Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 5 (2016) 53-66

Alzheimer's & Dementia

Neuroimaging

The effect of the top 20 Alzheimer disease risk genes on gray-matter density and FDG PET brain metabolism

Eddie Stage[a,1], Tugce Duran[a,1], Shannon L. Risacher[b], Naira Goukasian[c], Triet M. Do[c], John D. West[b], Holly Wilhalme[d], Kwangsik Nho[b], Meredith Phillips[a], David Elashoff[d], Andrew J. Saykin[b,d,e,f], Liana G. Apostolova[a,b,c,f,*], and for the Alzheimer's Disease Neuroimaging Initiative[2]

[a]*Department of Neurology, Indiana University School of Medicine, Indianapolis, IN, USA*
[b]*Department of Radiology and Imaging Sciences, Center for Neuroimaging, Indiana University School of Medicine, Indianapolis, IN, USA*
[c]*Department of Neurology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA*
[d]*Department of Medicine Statistics Core, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA*
[e]*Indiana University Network Science Institute, Indianapolis, IN, USA*
[f]*Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, IN, USA*

Abstract

Introduction: We analyzed the effects of the top 20 Alzheimer disease (AD) risk genes on gray-matter density (GMD) and metabolism.

Methods: We ran stepwise linear regression analysis using posterior cingulate hypometabolism and medial temporal GMD as outcomes and all risk variants as predictors while controlling for age, gender, and *APOE* ε4 genotype. We explored the results in 3D using Statistical Parametric Mapping 8.

Results: Significant predictors of brain GMD were *SLC24A4/RIN3* in the pooled and mild cognitive impairment (MCI); *ZCWPW1* in the MCI; and *ABCA7*, *EPHA1*, and *INPP5D* in the AD groups. Significant predictors of hypometabolism were *EPHA1* in the pooled, and *SLC24A4/RIN3, NME8*, and *CD2AP* in the normal control group.

Discussion: Multiple variants showed associations with GMD and brain metabolism. For most genes, the effects were limited to specific stages of the cognitive continuum, indicating that the genetic influences on brain metabolism and GMD in AD are complex and stage dependent.

Keywords: Genome-wide association studies (GWAS); Genetic variation; Imaging genetics; Magnetic resonance imaging (MRI); Fluorodeoxyglucose positron emission tomography (FDG PET); Atrophy; Brain metabolism; Risk genes; ADNI; Brain mapping; Statistical parametric mapping (SPM); Positron emission tomography (PET); Alzheimer disease; AD

1. Background

Alzheimer disease (AD) is a chronic neurodegenerative disease characterized by short-term memory loss in the early disease stages and progressive cognitive and functional deficits as the disease advances. The clinical symptoms result from the deposition of two toxic proteins, β-amyloid (Aβ) and tau, which give rise to neuritic plaques and neurofibrillary tangles, respectively [1]. The clinical appearance of AD is the direct result of neuronal dysfunction and death, which is manifested by brain atrophy and hypometabolism.

[1]Indicates co-first authorship. [2]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

*Corresponding author. Tel.: 317-963-7436; Fax: 317-963-7533.
E-mail address: lapostol@iu.edu

http://dx.doi.org/10.1016/j.dadm.2016.12.003

Brain imaging is increasingly used to measure AD-associated changes in vivo. Amyloid positron emission tomography (PET), a novel Food and Drug Administration–approved imaging technology, uses selective Aβ tracers to visualize brain amyloidosis and can reliably detect the presence of neuritic plaques in the symptomatic and presymptomatic stages. Brain atrophy is best evaluated with longitudinal studies of magnetic resonance imaging (MRI). The atrophic changes are first noticeable in the medial temporal lobe, eventually spreading through the remainder of the brain as the disease progresses [2]. Contributing to the neuronal death, brain hypometabolism, a decrease in the brain metabolic activity, can be visualized using F^{18}-fluorodeoxyglucose (FDG) PET or single photon emission tomography. The hallmark pattern in AD is early hypometabolism of the posterior cingulate, lateral temporal, and parietal lobes with spread to the frontal lobes as the disease progresses [3].

Seventy to eighty percent of sporadic AD can be attributed to genetic risk [4,5]. Recent large-scale genome-wide association studies (GWASs) have discovered more than 20 AD gene variants that confer genetic risk [6–11]. Among these variants is the apolipoprotein E (*APOE*) gene, which is the most established genetic risk factor for AD. Individuals with a single *APOE* ε4 allele have a three-fold increase in AD risk, whereas homozygotes have a 12-fold increase [12]. apoE is a major protein component of chylomicrons and is highly expressed in both liver and brain, where it plays a role in lipid metabolism and is thought to be involved in the breakdown of Aβ, both inside and outside of cells. The apoE4 protein is less effective in clearing Aβ, providing a possible explanation for the increased risk of amyloid buildup [13]. With the help of imaging studies, *APOE* ε4 allele was found to be strongly associated with brain amyloidosis [14,15], atrophy [16], and hypometabolism [17,18]. These data indicate that valuable observations related to gene function can be gathered with imaging phenotypes.

Many of the remaining top 20 AD variants have also been implicated in brain metabolism and neurodegeneration. Several *SORL1* variants, *EPHA1* rs11771145, and *CR1* rs6656401 were found to be associated with hippocampal atrophy and cerebrovascular or cardiovascular disease [19,20]. Additionally, various research groups have shown that *ABCA7* rs3764650, *MS4A6A* rs983392, *MS4A6A* rs610932 and rs11230161, *BIN1* rs6733839 and rs744373, *CR1* rs1408077, *CR1* rs6656401, *CR1* rs3818361, *PICALM* rs3851179, *CLU* rs11136000 and rs2279590, *CD2AP* rs10948363, and *CD33* rs3865444 are all associated with MRI-measured brain atrophy on MRI [21–27]. *BIN1* rs7561528 was found to be significantly associated with both hippocampal volume and FDG PET brain metabolism [28]. The studies mentioned have unquestionably contributed to the field of imaging genetics and AD research as a whole, but many of these studies have either analyzed the effect of a single gene variant at a time [19–22,24,26,27] or investigated the association between a polygenic risk score with the imaging trait, which does not allow us to interpret the individual contribution of genetic variants [23]. The commonly used univariate imaging genetics approach ignores the fact that in any given human subject, many of these risk variants are simultaneously present, and the genetic contribution of each variant should be investigated in the presence of the rest and not in isolation. In addition, these studies have investigated the effects in the pooled samples consisting of asymptomatic individuals, of whom only a portion harbor AD pathology, as well as symptomatic individuals who are in different stages of the disease. Such an approach would miss any stage-specific associations that might occur for genes that influence the timing and course of development of disease traits (e.g., early vs. late neurodegeneration or amyloidosis, early vs. late impairment in a specific cognitive domain) and explain, at least in part, AD heterogeneity.

Using a multivariable approach across the disease spectrum allows for accurate modeling of this complex polygenic disease that is constantly evolving. Here, we report a comprehensive analysis of the associations of all well-validated AD risk variants from recent large-scale GWAS studies with two markers of neurodegeneration—brain gray matter density (GMD) and brain glucose metabolism. Our goal was to establish the relative contribution of the top 20 AD risk genes to changes in GMD and metabolic dysfunction. We hypothesized that we would find gene variants that show a profound effect on these two neurodegenerative phenotypes and that some variants will show associations in a stage-specific manner.

2. Methods

2.1. Subjects

We sourced our study data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). ADNI is an international longitudinal study with approximately 50 sites across the United States and Canada that was launched in 2003. ADNI's goal is to track the progression of AD using clinical and cognitive tests, MRI, FDG PET, amyloid PET, cerebrospinal fluid, and blood biomarkers (http://adni.loni.usc.edu/study-design).

ADNI has undergone three study cycles: ADNI1, ADNI GO, and ADNI2. Our study population was composed of participants from all three stages [29]. The MRI and FDG PET analyses included all subjects with GWAS and baseline MRI or FDG PET data that were successfully preprocessed. A total of 1564 ADNI subject had baseline MRI and GWAS data. Of those, 65 failed in the MRI preprocessing steps and were excluded from our structural analyses. Our final MRI cohort consisted of 441 cognitively normal (NC) subjects, 764 mild cognitive impairment (MCI) subjects, and 294 dementia subjects (total $N = 1499$). As not all ADNI1 subjects received FDG PET, our FDG PET cohort was smaller and consisted of 381 NC, 634 MCI, and 243 dementia subjects (total $N = 1258$). There were 59 subjects with available