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

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INTRODUCTION

- Growing clinical research interest has been aimed towards identifying variation in genetic, epigenetic, and environmental markers that may 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 Apolipoprotien 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.

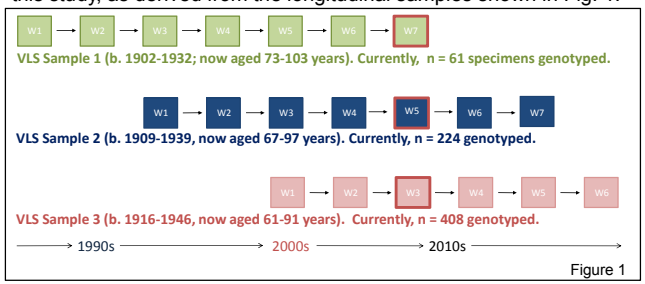

Figure 1

- 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.

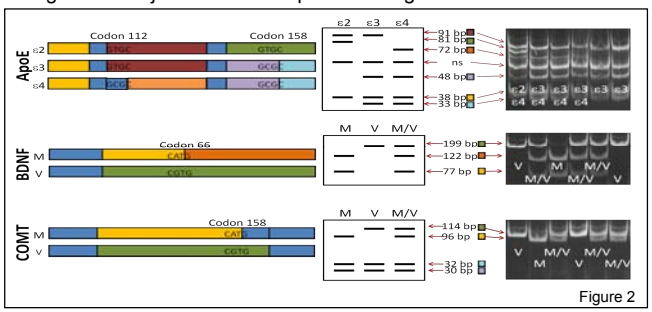

Figure 2

- 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 HhaI for *ApoE* and NlaIII for *BDNF* and *COMT*.

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 *IDE,* and n=175 for *CLU*.

BDNF	#	%
A	29	4.2
A/G	206	29.6
G	461	66.2
Total	696	100

COMT	#	%
A	156	22.4
A/G	371	53.3
G	169	24.3
Total	696	100

APOE	#	%
ε2	40	5.8
ε3	414	59.5
ε4	14	2.0
ε2/ε3	44	6.3
ε2/ε4	35	5.0
ε3/ε4	149	21.4
Total	696	100

CLU rs11136000	#	%
C	60	34.3
T/C	105	60.0
T	10	5.7
Total	175	100

IDE rs6583817	#	%
C	21	18.0
T/C	71	60.7
T	25	21.3
Total	117	100

LEGEND: *BDNF* and *COMT* snp
Purine Bases: A = Adenine; G = Guanine → Amino Acids: Met = Methionine; Val = Valine

- 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.

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.

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