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Journal of Alzheimer's Disease 39 (2014) 565–574
DOI 10.3233/JAD-131058
IOS Press

Polygenic Risk for Alzheimer's Disease is not Associated with Cognitive Ability or Cognitive Aging in Non-Demented Older People

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Handling Associate Editor: Emilio Di Maria

Accepted 29 September 2013

Abstract. Alzheimer's disease (AD) and non-pathological cognitive aging have phenotypic similarities which may be influenced by an overlapping set of genetic variants. Genome-wide complex trait analysis estimates that common genetic variants account for about 24% of the variation contributing to liability for AD. It is also estimated that 24% of the variance of non-pathological cognitive aging is accounted for by common single nucleotide polymorphisms. However, although the *APOE* locus is associated with both AD and cognitive aging, it is not known to what extent other common genetic variants, with smaller effect sizes that influence both, overlap. We test the hypothesis that polygenic risk for AD is associated with cognitive ability and cognitive change in about 3,000 non-demented older people (Cognitive Ageing Genetics England and Scotland-CAGES-consortium). We found no significant association of polygenic risk for AD with cognitive ability or cognitive change in CAGES, indicating that the genetic etiologies of AD and non-pathological cognitive decline differ.

Keywords: Aging, Alzheimer's disease, cognition, cohort studies, genetics, polygenic traits

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[1]Data used in the preparation of this article were obtained from the Genetic and Environmental Risk for Alzheimer's disease (GERAD1) Consortium. As such, the investigators within the GERAD1 consortia contributed to the design and implementation of GERAD1 and/or provided data but did not participate in analysis or writing of this report. A full list of GERAD1 investigators can be found in the acknowledgments.

ISSN 1387-2877/14/$27.50

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia and is predicted to affect over a million people in the UK by 2025 [1]. It is characterized by progressive loss of memory, mood changes, and problems with communication and reasoning [2]. Brain autopsies reveal extracellular plaques and intracellular neurofibrillary tangles, and these are considered hallmarks of the disease [3].

AD is a genetically heterogeneous disease. Candidate gene and genome-wide association studies have identified a number of genes which increase an individual's risk of developing the more common form of AD, late-onset AD (LOAD). These include *APOE*, *CR1*, *PICALM,* and *CLU*, with the *APOE* ε4 allele being by far the strongest genetic risk factor for LOAD [4, 5]. Mutations in three genes have been identified as causative in cases of the rarer familial early-onset AD (EOAD). These are *APP*, *PSEN1*, and *PSEN2* and all are involved in the amyloid-β (Aβ) pathway [6–8]. The mutations lead to an increase in $A\beta_{42}$ production, deposits of which accumulate in the extracellular plaques identified in the brains of AD patients. See references [9–11] for reviews of the genetics of AD.

Non-pathological cognitive aging shares some phenotypic similarities with AD including memory loss, and the greatest risk factor for developing AD is age. To date, the only gene with a replicated effect on normal cognitive aging is *APOE* [12], the gene which is the greatest genetic risk factor for LOAD. Based on genome-wide testing of single nucleotide polymorphisms (SNPs), it is estimated that common genetic variants account for about 40% to 50% of the variance in general cognitive functioning in later life, 24% of the variance in lifetime cognitive change (though this estimate had large standard errors), and 24% of the variation contributing to liability for AD [13–15]. The *APOE* locus alone accounts for about 5% of the variance in lifetime cognitive change and 4% of the variance in AD [16, 17]. We hypothesize that AD and non-pathological cognitive aging share common genetic risk factors.

A polygenic risk score for a particular disease can be calculated for each individual in a sample, from published genetic association data, by summing the known effect size of each individual SNP multiplied by the number of reference alleles present for that SNP in a particular individual. This technique has successfully been used to show, for example, that greater polygenic risk for schizophrenia is associated with more loss of cognitive function between childhood and old age in people who have neither dementia nor schizophrenia [18]. A recent study investigated a polygenic risk score, based on just 11 genes significantly associated with AD, and found only a marginal effect of these genes on memory scores in individuals aged 45–99 years, independent from *APOE* [19]. Here we test the hypothesis that a polygenic risk score created using data from a published AD genome-wide association study (GWAS) [4] is associated with cognitive ability in later life and non-pathological cognitive change in samples of older, non-demented people from England and Scotland.

MATERIALS AND METHODS

Cognitive Ageing Genetics in England and Scotland (CAGES) Consortium's cohorts

Five polygenic risk scores (created using different AD association criteria) were created in each of the five UK-based cohorts that make up the Cognitive Ageing Genetics in England and Scotland (CAGES) consortium.

Lothian Birth Cohort 1921 (LBC1921)

LBC1921 consists of 550 (234 men and 316 women) relatively healthy surviving members of the Scottish Mental Survey 1932 [20]. The majority of these individuals had their general cognitive ability assessed at ∼11 years of age using the Moray House Test (MHT) version 12. This test consists of 75 items of a variety of types: following directions (14 items), same-opposites (11 items), word classification (10 items), analogies (8 items), practical items (6 items), reasoning (5 items), proverbs (4 items), arithmetic (4 items), spatial items (4 items), mixed sentences (3 items), cypher decoding (2 items), and other items (4 items). At a mean age of 79.1 years (SD 0.6), they were recruited to a study to determine influences on normal cognitive aging and underwent a series of cognitive tests. This included retaking the MHT [21, 22]. A later-life general fluid cognitive functioning score (gf) was derived from principal components analysis of MHT, Raven's Matrices, Logical Memory, and Verbal Fluency [13]. Verbal declarative memory was assessed using the total Logical Memory score from the Wechsler Memory Scale-Revised [23]. Crystallized cognitive ability (vocabulary-based) was assessed using the National Adult Reading Test (NART) [24]. Cognitive measures were corrected for age at time of testing and gender prior to analysis. gf was adjusted for prior cognitive

ability using the MHT scores from age 11, thus providing a measure of relative cognitive change from age 11 to age 79. Both gf and age 11 MHT scores were adjusted for age in days at time of testing prior to the creation of the cognitive change measure. Cognitive change measures were extracted and standardized independently for males and females [16].

Lothian Birth Cohort 1936 (LBC1936)

LBC1936 consists of 1091 (548 men and 543 women) relatively healthy surviving members of the Scottish Mental Survey 1947 [25]. The majority of these individuals had their general cognitive ability assessed at ∼11 years of age using the MHT version 12. At a mean age of 69.5 years (SD 0.8), they were recruited to a study to determine influences on normal cognitive aging and underwent a series of cognitive tests, including re-taking the MHT [22, 26]. A general fluid (gf) cognitive ability score was derived from principal components analysis of six Wechsler Adult Intelligence Scale-III^{UK} (WAIS-III) [27] non-verbal subtests (matrix reasoning, letter number sequencing, block design, symbol search, digit symbol, and digit span backward), as described previously [28]. A general processing speed factor was similarly derived for the set of mental speed measures (symbol search, digit symbol, simple reaction time mean, choice reaction time mean, and inspection Time) [26] as described previously [28]. A general memory factor was derived from principal components analysis of the following subtests from Wechsler Memory Scale-III^{UK} (WMS-III) [29] and WAIS-III: logical memory I total recall score (A + B + B2), logical memory II delayed recall total score (A + B), spatial span forward and backward, verbal paired associates I (List A + B + C + D) and II (recall total score), letter-number sequencing, and digit span backward as described previously [30]. Crystallized cognitive ability (vocabulary-based) was assessed using the NART [24]. Cognitive measures were corrected for age at time of testing and gender prior to analysis. The gf was adjusted for prior cognitive ability using the MHT scores from age 11, thus providing a measure of relative cognitive change from age 11 to age 70. Both gf and age 11 MHT scores were adjusted for age in days at time of testing prior to the creation of the cognitive change measure. Cognitive change measures were extracted and standardized independently for males and females [16].

Aberdeen Birth Cohort 1936 (ABC1936)

ABC1936 consists of 498 (243 men and 255 women) relatively healthy surviving members of the Scottish Mental Survey 1947 [25]. The majority of these individuals had their general cognitive ability assessed at ∼11 years of age using the MHT version 12. At a mean age of 64.6 years (SD 0.9), they were recruited to a study to determine influences on normal cognitive aging and underwent a series of cognitive tests [21]. A general fluid (gf) cognitive ability score was derived from principal components analysis of Raven's Progressive Matrices, Digit Symbol, Uses of Common Objects, and Rey Auditory Verbal Learning Test (AVLT) [13]. Declarative memory was assessed by AVLT total score [31]. Crystallized cognitive ability (vocabulary-based) was assessed using the NART [24]. Cognitive measures were corrected for age at time of testing and gender prior to analysis. gf was adjusted for prior cognitive ability using the MHT scores from age 11, thus providing a measure of relative cognitive change from age 11 to age 64. Both gf and age 11 MHT scores were adjusted for age in days at time of testing prior to the creation of the cognitive change measure. Cognitive change measures were extracted and standardized independently for males and females [16].

Manchester and Newcastle Longitudinal Studies of Cognitive Ageing

The Manchester and Newcastle Longitudinal Studies of Cognitive Ageing began in 1983 with 6,063 (1,825 men and 4,238 women) individuals and documented longitudinal trajectories in older adults (44–93 years) for up to 20 years [32]. To create a general fluid cognitive ability (gf), empirical Bayes's estimates (EB) for each individual were obtained from a random effects model fitted by maximum likelihood (ML) to the standardized age-regressed residuals obtained for each gender from the Alice Heim 4 (AH4) parts 1 and 2 tests of general intelligence and the non-verbal Cattell Culture Fair test scores [13]. The AH4 parts 1 and 2 each consist of 65 problems. The AH4 part 1 consists of logic, arithmetic, and completion of number series and verbal comparisons. The AH4 part 2 consists of non-verbal problems in which participants must select among alternative solutions the correct completions of logical series defined by progressive mental rotation, or addition and subtraction, or other comparisons of line-drawn shapes. A general processing speed factor was created by a similar method using the Visual Search for letters and Savage (1984) Alphabet Coding Task tests. A general memory factor was derived from Verbal Free Recall for 30 words, Verbal Free Recall for 10 words, Cumulative Verbal Learning, Pictorial Recog-

nition Memory test, Memory for Shapes and Location, Propositions about people, Memory Circle. Individual EB estimates were obtained from the standardized age regressed residuals from each test using a one-factor model fitted by ML [33]. Crystallized cognitive ability (vocabulary) was assessed using the Mill Hill Vocabulary Test [34] corrected for age at time of testing and gender. Cognitive change measures were created independently for males and females by growth curve modeling as described in [16]. Briefly, growth curve models were estimated that took the 0 point on the age scale as 70 years and measured variation about it in units of 10 years. Data were available for up to four occasions of measurement.

DNA was extracted from whole blood for all cohorts. Ethical approval was obtained: for LBC1921 and LBC1936 from the Lothian Research Ethics Committee and for LBC1936 from Scotland's Multicentre Research Ethics Committee, for ABC1936 from the Grampian Research Ethics Committee and for the Manchester and Newcastle subjects from the University of Manchester Research Ethics Committee.

Creating Alzheimer's disease polygenic risk scores

The CAGES cohorts' members' DNA samples ($n = 3{,}511$ with cognitive data and DNA) were genotyped at the Wellcome Trust Clinical Research Facility using the Illumina 610-Quadv1 array (San Diego) [13]. Individuals were excluded based on unresolved gender discrepancy, relatedness, call rate (≤ 0.95), and evidence of non-Caucasian descent. SNPs were included in the analyses if they met the following conditions: call rate ≥ 0.98, minor allele frequency ≥ 0.01, and Hardy-Weinberg equilibrium test with $p \geq 0.001$. The first four components from a multidimensional scaling (MDS) analysis of the SNP data were extracted and used as covariates in the analyses to control for population stratification.

To obtain the data from which AD polygenic scores could be calculated, summary results were acquired from the Genetic and Environmental Risk for Alzheimer's disease (GERAD1) Consortium. This included 3,941 AD cases and 7,848 controls genotyped using the Illumina 610-quad chip, the Illumina HumanHap300 BeadChip, or the Illumina HumanHap550 Beadchip [4]. AD polygenic risk scores were created for each participant of the five CAGES cohorts using the method described elsewhere [35]. Briefly, all strand-ambiguous SNPs, SNPs with a minor allele frequency <0.02, and SNPs absent from the GERAD1 data were removed from each cohort. SNPs were then pruned to remove those in linkage disequilibrium (based on $r^2 > 0.25$ within a 200-SNP sliding window). SNPs that were identified as being called on the opposite strand to the GERAD1 data were flipped. Risk scores were then calculated for each individual in each cohort, using PLINK [36], by summing the log of the odds ratio from GERAD1, multiplied by the number of reference alleles carried by the individual. Missing SNPs were imputed based on the observed allele frequency in the cohort. A series of risk scores was created based on the inclusion of SNPs with varying AD association p-values: all SNPs, and SNPs with $p < 0.5$, $p < 0.1$, $p < 0.05$, or $p < 0.01$.

Statistical analyses

Partial correlations were calculated between the AD polygenic risk scores and the cognitive phenotypes described above. This was done within each of the five CAGES cohorts, correcting for the number of non-missing SNPs used to form the risk score, and population stratification (first four components from a MDS). Analyses were performed for risk scores calculated using each of the five SNP inclusion thresholds. Where cognitive phenotypes were derived separately for males and females, correlation analyses were performed separately for males and females. Correlation analyses were performed using IBM Statistical Package for the Social Sciences, Version 19.0 (SPSS Inc., Chicago, USA). Random effects meta-analyses of analyses of similar cognitive traits measured in the different cohorts were performed using Comprehensive Meta-Analysis, Version 2 (Biostat, Englewood, NJ, USA).

RESULTS

All cognitive traits were approximately normally distributed. At the varying SNP set criteria, the following range of SNPs across cohorts made up the scores: 119,702–121,500 (all SNPs), 60,924–61,718 ($p < 0.5$), 12,477–12,863 ($p < 0.1$), 6,372–6,583 ($p < 0.05$), and 1,359–1,422 ($p < 0.01$). SNP rs2075650 in the APOE locus, which was the top hit in both the GERAD1 AD GWAS ($p = 1.8 \times 10–157$) [4] and the CAGES cognitive aging GWAS ($p = 2.5 \times 10^{-8}$) [16], contributes to all scores.

MHT measured at age 11 in the Scottish cohorts was significantly positively correlated ($r = 0.050$, $p = 0.032$) with AD polygenic risk score generated only with SNPs with a p-value <0.1 (Table 1). No other significant correlations were found (Table 1).

Table 1
Meta-analysis correlations (with 95% CI) and significance between Alzheimer's disease polygenic risk scores (ADGRS) (calculated using different association *p*-values) and cognitive phenotypes

ADGRS: SNPs	Moray house test age 11 ($n = 1,835$)[a]	Moray house test ($n = 1,505$)[b]	General fluid ability ($n = 3,402$)	Memory[c] ($n = 3,392$)	General speed ability ($n = 2,515$)[d]	Crystallized ability[e] ($n = 3,482$)	Cognitive change ($n = 3,282$)
All SNPs	0.038 (−0.08–0.083) $p = 0.11$	0.016 (−0.082–0.11) $p = 0.75$	0.018 (−0.016–0.052) $p = 0.30$	−0.002 (−0.054–0.050) $p = 0.94$	0.025 (−0.014–0.064) $p = 0.21$	0.023 (−0.025–0.072) $p = 0.34$	0.003 (−0.031–0.038) $p = 0.85$
$p < 0.5$	0.035 (−0.013–0.084) $p = 0.16$	0.016 (−0.082–0.11) $p = 0.75$	0.019 (−0.017–0.055) $p = 0.30$	0.004 (−0.046–0.055) $p = 0.86$	0.024 (−0.016–0.063) $p = 0.24$	0.022 (−0.028–0.071) $p = 0.39$	0.000 (−0.034–0.035) $p = 0.98$
$p < 0.1$	**0.050 (0.004–0.096) p = 0.032**	0.018 (−0.075–0.11) $p = 0.71$	0.005 (−0.035–0.046) $p = 0.79$	−0.007 (−0.044–0.031) $p = 0.73$	0.007 (−0.034–0.048) $p = 0.74$	0.010 (−0.047–0.067) $p = 0.74$	−0.004 (−0.039–0.030) $p = 0.80$
$p < 0.05$	0.045 (−0.019–0.11) $p = 0.17$	0.018 (−0.073–0.11) $p = 0.70$	−0.004 (−0.045–0.037) $p = 0.86$	−0.025 (−0.075–0.025) $p = 0.32$	0.019 (−0.024–0.062) $p = 0.38$	−0.000 (−0.060–0.060) $p = 0.10$	−0.015 (−0.049–0.019) $p = 0.39$
$p < 0.01$	0.017 (−0.029–0.063) $p = 0.47$	0.015 (−0.042–0.072) $p = 0.60$	−0.005 (−0.039–0.028) $p = 0.76$	−0.017 (−0.065–0.031) $p = 0.49$	−0.017 (−0.08–0.046) $p = 0.59$	−0.005 (−0.044–0.034) $p = 0.80$	−0.026 (−0.026–0.008) $p = 0.13$

One *p*-value < 0.05 is in bold. All analyses were corrected for four multidimensional scaling components and number of non-missing genotypes used to calculate each risk score. [a]includes only Lothian Birth Cohort 1921 (LBC1921), Lothian Birth Cohort 1936 (LBC1936), and Aberdeen Birth Cohort 1936 (ABC1936). [b]includes only LBC1921 and LBC1936. [c]general memory ability used for: LBC1936 and the Manchester and Newcastle cohorts, Logical Memory used for LBC1921, and AVLT used for ABC1936. [d]includes only LBC1936 and the Manchester and Newcastle cohorts. [e]National Adult Reading Test used for LBC1921, LBC1936 and ABC1936; Mill Hill Vocabulary test used for the Manchester and Newcastle cohorts.

DISCUSSION

Polygenic risk scores for AD, created using a number of significance criteria, were not significantly associated with cognitive ability in later life or relative age-related cognitive change in the CAGES cohort. This indicates that, despite high frequency genetic variants accounting for approximately 24% of the variance of both AD and non-pathological cognitive aging, and 4–5% of the variance of both being accounted for by the *APOE* locus [14–16], the majority of the genetic variants might not overlap. This supports work from previous studies that found few significant effects of either single or multiple AD-associated genes on cognitive ability and or age-related cognitive decline in non-demented individuals [19, 38], although one study did find an association between *CR1* and cognitive decline [38]. The single significant result, of a positive association between one of the AD polygenic risk scores and childhood cognitive ability, in the Scottish cohorts, may be a type 1 error, given its relatively high p value. It requires replication in other childhood cohorts. It is possible that a more accurate AD polygenic risk score created using effect sizes generated from a GWAS of a larger number of individuals could be significantly associated with cognitive ability and cognitive aging in the CAGES cohort. A limitation of this study is that the cognitive tests were not exactly the same in each cohort. However, it is well documented that general factors derived from different test batteries rank people almost identically and that individual tests assessing the same cognitive domain are highly correlated [39]. For the cognitive aging traits, the English cohorts measured aging over a shorter period of time than the Scottish cohorts. However, the later-life change measured in the English cohorts will also have occurred in the Scottish cohorts. Therefore, all cohorts were appropriate for identifying associations with later-life cognitive aging. A second limitation is that a second AD cohort was not available to test whether or not a polygenic risk score for AD predicts AD in an independent AD cohort. In the future we plan to perform bivariate genome-wide complex trait analysis [40] to estimate the genetic correlation between AD in GERAD1 and cognitive aging in CAGES using genome-wide SNPs.

The results of this study indicate that the genetic etiologies of AD and non-pathological cognitive decline differ and that AD is not just the extreme end of a continuous spectrum of cognitive decline. We have >80% power to detect a correlation of $r = 0.05$ for the majority of the analyses and >90% power to detect a correlation of $r = 0.1$ for all analyses. However, it is possible that individuals in this study will go on to develop a variety of non-AD dementias, each with its own genetic etiology, thus reducing the power to identify an association between an AD genetic risk score and non-pathological cognitive decline. Although the *APOE* ε4 allele is a genetic risk factor for non-pathological cognitive aging in the CAGES cohorts [16], other genetic variants, not necessarily associated with AD, each with a very small effect, might ultimately contribute to the degree of cognitive decline that a non-demented individual experiences.

ACKNOWLEDGMENTS

We thank the cohort participants who contributed to these studies. Genotyping of the CAGES cohorts were supported by the UK's Biotechnology and Biological Sciences Research Council (BBSRC). Phenotype collection in the Lothian Birth Cohort 1921 was supported by the BBSRC, The Royal Society, and The Chief Scientist Office of the Scottish Government. Phenotype collection in the Lothian Birth Cohort 1936 was supported by Research Into Ageing (continues as part of Age UK's The Disconnected Mind project). Phenotype collection in the Aberdeen Birth Cohort 1936 was supported by BBSRC, the Wellcome Trust, and the Alzheimer's Research Trust. Phenotype collection in the Manchester and Newcastle Longitudinal Studies of Cognitive Ageing cohorts was supported by Social Science Research Council, Medical Research Council, Economic and Social Research Council, Research Into Ageing, Wellcome Trust and Unilever plc.

This study incorporated summary results from the GERAD1 genome-wide association study. GERAD1 acknowledgements: Cardiff University was supported by the Wellcome Trust, Medical Research Council (MRC), Alzheimer's Research Trust (ART) and the Welsh Assembly Government. ART supported sample collections at the Kings College London, the South West Dementia Bank, Universities of Cambridge, Nottingham, Manchester and Belfast. The Belfast group acknowledges support from the Alzheimer's Society, Ulster Garden Villages, N.Ireland R&D Office and the Royal College of Physicians/Dunhill Medical Trust. The MRC and Mercer's Institute for Research on Ageing supported the Trinity College group. The South West Dementia Brain Bank acknowledges support from Bristol Research into Alzheimer's and Care of the Elderly. The Charles Wolfson Charitable Trust supported the OPTIMA group. Washington University was funded by NIH grants, Barnes Jew-

ish Foundation and the Charles and Joanne Knight Alzheimer's Research Initiative. Patient recruitment for the MRC Prion Unit/UCL Department of Neurodegenerative Disease collection was supported by the UCLH/UCL Biomedical Centre. LASER-AD was funded by Lundbeck SA. The Bonn group was supported by the German Federal Ministry of Education and Research (BMBF), Competence Network Dementia and Competence Network Degenerative Dementia, and by the Alfried Krupp von Bohlen und Halbach-Stiftung. The GERAD1 Consortium also used samples ascertained by the NIMH AD Genetics Initiative. The KORA F4 studies were financed by Helmholtz Zentrum München; German Research Center for Environmental Health; BMBF; German National Genome Research Network and the Munich Center of Health Sciences. The Heinz Nixdorf Recall cohort was funded by the Heinz Nixdorf Foundation (Dr. jur. G.Schmidt, Chairman) and BMBF. Coriell Cell Repositories is supported by NINDS and the Intramural Research Program of the National Institute on Aging. We acknowledge use of genotype data from the 1958 Birth Cohort collection, funded by the MRC and the Wellcome Trust which was genotyped by the Wellcome Trust Case Control Consortium and the Type-1 Diabetes Genetics Consortium, sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Allergy and Infectious Diseases, National Human Genome Research Institute, National Institute of Child Health and Human Development and Juvenile Diabetes Research Foundation International. The work for this study was undertaken in The University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross council Lifelong Health and Wellbeing Initiative (G0700704/84698) and supported by researchers at the NIHR Queen Square Dementia BRU. Funding from the BBSRC, EPSRC, ESRC, and MRC is gratefully acknowledged.

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=1971).

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