Allelic Distributions of APOE, BDNF, COMT, IDE, and CLU: Toward Neurogenetic Analyses of Healthy Aging, Mild Cognitive Impairment, and Alzheimer’s Disease

Bonnie P. Whitehead1,4, David Vergote2, G. Peggy McFall1,5, Stuart W. S. MacDonald5,7, Richard Camicioli3,6, Kathy Lechelt4,6, Jack Jhamandas3, David Westaway2,3, Roger A. Dixon1,5

University of Alberta: 1Department of Psychology, 2Centre for Prions and Protein Folding Diseases, 3Division of Neurology, 4Division of Geriatric Medicine, Victoria Longitudinal Study; 5Edmonton: Glenrose Rehabilitation Hospital; 6University of Victoria: Department of Psychology

INTRODUCTION

Growing clinical research interest has been aimed towards identifying genetic, epigenetic, and environmental markers that influence aging-related diseases, including neurodegenerative conditions such as Alzheimer’s Disease (AD).

This is an interdisciplinary initiative of several groups, including the University of Alberta-based Victoria Longitudinal Study (VLS) and the Centre for Prions and Protein Folding Diseases (CPPFD), as well as Glenrose Rehabilitation Hospital (GRH).

The present poster reports ongoing interdisciplinary research on promising linkages among select genetic markers, clinical status, and neurocognitive performance in Healthy Aging, Mild Cognitive Impairment (MCI) and AD.

The selected genetic loci include Apolipoprotein E (ApoE), Brain Derived Neurotrophic Factor (BDNF), Catechol-O-Methyl Transferase (COMT), Insulin Degrading Enzyme (IDE), and Clusterin (CLU).

The ApoE gene has been associated with cognitive impairment, increased risk of dementia and AD.

COMT codes for a protein which degrades dopamine in the synaptic cleft. COMT protein activity is known to be an important link between the dopamine system and cognitive aging.

BDNF may play a role in learning and memory performance, and is known to be down-regulated in response to long-term beta amyloid exposure. Risk for clinical impairment and AD may vary according to BDNF alleles present.

IDE may degrade monomeric beta amyloid. Neuronal IDE expression is decreased in the brains of severe AD patients, making IDE a possible target for therapeutic interventions.

CLU has been associated with key aspects of AD pathology, including known roles in lipid and cholesterol metabolism and beta amyloid clearance.

GOALS

Assemble an interdisciplinary team for investigating genetic and environmental factors in Healthy Aging, MCI, and AD.

The present specific goals are to collect biosamples from these three clinical groups, perform DNA extraction and genotyping, and explore associations among identified genetic markers, clinical status, and neurocognitive performance and trajectories.

METHOD

We report progress in two related human data collections, both involving clinical aging populations, saliva samples (for initial genetic analysis), and neurocognitive batteries.

A collaborative initiative with the GRH is currently underway. Specifically, a saliva sample and a short neurocognitive and motor battery will be collected from ~100 individuals (ages 55-85) with AD, as recruited from the GRH Geriatric Clinic.

Data from the AD sample will be compared with genetic data from a corresponding collection of healthy aging and MCI participants enrolled in an ongoing epidemiological study (the VLS). We focus on data from this study, as derived from the longitudinal samples shown in Fig. 1.

New VLS genetic information will be merged with data from all three main VLS cohorts (see Fig. 1). We will examine genetic predictors of concurrent clinical status (Healthy Aging, MCI) and long-term longitudinal trajectories in multiple neurocognitive and health domains.

DISCUSSION

This project takes place in the context of other potential larger scale initiatives for this team. Goals include:

To make novel discoveries in the biological and clinical sciences of healthy aging, preclinical AD, and AD patients.

To assemble a framework of researchers and clinicians that will form the basis for a trans-Alberta consortium that will continue and expand beyond the present project.

Information on the environmental, genetic, biological and cognitive natural history of AD is invaluable towards identifying at-risk groups, planning interventions, and developing treatments. Interdisciplinary collaboration will increasingly make more data available.

FUNDING ACKNOWLEDGMENTS

We appreciate support from Alberta Health Services and the Faculty of Medicine and Dentistry, as well as from the University Hospital Foundation, CPPFD and VLS NIH. We also acknowledge the special contributions of CPPFD and VLS staff, especially Karrie Darichuk, Correne DeCarlo, Jill Friesen, and Terry Perkins.

CURRENT DATA

- Biosamples have been collected from n=700 VLS participants (ages 61-97 years). Genomic DNA have been extracted from 696 samples, and processed for genotypes APOE, COMT and BDNF.

- To date, n=117 samples have been processed for APOE and n=175 for CLU.

- Allelic distributions correspond to those observed in older adult samples.

- Risk Factor Alleles: Substantial portion of carriers were identified:
  - BDNF: 33.8% are carriers of the adenine (A) allele.
  - COMT: 77.6% are carriers of the guanine (G) allele.
  - APOE: 28.4% are carriers of the ε4 allele (23.4% - ε2).
  - CLU: 65.7% are carriers of the thymine (T) allele.
  - IDE: 78.6% are carriers of the cytosine (C) allele.

- Protection Factor Allele: 17.1% are carriers of APOE ε2 (12.1% - ε4).

- Future analyses will examine allelic distributions within normal aging, MCI, and AD groups.

- APOE ε2 will be tested within a VLS Cognitively Elite (“Superaging”) group.

![Image](image1.png)

VLS Sample 1 (b. 1907-1920; now aged 73-103 years). Currently, n = 61 specimens genotyped.

![Image](image2.png)

VLS Sample 2 (b. 1909-1939, now aged 67-97 years). Currently, n = 224 genotyped.

![Image](image3.png)

VLS Sample 3 (b. 1916-1946, now aged 61-91 years). Currently, n = 408 genotyped.

![Image](image4.png)

The diagram (Fig. 2) presents the PCR RFLP analysis for the 3 principal genes examined in this study. We represent the amplicon with the theoretical cleavage sites (left), the theoretical profiles for each genotype (middle), and the actual RFLP gels obtained (right). The restriction enzymes used are HinfI for APOE and NlaIII for BDNF and COMT.

![Image](image5.png)

VLS Sample 1990s - 2000s - 2010s Figure 1

![Image](image6.png)

APOE

![Image](image7.png)

BDNF

![Image](image8.png)

COMT

![Image](image9.png)

CLU

Legend: APOE and NlaIII for BDNF and COMT.