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Faster progression from MCI to probable AD for carriers of a single-nucleotide polymorphism associated with type 2 diabetes

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ABSTRACT

Sporadic Alzheimer's disease (AD), as opposed to its autosomal dominant form, is likely caused by a complex interaction of genetic, environmental, and health lifestyle factors. Twin studies indicate that sporadic AD heritability could be between 58% and 79%, around half of which is explained by the ε4 allele of the apolipoprotein E (APOE4). We hypothesized that genes associated with known risk factors for AD, namely hypertension, hypercholesterolemia, obesity, diabetes, and cardiovascular disease, would contribute significantly to the remaining heritability. We analyzed 22 AD-associated single-nucleotide polymorphisms (SNPs), associated with these risk factors, that were included in the sequencing data of the Alzheimer's Disease Neuroimaging Initiative 1 data set, which included 355 participants with mild cognitive impairment (MCI). We built survival models with the selected SNPs to predict progression of MCI to probable AD over the 10-year follow-up of the study. The rs391300 SNP, located on the serine racemase (SRR) gene and linked to increased susceptibility to type 2 diabetes, was associated with progression from MCI to probable AD.

1. Introduction

Alzheimer's disease (AD) is the major etiology behind cognitive impairment and dementia in the elderly population (Plassman et al., 2011). Its biggest risk factor is aging (Barnes and Yaffe, 2011), and thus, as the worldwide population is steadily getting older (Brodaty et al., 2011), a significant increase in the prevalence of AD seems imminent. In fact, what underlies aging as a risk factor in the sporadic form of AD, as opposed to its autosomal dominant form due to known amyloid precursor protein (APP), Presenilin 1 (PS1), or Presenilin 2 (PS2) genetic mutations, is likely the causal interaction(s) of genetic and environmental factors over an individual's lifetime.

Regarding genetic risk, twin studies indicate that AD heritability lies between 58% and 79% (Gatz et al., 2006). The only well-established factor linked to AD is the ε4 allele on the apolipoprotein E gene (APOE4), which is involved in the metabolism of triglyceride-rich lipoproteins (Kim et al., 2009). Carriers with only one copy of the ε4 allele have 2 to 3 times the risk of developing AD, whereas carriers of two ε4 alleles have 12 times the risk of developing AD (Roses, 1996). It is therefore estimated that APOE4 could be responsible for 50% of the genetic predisposition in AD (Ashford and Mortimer, 2002).

We postulate that the remaining half of the reported genetic heritability could be explained by genes associated not directly with AD, but with risk factors for AD. These include diabetes, hypercholesterolemia, hypertension, obesity, and coronary heart disease (Barnes and Yaffe, 2011). In particular,

(1) non-insulin dependent (type 2) diabetes mellitus (T2D), a chronic condition characterized by hyperglycemia either caused by insulin resistance or insufficient insulin production or both (Longo et al., 2012), is highly prevalent in the elderly population and has been linked to a 2-fold increased risk for AD (Ott et al., 1999). Twin studies have shown that onset of T2D

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during midlife (onset age <65 years) was more likely to be associated with dementia and AD than onset later in life (onset age ≥65 years) (Xu et al., 2009);
(2) increased plasma low-density lipoprotein (LDL) cholesterol concentrations in older adults (65–85 years) has been associated with poorer working memory performance (Meusel et al., 2017); increased serum cholesterol in midlife increases the risk of AD, and patients taking lipid-lowering agents have a lower risk of AD than patients taking no medication (Dufouil et al., 2005; Notkola et al., 1998);
(3) high blood pressure in midlife is a risk factor for late-life cognitive impairment and dementia (Qiu et al., 2005);
(4) obesity (body mass index [BMI] ≥30) in midlife has also been associated with AD (Whitmer et al., 2007), and a meta-analysis of prospective studies showed a 2-fold increase in risk for AD in obese individuals (Anstey et al., 2011); and
(5) coronary heart disease, defined as a history of myocardial infarction, angina, angiographic coronary stenosis, or coronary revascularization, has been associated with mild cognitive impairment (MCI) and progression to dementia (Roberts et al., 2010).

Based on these findings, we hypothesized that variants in genetic risk factors associated with diabetes, hypertension, lipid transport, obesity, and coronary heart disease would be associated with an increased risk of progression of MCI to AD. Our major contributions in this work include (1) identifying single-nucleotide polymorphism (SNP) variants known to be significantly associated with these risk factors for AD that were present in the Alzheimer's disease Neuroimaging Initiative (ADNI) database and (2) conducting survival analyses in a robust design to identify those SNPs and covariates significantly associated with risk for progression of MCI to AD.

2. Methods

2.1. Ethics

ADNI was launched in 2003 as a public-private partnership, led by M.W. Weiner (www.adni-info.org/). Approval from the local ethics board and informed consent of the participants were obtained as part of the ADNI study. Data used in the preparation of this article were obtained from ADNI in March 2015 (adni.loni.usc.edu).

2.2. Participant inclusion criteria

We included all participants enrolled in the ADNI-1 study who were evaluated as MCI at baseline. Criteria for the diagnosis of MCI included (1) Mini–Mental State Examination score between 24 and 30; (2) memory complaints and objective memory loss measured by education-adjusted scores obtained on the Wechsler Memory Scale Logical Memory II test; (3) Clinical Dementia Rating of 0.5; (4) absence of significant levels of impairment in other cognitive domains; (5) well-preserved activities of daily living; and (6) absence of dementia.

Probable AD was diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (McKhann et al., 1984) criteria, with a Clinical Dementia Rating of 0.5 or 1.

2.3. Genetic information

2.3.1. Genotyping

Genotyping was performed using the Human610-Quad BeadChip (Illumina, San Diego, CA, USA), including 620,901 SNP markers, and completed on all ADNI-1 participants following the protocol detailed in the study by (Saykin et al., 2010). APOE genotyping was performed at the time of participant enrollment. The 2 SNPs (rs429358 and rs7412) that define the ε2, ε3, and ε4 alleles of APOE are not on the Human610-Quad BeadChip and therefore were genotyped using extracted DNA (Saykin et al., 2010). Polymerase chain reaction amplification was followed by a methylation-sensitive restriction enzyme (HhaI), resolution on 4% MetaPhor gel, and visualization by ethidium bromide staining (Potkin et al., 2009). BeadStudio 3.2 software (Illumina) was used to generate SNP genotypes from bead intensity data. GenomeStudio v2009.1 (Illumina), an updated version of BeadStudio, was later used to reprocess the array data for all samples.

2.3.2. Selected SNPs

We selected 40 genetic variants that were shown in the literature to be significantly associated with risk for diabetes, hypertension, lipid transport dysfunction, obesity, and coronary heart disease in genome-wide association studies (Kato, 2013; Reitz et al., 2012; Roberts, 2014; Speliotes et al., 2010; Thorleifsson et al., 2009; Wing et al., 2011; Zhang et al., 2010). Eighteen of these variants were present on the Human610-Quad BeadChip used to genotype ADNI-1 participants, namely rs5945326, rs1048886, rs391300, rs7903146, and rs17584499 (diabetes); rs12413409 and rs3184504 (hypertension); rs11206510, rs2075650, and rs964184 (hypercholesterolemia); rs16945088, rs6499640, rs10852521, rs571312, and rs2867125 (obesity); and finally rs6725887, rs2306374, and rs1746048 (coronary heart disease). For the remaining missing genetic variants we used SNAP, a bioinformatics query tool, which identifies proxy SNPs (Johnson et al., 2008). We used the following search criteria: SNP data set = 1000 Genomes Pilot 1, r^2 threshold = 1, population panel = Utah residents with Northern and Western European ancestry from the CEPH collection (CEU), and distance limit = 500. Four SNP proxies were further identified in the ADNI database for diabetes (rs13081389 proxy: rs13089415; and rs7766070 proxy: rs7756992), cardiovascular disease (rs579459 proxy: rs495828), and obesity (rs713586 proxy: rs10182181).

2.4. Covariates

2.4.1. Sociodemographic and cognitive measures

Baseline clinical information for each participant included demographics, Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog; Rosen et al., 1984), Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964), and APOE genotype.

2.4.2. Morphometric regional brain measures

Baseline morphometric regional brain measures were derived from T1-weighted magnetic resonance imaging. Images were processed using FreeSurfer 5.3 (http://freesurfer.net; Fischl et al., 2009), and the measures were transformed into normative Z scores based on our normative morphometric regional brain values (Potvin et al., 2017, 2016). Morphometric brain measures included hippocampal, entorhinal, and global cortex volumes and thicknesses, all measures that have been widely reported as most sensitive to progression from MCI to probable AD.

2.4.3. Health conditions

Variables for baseline health conditions included treated diabetes, serum glucose and cholesterol levels, history of coronary heart disease, BMI, treated hypertension, and systolic and diastolic blood pressure.

2.5. Statistical analyses

Cox regression models for predicting conversion of MCI to AD were conducted. First, heterozygous genotypes were grouped with

the homozygous genotypes having the same univariate direction of association, unless there were less than 10 homozygous carriers in a category (Supplementary Table 1). Second, to identify relevant SNPs more robustly, the sample was randomly split into 2 subsamples with the same number of participants who converted to AD. A model was built for each subsample, with all SNPs and covariates (age, sex, ADAS-Cog, RAVLT delayed recall score, hippocampal volume, entorhinal cortex volume and thickness, global cortex volume and thickness, and APOE4) tested together with a backward elimination procedure keeping only those with p-values less than 10% at each iteration.

We built a final model from all participants including only SNPs selected in both subsample models, as well as all covariates retained by either one of the two subsample models and metrics related to the SNPs health condition (e.g., treated diabetes, glucose level, cholesterol level, CVD, BMI, treated hypertension, and blood pressure) using the same elimination procedure. This final model was tested for hazards proportionality and outliers. SAS 9.4 program was used for all statistical analyses (SAS Institute Inc, Cary, NC, USA).

3. Results

3.1. Sample characteristics

Table 1 shows participants' characteristics. There were 375 MCI participants enrolled at baseline. After removing participants without data for our selected genotype variants, the number of participants available was 355. The sample comprised 234 males and 121 females; at the 10-year maximum follow-up, 196 MCI participants had progressed to probable AD, with a mean time for conversion of 2.4 years (standard deviation = 1.9) and a maximum of 10 years.

Genotype frequencies for all SNPs were similar (Supplementary Table 1) to those observed in the literature and from the HapMap data set available on the NCBI website (https://www.ncbi.nlm.nih.gov/) (Kato, 2013; Roberts, 2014; Speliotes et al., 2010). Three variants had fewer than 5 participants with a homozygous variant: rs16945088 (G/G) with a genotype frequency of <1% (n = 3) and an allelic frequency (G) of 15%; rs12413409 (A/A) with a genotype frequency of 1% (n = 4) and an allelic frequency (A) of 15%; and rs6725887 (G/G) with a genotype frequency 1% (n = 4) and an allelic frequency (G) of 20%. Six SNPs had missing data: rs10182181 (n = 1), rs17584499 (n = 4), rs13089415 (n = 6), rs3184504 (n = 5), rs495828 (n = 2), and rs11206510 (n = 2). Missing data were also observed for ADAS-Cog scores (n = 3), BMI (n = 1), glucose levels (n = 23), and cholesterol levels (n = 22).

3.2. Association between SNPs and AD progression

Table 2 shows the selected predictors for each subsample model. In subsample 1, the selected allelic variants were rs391300 (diabetes) and rs6499640 (BMI). In subsample 2, the selected variants were rs391300 (diabetes), rs11206510 (hypercholesterolemia), rs964184 (hypercholesterolemia), and rs16945088 (obesity). In terms of covariates, ADAS-Cog was retained in both model subsamples. Meanwhile, entorhinal and cortical volumes and APOE4 were selected in subsample 1, and hippocampal volume and RAVLT were selected in subsample 2.

Thus, the only SNP robustly selected in both samples and retained for the final model was rs391300 (diabetes). All selected covariates are presented in Table 2. The only health condition retained in the final model that was related to one of the selected SNPs was cholesterol levels.

Table 1
Participant's characteristics (n = 355)

Characteristics	Mean or n	SD or %
Converted to AD	196	55.2
Demographics	74.8	7.3
Age	74.8	7.3
Women	121	34.1
Cognitive functioning		
ADAS-Cog score	18.7	6.2
RAVLT delayed recall score	2.7	3.2
Brain morphometry		
Cortical volume (Z score)	−1.1	1.1
Cortical thickness (Z score)	−0.9	1.1
Entorhinal volume (Z score)	−0.4	1.1
Entorhinal thickness (Z score)	−0.4	1.1
Hippocampal volume (Z score)	−1.4	1.3
Health-related variables		
Using diabetes medication	24	6.8
Serum glucose level (mg/dL)	100.2	26.8
Using antihypertensive medication	209	58.9
Diastolic blood pressure (mm Hg)	74.9	9.7
Systolic blood pressure (mm Hg)	135.8	18.0
Serum cholesterol level (mg/dL)	195.7	39.8
History of cardiovascular diseases	261	73.5
Body mass index	26.0	3.9

Key: AD, Alzheimer's disease; ADAS-Cog, AD Assessment Scale-cognitive subscale; RAVLT, Rey Auditory Verbal Learning Test; SD, standard deviation.

Fig. 1 shows the survival curves associated with rs391300 and APOE4. When covariates are kept constant, individuals with rs391300 AA variant and an APOE4 allele displayed the greatest risk of conversion (lowest survival), whereas those with rs391300 AG or GG variant and no APOE4 allele had the lowest risk (highest survival) of conversion to probable AD.

4. Discussion

It has been widely reported that the APOE4 genetic variant is the most significant genetic risk factor for AD and could explain 50% of total genetic risk (Ashford and Mortimer, 2002). Genome-wide association studies have revealed associations of AD with other genes, but of much smaller magnitudes than for APOE (Butler et al., 2009). Moreover, studies with twins indicate a disease heritability of 58%–79% (Gatz et al., 2006). Thus, an important portion of the genetic risk for AD remains unknown and could be linked to variations in genes associated with known health-related risk factors for AD.

We assessed the association of genetic variants linked to chronic conditions such as diabetes, hypertension, hypercholesterolemia, obesity, and coronary heart diseases with progression from MCI to probable AD over a 10-year observation period. Of the 22 SNPs included in our study, only one, linked to T2D, was significantly associated with progression from MCI to probable AD after adjusting for covariates (Fig. 2).

The rs391300 SNP is located in the serine racemase (SRR) gene. SRR generates D-serine from L-serine, a co-agonist with glutamate of the N-methyl-D-aspartate (NMDA) receptor. A variant in the SRR gene was significantly associated with schizophrenia susceptibility and T2D in a Chinese Han population (Labrie et al., 2009; Tsai et al., 2010). The rs391300 gene variant was also associated with therapeutic efficacy of metformin in T2D (Dong et al., 2011) and with risk of gestational diabetes mellitus in a Chinese Han population (Wang et al., 2011). However, another genome-wide association study in Hans did not confirm this relationship between SRR gene variants and T2D (Zhang et al., 2014).

Regarding the association between SRR and AD, a study investigating the role of D-serine in the pathophysiology of AD

Table 2
Cox proportional hazard models predicting MCI progression to AD

Variables	Hazard ratio	95% CI		*p*
Subsample 1 (n = 172)				
rs391300 (A/A)	2.18	1.26	3.79	0.0054
rs6499640 (G)	1.61	1.01	2.54	0.0440
APOE4	1.69	1.08	2.64	0.0216
Cortical volume (Z score)	0.59	0.48	0.72	<0.0001
Entorhinal volume (Z score)	0.81	0.65	0.99	0.0393
ADAS-Cog score	1.10	1.05	1.15	<0.0001
Subsample 2 (n = 167)				
rs391300 (A/A)	1.91	1.07	3.42	0.0294
rs11206510 (A/A)	1.63	1.01	2.62	0.0461
rs964184 (C)	1.68	1.07	2.63	0.0245
rs16945088 (A/A)	1.96	0.89	4.30	0.0948
Hippocampus volume (Z score)	0.78	0.66	0.92	0.0032
ADAS-Cog score	1.11	1.06	1.16	<0.0001
RAVLT delayed recall score	0.90	0.82	1.00	0.0547
Final model (n = 322)				
rs391300 (A/A)	1.85	1.24	2.75	0.0026
APOE4	1.32	0.96	1.82	0.0902
Cortical volume (Z score)	0.69	0.59	0.80	<0.0001
Hippocampus volume (Z score)	0.86	0.74	0.99	0.0427
ADAS-Cog	1.08	1.04	1.12	<0.0001
RAVLT delayed recall score	0.92	0.86	0.99	0.0190
Cholesterol level (mg/dL)	1.004	1.000	1.008	0.0745

Reference categories: rs391300, rs11206510, and rs16945088 = A/G + G/G; rs6499640 = A/A; rs964184 = G/G; and APOE4 = no ε4 allele.
Key: ADAS-Cog, Alzheimer's Disease Assessment Scale-cognitive subscale; RAVLT, Rey Auditory Verbal Learning Test.

(Hashimoto et al., 2004) concluded that reduced activity of SRR could play a role in the susceptibility to AD because serum levels of D-serine were decreased in AD patients compared with cognitively normal controls. D-Serine is a co-agonist of NMDA receptors, which have been shown to be decreased in brain regions affected in AD, particularly the hippocampus and entorhinal cortex (Sze et al., 2001). A dysfunction in glutamatergic neurotransmission in relation to NMDA receptors could also be involved in the pathophysiology of AD (Kornhuber and Weller, 1997; Olney et al., 1997).

Currently, the effect of rs391300 on the SRR gene remains unknown; only that the effect of this SNP on certain phenotypes was investigated, and not on the functionality of SRR itself. The SNP rs391300 could impact activity or expression of SRR, subsequently altering the metabolism of D/L-serine and thereby influencing conversion of MCI to AD via an NMDA receptor effect. Alternatively, an association with another SNP not included in our analysis is also a possibility because an exhaustive analysis of all SNPs associated with risk factors for AD was not performed.

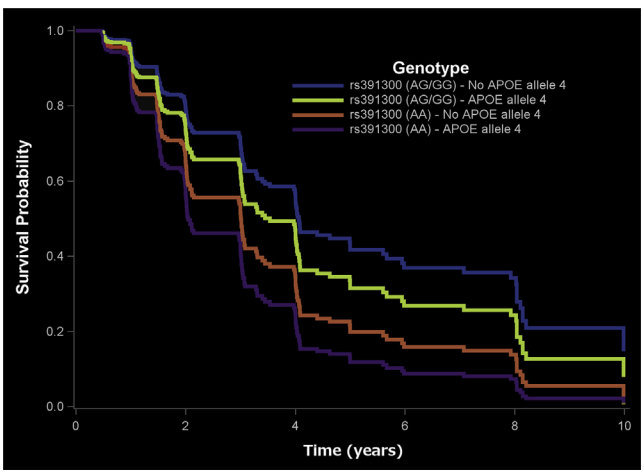

Fig. 1. Survival curve showing association between genetic variants and progression from mild cognitive impairment to Alzheimer's disease.

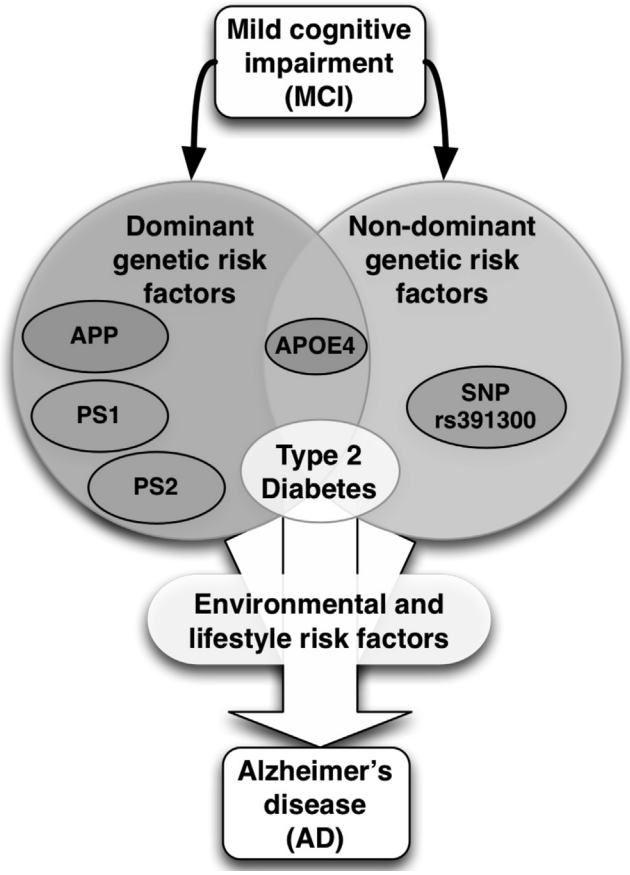

Fig. 2. Pathways illustrating dominant versus nondominant risk factors for the development of Alzheimer's disease. SNP rs391300 interruption results in reduced N-methyl-D-aspartate receptor activation. Abbreviations: APOE4, ε4 allele of the apolipoprotein E; APP, amyloid precursor protein; PS1, Presenilin 1; PS2, Presenilin 2; SNP, single-nucleotide polymorphisms.

The relationship between AD and T2D remains unclear but is currently a very dynamic area of research. While hyperglycemia has been associated with accelerated cognitive decline (Crane et al., 2013), the association of suboptimal cognitive performance with insulin resistance/T2D could also be partly explained by reactive oxygen species that contribute to microvascular damage (de Bresser et al., 2010; Segura et al., 2009; Unoki and Yamagishi, 2008) and beta amyloid and tau accumulation (Chen et al., 2003) within the brain. In addition to oxidative stress, insulin and insulin-like growth factor 1 stimulate beta amyloid release from neurons, and insulin resistance impairs brain amyloid clearance and phosphorylated tau clearance (Carro and Torres-Aleman, 2004; Craft and Watson, 2004; De Felice et al., 2014; Kang et al., 2017a). Increased amounts of proinflammatory factors and ceramides produced in the liver of T2D may also cross the blood-brain barrier and cause or exacerbate neurological insults (de la Monte, 2009; Diehl et al., 2017). More recently, the role of amylin, an amyloidogenic protein cosecreted with insulin by pancreatic β-cells, has been supported by several studies as a potential connection between T2D and AD (Bharadwaj et al., 2017; de Matos et al., 2017; Zhang and Song, 2017). Amylin exerts its neurotoxicity by directly interacting with beta amyloid and causing its aggregation (Ono et al., 2014). Interestingly, decreased brain volumes (Brundel et al., 2010; den Heijer et al., 2003; Moran et al., 2013; Scheltens et al., 2002) and functional connectivity (Chen et al., 2014; Musen et al., 2012) assessed by magnetic resonance imaging were found in similar brain regions for both T2D and AD patients. These 2 conditions share many common

risk factors (i.e., aging, dyslipidemia, genetic predisposition, hypertension, and obesity) and pathological processes (i.e., inflammation, oxidative stress, and mitochondrial dysfunction) (Zhang and Song, 2017; de la Monte and Wands, 2008; Kang et al., 2017b).

5. Conclusion

The present study found a significant association between an SNP (rs391300) linked to T2D and conversion of MCI to AD, even after correction for APOE genotype.

One goal of being able to better identify those at risk of AD is to allow intervention before damage is irreversible. Multimodal prevention-type treatments for AD are emerging (Ngandu et al., 2015) and commonly suggest lowering the risk for coronary heart disease and/or T2D. Increased risk of T2D due to SRR may therefore be an important target for AD preventative measures.

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Supplementary data

Supplementary Data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurobiolaging.2017.11.013.

Disclosure statement

H.G., O.P., S.N., C.D.-T., and S.C. declare no competing financial interests. S.D. is an officer and a shareholder of True Positive Medical Devices, Inc.

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