Journal of Molecular Neuroscience (2020) 70:1574–1588
https://doi.org/10.1007/s12031-020-01588-7

Selected *LDLR* and *APOE* Polymorphisms Affect Cognitive and Functional Response to Lipophilic Statins in Alzheimer's Disease

Fabricio Ferreira de Oliveira[1] · Elizabeth Suchi Chen[2] · Marilia Cardoso Smith[2] · Paulo Henrique Ferreira Bertolucci[1]

Received: 12 February 2020 / Accepted: 13 May 2020 / Published online: 31 May 2020

Abstract

Effects of statins over clinical changes in Alzheimer's disease (AD) are usually non-significant, but epistatic interactions between genetic variants involved in cholesterol metabolism could be important for such effects. We aimed to investigate whether *LDLR* single-nucleotide polymorphisms rs11669576 (LDLR8), rs5930 (LDLR10), and rs5925 (LDLR13) are associated with cognitive and functional changes in AD, while also considering *APOE* haplotypes and lipid-lowering treatment with lipophilic statins for stratification. Consecutive outpatients with late-onset AD were screened with cognitive tests, while caregivers scored functionality and caregiver burden, with prospective neurotranslational correlations documented for 1 year. For 179 patients, minor allele frequencies were 0.078 for rs11669576–A (14.5% heterozygotes), 0.346 for rs5930–A (42.5% heterozygotes), and 0.444 for rs5925–C (56.4% heterozygotes), all in Hardy-Weinberg equilibrium; 134 patients had hypercholesterolemia, and 133 used lipophilic statins. Carriers of rs11669576–G had faster cognitive decline, while functional decline was slower for carriers of rs11669576–A who used lipophilic statins. *APOE*-ε4 carriers who also carried rs5930–AA had improved caregiver burden, while carriers of haplotypes that included rs5930–AG had worse cognitive and functional outcomes, though carriers of the A allele of rs5930 had better cognitive and functional response to lipophilic statins. *APOE*-ε4 non-carriers who carried rs5925–TT had slower cognitive decline, while lipophilic statins protected carriers of the other genotypes. We preliminarily conclude that reportedly protective variants of *LDLR* and *APOE* against risk of AD also slowed cognitive decline, regardless of cholesterol variations, while therapy with lipophilic statins might benefit carriers of specific genetic variants.

Keywords Alzheimer disease · Dementia · Drug therapy · Neuropsychiatry · Pharmacogenetics · Hydroxymethylglutaryl-CoA reductase inhibitors

Introduction

The brain has the richest availability of cholesterol in the human body, particularly due to its importance for both myelin biosynthesis and synaptogenesis (Petek et al. 2018). In the peripheral blood, accumulating evidence shows that lipid profile variations are genetically mediated, though intimately associated with Alzheimer's disease (AD) onset (De Oliveira et al. 2014b) and progression (De Oliveira et al. 2015b) when in combination with other cerebrovascular risk factors.

The apolipoprotein E is the primary cholesterol transporter in the brain (Querfurth and LaFerla 2010); it is involved in cholinergic dysfunction, atherogenesis, and amyloidogenesis, while finding a strong affinity in the low-density lipoprotein receptor within the central nervous system (Oliveira et al. 2017). *APOE*-ε4 is the most important genetic risk factor for incidence (Smith 1999) and earlier onset of late-onset AD (De Oliveira et al. 2014b), despite also affecting behavioral

✉ Fabricio Ferreira de Oliveira
fabricioferreiradeoliveira@hotmail.com

Elizabeth Suchi Chen
eschen@unifesp.br

Marilia Cardoso Smith
macsmith@unifesp.br

Paulo Henrique Ferreira Bertolucci
bertolucci.paulo@unifesp.br

[1] Department of Neurology and Neurosurgery, Escola Paulista de Medicina, Federal University of São Paulo (UNIFESP), Sao Paulo, SP, Brazil

[2] Department of Morphology and Genetics, Escola Paulista de Medicina, Federal University of São Paulo (UNIFESP), Sao Paulo, SP, Brazil

performance (Oliveira et al. 2017) and effects of cerebrovascular risk factors over clinical changes, particularly considering lipid profile variations (De Oliveira et al. 2017). However, *APOE*-ε4 carrier status is not required or sufficient for development of the disease (Smith 1999), possibly due to variable expressivity caused by other genetic factors, such as the *TOMM40* poly-T polymorphisms linked to *APOE* (Roses 2010); actually, genetic heterogeneity causes opposite effects of *APOE*-ε4 alleles in early-onset and late-onset AD (De Luca et al. 2016). Furthermore, *APOE*-ε4 alleles do not affect cognitive or functional response to lipophilic statins by themselves (De Oliveira et al. 2017), but other genetic variants could be important for such effects.

The amyloid-β-induced increase in astrocytic expression of *APOE* is mediated by the low-density lipoprotein receptor (Oliveira et al. 2017), whereas storage and transport of cholesterol depend upon the expression of *LDLR*, consisting of 18 exons spanning 45 kb in a region linked to AD; rs11669576 (Yan et al. 2014), rs5930, and rs5925 (Gopalraj et al. 2005) are the most important genetic variants of the epidermal growth factor precursor homology domain of *LDLR* to be associated with dysfunctional cholesterol metabolism and variability in the risk of AD (Oliveira et al. 2017). The *LDLR* gene resides within ~ 1 cM (1 Mb) of a strong *APOE*-independent linkage signal in 19p13.3 and is an interesting AD candidate because it encodes an apolipoprotein E receptor (with the apolipoprotein E2 isoform having the weakest binding to the low-density lipoprotein receptor at less than 2% relative to the E3 and E4 isoforms) (Leon et al. 2018) and is pathogenetically involved in cholesterol homeostasis and response to statins (Cacabelos et al. 2016).

Most well-designed studies show no adverse effects of statins on cognition, but evidence of benefits of statin therapy over clinical changes in AD is usually non-significant (McGuiness et al. 2014). Statins could benefit these patients by lowering cholesterol levels, but also by the following alternative mechanisms: their anti-oxidant, anti-thrombotic, and vasodilatory properties (Loera-Valencia et al. 2019); neuroprotective effects that reduce production of amyloid-β while boosting the activity of the α-secretase and stimulating the non-amyloidogenic pathway of the amyloid precursor protein (Petek et al. 2018); and degradation of amyloid-β when stimulating the release of the insulin-degrading enzyme (which degrades insulin and amyloid-β) from microglia (Ozudogru and Lippa 2012) and increasing the secretion of neprilysin (another amyloid-β-degrading enzyme) from astrocytes independently of cholesterol-lowering effects (Yamamoto et al. 2016).

Most genome-wide association studies have not supported the role of *LDLR* genotypes as risk factors for late-onset AD, though their effects could be mediated via epistatic interactions with other variants of risk, such as *APOE* haplotypes. Correlations of clinical response with genetic data might explain the diversity of results in studies of lipophilic statin therapy in AD. In this preliminary observational translational study, we aimed to investigate whether *LDLR* gene polymorphisms rs11669576 (LDLR8), rs5930 (LDLR10), and rs5925 (LDLR13) are associated with cognitive and functional changes in patients with AD, while also taking *APOE* haplotypes and lipid-lowering treatment with lipophilic statins into account for stratification.

Methods

Participants and Clinical Assessment

In this uncontrolled cohort, consecutive outpatients with late-onset AD according to National Institute on Aging–Alzheimer's Association criteria (Sperling et al. 2011) were prospectively recruited from November 2010 to May 2014 at the Behavioral Neurology Section of *Hospital São Paulo*, Federal University of São Paulo (UNIFESP). Each patient was followed for 1 year, and all patients had a magnetic resonance exam to evaluate either medial parietal or medial, basal or lateral temporal atrophy or, in cases of claustrophobia or use of pacemakers, a computed tomography scan to exclude vascular lesions. Late-onset AD was considered when the dementia syndrome began after patients turned 60 years old (De Oliveira et al. 2014b).

After diagnostic confirmation, all patients had at least three yearly consultations; in the first one, they were evaluated for sex, schooling, and estimated age at dementia onset, while lipid profile evaluations and assessments of pharmacological therapy (use of lipid-lowering drugs, cholinesterase inhibitors, and/or Memantine) were conducted in all consultations. Information concerning age at dementia onset was determined following a review of medical records for cognitive and functional decline and confirmed after an interview with the caregiver, who should have frequent visits with the patient (preferably a family member), so that patients with mild cognitive impairment would not be included (Grundman et al. 2004). Diagnosis of hypercholesterolemia was based on the results of blood tests, while specific guidelines (Grundy et al. 2004) were employed for its management. Essentially, goals of total cholesterol and LDL-cholesterol were based on the presence or not of coronary heart disease, clinical manifestations of non-coronary forms of atherosclerotic disease, diabetes *mellitus*, and other vascular risk factors in general. Unless the 10-year estimated coronary heart disease risk was higher than 10%, drug therapy was introduced only if lifestyle therapy was unsuccessful after 3 months. Non-pharmacological recommendations including body weight control, regular physical activity, dietary therapy, and smoking cessation were simultaneously employed, whereas pharmacological therapy would be discontinued in case of side effects. All efforts were

directed to control hypercholesterolemia for all patients rather than just lowering cholesterol levels. Participation of each patient was concluded when follow-up completed 1 year.

All participants were prospectively evaluated by way of the Mini-Mental State Examination (MMSE) (Bertolucci et al. 1994) and a 15-item Clock Drawing Test (free drawing) (CDT) (De Oliveira et al. 2015a), while their caregivers were queried for scores on the Index of Independence in Activities of Daily Living (ADL) (Katz and Akpom 1976), Lawton's Scale for Instrumental Activities of Daily Living (IADL) (Lawton 1988), the Clinical Dementia Rating sum-of-boxes (CDR-SOB) (Lima et al. 2017), and the Brazilian Version of the Zarit Caregiver Burden Interview (Zarit) (Taub et al. 2004). Scoring guidelines for these tests have been previously described (De Oliveira et al. 2015a); essentially, cognition and functionality are usually correlated, while caregiver burden is more affected by behavioral features. All assessments were conducted on weekdays at morning time, by the same examiner (FFO). For statistics, only the baseline and the final scores were taken into account.

Genotyping Procedures

After blood was collected from all patients in tubes with ethylenediaminetetraacetic acid 0.1%, genomic DNA was extracted using a standard salting-out procedure for determination of rs11669576, rs5930, rs5925, rs7412, and rs429358 by way of real-time polymerase chain reactions using TaqMan® SNP Genotyping Assays on the Applied Biosystems 7500 Fast Real-Time PCR System (Applied Biosystems®, USA), following the standard protocols of the manufacturer. After *APOE* haplotypes were determined by genotypes of rs7412 and rs429358, the presence of *LDLR* genotypes of rs11669576, rs5930, or rs5925, or their represented haplotypes, was correlated with lipid-lowering therapy using lipophilic statins. All genotyping procedures were carried out only after clinical data were collected from all patients.

Outcome Measures

The main outcome measure was the score variation in 1 year regarding cognition (CDT, MMSE), functionality (ADL, IADL), global ratings (CDR-SOB), or caregiver burden (Zarit), taking into account the following independent variables: use of a lipophilic statin and *LDLR* genotypes or haplotypes. When the impacts of lipophilic statin therapy or *LDLR* genotypes were measured, patients were divided into groups of *APOE*-ε4 carriers or *APOE*-ε4 non-carriers.

Statistical Analyses

Paired Student's *t* test was employed for yearly variations of weight, total cholesterol, and test scores (taking baseline and final scores after 1 year into account). The Hardy-Weinberg equilibrium for *LDLR* genotypes was estimated by way of the *Chi*-square test. A general linear model with post hoc Hochberg's GT2, separately for *APOE*-ε4 carriers and for *APOE*-ε4 non-carriers, was employed for test score variations in 1 year, according to *LDLR* genotypes or haplotypes and use or not of a lipophilic statin. The general linear model was adjusted for sex, years of schooling, age, estimated length of the dementia syndrome, total cholesterol, and weight variations in 1 year. Univariate analyses disclosed the effects of genetic variants over each test score variation regardless of pharmacological treatment, while multivariate analyses showed results of interactions between genetic variants and use or not of lipophilic statins. The threshold of significance was set at $p < 0.05$.

Results

By the end of the recruitment, 216 patients had been included. During follow-up, 15 patients (6.9%) passed away, and 9 patients (4.2%) abandoned the study; at the end, other 13 patients (6.0%) had to be excluded due to insufficient clinical data, resulting in a final sample of 179 patients.

Table 1 shows clinical and demographic results for all patients. Almost 94% of them used a cholinesterase inhibitor during the study, while almost 75% used a lipophilic statin (Atorvastatin, a synthetic statin, or Simvastatin, a natural one) as lipid-lowering therapy (Maxwell et al. 2017). All patients who used Ezetimibe were also treated with a statin. Weight and levels of total cholesterol were significantly lowered after 1 year. Significant changes were found for most test scores, except for the Zarit.

Table 2 shows genetic frequencies for the final sample. Minor allele frequencies were 0.078 for rs11669576 (A), 0.346 for rs5930 (A), and 0.444 for rs5925 (C). All single-nucleotide polymorphisms were in Hardy-Weinberg equilibrium. Of 27 possible *LDLR* haplotypes, 21 were represented in the sample.

Table 3 shows test score variations according to genetic variants only. *APOE*-ε4 non-carriers who carried rs5930-AG had faster worsening of CDR-SOB scores, while those who carried rs5925-TT had slower worsening of MMSE scores. *APOE*-ε4 carriers who carried rs5930-AA had improved caregiver burden.

Table 4 shows that lipophilic statins protected non-carriers of rs11669576-GG against functional decline: a slower worsening of instrumental functionality was observed for *APOE*-ε4 carriers who also carried rs11669576-AG, while a slower worsening of basic functionality and CDR-SOB scores was observed for *APOE*-ε4 non-carriers who also carried rs11669576-AG; the AA genotype was underrepresented in the sample. Table 5 shows that lipophilic statins were harmful

Table 1 Demographic and clinical results

Assessed factors, $n = 179$		n (%)	Mean ± SD	p^a
Sex	Women	124 (69.3%)	–	–
	Men	55 (30.7%)	–	–
Schooling		–	4.30 ± 3.7 years	–
Estimated age at dementia onset		–	72.78 ± 6.5 years old	–
Age at inclusion in the study		–	77.80 ± 5.9 years old	–
Length of dementia at inclusion in the study		–	2.95 ± 2.3 years	–
Weight	Baseline values	–	62.79 ± 12.4 kgf	*p < 0.0001*
	Final values	–	61.32 ± 13.2 kgf	
	Variation	–	− 1.47 ± 5.2 kgf	–
Diabetes *mellitus*		49 (27.4%)	–	–
Hypercholesterolemia		134 (74.9%)	–	–
Lipid-lowering therapy	Atorvastatin	13	29.23 ± 23.6 mg/day	–
	Rosuvastatin	1	10.00 ± 0.0 mg/day	–
	Simvastatin	120	18.25 ± 9.0 mg/day	–
	Ezetimibe	3	10.00 ± 0.0 mg/day	–
Total cholesterol	Baseline values	–	198.90 ± 47.1 mg/dl	*p < 0.0001*
	Final values	–	182.34 ± 39.0 mg/dl	
	Variation	–	− 16.56 ± 36.8 mg/dl	–
Use of a cholinesterase inhibitor		168 (93.9%)	–	–
Use of Memantine		134 (74.9%)	–	–
Clinical Dementia Rating sum-of-boxes (0.0–18.0 points)	Baseline scores	–	10.13 ± 3.8	*p < 0.0001*
	Final scores	–	11.69 ± 4.0	
	Variation	–	1.55 ± 2.5	–
Index of Independence in Activities of Daily Living (0–6 points)	Baseline scores	–	5.04 ± 1.5	*p < 0.0001*
	Final scores	–	4.47 ± 2.0	
	Variation	–	− 0.57 ± 1.5	–
Lawton's Scale for Instrumental Activities of Daily Living (9–27 points)	Baseline scores	–	13.94 ± 4.7	*p < 0.0001*
	Final scores	–	12.34 ± 4.1	
	Variation	–	− 1.61 ± 3.0	–
Clock Drawing Test (0–15 points)	Baseline scores	–	6.31 ± 4.5	*p = 0.023*
	Final scores	–	5.83 ± 4.7	
	Variation	–	− 0.48 ± 2.8	–
Mini-Mental State Examination (0–30 points)	Baseline scores	–	15.57 ± 5.5	*p < 0.0001*
	Final scores	–	14.31 ± 6.3	
	Variation	–	− 1.26 ± 3.1	–
Brazilian Version of the Zarit Caregiver Burden Interview (0–56 points)	Baseline scores	–	15.47 ± 9.8	$p = 0.902$
	Final scores	–	15.55 ± 10.4	
	Variation	–	0.08 ± 8.4	–

SD standard deviation

[a] Paired Student's *t* test for baseline scores and final scores after 1 year

Significant values are outlined in italics

regarding caregiver burden for *APOE*-ε4 carriers who also carried rs5930-AA, while marginally significant effects toward slower cognitive decline were observed for non-carriers of rs5925-TT.

Table 6 shows *LDLR* haplotype effects for the entire sample. Carriers of rs11669576-AG/rs5930-AG had better outcomes regarding instrumental functionality when using lipophilic statins. Carriers of rs11669576-GG/rs5930-AA had better outcomes regarding MMSE and CDR-SOB scores when using lipophilic statins and caused lower caregiver burden even when not using lipophilic statins. Carriers of rs11669576-GG/rs5930-AG had worse outcomes regarding CDT and CDR-SOB scores and also regarding MMSE scores mostly when not using lipophilic statins. Carriers of rs5930-

Table 2 Genetic results

Genotypes and haplotypes, $n = 179$			n (%)	p^a
APOE haplotypes	*APOE*-ε4 carriers, $n = 96$	ε4/ε4	21 (11.7%)	–
		ε4/ε3	68 (38.0%)	–
		ε4/ε2	7 (3.9%)	–
	APOE-ε4 non-carriers, $n = 83$	ε3/ε3	76 (42.5%)	–
		ε3/ε2	7 (3.9%)	–
		ε2/ε2	0 (0.0%)	–
(LDLR8): rs11669576 genotypes	*APOE*-ε4 carriers, $n = 96$	AA	1 (0.6%)	$p = 0.922$
		AG	18 (10.0%)	
		GG	77 (43.0%)	
	APOE-ε4 non-carriers, $n = 83$	AA	0 (0.0%)	
		AG	8 (4.5%)	
		GG	75 (41.9%)	
(LDLR10): rs5930 genotypes	*APOE*-ε4 carriers, $n = 96$	AA	13 (7.2%)	$p = 0.405$
		AG	41 (22.9%)	
		GG	42 (23.5%)	
	APOE-ε4 non-carriers, $n = 83$	AA	11 (6.2%)	
		AG	35 (19.5%)	
		GG	37 (20.7%)	
(LDLR13): rs5925 genotypes	*APOE*-ε4 carriers, $n = 96$	CC	14 (7.8%)	$p = 0.056$
		CT	53 (29.6%)	
		TT	29 (16.2%)	
	APOE-ε4 non-carriers, $n = 83$	CC	15 (8.4%)	
		CT	48 (26.8%)	
		TT	20 (11.2%)	
LDLR haplotypes	rs11669576 AA/rs5930 GG		1 (0.6%)	–
	rs11669576 AA/rs5925 TT		1 (0.6%)	–
	rs11669576 AG/rs5930 AG		9 (5.0%)	–
	rs11669576 AG/rs5930 GG		17 (9.5%)	–
	rs11669576 AG/rs5925 CC		1 (0.6%)	–
	rs11669576 AG/rs5925 CT		13 (7.3%)	–
	rs11669576 AG/rs5925 TT		12 (6.7%)	–
	rs11669576 GG/rs5930 AA		24 (13.4%)	–
	rs11669576 GG/rs5930 AG		67 (37.4%)	–
	rs11669576 GG/rs5930 GG		61 (34.1%)	–
	rs11669576 GG/rs5925 CC		28 (15.6%)	–
	rs11669576 GG/rs5925 CT		88 (49.1%)	–
	rs11669576 GG/rs5925 TT		36 (20.1%)	–
	rs5930 AA/rs5925 CT		7 (3.9%)	–
	rs5930 AA/rs5925 TT		17 (9.5%)	–
	rs5930 AG/rs5925 CC		5 (2.8%)	–
	rs5930 AG/rs5925 CT		53 (29.6%)	–
	rs5930 AG/rs5925 TT		18 (10.0%)	–
	rs5930 GG/rs5925 CC		24 (13.5%)	–
	rs5930 GG/rs5925 CT		41 (22.9%)	–
	rs5930 GG/rs5925 TT		14 (7.8%)	–

APOE apolipoprotein E gene, *LDLR* low-density lipoprotein cholesterol receptor gene

[a] Hardy-Weinberg equilibrium (*Chi*-square test)

Table 3 Effects of genetic variants over test score variations in 1 year independently of pharmacological treatment

Genotypes		CDR-SOB variations		ADL variations		IADL variations		MMSE variations		CDT variations		Zarit variations	
		Mean ± SD	p^a	Mean ± SD	p^a	Mean ± SD	p^a	Mean ± SD	p^a	Mean ± SD	p^a	Mean ± SD	p^a
rs11669576 genotypes (*APOE*-ε4 carriers[b])	AA	2.00 ± 0.0	0.411	− 2.00 ± 0.0	0.234	− 2.00 ± 0.0	0.921	− 4.00 ± 0.0	0.282	0.00 ± 0.0	0.664	6.00 ± 0.0	0.387
	AG	1.89 ± 2.6	0.616	− 0.44 ± 1.6	0.218	− 1.11 ± 3.1	0.890	− 1.56 ± 3.6	0.270	0.28 ± 2.8	0.932	0.94 ± 6.4	0.600
	GG	1.36 ± 2.5	0.254	− 0.61 ± 1.6	0.798	− 2.09 ± 3.1	0.877	− 1.40 ± 3.2	0.847	− 1.04 ± 3.0	0.203	− 1.21 ± 7.7	0.228
rs11669576 genotypes (*APOE*-ε4 non--carriers[c])	AA	–	–	–	–	–	–	–	–	–	–	–	–
	AG	0.56 ± 3.2	0.272	− 0.50 ± 1.9	0.680	− 1.87 ± 2.1	0.637	− 0.75 ± 2.1	0.407	0.25 ± 1.6	0.430	− 1.00 ± 5.3	0.485
	GG	1.77 ± 2.3	0.272	− 0.55 ± 1.5	0.680	− 1.20 ± 3.0	0.637	− 1.07 ± 3.0	0.407	− 0.17 ± 2.6	0.430	1.23 ± 9.8	0.485
rs5930 genotypes (*APOE*-ε4 carriers[b])	AA	0.15 ± 2.5	0.144	− 0.15 ± 1.3	0.145	− 1.62 ± 3.0	0.102	0.31 ± 2.9	0.326	− 0.31 ± 3.2	0.465	− 5.85 ± 10.6	*0.001*
	AG	1.59 ± 2.4	0.384	− 0.51 ± 1.6	0.411	− 1.49 ± 2.5	0.373	− 1.93 ± 2.9	0.136	− 0.90 ± 2.8	0.767	0.54 ± 5.2	*< 0.001*
	GG	1.75 ± 2.5	0.386	− 0.81 ± 1.6	0.349	− 2.40 ± 3.6	0.271	− 1.55 ± 3.6	0.410	− 0.81 ± 3.2	0.520	− 0.38 ± 7.7	0.417
rs5930 genotypes (*APOE*-ε4 non--carriers[c])	AA	0.77 ± 2.2	0.379	− 0.27 ± 0.9	0.856	− 0.09 ± 3.0	0.806	0.18 ± 2.0	0.686	− 0.27 ± 1.7	0.462	− 4.00 ± 11.9	0.123
	AG	2.47 ± 2.5	*0.021*	− 0.91 ± 1.9	0.318	− 2.11 ± 3.5	0.697	− 1.80 ± 3.1	0.227	− 0.54 ± 2.9	0.985	1.34 ± 9.1	0.150
	GG	1.15 ± 2.2	0.523	− 0.27 ± 1.2	0.070	− 0.81 ± 2.0	0.327	− 0.68 ± 2.7	0.215	0.30 ± 2.3	0.243	2.19 ± 8.7	0.864
rs5925 genotypes (*APOE*-ε4 carriers[b])	CC	1.61 ± 1.9	0.237	− 0.79 ± 1.5	0.175	− 2.71 ± 3.2	0.075	− 1.93 ± 2.4	0.498	− 1.07 ± 2.9	0.206	0.57 ± 4.3	0.275
	CT	1.58 ± 2.5	0.331	− 0.77 ± 1.7	0.805	− 2.02 ± 3.2	0.317	− 1.36 ± 3.4	0.630	− 0.75 ± 3.3	0.335	− 0.85 ± 7.3	0.700
	TT	1.19 ± 2.6	0.711	− 0.17 ± 1.3	0.141	− 1.31 ± 2.7	0.258	− 1.41 ± 3.4	0.763	− 0.69 ± 2.4	0.624	− 1.14 ± 9.0	0.337
rs5925 genotypes (*APOE*-ε4 non--carriers[c])	CC	1.80 ± 1.8	0.417	− 0.53 ± 0.8	0.866	− 1.33 ± 1.8	0.980	− 0.93 ± 3.2	0.192	− 0.33 ± 3.2	0.443	3.87 ± 6.3	0.134
	CT	1.62 ± 2.5	0.310	− 0.60 ± 1.7	0.762	− 1.33 ± 3.4	0.641	− 1.46 ± 3.0	0.717	− 0.23 ± 2.4	0.758	1.60 ± 9.5	0.563
	TT	1.62 ± 2.7	0.892	− 0.40 ± 1.5	0.889	− 1.05 ± 2.4	0.596	− 0.10 ± 2.4	*0.030*	0.25 ± 2.2	0.507	− 2.55 ± 10.6	0.184

CDR-SOB Clinical Dementia Rating sum-of-boxes, *ADL* Index of Independence in Activities of Daily Living, *IADL* Lawton's Scale for Instrumental Activities of Daily Living, *MMSE* Mini-Mental State Examination, *CDT* Clock Drawing Test, *Zarit* Brazilian Version of the Zarit Caregiver Burden Interview, *SD* standard deviation

[a] Inter-genotype comparisons (general linear model adjusted for sex, years of schooling, age, estimated length of the dementia syndrome, total cholesterol, and weight variations in 1 year)

[b] *APOE*-ε4 carriers ($n = 96$) = carriers of *APOE*-ε4/ε4, *APOE*-ε4/ε3 or *APOE*-ε4/ε2: for rs11669576 AA, $n = 1$; for rs11669576 AG, $n = 18$; for rs11669576 GG, $n = 77$; for rs5930 AA, $n = 13$; for rs5930 AG, $n = 41$; for rs5930 GG, $n = 42$; for rs5925 CC, $n = 14$; for rs5925 CT, $n = 53$; for rs5925 TT, $n = 29$

[c] *APOE*-ε4 non-carriers ($n = 83$) = carriers of *APOE*-ε3/ε3 or *APOE*-ε3/ε2 (*APOE*-ε2/ε2 was not represented in this sample): for rs11669576 AG, $n = 8$; for rs11669576 GG, $n = 75$; for rs5930 AA, $n = 11$; for rs5930 AG, $n = 35$; for rs5930 GG, $n = 37$; for rs5925 CC, $n = 15$; for rs5925 CT, $n = 48$; for rs5925 TT, $n = 20$

Significant values are outlined in italics

GG/rs5925-TT had increasing MMSE scores when not using lipophilic statins, but better CDT scores particularly when using lipophilic statins. Carriers of rs5930-AG/rs5925-CC had worse functionality when not using lipophilic statins. Carriers of rs11669576-GG/rs5925-TT and rs5930-AA/rs5925-TT caused lower caregiver burden mostly when not using lipophilic statins.

According to MMSE scores, carriers of rs11669576-GG/rs5925-CT ($p = 0.042$) and rs5930-AG/rs5925-CT ($p = 0.029$) had faster cognitive decline, while carriers of rs5930-AA/rs5925-CT ($p = 0.033$) had slower cognitive decline, regardless of use of lipophilic statins.

Graphical representations of the most significant results of the analyses are illustrated in Fig. 1; each graph represents test score variations in 1 year according to specific genotypes and pharmacological treatment. Figure 2 shows the mechanisms underlying the bound ligand of apolipoprotein E4 to the low-density lipoprotein receptor.

Discussion

Conventional treatment for AD is still based on cholinesterase inhibitors and Memantine (De Oliveira et al. 2014a).

Table 4 Functional staging response to lipophilic statins in 1 year according to genotype frequencies for *LDLR* polymorphisms in *APOE*-ε4 carriers and non-carriers

Genotypes		CDR-SOB variations (mean ± SD)			ADL variations (mean ± SD)			IADL variations (mean ± SD)		
		Lipophilic statin	No lipophilic statin	p^a	Lipophilic statin	No lipophilic statin	p^a	Lipophilic statin	No lipophilic statin	p^a
rs11669576 genotypes (*APOE*-ε4 carriers[b])	AA	2.00 ± 0.0	–	–	− 2.00 ± 0.0	–	–	− 2.00 ± 0.0	–	–
	AG	1.79 ± 2.6	2.08 ± 2.7	0.675	− 0.17 ± 1.3	− 1.00 ± 2.0	0.291	− 0.17 ± 2.7	− 3.00 ± 3.2	*0.035*
	GG	1.54 ± 2.5	0.91 ± 2.5	0.504	− 0.56 ± 1.5	− 0.73 ± 1.8	0.454	− 2.51 ± 3.3	− 1.05 ± 2.3	0.171
rs11669576 genotypes (*APOE*-ε4 non-carriers[c])	AA	–	–	–	–	–	–	–	–	–
	AG	− 0.90 ± 3.0	3.00 ± 1.7	*0.029*	0.60 ± 1.3	− 2.33 ± 1.2	*0.015*	− 1.40 ± 1.5	− 2.67 ± 3.1	0.586
	GG	1.65 ± 2.5	2.27 ± 1.5	0.516	− 0.58 ± 1.5	− 0.40 ± 1.5	0.865	− 1.00 ± 3.0	− 2.00 ± 2.8	0.340
rs5930 genotypes (*APOE*-ε4 carriers[b])	AA	− 0.10 ± 2.4	1.00 ± 3.0	0.630	− 0.30 ± 1.3	0.33 ± 1.5	0.564	− 2.50 ± 2.8	1.33 ± 1.5	0.063
	AG	1.84 ± 2.3	0.80 ± 2.4	0.361	− 0.45 ± 1.7	− 0.70 ± 1.3	0.545	− 1.32 ± 2.5	− 2.00 ± 2.5	0.368
	GG	1.93 ± 2.4	1.43 ± 2.6	0.746	− 0.67 ± 1.4	− 1.07 ± 2.1	0.318	− 2.81 ± 4.0	− 1.67 ± 2.5	0.537
rs5930 genotypes (*APOE*-ε4 non-carriers[c])	AA	0.28 ± 2.1	3.00 ± 0.0	0.186	− 0.33 ± 1.0	0.00 ± 0.0	0.915	0.78 ± 2.6	− 4.00 ± 1.4	0.053
	AG	2.31 ± 2.8	3.00 ± 0.8	0.445	− 0.78 ± 1.9	− 1.37 ± 1.8	0.293	− 2.26 ± 3.7	− 1.62 ± 2.5	0.586
	GG	1.02 ± 2.3	1.62 ± 2.0	0.837	− 0.28 ± 1.2	− 0.25 ± 1.3	0.932	− 0.45 ± 1.4	− 2.12 ± 3.2	0.188
rs5925 genotypes (*APOE*-ε4 carriers[b])	CC	1.67 ± 0.6	2.40 ± 3.0	0.187	− 0.56 ± 1.2	− 1.20 ± 1.9	0.320	− 2.67 ± 3.5	− 2.80 ± 3.1	0.795
	CT	1.72 ± 2.6	1.18 ± 2.5	0.472	− 0.64 ± 1.6	− 1.14 ± 2.1	0.297	− 2.15 ± 3.5	− 1.64 ± 2.5	0.811
	TT	1.52 ± 2.8	0.44 ± 2.2	0.370	− 0.25 ± 1.4	0.00 ± 0.9	0.757	− 1.70 ± 2.9	− 0.44 ± 2.2	0.549
rs5925 genotypes (*APOE*-ε4 non-carriers[c])	CC	2.08 ± 1.9	0.67 ± 1.5	0.451	− 0.67 ± 0.9	0.00 ± 0.0	0.592	− 1.17 ± 1.8	− 2.00 ± 1.7	0.659
	CT	1.32 ± 2.6	2.80 ± 1.6	0.122	− 0.55 ± 1.7	− 0.80 ± 1.7	0.557	− 1.05 ± 3.4	− 2.40 ± 3.1	0.215
	TT	1.30 ± 3.1	2.60 ± 0.5	0.647	− 0.20 ± 1.4	− 1.00 ± 1.9	0.316	− 0.87 ± 2.4	− 1.60 ± 2.7	0.991

CDR-SOB Clinical Dementia Rating sum-of-boxes, *ADL* Index of Independence in Activities of Daily Living, *IADL* Lawton's Scale for Instrumental Activities of Daily Living, *SD* standard deviation

[a] General linear model adjusted for sex, years of schooling, age, estimated length of the dementia syndrome, total cholesterol, and weight variations in 1 year

[b] *APOE*-ε4 carriers ($n = 96$) = carriers of *APOE*-ε4/ε4, *APOE*-ε4/ε3 or *APOE*-ε4/ε2: for rs11669576 AA ($n = 1$): 1 used a lipophilic statin; for rs11669576 AG ($n = 18$): 12 used a lipophilic statin; for rs11669576 GG ($n = 77$): 55 used a lipophilic statin; for rs5930 AA ($n = 13$): 10 used a lipophilic statin; for rs5930 AG ($n = 41$): 31 used a lipophilic statin; for rs5930 GG ($n = 42$): 27 used a lipophilic statin; for rs5925 CC ($n = 14$): 9 used a lipophilic statin; for rs5925 CT ($n = 53$): 39 used a lipophilic statin; for rs5925 TT ($n = 29$): 20 used a lipophilic statin

[c] *APOE*-ε4 non-carriers ($n = 83$) = carriers of *APOE*-ε3/ε3 or *APOE*-ε3/ε2 (*APOE*-ε2/ε2 was not represented in this sample): for rs11669576 AG ($n = 8$): 5 used a lipophilic statin; for rs11669576 GG ($n = 75$): 60 used a lipophilic statin; for rs5930 AA ($n = 11$): 9 used a lipophilic statin; for rs5930 AG ($n = 35$): 27 used a lipophilic statin; for rs5930 GG ($n = 37$): 29 used a lipophilic statin; for rs5925 CC ($n = 15$): 12 used a lipophilic statin; for rs5925 CT ($n = 48$): 38 used a lipophilic statin; for rs5925 TT ($n = 20$): 15 used a lipophilic statin

Significant values are outlined in italics

Pharmacogenetic studies are useful to identify genetic factors that participate in the heterogeneity of response to conventional and unconventional drugs, thus leading to personalized medicine (Park and Choi 2009). Considering the low cost and the wide availability of lipophilic statins, the pharmacogenetic study of these drugs might be useful for healthcare systems worldwide.

Significant findings from this cohort demonstrate that clinical outcomes in patients with AD depend upon specific genetic profiles, which may impact cognitive and functional response to lipophilic statins. The G allele of rs11669576 usually led to faster cognitive decline, while lipophilic statins protected carriers of the A allele against functional decline. *APOE*-ε4 carriers who carried rs5930-AA had improved caregiver burden, while carriers of haplotypes that included rs5930-AG had mostly worse cognitive and functional outcomes, but carriers of the A allele of rs5930 had better cognitive and functional response to lipophilic statins. *APOE*-ε4 non-carriers who carried rs5925-TT had slower cognitive decline, while lipophilic statins protected carriers of the other genotypes. Some of these effects were boosted when haplotypes were present to strengthen the actions of independent genotypes or alleles.

We observed a significant difference between improvement in caregiver burden for *APOE*-ε4 carriers who carried rs5930-AA and the worsening caregiver burden of *APOE*-ε4 carriers who carried the G allele of rs5930. On the other hand, *APOE*-ε4 non-carriers who carried rs5930-AA also had improved caregiver

Table 5 Cognitive and caregiver burden variation responses to lipophilic statins in 1 year according to genotype frequencies for *LDLR* polymorphisms in *APOE*-ε4 carriers and non-carriers

Genotypes		MMSE variations (mean ± SD)			CDT variations (mean ± SD)			Zarit variations (mean ± SD)		
		Lipophilic statin	No lipophilic statin	p^a	Lipophilic statin	No lipophilic statin	p^a	Lipophilic statin	No lipophilic statin	p^a
rs11669576 genotypes (*APOE*-ε4 carriers[b])	AA	−4.00 ± 0.0	–	–	0.00 ± 0.0	–	–	6.00 ± 0.0	–	–
	AG	−1.83 ± 3.6	−1.00 ± 3.8	0.630	0.75 ± 2.6	−0.67 ± 3.1	0.478	0.58 ± 7.3	1.67 ± 4.6	0.898
	GG	−1.16 ± 3.3	−2.00 ± 3.0	0.354	−1.04 ± 3.0	−1.05 ± 3.1	0.824	−0.89 ± 7.0	−2.00 ± 9.2	0.542
rs11669576 genotypes (*APOE*-ε4 non-carriers[c])	AA	–	–	–	–	–	–	–	–	–
	AG	−0.20 ± 1.3	−1.67 ± 3.2	0.636	0.00 ± 2.0	0.67 ± 0.6	0.874	−0.20 ± 2.4	−2.33 ± 9.0	0.684
	GG	−0.85 ± 3.0	−1.93 ± 3.0	0.127	−0.12 ± 2.7	−0.40 ± 2.3	0.484	1.35 ± 10.2	0.73 ± 8.3	0.552
rs5930 genotypes (*APOE*-ε4 carriers[b])	AA	0.80 ± 2.3	−1.33 ± 4.5	0.445	−0.50 ± 3.7	0.33 ± 0.6	0.891	−2.60 ± 6.7	−16.67 ± 15.5	*0.005*
	AG	−1.65 ± 3.1	−2.80 ± 2.0	0.362	−1.16 ± 2.5	−0.10 ± 3.5	0.303	0.10 ± 5.4	1.90 ± 4.8	0.560
	GG	−1.74 ± 3.7	−1.20 ± 3.5	0.566	−0.26 ± 3.3	−1.80 ± 2.9	0.097	−0.48 ± 8.7	−0.20 ± 5.6	0.971
rs5930 genotypes (*APOE*-ε4 non-carriers[c])	AA	0.33 ± 1.9	−0.50 ± 3.5	0.398	−0.11 ± 1.8	−1.00 ± 1.4	0.663	−3.89 ± 13.0	−4.50 ± 7.8	0.847
	AG	−1.56 ± 3.1	−2.62 ± 3.3	0.342	−0.56 ± 3.1	−0.50 ± 2.4	0.803	1.67 ± 8.7	0.25 ± 11.1	0.576
	GG	−0.45 ± 2.8	−1.50 ± 2.7	0.402	0.31 ± 2.4	0.25 ± 2.0	0.817	2.41 ± 9.5	1.37 ± 4.7	0.579
rs5925 genotypes (*APOE*-ε4 carriers[b])	CC	−1.89 ± 1.6	−2.00 ± 3.6	0.880	0.00 ± 2.4	−3.00 ± 2.9	0.056	0.56 ± 5.0	0.60 ± 3.1	0.968
	CT	−0.92 ± 3.5	−2.57 ± 2.8	0.161	−0.72 ± 3.3	−0.86 ± 3.5	0.945	−1.36 ± 7.5	0.57 ± 6.8	0.526
	TT	−1.85 ± 3.5	−0.44 ± 3.2	0.279	−1.00 ± 2.6	0.00 ± 1.8	0.469	0.60 ± 7.0	−5.00 ± 11.9	0.065
rs5925 genotypes (*APOE*-ε4 non-carriers[c])	CC	−0.75 ± 3.2	−1.67 ± 3.8	0.449	−0.17 ± 3.4	−1.00 ± 2.6	0.578	4.00 ± 7.0	3.33 ± 3.2	0.804
	CT	−1.08 ± 3.0	−2.90 ± 2.6	0.071	−0.26 ± 2.5	−0.10 ± 2.4	0.888	1.76 ± 9.6	1.00 ± 9.4	0.636
	TT	−0.13 ± 2.4	0.00 ± 2.7	0.981	0.33 ± 2.5	0.00 ± 1.2	0.586	−2.33 ± 11.7	−3.20 ± 7.6	0.807

MMSE Mini-Mental State Examination, *CDT* Clock Drawing Test, *Zarit* Brazilian Version of the Zarit Caregiver Burden Interview, *SD* standard deviation

[a] General linear model adjusted for sex, years of schooling, age, estimated length of the dementia syndrome, total cholesterol and weight variations in 1 year

[b] *APOE*-ε4 carriers ($n = 96$) = carriers of *APOE*-ε4/ε4, *APOE*-ε4/ε3 or *APOE*-ε4/ε2: for rs11669576 AA ($n = 1$): 1 used a lipophilic statin; for rs11669576 AG ($n = 18$): 12 used a lipophilic statin; for rs11669576 GG ($n = 77$): 55 used a lipophilic statin; for rs5930 AA ($n = 13$): 10 used a lipophilic statin; for rs5930 AG ($n = 41$): 31 used a lipophilic statin; for rs5930 GG ($n = 42$): 27 used a lipophilic statin; for rs5925 CC ($n = 14$): 9 used a lipophilic statin; for rs5925 CT ($n = 53$): 39 used a lipophilic statin; for rs5925 TT ($n = 29$): 20 used a lipophilic statin

[c] *APOE*-ε4 non-carriers ($n = 83$) = carriers of *APOE*-ε3/ε3 or *APOE*-ε3/ε2 (*APOE*-ε2/ε2 was not represented in this sample): for rs11669576 AG ($n = 8$): 5 used a lipophilic statin; for rs11669576 GG ($n = 75$): 60 used a lipophilic statin; for rs5930 AA ($n = 11$): 9 used a lipophilic statin; for rs5930 AG ($n = 35$): 27 used a lipophilic statin; for rs5930 GG ($n = 37$): 29 used a lipophilic statin; for rs5925 CC ($n = 15$): 12 used a lipophilic statin; for rs5925 CT ($n = 48$): 38 used a lipophilic statin; for rs5925 TT ($n = 20$): 15 used a lipophilic statin

Significant values are outlined in italics

burden in comparison to *APOE*-ε4 non-carriers who carried the G allele of rs5930, but the difference was non-significant. In view of the fact that behavioral features tend to be more severe in *APOE*-ε4 carriers (Oliveira et al. 2017), potentially affecting caregiver burden, we conclude that the protective effect of rs5930-AA could be observed more easily in these patients.

In line with our findings, the A alleles of rs11669576 and rs5930 have usually been associated with prospectively improved vascular profiles (De Oliveira et al. 2019) and less behavioral symptoms in AD (Oliveira et al. 2017), possibly attesting their protective roles in this dementia syndrome. Still, the A allele of rs5930 and the T allele of rs5925 have been associated with reduced odds of AD when represented in haplotypes (Gopalraj et al. 2005).

Whereas *APOE*-ε4 non-carriers had more benefits from lipophilic statins than *APOE*-ε4 carriers, *APOE*-ε4 alleles have been strongly associated with both AD and vascular dementia (Chapman et al. 1998). The apolipoprotein E promotes the proteolytic degradation of amyloid-β (Jiang et al. 2008), more efficiently regarding the more lipidated E2 isoform and less efficiently regarding the less lipidated E4 isoform (Lee and Landreth 2010), though amyloidosis is reportedly more important for cognitive decline than *APOE*-ε4 carrier status (Lim et al. 2012). Nevertheless, AD expression is modulated by *APOE* haplotypes, translated into *APOE*-dependent cognitive and structural phenotypes (Morgen et al. 2013), thus reaffirming the importance of sample stratification according to *APOE*-ε4 carrier status.

Table 6 Response to lipophilic statins in 1 year according to each represented *LDLR* haplotype with variability

LDLR haplotypes		Variations in test scores in 1 year (mean ± SD)											
		CDR-SOB		ADL		IADL		MMSE		CDT		Zarit	
		Lipophilic statin[a]		Lipophilic statin[a]		Lipophilic statin[a]		Lipophilic statin[a]		Lipophilic statin[a]		Lipophilic statin[a]	
		Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
rs11669576 AG/rs5930 AG	Yes ($n = 9$)	1.33 ± 2.7	2.00 ± 1.0	0.17 ± 0.4	− 1.33 ± 1.5	0.67 ± 2.7	− 2.00 ± 2.0	− 2.67 ± 3.9	0.00 ± 1.7	− 0.17 ± 2.6	1.67 ± 1.2	− 1.33 ± 3.3	− 3.00 ± 8.5
	No ($n = 170$)	1.53 ± 2.5	1.62 ± 2.3	− 0.54 ± 1.5	− 0.72 ± 1.7	− 1.68 ± 3.1	− 1.70 ± 2.7	− 0.99 ± 3.1	− 1.95 ± 3.1	− 0.43 ± 2.8	− 0.84 ± 2.7	0.41 ± 8.7	− 0.49 ± 8.4
	p^b	0.567	0.688	0.259	0.553	*0.020*	0.863	0.320	0.316	0.588	0.106	0.680	0.661
rs11669576 AG/rs5930 GG	Yes ($n = 17$)	0.82 ± 2.6	2.58 ± 2.8	0.00 ± 1.7	− 1.50 ± 2.1	− 1.18 ± 2.1	− 3.33 ± 3.4	− 0.64 ± 2.6	− 1.83 ± 4.1	0.91 ± 2.3	− 1.17 ± 2.6	1.27 ± 7.3	2.00 ± 4.6
	No ($n = 162$)	1.59 ± 2.5	1.50 ± 2.2	− 0.55 ± 1.5	− 0.65 ± 1.6	− 1.61 ± 3.2	− 1.47 ± 2.4	− 1.11 ± 3.2	− 1.82 ± 2.9	− 0.53 ± 2.8	− 0.60 ± 2.7	0.25 ± 8.6	− 1.05 ± 8.7
	p^b	0.336	0.460	0.205	0.461	0.789	0.169	0.600	0.760	0.136	0.799	0.649	0.419
rs11669576 AG/rs5925 CT	Yes ($n = 13$)	0.78 ± 3.3	3.62 ± 2.9	− 0.44 ± 1.4	− 1.75 ± 2.2	− 0.67 ± 3.0	− 4.25 ± 4.0	− 0.33 ± 2.1	− 3.75 ± 2.5	0.56 ± 2.7	− 1.25 ± 3.8	− 2.11 ± 4.3	1.00 ± 5.4
	No ($n = 166$)	1.58 ± 2.5	1.45 ± 2.1	− 0.51 ± 1.5	− 0.67 ± 1.6	− 1.64 ± 3.2	− 1.48 ± 2.4	− 1.12 ± 3.2	− 1.64 ± 3.0	− 0.48 ± 2.8	− 0.62 ± 2.6	0.51 ± 8.7	− 0.81 ± 8.6
	p^b	0.238	0.238	0.642	0.377	0.450	0.167	0.245	0.523	0.339	0.952	0.318	0.673
rs11669576 AG/rs5925 TT	Yes ($n = 12$)	1.43 ± 2.9	1.40 ± 1.3	0.71 ± 1.1	− 1.20 ± 1.6	0.00 ± 1.6	− 1.80 ± 1.5	− 2.71 ± 4.1	0.80 ± 2.8	1.00 ± 1.9	0.60 ± 0.9	3.43 ± 7.5	− 0.20 ± 7.3
	No ($n = 167$)	1.53 ± 2.5	1.67 ± 2.3	− 0.57 ± 1.5	− 0.71 ± 1.7	− 1.66 ± 3.2	− 1.71 ± 2.7	− 0.98 ± 3.0	− 2.15 ± 2.9	− 0.49 ± 2.9	− 0.83 ± 2.8	0.16 ± 8.5	− 0.71 ± 8.5
	p^b	0.890	0.969	0.051	0.612	0.065	0.688	0.114	0.071	0.090	0.317	0.167	0.922
rs11669576 GG/rs5930 AA	Yes ($n = 24$)	0.08 ± 2.2	1.80 ± 2.4	− 0.32 ± 1.1	0.20 ± 1.1	− 0.95 ± 3.1	− 0.80 ± 3.2	0.58 ± 2.1	− 1.00 ± 3.7	− 0.32 ± 2.9	− 0.20 ± 1.1	− 3.21 ± 9.9	− 11.80 ± 13.4
	No ($n = 155$)	1.76 ± 2.5	1.62 ± 2.3	− 0.54 ± 1.5	− 0.88 ± 1.7	− 1.68 ± 3.1	− 1.83 ± 2.6	− 1.34 ± 3.2	− 1.93 ± 3.0	− 0.43 ± 2.8	− 0.73 ± 2.8	0.92 ± 8.1	0.71 ± 6.5
	p^b	*0.022*	0.887	0.791	0.195	0.371	0.450	*0.031*	0.582	0.985	0.711	*0.036*	*0.002*
rs11669576 GG/rs5930 AG	Yes ($n = 67$)	2.14 ± 2.4	1.73 ± 2.3	− 0.69 ± 1.8	− 0.93 ± 1.6	− 2.04 ± 3.1	− 1.80 ± 2.6	− 1.48 ± 3.0	− 3.27 ± 2.4	− 0.96 ± 2.8	− 0.67 ± 3.1	1.08 ± 7.4	2.00 ± 7.9
	No ($n = 112$)	1.12 ± 2.5	1.60 ± 2.2	− 0.38 ± 1.2	− 0.68 ± 1.7	− 1.27 ± 3.2	− 1.68 ± 2.7	− 0.80 ± 3.2	− 1.13 ± 3.1	− 0.06 ± 2.8	− 0.68 ± 2.5	− 0.15 ± 9.2	− 1.94 ± 8.3
	p^b	*0.034*	0.824	0.343	0.613	0.107	0.845	0.300	*0.028*	*0.048*	0.951	0.441	0.130
rs11669576 GG/rs5930 GG	Yes ($n = 61$)	1.60 ± 2.4	1.12 ± 2.2	− 0.55 ± 1.2	− 0.53 ± 1.7	− 1.68 ± 3.4	− 1.29 ± 2.3	− 1.11 ± 3.5	− 1.12 ± 2.9	− 0.18 ± 3.0	− 1.06 ± 2.8	0.84 ± 9.8	− 0.24 ± 5.5
	No ($n = 118$)	1.48 ± 2.6	1.95 ± 2.3	− 0.48 ± 1.6	− 0.90 ± 1.7	− 1.52 ± 3.0	− 1.97 ± 2.8	− 1.05 ± 2.9	− 2.24 ± 3.1	− 0.53 ± 2.8	− 0.45 ± 2.7	0.08 ± 7.9	− 0.90 ± 9.7
	p^b	0.876	0.319	0.834	0.647	0.889	0.470	0.905	0.306	0.389	0.409	0.607	0.836
rs11669576 GG/rs5925 CC	Yes ($n = 28$)	1.77 ± 1.5	1.75 ± 2.6	− 0.65 ± 1.0	− 0.75 ± 1.6	− 1.75 ± 2.7	− 2.50 ± 2.6	− 1.25 ± 2.7	− 1.87 ± 3.4	0.05 ± 3.0	− 2.25 ± 2.8	2.60 ± 6.5	1.62 ± 3.2
	No ($n = 151$)	1.48 ± 2.7	1.62 ± 2.2	− 0.48 ± 1.6	− 0.76 ± 1.7	− 1.54 ± 3.2	− 1.55 ± 2.6	− 1.04 ± 3.2	− 1.82 ± 3.0	− 0.50 ± 2.8	− 0.34 ± 2.6	− 0.07 ± 8.8	− 1.13 ± 9.0
	p^b	0.745	0.740	0.617	0.873	0.859	0.454	0.855	0.856	0.354	0.081	0.179	0.361
rs11669576 GG/rs5925 CT	Yes ($n = 88$)	1.62 ± 2.5	1.50 ± 2.1	− 0.62 ± 1.7	− 0.85 ± 1.8	− 1.74 ± 3.5	− 1.50 ± 2.3	− 1.09 ± 3.4	− 2.50 ± 2.7	− 0.63 ± 3.0	− 0.40 ± 3.0	0.49 ± 9.1	0.70 ± 8.3
	No ($n = 91$)	1.42 ± 2.6	1.75 ± 2.4	− 0.38 ± 1.3	− 0.69 ± 1.6	− 1.40 ± 2.7	− 1.88 ± 2.9	− 1.05 ± 2.8	− 1.31 ± 3.2	− 0.18 ± 2.7	− 0.88 ± 2.5	0.17 ± 7.9	− 1.69 ± 8.4
	p^b	0.800	0.752	0.550	0.606	0.487	0.918	0.926	0.143	0.364	0.858	0.908	0.482
rs11669576 GG/rs5925 TT	Yes ($n = 36$)	1.41 ± 3.0	1.11 ± 2.4	− 0.41 ± 1.4	0.11 ± 0.9	− 1.67 ± 2.9	− 0.33 ± 2.6	− 0.59 ± 2.8	− 0.89 ± 3.0	− 0.81 ± 2.7	− 0.33 ± 1.8	− 1.96 ± 9.5	− 6.67 ± 11.4
	No ($n = 143$)	1.55 ± 2.4	1.77 ± 2.2	− 0.53 ± 1.5	− 0.97 ± 1.8	− 1.55 ± 3.2	− 2.05 ± 2.5	− 1.19 ± 3.2	− 2.05 ± 3.0	− 0.31 ± 2.9	− 0.76 ± 2.9	0.92 ± 8.2	0.81 ± 6.8
	p^b	0.823	0.421	0.995	0.073	0.722	0.062	0.636	0.266	0.299	0.505	0.117	*0.029*
	Yes ($n = 7$)	0.21 ± 1.3	–	− 0.43 ± 1.1	–	− 1.14 ± 4.8	–	0.86 ± 2.6	–	0.00 ± 4.4	–	− 3.29 ± 5.6	–

Table 6 (continued)

LDLR haplotypes		Variations in test scores in 1 year (mean ± SD)											
		CDR-SOB		ADL		IADL		MMSE		CDT		Zarit	
		Lipophilic statin[a]		Lipophilic statin[a]		Lipophilic statin[a]		Lipophilic statin[a]		Lipophilic statin[a]		Lipophilic statin[a]	
		Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
rs5930 AA/rs5925 CT	No ($n = 172$)	1.60 ± 2.6	1.64 ± 2.2	− 0.51 ± 1.5	− 0.76 ± 1.7	− 1.60 ± 3.0	− 1.72 ± 2.6	− 1.17 ± 3.1	− 1.83 ± 3.0	− 0.44 ± 2.7	− 0.67 ± 2.7	0.53 ± 8.6	− 0.65 ± 8.3
	p[b]	0.132	–	0.927	–	0.532	–	0.066	–	0.548	–	0.288	–
rs5930 AA/rs5925 TT	Yes ($n = 17$)	0.00 ± 2.7	1.80 ± 2.4	− 0.25 ± 1.1	0.20 ± 1.1	− 0.83 ± 1.8	− 0.80 ± 3.2	0.42 ± 1.8	− 1.00 ± 3.7	− 0.50 ± 1.7	− 0.20 ± 1.1	− 3.17 ± 12.0	− 11.80 ± 13.4
	No ($n = 162$)	1.67 ± 2.5	1.62 ± 2.3	− 0.53 ± 1.5	− 0.88 ± 1.7	− 1.64 ± 3.2	− 1.83 ± 2.6	− 1.21 ± 3.2	− 1.93 ± 3.0	− 0.41 ± 2.9	− 0.73 ± 2.8	0.68 ± 8.1	0.71 ± 6.5
	p[b]	0.110	0.895	0.798	0.195	0.546	0.448	0.234	0.576	0.651	0.705	0.088	*0.002*
rs5930 AG/rs5925 CC	Yes ($n = 5$)	2.62 ± 1.7	5.00 ± 0.0	− 0.75 ± 1.5	− 4.00 ± 0.0	− 2.75 ± 1.7	− 7.00 ± 0.0	− 2.75 ± 1.5	− 3.00 ± 0.0	− 0.25 ± 4.8	− 4.00 ± 0.0	2.75 ± 3.6	4.00 ± 0.0
	No ($n = 174$)	1.49 ± 2.5	1.57 ± 2.2	− 0.50 ± 1.5	− 0.69 ± 1.6	− 1.53 ± 3.2	− 1.60 ± 2.5	− 1.02 ± 3.1	− 1.80 ± 3.0	− 0.42 ± 2.8	− 0.60 ± 2.7	0.26 ± 8.6	− 0.76 ± 8.4
	p[b]	0.609	0.252	0.906	*0.047*	0.383	0.105	0.454	0.939	0.951	0.312	0.593	0.562
rs5930 AG/rs5925 CT	Yes ($n = 53$)	1.90 ± 2.3	1.92 ± 1.8	− 0.65 ± 1.9	− 0.77 ± 1.5	− 1.63 ± 3.3	− 1.62 ± 2.1	− 1.22 ± 2.9	− 3.23 ± 2.6	− 0.65 ± 2.6	− 0.31 ± 3.2	0.75 ± 7.6	1.46 ± 8.7
	No ($n = 126$)	1.36 ± 2.6	1.53 ± 2.4	− 0.44 ± 1.3	− 0.76 ± 1.8	− 1.55 ± 3.1	− 1.76 ± 2.8	− 1.00 ± 3.2	− 1.27 ± 3.0	− 0.31 ± 2.9	− 0.82 ± 2.5	0.15 ± 8.9	− 1.48 ± 8.2
	p[b]	0.294	0.552	0.576	0.931	0.788	0.896	0.841	0.052	0.448	0.829	0.726	0.281
rs5930 AG/rs5925 TT	Yes ($n = 18$)	2.36 ± 3.4	0.50 ± 2.6	− 0.43 ± 1.6	− 1.00 ± 1.4	− 1.86 ± 3.1	− 1.25 ± 2.5	− 2.36 ± 3.8	− 1.00 ± 2.4	− 1.71 ± 2.6	0.75 ± 2.1	0.50 ± 6.3	− 0.50 ± 7.3
	No ($n = 161$)	1.42 ± 2.4	1.75 ± 2.2	− 0.51 ± 1.5	− 0.74 ± 1.7	− 1.54 ± 3.2	− 1.76 ± 2.6	− 0.92 ± 3.0	− 1.90 ± 3.1	− 0.26 ± 2.8	− 0.81 ± 2.7	0.31 ± 8.7	− 0.67 ± 8.5
	p[b]	0.255	0.395	0.885	0.835	0.889	0.548	0.108	0.722	0.088	0.111	0.901	0.886
rs5930 GG/rs5925 CC	Yes ($n = 24$)	1.47 ± 1.4	1.29 ± 2.4	− 0.59 ± 0.9	− 0.29 ± 1.0	− 1.59 ± 2.9	− 1.86 ± 2.0	− 0.88 ± 2.7	− 1.71 ± 3.6	− 0.06 ± 2.6	− 2.00 ± 2.9	2.47 ± 6.9	1.29 ± 3.4
	No ($n = 155$)	1.53 ± 2.6	1.71 ± 2.2	− 0.49 ± 1.6	− 0.85 ± 1.8	− 1.57 ± 3.2	− 1.69 ± 2.7	− 1.09 ± 3.2	− 1.85 ± 3.0	− 0.47 ± 2.9	− 0.44 ± 2.6	0.02 ± 8.7	− 1.00 ± 8.9
	p[b]	0.956	0.913	0.701	0.530	0.928	0.887	0.889	0.869	0.489	0.154	0.254	0.462
rs5930 GG/rs5925 CT	Yes ($n = 41$)	1.32 ± 3.0	1.77 ± 2.9	− 0.57 ± 1.4	− 1.27 ± 2.3	− 1.70 ± 3.4	− 2.36 ± 3.4	− 1.13 ± 3.7	− 2.09 ± 2.8	− 0.40 ± 3.0	− 0.82 ± 3.0	0.23 ± 10.4	− 0.09 ± 6.9
	No ($n = 138$)	1.58 ± 2.4	1.60 ± 2.1	− 0.49 ± 1.5	− 0.60 ± 1.4	− 1.53 ± 3.1	− 1.51 ± 2.3	− 1.05 ± 2.9	− 1.74 ± 3.1	− 0.42 ± 2.8	− 0.63 ± 2.6	0.36 ± 7.9	− 0.83 ± 8.8
	p[b]	0.432	0.832	0.900	0.277	0.686	0.510	0.951	0.909	0.997	0.997	0.774	0.987
rs5930 GG/rs5925 TT	Yes ($n = 14$)	1.89 ± 1.3	1.20 ± 1.3	0.11 ± 1.5	− 0.40 ± 1.5	− 1.22 ± 3.1	− 0.60 ± 1.7	− 1.22 ± 2.9	1.00 ± 2.6	1.67 ± 2.3	− 0.40 ± 1.7	0.89 ± 9.3	0.00 ± 4.0
	No ($n = 165$)	1.50 ± 2.6	1.70 ± 2.3	− 0.55 ± 1.5	− 0.80 ± 1.7	− 1.60 ± 3.2	− 1.85 ± 2.7	− 1.06 ± 3.1	− 2.17 ± 2.9	− 0.56 ± 2.8	− 0.71 ± 2.8	0.29 ± 8.5	− 0.73 ± 8.7
	p[b]	0.396	0.724	0.411	0.490	0.587	0.483	0.673	*0.023*	*0.013*	0.913	0.513	0.725

SD standard deviation, *CDR-SOB* Clinical Dementia Rating sum-of-boxes, *ADL* Index of Independence in Activities of Daily Living, *IADL* Lawton's Scale for Instrumental Activities of Daily Living, *MMSE* Mini-Mental State Examination, *CDT* Clock Drawing Test, *Zarit* Brazilian Version of the Zarit Caregiver Burden Interview

[a] Lipophilic Statins: for rs11669576 AA ($n = 1$): 1 used a lipophilic statin; for rs11669576 AG ($n = 26$): 17 used a lipophilic statin; for rs11669576 GG ($n = 152$): 115 used a lipophilic statin; for rs5930 AA ($n = 24$): 19 used a lipophilic statin; for rs5930 AG ($n = 76$): 58 used a lipophilic statin; for rs5930 GG ($n = 79$): 56 used a lipophilic statin; for rs5925 CC ($n = 29$): 21 used a lipophilic statin; for rs5925 CT ($n = 101$): 77 used a lipophilic statin; for rs5925 TT ($n = 49$): 35 used a lipophilic statin

[b] Differences regarding use of a lipophilic statin for carriers versus non-carriers of each haplotype: general linear model adjusted for sex, years of schooling, age, estimated length of the dementia syndrome, total cholesterol, and weight variations in 1 year

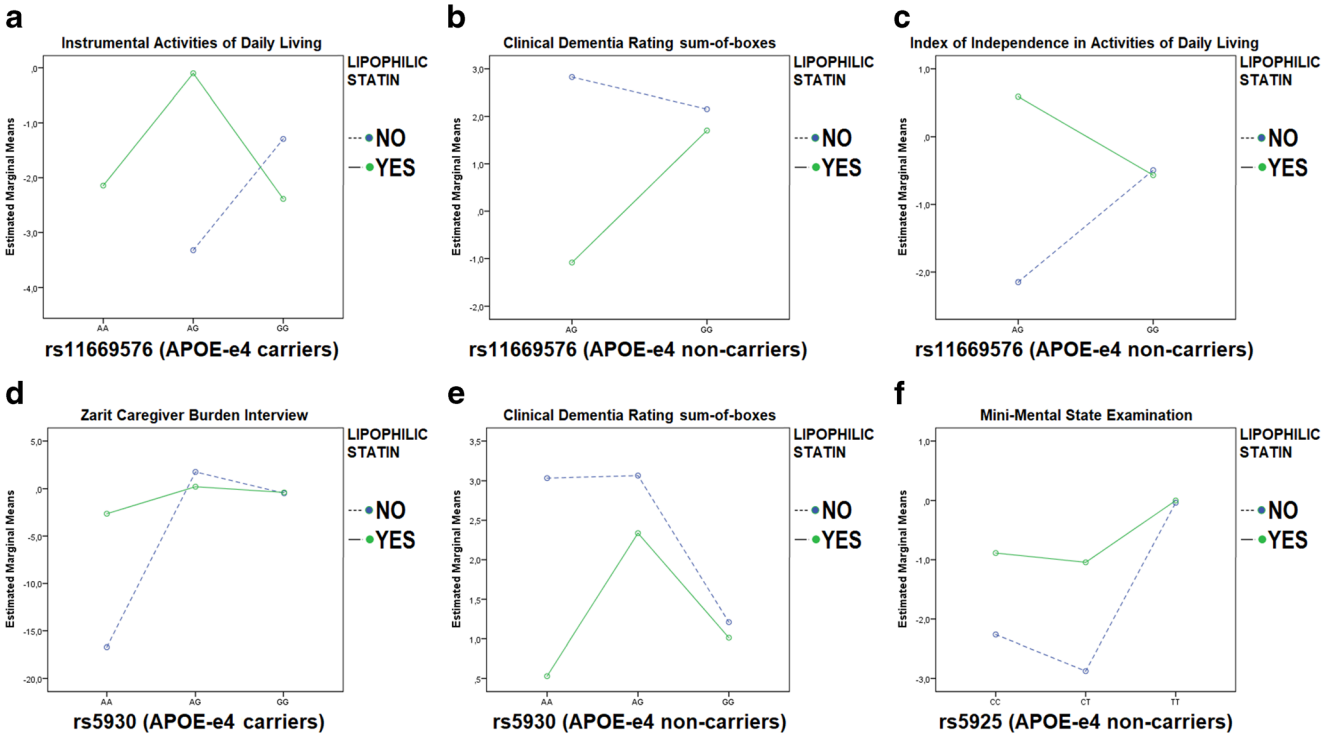

Fig. 1 The most significant results of the neurotranslational analyses are illustrated. Test score variations in 1 year according to specific genotypes and pharmacological treatment are graphically represented. **a** Regarding Instrumental Activities of Daily Living score variations, lipophilic statins protected *APOE*-ε4 carriers who also carried rs11669576-AG ($p = 0.035$). **b** Regarding Clinical Dementia Rating sum-of-boxes score variations, lipophilic statins protected *APOE*-ε4 non-carriers who also carried rs11669576-AG ($p = 0.029$). **c** Regarding Index of Independence in Activities of Daily Living score variations, lipophilic statins protected *APOE*-ε4 non-carriers who also carried rs11669576-AG ($p = 0.015$). **d** Regarding the Zarit Caregiver Burden Interview, *APOE*-ε4 carriers who also carried rs5930-AA had improved scores after 1 year ($p = 0.001$). **e** Regarding Clinical Dementia Rating sum-of-boxes score variations, lipophilic statins non-significantly protected *APOE*-ε4 non-carriers who also carried rs5930-AA ($p = 0.186$), while *APOE*-ε4 non-carriers who also carried rs5930-AG had worse prognosis regardless of statin therapy ($p = 0.021$). **f** Regarding Mini-Mental State Examination score variations, lipophilic statins marginally significantly protected *APOE*-ε4 non-carriers who also carried rs5925-CT ($p = 0.071$), while *APOE*-ε4 non-carriers who also carried rs5925-TT had better prognosis regardless of statin therapy ($p = 0.030$). *APOE*-ε4 carriers ($n = 96$) = carriers of *APOE*-ε4/ε4, *APOE*-ε4/ε3 or *APOE*-ε4/ε2; *APOE*-ε4 non-carriers ($n = 83$) = carriers of *APOE*-ε3/ε3 or *APOE*-ε3/ε2 (*APOE*-ε2/ε2 was not represented in this sample)

Low-density lipoprotein receptors supply cholesterol to cells and remove cholesterol-rich lipoprotein particles from the circulation (Maxwell et al. 2017); they also bind the apolipoprotein E, which by itself may bind amyloid-β (Jiang et al. 2008) and induce cholinergic compensatory synaptogenesis caused by entorhinal cortex deafferentation (Poirier 1999). Different binding affinities of apolipoprotein E isoforms to the low-density lipoprotein receptors suggest that the receptor may trap the apolipoprotein E4 and reduce its transfer to lipoproteins for clearance, resulting in increased levels of plasma low-density lipoproteins (Petek et al. 2018) and amyloidogenesis (Leon et al. 2018). High levels of cholesterol increase insoluble amyloid-β formation, while older people with increased plasma cholesterol levels are at higher risk for dementia (Loera-Valencia et al. 2019), despite the largest amount of brain cholesterol resulting from local production by astrocytes, oligodendrocytes, and also neurons (Petek et al. 2018). The polymorphisms in the epidermal growth factor precursor homology domain of *LDLR* may prevent the internalization of the bound ligand and subsequent release in the acidic endosome, while also foiling the recycling of the receptor. Moreover, these polymorphisms may indirectly affect cholesterol metabolism by way of functional variants in this same gene or in closely linked genes, thus resulting in pleiotropic effects over pathogenesis of AD (Cacabelos et al. 2016).

Overall, 74.9% of all patients had hypercholesterolemia in this study, almost all of them using lipophilic statins (thereby crossing the blood-brain barrier), thus confirming the burden of this vascular risk factor in older people (De Oliveira et al. 2017). Since only one patient used a hydrophilic statin (Rosuvastatin), and only three used Ezetimibe, we could not specifically assess the effects of such therapies. Some associations may have been biased by the high rates of statin therapy, but management recommendations regarding lipid-lowering therapy were strictly followed.

Statins lower plasma cholesterol concentrations by inhibiting 3-hydroxy-3-methylglutaryl-CoA reductase, thus blocking cholesterol biosynthesis (Cacabelos et al.

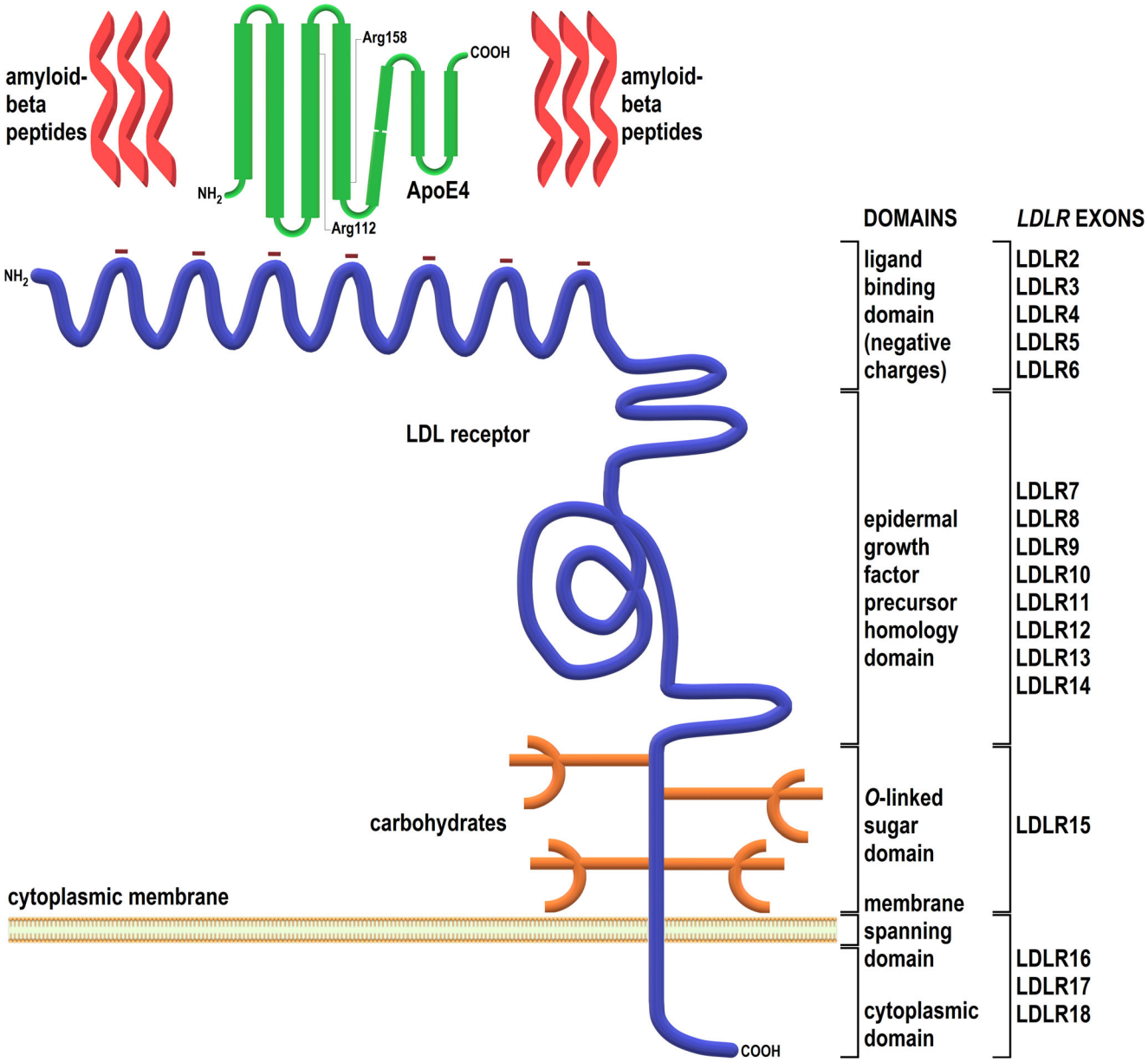

Fig. 2 The *LDLR* gene consists of 18 exons, whereas exons 7 to 14 correspond to the epidermal growth factor precursor homology domain. Single-nucleotide polymorphisms rs11669576 (LDLR8), rs5930 (LDLR10), and rs5925 (LDLR13) are the most important genetic variants of the epidermal growth factor precursor homology domain of *LDLR* to be associated with dysfunctional cholesterol metabolism and variable risk of Alzheimer's disease. The apolipoprotein E4 (green) has the highest binding affinity to the low-density lipoprotein receptor (blue). Presence of the G allele of rs11669576, the G allele of rs5930, or the C allele of rs5925 translates an abnormal low-density lipoprotein receptor that inhibits the internalization of apolipoprotein E4 (thus reducing its transfer to lipoproteins for clearance), resulting in increased synthesis of low-density lipoproteins and reduced storage of intracellular cholesterol while precluding recycling of the low-density lipoprotein receptor and activating the amyloidogenic pathway of amyloid precursor protein processing. The apolipoprotein E may also bind amyloid-β peptides (red) and induce cholinergic synaptogenesis caused by cortical deafferentation while increasing the expression of the *APOE* gene

2016). In cell cultures, decreased amyloid-β load follows cholesterol lowering by lipophilic statins (Eckert et al. 2005). Earlier prospective studies showed that statins could prevent dementia independently of cholesterol variations (Larsson & Markus 2018), as well as increase cerebral perfusion (Petek et al. 2018), reduce *tau* pathology and amyloidosis (Loera-Valencia et al. 2019). Some intraclass differences for patients with mild to moderate AD have been reported, though, with cognitive benefits and aggressive cholesterol reductions following high-dose Atorvastatin treatment at 6 months up to 1 year (Sparks et al. 2005), but not with dose escalation of Simvastatin even after 18 months (Sano et al. 2011). However, lipophilic statin therapy has been shown to protect

hippocampal neurons via inhibition of oxidative stress-induced apoptosis and regulation of mitochondrial function while also upregulating low-density lipoprotein receptors (Petek et al. 2018).

Due to operational and funding restrictions, we only studied *APOE* and *LDLR* as potential modifiers of progression of AD in this cohort. Other cholesterol-related genes have shown importance for AD pathogenesis, such as *HMGCR* (Leduc et al. 2016), *CETP* (Chen et al. 2008), *PPARα* (Chen et al. 2010), *APOA5* (Barbosa et al. 2006), *MEOX2* (Wu et al. 2005) and *DHCR24* (Crameri et al. 2006), and should be assessed in future pharmacogenetic studies.

Major strengths of this study include the longitudinal design and the fact that assessments of functional and cognitive decline, as well as lipid profile variations, were well documented all along the follow-up, thus avoiding a classification bias that could have resulted from self-reports. Except for caregiver burden, all other test scores were significantly different after 1 year, thus confirming that this length of follow-up was proper for most measures. Though it is unknown whether age affects the brain distribution of lipophilic statins, our general linear model was adjusted for age, while adjustment for cholesterol variations allowed us to isolate the pharmacogenetic effects of these medications over cognition and functionality.

Limitations of this preliminary study include the fact that it was conducted in a single center, with a short follow-up and no randomization, and the absence of stratification according to environmental factors (the full spectrum of which is hardly incorporated into genetic studies). Still, the small subgroup sizes affected the power of the associations we found; thus, further studies with larger samples are recommended to validate our findings. Though functionality may be affected by cognitive performance, we only assessed one test score variation at a time in our analyses. Also, it is unknown whether the cognitive and functional effects of lipophilic statins are either different from those of hydrophilic statins or dose-dependent, or more significant at the start of lipid-lowering therapy (because many patients were already under treatment when they were included in the study). We tried to minimize these limitations by keeping observers blinded to genetic data during the neurological evaluations, and also by indicating lipophilic statins only for patients with hypercholesterolemia. We also sustained the use of cholinesterase inhibitors for most patients who did not have side effects to these medications, so that the results of this study may be attributed to the effects of lipophilic statins only. Nonetheless, this is a pioneering study on the evaluation of effects of lipophilic statins during the course of AD while taking into account *APOE* and *LDLR* genotypes and haplotypes. Future studies should also prospectively analyze parameters of neuroimaging exams and gene expression according to the use of these drugs.

We conclude that therapy with lipophilic statins might be beneficial for carriers of specific genetic variants, such as the A allele of rs11669576, the A allele of rs5930, or the CC and CT genotypes of rs5925. Overall, variants of *LDLR* and *APOE* that reportedly protected against risk of AD also seemed to slow cognitive decline in epistatic interactions, regardless of cholesterol variations. Further molecular studies and randomized controlled trials will be required to confirm any disease-modifying or pharmacogenetic effects of lipophilic statins in AD.

Funding Information This work was sponsored by CAPES–*Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (grant #1067/10) and FAPESP–The State of São Paulo Research Foundation (grant #2015/10109-5 and grant #2015/18125-0).

Compliance with Ethical Standards

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

Ethics Approval All procedures were in accordance with the ethical standards of the Ethics Committee of *Hospital São Paulo*, Federal University of São Paulo–UNIFESP, according to the research project 1067/10 (CAAE 0540.0.174.000-10), and followed The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. All invited patients and their legal representatives agreed to participate on the research and signed the Informed Consent Form before the evaluation.

References

Barbosa FAF, de Labio RW, Rigolin VOS, Minett T, Bertolucci PHF, Smith MAC, Payão SLM (2006) Apolipoprotein A-V gene polymorphism –1131T>C and Alzheimer's disease. J Alzheimers Dis 10:365–369

Bertolucci PHF, Brucki SMD, Campacci SR, Juliano Y (1994) The mini-mental state examination in an outpatient population: influence of literacy. Arq Neuropsiquiatr 52:1–7

Cacabelos R, Torrellas C, Tejido O, Carril JC (2016) Pharmacogenetic considerations in the treatment of Alzheimer's disease. Pharmacogenomics 17:1041–1074

Chapman J, Wang N, Treves TA, Korczyn AD, Bornstein NM (1998) ACE, MTHFR, factor V Leiden, and APOE polymorphisms in patients with vascular and Alzheimer's dementia. Stroke 29:1401–1404

Chen DW, Yang JF, Tang Z, Dong XM, Feng XL, Yu S, Chan P (2008) Cholesteryl ester transfer protein polymorphism D442G associated with a potential decreased risk for Alzheimer's disease as a modifier for APOE ε4 in Chinese. Brain Res 1187:52–57

Chen ES, Mazzotti DR, Furuya TK, Cendoroglo MS, Ramos LR, Araujo LQ, Burbano RR, Smith MAC (2010) Association of *PPARα* gene polymorphisms and lipid serum levels in a Brazilian elderly population. Exp Mol Pathol 88:197–201

Crameri A, Biondi E, Kuehnle K, Lütjohann D, Thelen KM, Perga S, Dotti CG, Nitsch RM, Ledesma MD, Mohajeri MH (2006) The role of seladin-1/DHCR24 in cholesterol biosynthesis, APP processing and Aβ generation *in vivo*. EMBO J 25:432–443

De Luca V, Orfei MD, Gaudenzi S, Caltagirone C, Spalletta G (2016) Inverse effect of the APOE epsilon4 allele in late- and early-onset

Alzheimer's disease. Eur Arch Psychiatry Clin Neurosci 266:599–606

De Oliveira FF, Bertolucci PHF, Chen ES, Smith MAC (2014a) Pharmacological modulation of cognitive and behavioral symptoms in patients with dementia due to Alzheimer's disease. J Neurol Sci 336:103–108

De Oliveira FF, Bertolucci PHF, Chen ES, Smith MC (2014b) Risk factors for age at onset of dementia due to Alzheimer's disease in a sample of patients with low mean schooling from São Paulo, Brazil. Int J Geriatr Psychiatry 29:1033–1039

De Oliveira FF, Wajman JR, Bertolucci PHF, Chen ES, Smith MC (2015a) Correlations among cognitive and behavioural assessments in patients with dementia due to Alzheimer's disease. Clin Neurol Neurosurg 135:27–33

De Oliveira FF, Pivi GAK, Chen ES, Smith MC, Bertolucci PHF (2015b) Risk factors for cognitive and functional change in one year in patients with Alzheimer's disease dementia from São Paulo, Brazil. J Neurol Sci 359:127–132

De Oliveira FF, Chen ES, Smith MC, Bertolucci PHF (2017) Longitudinal lipid profile variations and clinical change in Alzheimer's disease dementia. Neurosci Lett 646:36–42

De Oliveira FF, Berretta JM, Almeida Junior GV, Almeida SS, Chen ES, Smith MC, Bertolucci PHF (2019) Pharmacogenetic analyses of variations of measures of cardiovascular risk in Alzheimer's dementia. Indian J Med Res 150:261–271

Eckert GP, Wood WG, Müller WE (2005) Statins: drugs for Alzheimer's disease? J Neural Transm 112:1057–1071

Gopalraj RK, Zhu H, Kelly JF, Mendiondo M, Pulliam JF, Bennett DA, Estus S (2005) Genetic association of low density lipoprotein receptor and Alzheimer's disease. Neurobiol Aging 26:1–7

Grundman M, Petersen RC, Ferris SH, Thomas RG, Aisen PS, Bennett DA, Foster NL, Jack CR Jr, Galasko DR, Doody R, Kaye J, Sano M, Mohs R, Gauthier S, Kim HT, Jin S, Schultz AN, Schafer K, Mulnard R, van Dyck CH, Mintzer J, Zamrini EY, Cahn-Weiner D, Thal LJ (2004) Mild cognitive impairment can be distinguished from Alzheimer disease and normal aging for clinical trials. Arch Neurol 61:59–66

Grundy SM, Cleeman JI, Merz CNB, Brewer HB Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC Jr, Stone NJ (2004) Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. Circulation 110:227–239

Jiang Q, Lee CYD, Mandrekar S, Wilkinson B, Cramer P, Zelcer N, Mann K, Lamb B, Willson TM, Collins JL, Richardson JC, Smith JD, Comery TA, Riddell D, Holtzman DM, Tontonoz P, Landreth GE (2008) ApoE promotes the proteolytic degradation of Aβ. Neuron 58:681–693

Katz S, Akpom CA (1976) A measure of primary socio-biological functions. Int J Health Serv 6:493–508

Larsson SC, Markus HS (2018) Does treating vascular risk factors prevent dementia and Alzheimer's disease? A systematic review and meta-analysis. J Alzheimers Dis 64:657–668

Lawton MP (1988) Instrumental Activities of Daily Living (IADL) Scale: self-reported version. Psychopharmacol Bull 24:789–791

Leduc V, Théroux L, Dea D, Dufour R, Poirier J (2016) Effects of rs3846662 variants on HMGCR mRNA and protein levels and on markers of Alzheimer's disease pathology. J Mol Neurosci 58:109–119

Lee CYD, Landreth GE (2010) The role of microglia in amyloid clearance from the AD brain. J Neural Transm 117:949–960

Leon M, Sawmiller D, Giunta B, Tan J (2018) Therapeutic approach targeting apolipoprotein E binding region and low-density lipoprotein receptor for Alzheimer's disease. Neuroimmunol Neuroinflammation 5:30

Lim YY, Ellis KA, Pietrzak RH, Ames D, Darby D, Harrington K, Martins RN, Masters CL, Rowe C, Savage G, Szoeke C, Villemagne VL, Maruff P (2012) Stronger effect of amyloid load than *APOE* genotype on cognitive decline in healthy older adults. Neurology 79:1645–1652

Lima APV, Castilhos R, Chaves MLF (2017) The use of the clinical dementia rating scale sum of boxes scores in detecting and staging cognitive impairment/dementia in Brazilian patients with low educational attainment. Alzheimer Dis Assoc Disord 31:322–327

Loera-Valencia R, Goikolea J, Parrado-Fernandez C, Merino-Serrais P, Maioli S (2019) Alterations in cholesterol metabolism as a risk factor for developing Alzheimer's disease: potential novel targets for treatment. J Steroid Biochem Mol Biol 190:104–114

Maxwell WD, Ramsey LB, Johnson SG, Moore KG, Shtutman M, Schoonover JH, Kawaguchi-Suzuki M (2017) Impact of pharmacogenetics on efficacy and safety of statin therapy for dyslipidemia. Pharmacotherapy 37:1172–1190

McGuiness B, Craig D, Bullock R, Malouf R, Passmore P (2014) Statins for the treatment of dementia (review). Cochrane Database Syst Rev 7:CD007514

Morgen K, Frölich L, Tost H, Plichta MM, Kölsch H, Rakebrandt F, Rienhoff O, Jessen F, Peters O, Jahn H, Luckhaus C, Hüll M, Gertz HJ, Schröder J, Hampel H, Teipel SJ, Pantel J, Heuser I, Wiltfang J, Rüther E, Kornhuber J, Maier W, Meyer-Lindenberg A (2013) APOE-dependent phenotypes in subjects with mild cognitive impairment converting to Alzheimer's disease. J Alzheimers Dis 37:389–401

Oliveira FF, Chen ES, Smith MC, Bertolucci PH (2017) Associations of cerebrovascular metabolism genotypes with neuropsychiatric symptoms and age at onset of Alzheimer's disease dementia. Rev Bras Psiquiatr 39:95–103

Ozudogru SN, Lippa CF (2012) Disease modifying drugs targeting β-amyloid. Am J Alzheimers Dis Other Dement 27:296–300

Park SK, Choi JY (2009) Risk assessment and pharmacogenetics in molecular and genomic epidemiology. J Prev Med Public Health 42: 371–376

Petek B, Villa-Lopez M, Loera-Valencia R, Gerenu G, Winblad B, Kramberger MG, Ismail MAM, Eriksdotter M, Garcia-Ptacek S (2018) Connecting the brain cholesterol and renin-angiotensin systems: potential role of statins and RAS-modifying medications in dementia. J Intern Med 284:620–642

Poirier J (1999) Apolipoprotein E4, cholinergic integrity and the pharmacogenetics of Alzheimer's disease. J Psychiatry Neurosci 24:147–153

Querfurth HW, LaFerla FM (2010) Alzheimer's disease. N Engl J Med 362:329–344

Roses AD (2010) An inherited variable poly-T repeat genotype in *TOMM40* in Alzheimer disease. Arch Neurol 67:536–541

Sano M, Bell KL, Galasko D, Galvin JE, Thomas RG, van Dyck CH, Aisen PS (2011) A randomized, double-blind, placebo-controlled trial of simvastatin to treat Alzheimer disease. Neurology 77:556–563

Smith MAC (1999) Doença de Alzheimer. Rev Bras Psiquiatr 21:S03–S07

Sparks DL, Sabbagh MN, Connor DJ, Lopez J, Launer LJ, Browne P, Wasser D, Johnson-Traver S, Lochhead J, Ziolwolski C (2005) Atorvastatin for the treatment of mild to moderate Alzheimer disease: preliminary results. Arch Neurol 62:753–757

Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, Iwatsubo T, Jack CR Jr, Kaye J, Montine TJ, Park DC, Reiman ER, Rowe CC, Siemers E, Stern Y, Yaffe K, Carrillo MC, Thies B, Morrison-Bogorad M, Wagster MV, Phelps CH (2011) Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7:280–292

Taub A, Andreoli SB, Bertolucci PHF (2004) Dementia caregiver burden: reliability of the Brazilian version of the Zarit caregiver burden interview. Cad Saude Publica 20:372–376

Wu Z, Guo H, Chow N, Sallstrom J, Bell RD, Deane R, Brooks AI, Kanagala S, Rubio A, Sagare A, Liu D, Li F, Armstrong D, Gasiewicz T, Zidovetzki R, Song X, Hofman F, Zlokovic BV (2005) Role of the *MEOX2* homeobox gene in neurovascular dysfunction in Alzheimer disease. Nat Med 11:959–965

Yamamoto N, Fujii Y, Kasahara R, Tanida M, Ohora K, Ono Y, Suzuki K, Sobue K (2016) Simvastatin and atorvastatin facilitates amyloid β-protein degradation in extracellular spaces by increasing neprilysin secretion from astrocytes through activation of MAPK/Erk1/2 pathways. Glia 64:952–962

Yan HC, Wang W, Dou CW, Tian FM, Qi ST (2014) Relationships of *LDLR* genetic polymorphisms with cerebral infarction: a meta-analysis. Mol Biol Rep 41:4425–4434

Prior Presentation of Information from the Paper

Preliminary aspects of this study were previously presented (and published in the form of abstracts) at the following meetings:

1. AAIC>14 – Alzheimer's Association International Conference 2014

(with an Alzheimer's Association Travel Fellowship to the first author)

(Alzheimer's Association, Copenhagen/DENMARK, July 2014):

https://doi.org/10.1016/j.jalz.2014.05.698

2. 29th CINP World Congress of Neuropsychopharmacology

(*Collegium Internationale Neuro-Psychopharmacologicum*, Vancouver/CANADA, June 2014)

https://doi.org/10.1017/S1461145714000741

3. 66th Annual Meeting of the American Academy of Neurology

(American Academy of Neurology, Philadelphia/USA, April 2014):

http://www.neurology.org/content/82/10_Supplement/P5.223.abstract?sid=adf1feeb-3dc6-43f6-9e1beea01faca6d1

4. AD/PD 2013 – The 11th International Conference on Alzheimer's & Parkinson's Diseases

(Kenes International, Florence/ITALY, March 2013)

Alzheimer's and Parkinson's Diseases: Mechanisms, Clinical Strategies, and Promising Treatments of Neurodegenerative Diseases. Basel: Karger, 2013, v.11, p. 700.