The relationship between early Alzheimer’s Disease, Apolipoprotein E genotyping & Hippocampal MRI Volumes

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Thesis submission for the degree of Master of Philosophy (Clinical Epidemiology), University of Newcastle, Australia.

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Declarations:

Statement of Originality:

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to this copy of my thesis, when deposited in the University Library, being made available for loan and photocopying subject to the provisions of the Copyright Act 1968.

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**Statement of Collaboration:**

I hereby certify that the work embodied in this thesis has been done in collaboration with another researcher, Dr Stuart Slater, senior radiologist, Hunter Imaging Group, Newcastle Australia, whose input involved performing all cerebral MRI scanning and associated medial temporal lobe volume estimations conducted on the research subjects in this thesis.

Signed

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Bernard Anthony Walsh

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**Statement of Authorship:**

I hereby certify that the work embodied in this thesis contains published work of which I am a joint author. As part of thesis I provide the written statement, endorsed by my principal supervisor Professor Balakrishnan Nair, School of Medicine and Public Health, University of Newcastle, that I was the primary contributor and author of these publications.

Signed

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Bernard Anthony Walsh
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Hunter New England Health Service
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List of Abbreviations:

Amnesic Mild Cognitive Impairment Syndrome  Amnesic MCI
ALlele FREquency Database (US Nat. Science Foundation)  ALFRED
Alzheimer’s Disease  AD
One Way Analysis of Variance  ANOVA
Amyloid Precursor Protein  APP
Apolipoprotein E  Apo E
Apolipoprotein E epsilon 2 allele  ApoE ε2
Apolipoprotein E epsilon 3 allele  ApoE ε3
Apolipoprotein E epsilon 4 allele  ApoE ε4
Apolipoprotein E2 protein isoform (coded by ApoE ε2 allele)  Apo E2
Apolipoprotein E2 protein isoform (coded by ApoE ε3 allele)  Apo E3
Apolipoprotein E2 protein isoform (coded by ApoE ε4 allele)  Apo E4
Cerebral Spinal Fluid  CSF
Clinical Dementia Rating scale  CDR
FluoroDeoxyGlucose  FDG
Medial Temporal Lobe (of the cerebrum)  MTL
Magnetic Resonance Imaging  MRI
Dementia of the Alzheimer’s Type  DAT
Mini Mental State Examination  MMSE
Positron Emission Tomography  PET
Pittsburgh Compound-B  PIB
Relative Ratio  RR
Single Photon Emission Computerised Tomography  SPECT
Tau family of intraneuronal proteins  Tau
Vascular Dementia  VasD
Abstract:

This thesis attempts to improve the clinical probability of correctly staging the degree of Alzheimer’s Disease (AD) neuropathology in an individual presenting with the syndrome of early Dementia, by exploring the relationship between the known subtypes of the cerebral protein Apolipoprotein E (ApoE) and the extent of AD neuropathology in such persons, using the surrogate of cerebral MRI volume loss within the Medial Temporal Lobe (MTL) regions as the maker of severity of AD neuropathology.

In this thesis Early Dementia is defined as “CDR 1.0” using the Clinical Dementia Rating scale (CDR), this being the classification in most common use by Dementia clinicians. The research subjects were drawn from CDR 1.0 persons residing within the community (as opposed to more serve dementia persons typically needing to reside within assisted care programs and who typically have more advanced neurodegeneration). These subjects are the most likely group where improved definition of the degree of neurodegeneration within an early AD individual would be of most clinical use.

No demonstrable relationship between the ApoE ε4 allele and increasing MTL volume loss in early AD was found in the research studies of this thesis and hence the presence of one or more ε4 alleles cannot be used by the clinician to estimate pathological disease load within an equivalent degree of cognitive impairment in early AD.

One peer reviewed medical literature publication and one published abstract resulted from this thesis work.