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Featured Article

Alzheimer's disease risk variants modulate endophenotypes in mild cognitive impairment

Eva Louwersheimer[a,*,1], Steffen Wolfsgruber[b,c,1], Ana Espinosa[d], André Lacour[c], Stefanie Heilmann-Heimbach[e,f], Montserrat Alegret[d], Isabel Hernández[d], Maitée Rosende-Roca[d], Lluís Tárraga[d], Mercè Boada[d], Johannes Kornhuber[g], Oliver Peters[h], Lutz Frölich[i], Michael Hüll[j], Eckart Rüther[k], Jens Wiltfang[k], Martin Scherer[l], Steffi Riedel-Heller[m], Frank Jessen[n], Markus M. Nöthen[e,f], Wolfgang Maier[b,c], Ted Koene[a,o], Philip Scheltens[a], Henne Holstege[p], Michael Wagner[b,c], Agustín Ruiz[d], Wiesje M. van der Flier[a,q], Tim Becker[r], Alfredo Ramirez[b,e,**]

[a]*Alzheimer Center and Department of Neurology, Neuroscience Campus Amsterdam, VU University Medical Centre, Amsterdam, The Netherlands*
[b]*Department of Psychiatry and Psychotherapy, University of Bonn, Bonn, Germany*
[c]*German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany*
[d]*Alzheimer Research Center and Memory Clinic of Fundació ACE, Institut Català de Neurociències Aplicades, Barcelona, Spain*
[e]*Institute of Human Genetics, University of Bonn, Bonn, Germany*
[f]*Department of Genomics, Life & Brain Center, University of Bonn, Bonn, Germany*
[g]*Department of Psychiatry and Psychotherapy, University Clinic Erlangen, Friedrich-Alexander University Erlangen-Nürnberg, Erlangen, Germany*
[h]*Department of Psychiatry, Charité University Medicine, Berlin, Germany*
[i]*Department of Geriatric Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany*
[j]*Centre for Geriatric Medicine and Section of Gerontopsychiatry and Neuropsychology, Medical School, University of Freiburg, Freiburg, Germany*
[k]*Department of Psychiatry and Psychotherapy, University of Göttingen, Göttingen, Germany*
[l]*Department of Primary Medical Care, University Medical Center Hamburg-Eppendorf, Hamburg, Germany*
[m]*Institute of Social Medicine, Occupational Health and Public Health, University of Leipzig, Leipzig, Germany*
[n]*Department of Psychiatry and Psychotherapy, University of Cologne, Cologne, Germany*
[o]*Alzheimer Center and Department of Medical Psychology, VU University Medical Center, Amsterdam, The Netherlands*
[p]*Alzheimer Center and Department of Clinical Genetics, Neuroscience Campus Amsterdam, VU University Medical Centre, Amsterdam, The Netherlands*
[q]*Department of Epidemiology & Biostatistics, VU University Medical Center, Amsterdam, The Netherlands*
[r]*Institute for Community Medicine, Ernst Moritz Arndt University Greifswald, Greifswald, Germany*

Abstract

Introduction: We evaluated the effect of Alzheimer's disease (AD) susceptibility loci on endophenotypes closely related with AD pathology in patients with mild cognitive impairment (MCI).
Methods: We selected 1730 MCI patients from four independent data sets. Weighted polygenic risk scores (PGS) were constructed of 18 non-apolipoprotein E (*APOE*) AD risk variants. In addition, we determined *APOE* genotype. AD endophenotypes were cognitive decline over time and cerebrospinal fluid (CSF) biomarkers (aβ, tau, ptau).
Results: PGS was modestly associated with cognitive decline over time, as measured by mini-mental state examination (MMSE) ($\beta \pm SE$: -0.24 ± 0.10; $P = .012$), and with CSF levels of tau and ptau (tau: 1.38 ± 0.36, $P = 1.21 \times 10^{-4}$; ptau: 1.40 ± 0.36, $P = 1.02 \times 10^{-4}$).
Discussion: In MCI, we observed a joint effect of AD susceptibility loci on nonamyloid endophenotypes, suggesting a link of these genetic loci with neuronal degeneration in general rather than with Alzheimer-related amyloid deposition.

Keywords: Alzheimer's disease; Mild cognitive impairment; Polygenic risk score; Endophenotypes; Genetic risk variants

[1]These authors contributed equally.

*Corresponding author. Tel.: +31-0-204440823; Fax: +31-0-204448529.
**Corresponding author. Tel.: +49-0-228-287-19323; Fax: +49-0-228-287-16097.
E-mail address: e.louwersheimer@vumc.nl (E.L.), alfredo.ramirez@ukb.uni-bonn.de (A.R.)

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1. Introduction

Alzheimer's disease (AD) is a complex neurodegenerative disease caused by genetic and environmental factors. The estimated genetic component (heritability) of sporadic late onset AD is 60%–80% [1]. Over the past 5 years, an increasing number of common genetic AD risk variants (minor allele frequency >5%) has been identified by genome wide association studies (GWAS) [2–6]. Each of the identified variants individually confers a small effect (odds ratio <1.5) on susceptibility to AD, thereby limiting their predictive value in clinical setting. Computation of a polygenic risk score (PGS) appears a suited strategy to improve predictive value of these genetic effects, because it provides a cumulative effect score based on the individual susceptibility variants. The robustness of this strategy has been shown in psychiatric disorders, including schizophrenia and bipolar disorders [7], and previous studies have investigated the usability of PGS in the prediction of conversion from mild cognitive impairment (MCI) to AD [8,9]. A complementary approach assesses the relationship between genetic risk variants and intermediate phenotypes (endophenotypes), such as cerebrospinal fluid (CSF) biomarkers or cognitive decline, which are more proximal to specific events in the pathologic pathways involved in AD pathogenesis [10]. This strategy enhances further identification of the underlying molecular mechanisms associated with the AD susceptibility loci. Research has shown that a PGS without apolipoprotein E (*APOE*) (non-*APO*E PGS) was significantly associated with lower levels of CSF amyloid-beta-42 (Aβ) in AD patients (n = 222) but not with CSF levels of total tau (tau) or tau phosphorylated at threonine-181 (ptau) [11]. A finding contradicted by a study with 338 AD patients, which showed an association between non-*APOE* PGS and increased CSF levels of tau and ptau but not with CSF levels of Aβ [12]. In addition, a large population-based study with non-demented subjects from the Rotterdam Study (n = 5171) has identified a marginal joint effect of non-*APOE* PGS on memory [13].

To date, little research has been performed on the effect of PGS on endophenotypes of AD in patients with MCI. Linking genetic risk factors of AD to pathologic pathways acting at the MCI stage will be crucial for the development of effective treatments and improved definitions of at-risk groups.

The work described here used an alternative approach by exploring the effect of joined AD susceptibility variants on different endophenotypes of AD in patients with MCI. A PGS out of 18 known AD risk GWAS loci (i.e. *CR1, BIN1, INPP5D, MEF2C, CD2AP, NME8, ZCWPW1, EPHA1, PTK2B, CLU, MS4A6A, PICALM, SORL1, FERMT2, SLC24A4/RIN3, ABCA7, CD33, CASS4*) was created, and we investigated associations with two types of endophenotypic markers of AD; CSF biomarkers (Aβ, tau, and ptau) and cognitive decline over time (as measured by the mini-mental state examination [MMSE] [14], and the word list learning test with immediate and delayed recall).

2. Methods

2.1. Participants

For the present study, 1730 MCI patients were selected from four cohorts: 242 patients from the Amsterdam Dementia Cohort (ADC), 421 from the Dementia Competence Network (DCN), 342 from the study on Aging, Cognition, and Dementia (AgeCoDe), and 725 from Fundació ACE (ACE) (Table 1). The patients were included based on the following inclusion criteria: (1) baseline diagnosis of MCI; (2) availability of longitudinal cognitive assessment including MMSE and word list learning test with immediate and delayed verbal recall; (3) availability of genotyped single-nucleotide polymorphisms (SNPs) for PGS; (4) availability of information concerning conversion (yes/no); and (5) at least 1-year follow-up.

The ADC cohort included 242 MCI patients who visited the memory clinic of the Alzheimer center of the VU University Medical Center (VUmc) between 2000 and 2013 [19]. In short, all patients underwent an extensive standardized dementia assessment, including medical history, informant-based history, physical and neurologic examination, laboratory tests, neuropsychological assessment including the MMSE, and the Dutch version of the Rey auditory verbal learning task (including immediate and delayed recall) [15], CSF investigation and magnetic resonance investigation (MRI) of the brain. Diagnosis was made in a consensus meeting without prior knowledge of the CSF results. For the diagnosis of MCI, Petersen's criteria were used until the beginning of 2012 [20], when the National Institute on Aging–Alzheimer's Association (NIA-AA) criteria for MCI [21] were implemented. In general, follow-up is organized in such a way that patients are monitored on an annual basis in a standardized fashion. Progression to probable AD was diagnosed based on the NINCDS-ADRDA criteria [22,23].

The DCN cohort included 421 MCI patients who were recruited at 14 university hospital memory clinics across Germany between 2003 and 2005 [24]. Baseline assessment comprised extensive neuropsychological tests, including those of the consortium to establish a registry for Alzheimer's disease (CERAD) [16], MMSE and immediate and delayed verbal recall and structural MRI scans of the brain. CSF was collected from all consenting participants. MCI was diagnosed according to the consensus criteria by the international working group (IWG) on MCI [25]. Minor changes in complex activities of daily living were tolerated. Clinical diagnoses of MCI subtypes were made by team conferences at the local study centers. Follow-up assessments were performed at 12 and 24 months. Conversion to probable AD was diagnosed based on the NINCDS-ADRDA criteria.

The AgeCoDe cohort included 342 MCI patients who were recruited from general practice registries across six study centers in Germany between 2002 and 2003 [26,27]. All AgeCoDe participants were assessed using the