ± 6.8	>28

MMSE Mini-Mental State Examination

Table 2 Case-control genotype and allelic distribution in the Greek and total samples

	Cases	Controls	χ^2	*p*
Greek sample				
C//C	28 (29.5 %)	45 (34.4 %)	0.599	0.741
C//T	49 (51.6 %)	63 (48.1 %)		
T//T	18 (18.9 %)	23 (17.6 %)		
C	105 (54.7 %)	153 (58.4 %)	0.620	0.431
T	87 (45.3%)	109 (41.6%)		
Italian sample				
C//C	18 (41.9 %)	48 (34.8 %)	0.869	0.647
C//T	17 (39.5 %)	65 (47.1 %)		
T//T	8 (18.6 %)	25 (18.1 %)		
C	53 (61.6 %)	161 (58.3 %)	0.294	0.588
T	33 (38.4 %)	115 (41.7 %)		
Total sample				
C//C	46 (33.6 %)	93 (34.6 %)	0.041	0.979
C//T	66 (48.2 %)	128 (47.6 %)		
T//T	25 (18.2 %)	48 (17.8 %)		
C	158 (57.7 %)	314 (58.4 %)	0.037	0.848
T	116 (42.3 %)	224 (41.6 %)		

SIRT2 rs10410544 polymorphism (Genotype and allele percentages are in brackets)

but they likely be false positive results since no associations were detected among SIRT2 genotype and the count of both eosinophil and basophil granulocytes (see supplementary table 2).

Discussion

AD is a growing problem because of population aging. Among genetic liability factors, SIRT genes have been recently proposed as promising candidate genes because of their function and their effects on inflammatory system. Consistently, SIRT2 rs10410544 was found associated with AD (Polito et al. 2012). Interestingly, it was associated also with mood disorders (Abe et al. 2011), which have been in turn associated with inflammatory activity as well (Bufalino et al. 2012; Eyre and Baune 2012).

Taking into account these data, in the present study we investigated the association among SIRT2 rs104110544 and both AD and depressive symptomatology in AD patients in two independent samples. Further, we performed some exploratory analysis in order to detect possible associations with other clinical features and parameters (e.g. inflammatory markers).

We did not find any association among rs10410544 and AD in the two samples, not confirming previous findings (Polito et al. 2012). Taking into account that the study of Polito et al. was the first which investigated this SNP in AD, further studies are needed to clarify this association. On the other hand, we found that rs10410544 was associated with depression in our samples, consistently with the results reported by Abe et al. (2011). Particularly, TT genotype was associated with a lower risk to develop depression. Interestingly, this association was found to be modulated by the TNF values, suggesting a possible effect of the SNP on mood through the modulation of the inflammatory system, as hypothesized by Abe et al. (2011). Moreover, in the exploratory analyses in the Greek sample we found that rs10410544 was associated with both age of onset and duration of illness. Particularly, TT genotype was associated with both an earlier onset and to a longer duration of the illness. Although these findings could be seen as contradictory since TT genotype was associated to a lower inflammatory status (Abe et al. 2011), and thus to a lower risk of developing mood disorders as well as AD (Bufalino et al. 2012; Eyre and Baune 2012; Rubio-Perez and Morillas-Ruiz 2012), an alternative explanation is possible. Indeed, we could hypothesize that C carriers showed a less clear symptomatology at the onset, causing a delay in the diagnosis of AD. Particularly, C carriers could show at the onset only depressive symptoms, which could likely cover the core symptoms of AD, as the impairment in memory functions. Therefore, the late diagnosis observed in C carriers may be due to a delay in the correct diagnosis of AD rather than to a severe predisposition in TT subjects. Obviously, this hypothesis required further studies in order to be demonstrated.

Although we examined and replicated our results in two homogeneous, independent samples, our study has undeniably some limitations. At first, we performed many analyses without using any statistical correction. Nonetheless, the primary analyses were few, allowing to avoid the use of any statistical correction, while the secondary analyses were performed only to better understand the main associations identified. Obviously, these secondary results have to be further investigated in target studies in order to be confirmed. Secondarily, the examination of only one SNP within the SIRT2 gene represents a limit of this research. However, since this polymorphism has been yet associated with AD, it represents a promising candidate for genetic analysis in the field. Furthermore, we were not able to investigate the associations among the genetic variant and other clinical variables and parameters in the entire sample, C-RP and MMSE scores apart, because of the different clinical data available for the two samples. Finally, we cannot completely exclude an ethnic stratification bias in the recruitment, even if the two samples in exam (Greek and Italian) could be considered genetically homogeneous since European population is characterized by a substantial genetic homogeneity and there are more differences among southern and northern population than western and eastern ones (Wang et al. 2012).

Table 3 Presence of depressive/psychotic symptoms in three samples considered

	CC	CT	TT	All gen	CC vs. CT vs. TT		CC + TT vs. CT		CC + CT vs. TT		TTCC + CT vs. TTCC	
					χ^2_{ML}	p	χ^2_{ML}	p	χ^2_{ML}	p	χ^2_{ML}	p
Greek Sample												
Depressive symptoms												
Yes	13 (15.1 %)	19 (22.1 %)	2 (2.3 %)	33 (38.4 %)	**7.68**	**0.02**	0.93	0.33	**6.62**	**0.01**	1.35	0.25
No	14 (16.3 %)	24 (27.9 %)	15 (17.4 %)	53 (61.6 %)								
Psychotic symptoms												
Yes	8 (11.4 %)	11 (15.7 %)	4 (5.7 %)	23 (32.9 %)	0.18	0.91	0.07	0.80	0.03	0.86	0.18	0.67
No	14 (20 %)	24 (34.3 %)	9 (12.9 %)	47 (67.1 %)								
Italian Sample												
Depressive symptoms												
Yes	4 (10.3 %)	7 (17.9 %)	0 (0 %)	11 (28.2 %)	**7.07**	**0.03**	3.24	0.07	**3.95**	**0.05**	0.03	0.87
No	11 (28.2 %)	9 (23.1 %)	8 (20.5 %)	28 (71.2 %)								
Psychotic symptoms												
Yes	2 (5.7 %)	2 (5.7 %)	0 (0 %)	4 (11.4 %)	1.93	0.38	0.32	0.57	1.13	0.28	0.09	0.76
No	13 (37.1 %)	11 (31.4 %)	7 (20 %)	31 (88.6 %)								
Total Sample												
Depressive symptoms												
Yes	17 (13.6 %)	26 (20.8 %)	2 (1.6 %)	45 (36 %)	**11.94**	**0.002**	3.16	0.07	**9.87**	**0.002**	0.55	0.46
No	25 (20 %)	33 (26.4 %)	22 (17.6 %)	80 (64 %)								
Psychotic symptoms												
Yes	10 (9.3 %)	13 (12.1 %)	4 (3.7 %)	27 (25.2 %)	0.37	0.83	0.08	0.77	0.36	0.55	0.04	0.85
No	28 (26.3 %)	36 (33.6 %)	16 (15 %)	80 (74.8 %)								

In bold are reported significant p values (<0.05) and χ^2 values. Percentages of patients with or without symptoms are in brackets

In conclusion our results did not confirm the association between rs10410544 within the SIRT2 gene and AD. On the other hand, a role of SIRT2 gene in the pathogenesis of mood disorders was confirmed. Secondary analyses suggested that rs10410544 TT carriers may be protected from depressive symptoms and, thus, it could be easier make a diagnosis of AD in these subjects, justifying the earlier onset found in our studies for these patients. The knowledge of a higher risk of confounding depressive symptoms in C carriers may have a relevant clinical impact in diagnostic and therapeutic approaches thus modifying expectancy and quality of life of AD patients.

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Conflict of interest No conflict of interest is present for the authors.

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