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Cognitive gene risk profile for the prediction of cognitive decline in presymptomatic Alzheimer's disease

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ABSTRACT

Introduction: In cognitively normal (CN) older adults, high levels of Aβ-amyloid are associated with significant decline in cognition, especially episodic memory. Several genes have previously been associated with cognition, including *APOE*, *KIBRA*, *KLOTHO*, *BDNF*, *COMT*, *SPON1* and *CSMD1*. While some of this variation has been attributed to some of these genes individually, the combined effects of these genes on rates of cognitive decline, particularly in preclinical Alzheimer's Disease remain largely unknown.

Methods: To elucidate if risk alleles within these genes can be suitably combined to predict cognitive decline 127 CN older adults with elevated PET-ascertained Aβ-amyloid were included in a decision tree analysis to define a "Cognitive Gene Risk Profile" for decline in a verbal episodic memory composite.

Results: The episodic memory-derived Cognitive Gene Risk Profile defined four groups: *APOE* ε4+ Risk, ε4+ Resilient, ε4− Risk, ε4− Resilient, with the ε4+ Risk group declining significantly faster than all other groups (ε4+ Resilient, p = 0.0008; ε4− Risk, p = 0.025; ε4− Resilient, p = 0.0006). The ε4+ Risk group also declined significantly faster than all other groups on Global, Clinical Progression and Pre-Alzheimer's cognitive composites.

Discussion: The defined Cognitive Gene Risk Profile has potential utility in participant selection/stratification for

Abbreviations: AIBL, Australian Imaging Biomarkers and Lifestyle study of Ageing; CN, Cognitive Normal; Cog-GRP, Cognitive Gene Risk Profile; PACC, Pre-Alzheimer's Cognitive Composite

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preclinical AD trials that incorporate Aβ-amyloid and where decline in cognition is essential to determine therapeutic effectiveness.

Introduction

Evidence from prospective longitudinal cohort studies suggests that the pathological changes in Alzheimer's Disease (AD) commence decades before the onset of clinical symptomology [1]. Further, it has been established that higher levels of Aβ-amyloid (Aβ) in cognitively normal (CN) older adults is associated with accelerated decline in cognition [2]. As such, cerebrospinal fluid (CSF) and imaging biomarkers of Aβ are used to define the preclinical stage of AD [3,4]. However, at the preclinical stage of AD there is considerable interpersonal variability in the rate of cognitive decline, suggesting that while Aβ is a necessary condition for AD, other factors influence the relationship between this biomarker and clinical disease progression. Cognition has been shown to be both highly heritable and highly polygenic [5] and allelic variation in several genes associated with cognition has been shown to explain some variation in cognitive function in older adults and in Aβ related cognitive decline in early AD [6–8]. Thus suggesting that genetics could help inform and predict rates of cognitive decline and identify groups of CN older adults that are at a higher risk of a more rapid decline in cognition.

There have been several individual genes associated with cognitive performance and decline. The major genetic risk factor for AD, the ε4 allele of apolipoprotein E (*APOE*) [9], has been consistently associated with accelerated rates of episodic memory decline and hippocampal atrophy (reviewed in [10]). The non-synonymous rs6265 (Val66Met) single nucleotide polymorphism (SNP) in the brain derived neurotropic factor (*BDNF*), has been linked with altered rates of decline in several cognitive domains, and hippocampal atrophy [7,8]. A further non-synonymous SNP that regulates dopamine availability in the central nervous system, rs4680 (Val158Met) within Catechol-O-methyltransferase (*COMT*), has also been associated with cognitive performance [11]. The Klotho gene (*KL*), initially discovered in transgenic mice with a phenotype resembling human aging [12], has a functional variant, *KL*-VS that has been associated with life expectancy [13], global cognition [14], processing speed [14], and brain volume [15].

A further gene, *KIBRA*, that encodes the KIdney and BRAin expressed protein has recently been shown to be involved in the mediation of tau-induced memory loss and synaptic plasticity [16]. Allelic variation in the *KIBRA* gene, specifically a substitution of C for T in the 9th intron (rs17070145), has been reported to be associated with memory performance [17], hippocampal atrophy [18] and measurable differences in brain activation [17]. We have described recently how this gene contributes to moderating Aβ driven cognitive decline [19]. Additionally, several SNPs in the *CSMD1* (CUB and Sushi Multiple Domains 1) gene, involved in the regulation of complement and inflammation [20], have been associated with episodic memory and general cognition in a cognitively normal sample [21]. Finally, multiple SNPs within the Spondin 1 (*SPON1*) gene, involved in the processing of amyloid precursor protein (APP) [22], have been associated with disease severity [23] and rates of cognitive decline [24], though only in AD individuals.

Several studies have investigated the extent to which combinations of genes can influence cognitive decline and clinical progression in AD [25–28]. However, most of these studies focused on genes shown previously to be associated with risk for AD, with gene weighting based on AD risk [25,26]. Thus these polygenic approaches may have resulted in exclusion of genes associated with cognitive performance, or if included, their influence diluted due to a disease risk based weighting [26]. Further, few studies have taken brain Aβ burden into consideration and investigated combining genes associated with cognitive performance in preclinical AD [8,29].

This study hypothesised that combining genes shown to be associated with cognition would explain variance in Aβ related cognitive decline in preclinical AD. This study aimed to combine these genes into a straightforward profile able to discriminate individuals based on cognition, and particularly episodic memory, which is one of the earliest cognitive domains to decline [30]. The profile was created in CN older adults, signified at risk of cognitive decline based on brain imaging biomarkers, enrolled in the Australian Imaging, Biomarkers and Lifestyle (AIBL) Study. Extensive 18-monthly assessment, including cognitive and neuroimaging, within the AIBL Study allows for the longitudinal evaluation of this profile. Such a genetic profile could be easily implemented for the identification of individuals with accelerated rates of cognitive decline, which could have utilisation for clinical trial design, leading to more efficient clinical trials and secondary prevention studies.

Material and methods

Study participants

One hundred and thirty-three CN biomarker positive (based on brain imaging) older adults enrolled in the AIBL Study, a prospective longitudinal study of ageing, were included in this study. The study design, enrolment process, neuropsychological assessments, and diagnostic criteria of the AIBL Study have been previously described [31]. Approval of the AIBL Study has been granted by each of the ethics committees of each of the member institutions: Austin Health, St Vincent's Health, Hollywood Private Hospital, and Edith Cowan University, and all volunteers gave informed written consent. Assessments occurred every 18 months, with cognitive, neuroimaging and laboratory assessment achieved within 3 months of each other.

Cognitive measures

Burnham et al. previously calculated cognitive composite scores using the AIBL neuropsychological test battery and the Clinical Dementia Rating (CDR) scale [32]. These composite scores were used in this study to assess cognitive performance. The AIBL neuropsychological test battery consists of Mini-Mental State Examination (MMSE), Clock Drawing Test, California Verbal Learning Test-Second edition (CVLT-II), Logical Memory I and II (LMI; LMII; Story A only), D-KEFS verbal fluency, a 30-item version of the Boston Naming Test (BNT), Wechsler Test of Adult Reading (WTAR), Digit Span and Digit Symbol-Coding subtests of the Wechsler Adult Intelligence Scale-Third edition (WAIS-III), the Stroop task (Victoria version), and the Rey Complex Figure Test (RCFT) [31]. Briefly, a verbal episodic memory composite (CDR sum of boxes (CDR_{SB}), LMII, CVLT-II recognition false positives ($CVLT_{FP}$) and long delay free recall ($CVLT_{LDFR}$)) was used as the primary cognitive measure for defining groups with different rates of decline. Groups defined by decline in episodic memory were also assessed against a global cognition composite (CDR_{SB}, MMSE, LMII, $CVLT_{FP}$ and Clock), and a composite measure of clinical progression (CDR_{SB}, MMSE) [32]. In addition, the Pre-Alzheimer's cognitive composite (PACC) previously calculated by Donohue et al. was also investigated [33]. In the calculation of the statistically driven composites there were corrections for age, sex, years of education, premorbid IQ (WTAR-estimated WAIS-III Full Scale Intelligence Quotient (FSIQ)) and depressive symptoms (Geriatric Depression Scale (GDS)) [34]. Five cognitive assessment time points were used: baseline, 18, 36, 54 and 72 months.