Polygenic Disease: A Study of Genetic Risk in an Australian Stroke Population

The Adelaide Genetic Stroke Study

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Thesis Abstract

Twin, family and animal studies support this thesis that ischemic stroke is a polygenic disease. The magnitude of this predisposition varies according to stroke subtype, with the greatest risk associated with lacunar and atherothromboembolic stroke. To date, the precise genetic determinants remain unknown.

The primary aim of this thesis was to determine the risk of ischemic stroke associated with eight single nucleotide polymorphisms (SNPs) that were selected using a candidate gene approach: Paraoxonase (PON1) –107T/C and M54L, Glycoprotein 1b 145Thr/Met, Glycoprotein IIb/IIIa PlA1/A2, β fibrinogen –148 C/T, Prothrombin 20210 G/A, Tissue Plasminogen Activator (TPA) –7,351 C/T and Plasminogen Activator Inhibitor (PAI-1) 5G/4G. This thesis also aimed to determine the relevance of each SNP to ischemic stroke subtypes and to determine the effect of interaction between each SNP and known cerebrovascular risk factors.

The objectives were met using a case-control study that recruited hospital inpatients with a diagnosis of acute ischemic stroke. Patients were evaluated for known cerebrovascular risk factors and classified for stroke subtype. A cerebrovascular risk factor profile was also determined in a randomly selected, age and gender matched control group. The SNP genotypes were determined using a polymerase chain reaction (PCR) method. Logistic regression was used to determine the risk of ischemic stroke associated with each SNP.

During a 26-month period, 182 patients and 301 non-hospitalised controls consented to participate. In a multivariate model that adjusted for important confounders, a 1.9-fold (95%CI 1.01-3.6) increased risk of ischemic stroke was associated with the TPA –7,351 TT genotype. This association, however, was not significant in a multivariate model that incorporated all potential confounders (OR 1.8, 95%CI 0.9-3.4). In a subgroup analysis, a statistically significant 2.6 and 2.4-fold increased risk of lacunar

stroke was associated with the TPA –7,351 TT and PON1 -107 CC genotypes respectively. No other association or effect of interaction was observed.

The findings suggest that TPA –7,351 C/T and PON1 -107 T/C SNP's may play a role in the pathogenesis of lacunar stroke. Confirmation by a larger study of greater statistical power is required, which may then provide a better means to predict the risk of lacunar stroke.

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Declaration

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 is made in the text.

I give consent to this copy of my thesis, when deposited in the University Library, being available for loan and photocopying.

Signed:..... ..... Date: 24/2/04.....

Conference Presentations

Poster Presentation:
"Polygenic Disease: A Study of Genetic Risk in an Australian Stroke Population" Australasian Association of Neurologists Annual Scientific Meeting, Adelaide, May 2000.

Poster Presentation:
"Polygenic Disease: A Study of Genetic Risk in an Australian Stroke Population" Australian Neuroscience Society, 23rd Annual Scientific Meeting, Adelaide, January 2003.

Platform Presentation:
"Tissue Plasminogen Activator –7,351 Enhancer Polymorphism is a Risk Factor for Lacunar Stroke". The Stroke Society of Australasia Annual Scientific Meeting, Sydney, September 2003.
Recipient of the "New Investigator Award for Scientific Research"

Platform Presentation:
"Tissue Plasminogen Activator –7,351 Enhancer Polymorphism is a Risk Factor for Lacunar Stroke". The Queen Elizabeth Hospital Research Day, Adelaide, October 2003.
Recipient of the "Best Higher Degree Research Award" and the "Allan Kerr Grant Most Outstanding Postgraduate Learner Award".

Platform Presentation:
"Tissue Plasminogen Activator –7,351 Enhancer Polymorphism is a Risk Factor for Lacunar Stroke". ASMR 42nd National Scientific Conference, Adelaide, November 2003.

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Abbreviations

Adenosine	A
Adenosine Diphosphate	ADP
Computerised Tomography	CT
Cytosine	C
Deoxyribonucleic Acid	DNA
Diastolic Blood Pressure	DBP
Disability Adjusted Life Year	DALY
Glycoprotein	Gp
Guanine	G
High Density Lipoprotein	HDL
Human Platelet Alloantigen	HPA
Lacunar Syndrome	LS
Leucine	L
Low Density Lipoprotein	LDL
Magnetic Resonance Imaging	MRI
Messenger Ribodeoxynucleic Acid	MRNA
Metaloproteases	MMP
Methionine	M
National Heart Foundation	NHF
North East Melbourne Stroke Incidence Study	NEMESIS
Oxfordshire Community Stroke Project	OCSP
Paraoxonase	PON1
Partial Anterior Circulation Syndrome	PACS
Patent Foramen Ovale	PFO
Perth Community Stroke Study	PCSS
Plasminogen Activator Inhibitor	PAI
Polymerase Chain Reaction	PCR
Population Research and Outcome Studies	PROS
Posterior Circulation Syndrome	PCS

Ribonucleic Acid	RNA
Sequence Specific Primer Polymerase Chain Reaction	SSP-PCR
Sibling Transmission Disequilibrium Test	S-TDT
Single Nucleotide Polymorphism	SNP
Spontaneously Hypertensive Rat	SHR
Stroke Prone Spontaneously Hypertensive Rat	SP-SHR
Systolic Blood Pressure	SBP
The Trial of ORG 10172 in Acute Stroke Treatment	TOAST
Threonine	Thr
Thymidine	T
Tissue Plasminogen Activator	TPA
Total Anterior Circulation Syndrome	TACS
Transcription factor IID	TFIID
Transient Ischemic Attack	TIA
Transmission Disequilibrium Test	TDT
World Health Organization	WHO