ASCERTAINMENT, DIAGNOSTIC EVALUATION AND GENE MAPPING OF SOUTH AUSTRALIAN FAMILIES WITH POSSIBLE X-LINKED MENTAL RETARDATION

By

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A thesis submitted for the degree of

Master in Clinical Medicine (by Research)

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November 2008

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ABSTRACT

Mental retardation is a disorder that affects the lives of many individuals and their families worldwide. The underlying causes are heterogeneous and despite efforts to reveal them, the aetiology remains unknown for 50% of cases.

Estimates of the prevalence of MR have varied between one and three percent in different studies, because of differences in definition, classification and approach to ascertainment. Most studies show that MR is about 30% more prevalent in males than females suggesting that XLMR is an important contributor to MR. Previous studies estimated that XLMR has a prevalence of 1.83 males (Herbst et al., 1980).

The aim of the thesis was the ascertainment, diagnostic evaluation and gene mapping of South Australian families with possible XLMR. The South Australian Clinical Genetics Service's database (Kintrak) identified 33 families with possible XLMR of unknown cause. The clinical features and diagnostic evaluation of these families were documented.

Six of these families were large enough for linkage mapping but only 2 of them agreed to participate in the current study. For one family the gene was localised between markers DXS8067 and DXS1062. Two candidate genes within the linkage interval, PHF6 and GRIA3 were screened for a mutation but no pathological mutation was found. The linkage mapping of the second family is still in progress. One of the 33 families was suspected to have Borjeson-Forssman-Lehmann syndrome and was screened for PHF6 but no mutation was found.

Tarpey et al. (2007) identified protein truncating mutations in UPF3B in some patients with Lujan Fryns Syndrome (XLMR with Marfanoid body build). Therefore, the South Australian Clinical Genetics Service's database (Kintrak) was searched for males with a diagnosis of MR

and Marfanoid body build and 14 individuals were found. They were screened for mutations in UPF3B gene but no pathological mutation was found.

STATEMENT

This work 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 available for loan and photocopying.

Zahiya Abdul Hameed Al Raisi

ACKNOWLEDGMENTS

I would like to thank Professor Eric Haan and Associate Professor Jozef Gecz for their help, advice and encouragement during my research period and for giving their valuable time and expertise to review this thesis. They were always there when I needed them and I consider myself very lucky to have them as my supervisors.

I would like to thank all the members of the Department of Genetic Medicine who made my stay enjoyable and memorable (Stephanie Singer, Anne Baxendale, Hayley Salvemini, Tania Straga, Lara Fitzgerald, Christine Clift and Jill Lee) with a special thanks to Vicky Dancer for her help, kindness and care from the first day.

I would like to thank the clinical geneticists for introducing me to some of the families and for their valuable guidance during the clinics (Professor Eric Haan, Dr. Elizabeth Thompson, Dr. Jan Liebelt, Dr. Lesley McGregor and Dr Graeme Suthers).

I am grateful to Mr Lam Sonny Nguyen for his help and guidance in the Neurogenetics Research Laboratory and to Dr Sinitdhorn Rujirabanjerd and Dr Marie Shaw for their help with the GOLD SA project.

I would like to thank Ms Lucianne Vandeleur for arranging the lymphoblastoid cell lines and Dr Kathie Friend for her help with the linkage analysis of the two large mappable families.

A special thanks to all the families for their participation and cooperation.

DEDICATION

To my loving parents and my brothers and sisters whose love, support and encouragement was overwhelming

To my loving husband for his continuous encouragement, support and for being always there for me when I needed him

To my angels my daughters Sara and Fatma for filling my life with joy and happiness.

Zahiya Al Raisi

GLOSSARY OF ABBREVIATIONS

A, C, G, T	-	nucleotides: adenine, cytosine, guanine, thymine
AGRF	-	Australian Genome Research Facility
Array CGH	-	array comparative genomic hybridisation
ARHGEF6	-	Rac/Cdc42 guanine nucleotide exchange factor (GEF)
ARX	-	aristaless related homeobox
ATRX	-	alpha thalassemia/mental retardation syndrome
BAC	-	bacterial artificial chromosome
BLAST	-	basic local alignment search tool
bp	-	base pairs
˚C	-	degrees centigrade
cDNA	-	complementary deoxyribonucleic acid
cm	-	centimetre
cM	-	centiMorgans
CNPs	-	copy number polymorphisms
CT	-	computed tomography
DNA	-	deoxyribonucleic acid
dNTP	-	deoxynucleoside triphosphate
EDTA	-	ethylenediamine tetra-acetic acid
ESD	-	esterase D
FGFR	-	fibroblast growth factor receptor
FISH	-	fluorescence *in situ* hybridisation

gDNA	-	genomic DNA
GOLD SA	-	Genetics Of Learning Disability South Australia
GRIA3	-	glutamate receptor, ionotrophic, AMPA 3
IMVS	-	Institute of Medical and Veterinary Science
IQ	-	intelligence quotient
Kb	-	kilobase pairs
LCL	-	lymphoblastoid cell line
Lod	-	logarithm of the odds
Mb	-	megabase
$MgCl_2$	-	magnesium chloride
MR	-	mental retardation
MRI	-	Magnetic Resonance Imaging
mRNA	-	messenger RNA
MRX	-	non-specific X linked mental retardation
MRXS	-	specific X linked mental retardation
NCBI	-	National Centre for Biotechnology Information
NSXLMR	-	non syndromic X linked mental retardation
OMIM	-	Online Mendelian Inheritance in Man
ORF	-	open reading frame
PAC	-	p1 artificial chromosome
PCR	-	polymerase chain reaction
RNA	-	ribonucleic acid
rpm	-	revolutions per minute
RT	-	reverse transcriptase
SNP	-	single nucleotide polymorphism

SXLMR	-	syndromic X linked mental retardation
U	-	units
WCH	-	Women's and Children's Hospital (North Adelaide)
XLMR	-	X linked mental retardation
YAC	-	yeast artificial chromosome
µg	-	microgram
µl	-	microlitre