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Translational gene mapping of cognitive decline

Beth Wilmot [a,*], Shannon K. McWeeney [b], Randal R. Nixon [c], Thomas J. Montine [d], Jamie Laut [e], Christina A. Harrington [f], Jeffrey A. Kaye [e], Patricia L. Kramer [a,e]

[a] *Department of Molecular and Medical Genetics, Oregon Health and Sciences University, Portland, OR, United States*
[b] *Division of Biostatistics, Department of Public Health and Preventive Medicine, Oregon Health and Sciences University, Portland, OR, United States*
[c] *Department of Pathology, Oregon Health and Sciences University, Portland, OR, United States*
[d] *Department of Pathology, University of Washington, Seattle, WA, United States*
[e] *Department of Neurology, Oregon Health and Sciences University, Portland, OR, United States*
[f] *Gene Microarray Shared Resource, Oregon Health and Sciences University, Portland, OR, United States*

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Abstract

The ability to maintain cognitive function during aging is a complex process subject to genetic and environmental influences. Alzheimer's disease (AD) is the most common disorder causing cognitive decline among the elderly. Among those with AD, there is broad variation in the relationship between AD neuropathology and clinical manifestations of dementia. Differences in expression of genes involved in neural processing pathways may contribute to individual differences in maintenance of cognitive function.

We performed whole genome expression profiling of RNA obtained from frontal cortex of clinically non-demented and AD subjects to identify genes associated with brain aging and cognitive decline. Genetic mapping information and biological function annotation were incorporated to highlight genes of particular interest. The candidate genes identified in this study were compared with those from two other studies in different tissues to identify common underlying transcriptional profiles. In addition to confirming sweeping transcriptomal differences documented in previous studies of cognitive decline, we present new evidence for up-regulation of actin-related processes and down-regulation of translation, RNA processing and localization, and vesicle-mediated transport in individuals with cognitive decline.

Keywords: Cognitive reserve; Cognitive decline; Alzheimer's disease; Healthy brain aging; Gene expression profiling; Synaptic plasticity; Intersectin 1

1. Introduction

Finding the genes involved in a complex phenotype such as healthy brain aging is challenging due to the biological complexity of the underlying genetic and environmental components. A primary challenge is presented by the heterogeneity of the phenotype itself. Individuals exhibit broad variation in the ability to maintain cognitive function during the aging process. Clinically significant cognitive decline in the elderly is most commonly caused by Alzheimer's disease (AD). Diagnostic neuropathological features of AD include extracellular amyloid plaques and intracellular neurofibrillary tangles (NFTs). However, there is considerable neuropathological heterogeneity across individuals with clinical AD and individuals with no clinical signs of dementia, making division into "cases" and "controls" based on neuropathology problematic. In particular, there is tremendous variability in the relationship between the amount and location of AD neuropathology in the brain

* Corresponding author at: Department of Molecular and Medical Genetics, L103, Oregon Health and Sciences University, 3181 SW Sam Jackson Park Road, Portland, OR 97239, United States. Tel.: +1 503 494 4362; fax: +1 503 494 7499.
E-mail addresses: wilmotb@ohsu.edu (B. Wilmot), mcweeney@ohsu.edu (S.K. McWeeney), nixonr@ohsu.edu (R.R. Nixon), tmontine@u.washington.edu (T.J. Montine), lautj@ohsu.edu (J. Laut), harringc@ohsu.edu (C.A. Harrington), kaye@ohsu.edu (J.A. Kaye), kramer@ohsu.edu (P.L. Kramer).

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and the clinical manifestation of AD symptoms (Schmitt et al., 2000). Individuals without loss of cognitive function may tolerate high levels of brain tissue injury presumptively indexed by amyloid plaques and NFTs, while others demonstrate loss of cognition with similar or even lower levels of lesion burden. These differences in protection from the effects of AD neuropathology may be due to genetic differences at several levels including the expression of gene products.

According to cognitive reserve theory, individuals differ in their capacity to maintain normative cognitive function and, accordingly, those with greater capacity are better equipped to delay or circumvent the damaging effects of brain lesions that in other less equipped individuals, lead to clinical manifestations of AD. The theory postulates that this natural variability across individuals is due to differences in neural processing mechanisms (Katzman et al., 1988). The physiological basis of this mechanism is unknown, although it is likely to reflect environmental as well as genetic factors (Lee, 2003; Scarmeas and Stern, 2004). Genetic variations can contribute to individual differences in normal cognitive function. Interaction between these genetic differences and environmental factors over the lifespan can amplify variation in cognitive function later in life.

There is growing evidence that variation in the quantity of a gene product, rather than simply presence or absence of product, can be responsible for the subtle effects of complex traits (Farrall, 2004; Jais, 2005; Singleton et al., 2004). Several recent studies have shown that variation in gene expression is heritable (Cheung et al., 2003; Morley et al., 2004; Yan et al., 2002) and can be mapped as a quantitative trait (Morley et al., 2004). We suggest that differences in expression of genes in neural processing pathways are responsible for differences in the maintenance of cognitive function, and at least in part account for an important component of cognitive reserve.

To address this assertion, we performed whole genome expression profiling on a set of well characterized, clinically non-demented and AD subjects in order to identify genes, or gene pathways, that contribute to cognitive decline. Subjects were stratified into four groups based on cognitive status prior to death (non-demented or AD) and neuropathological status defined by three categories of NFT burden (Braak stage I/II, III/IV, and V/VI) (Fig. 1A). Non-demented subjects were represented in all three Braak-stage categories, whereas AD subjects were represented only in Braak stage V/VI. We designed three comparisons to test three hypotheses (Fig. 1B). In the first comparison, we postulated that all non-demented subjects, taken as a whole (groups 1–3), would exhibit different gene expression profiles compared to AD subjects (group 4), irrespective of NFT burden. We refer to this as the extreme cognitive phenotypes hypothesis (hypothesis I). In the second comparison, we proposed that individuals with lower NFT burden (Braak stage I/II and III/IV, groups 1 and 2) would display different expression profiles than those with higher NFT burden (Braak stage V/VI, groups 3 and 4), irrespective of cognitive ability. We refer to this as the neuropathologic process hypothesis (hypothesis II). In the third comparison, we postulated that expression profiles in non-demented subjects with a high NFT burden (group 3) would differ from those in AD subjects with similar NFT pathology (group 4). We refer to this as the cognitive reserve hypothesis (hypothesis III).

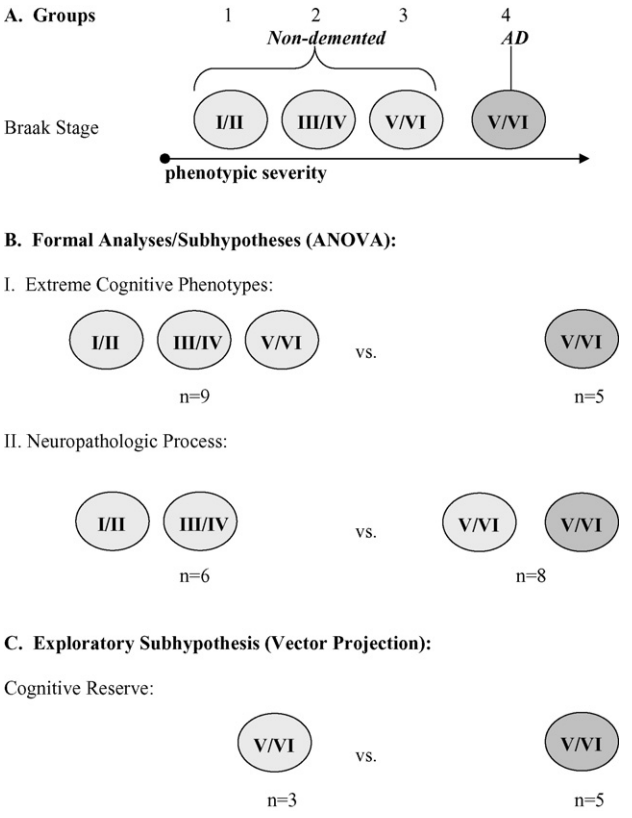

Fig. 1. Subject comparisons. (A) Subjects were separated into four groups based on Braak stage and cognitive health. (B) Two separate ANOVA comparisons performed. (I) Extreme cognitive phenotypes were assessed by combining all non-demented subjects compared to AD subjects; (II) neuropathological process was assessed by comparing low Braak stage subjects with high Braak stage subjects regardless of cognitive ability; (III) cognitive reserve was assessed using vector projection comparing non-demented, Braak V/VI subjects with AD subjects.

We interpret our gene expression results in the context of prior evidence from genetic linkage studies and biological function annotations to identify possible candidate susceptibility genes. Furthermore, since genes that are differentially expressed across tissues involved in AD pathology would provide valuable insight into common underlying genetic mechanisms in brain aging, we compared genes identified in this study, using frontal cortex, with genes identified in two other expression studies using hippocampus (Blalock et al., 2004) and entorhinal cortex (Dunckley et al., 2005). Genes that were differentially expressed across the three studies, emphasizing common themes of pathology underlying dementia, are key candidates for further studies of genetic risk factors for cognitive decline.