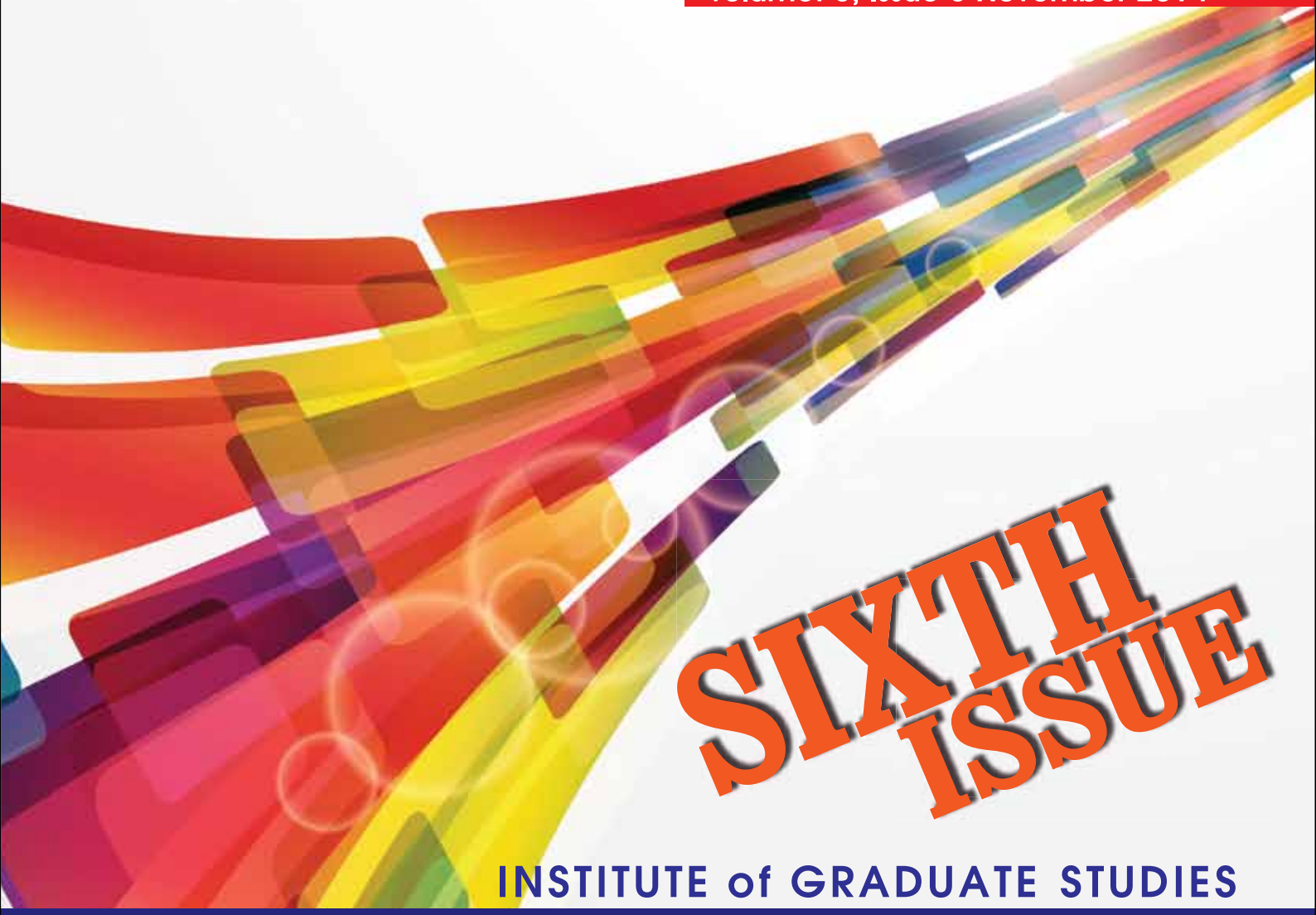
UNIVERSITI TEKNOLOGI MARA

THE DOCTORAL RESEARCH ABSTRACTS

Volume: 6, Issue 6 November 2014



SIXTH ISSUE

INSTITUTE of GRADUATE STUDIES

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Title :
Development Of An Allele-Specific Polymerase Chain Reaction Genotyping Test And Association Of Selected Single Nucleotide Polymorphisms And Analytes With The Risk Of Alzheimer's Disease

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The incidence of Alzheimer"s disease (AD) is expected to increase exponentially as the population ages. Continuing research in this area is essential to better understand this disease and develop strategies for prevention and treatment. Recent genome-wide association studies have identified several novel loci as genetic risk factors of AD. Previous studies also suggest the total plasma homocysteine (tHcy) level and its biological determinants such as folate and vitamin B_{12} contribute to the risk of AD. Some of them highlight the correlation between AD risk and genetic polymorphisms of methylenetetrahydrofolate reductase (*MTHFR*) and transcobalamin (*TCN II*) since they are directly associated with the Hcy metabolism. Replication studies of these loci are performed actively in developed countries. Thus, the present study is focused on a selected Malaysian population. As genetic research in developing countries is often limited by lack of funding and expertise, this study has also developed a cost-effective polymerase chain reaction (PCR) based technique to determine these single nucleotide polymorphisms (SNPs). The study was conducted with the approval of human ethic committees. An allele-specific PCR method was developed to detect SNPs of Top 10 Alzgene Results (updated 18 April 2011), *MTHFR* rs1801133, *MTHFR* rs1801131 and *TCN II* rs1801198. Validation was by direct DNA sequencing. A

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hundred-and-twelve cases and a hundred-and-nineteen controls were successfully recruited and analyzed for the selected SNPs and analytes. Cross tabulation analyses and logistic regression were performed in four different models. Genetic analyses showed that APOE ε4, *APOE* rs429358, *ABCA7* rs3764650, *MS4A4E* rs670139, *MS4A6A* rs610932, and *CD2AP* rs9349407 were statistically significantly associated with AD risk. The distribution of all selected SNPs was also determined after stratifying all samples by the presence of *APOE ε4* copy. In the stratified samples, statistically significantly different values were observed only in subjects without *APOE ε4* copy for *ABCA7* rs3764650 and *MS4A4E* rs670139. The AD risk of a person with GG genotype for *ABCA7* rs3764650 is increased to around 3.7-fold in model I and 5.2-fold in model III. Whereas, the AD risk of a person with AA genotype for *MS4A4E* rs670139 is increased to around 3.3-fold in model I and III. The mean tHcy levels were statistically significantly higher in cases than in controls while the mean serum holotranscobalamin (holoTC) levels were statistically significantly lower in cases than in controls. The logistic regression analysis showed that the *APOE* rs429358 is the main predictor variable. Other significant predictor variables were age at assessment, social class, holoTC, *ABCA7* rs3764650, *MS4A6A* rs610932, folate and LDL. The combination of them significantly predicted 35.8% of variance in the model. The developed method will enable researchers to study AD-related SNPs using an inexpensive method. Our findings show that the significant SNPs may influence the AD risk in the population. It is plausible that the effect of other SNPs on AD risk is specific to certain ethnic group or that effect is not large enough to be identified reliably by a cohort of our size. To the best of our knowledge, this is the first study aimed to determine the potential contribution of the SNPs to AD in a Malaysian population.