

UNIVERSITY OF NEWCASTLE

# The Complex Genetics of Multiple Sclerosis

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BSc (Biotech) (Hons)

**Doctor of Philosophy, Medical Genetics**

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## **Declaration**

The 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 the final version of my thesis being made available worldwide when deposited in the University's Digital Repository, subject to the provisions of the Copyright Act 1968.

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I hereby certify that this thesis is submitted in the form of a series of published papers of which I am a joint author. I have included as part of the thesis a written statement from each co-author; and endorsed by the Faculty Assistant Dean (Research Training), attesting to my contribution to the joint publications

Mathew B. Cox

Date

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# **Table of Contents**

Declaration.....	i
Acknowledgements.....	ii
Publications included as part of the thesis .....	iii
Copyright statement .....	iii
Additional publications which have relevance to the thesis .....	iv
Conference presentations which have relevance to the thesis.....	vii
Abstract.....	1
Chapter One – Introduction: The Complex Genetics of Multiple Sclerosis .....	3
Multiple Sclerosis .....	5
Prevalence.....	5
Subtypes.....	6
Pathology .....	6
Aetiology .....	8
Current disease modifying therapies and pharmacogenomics .....	20
Future.....	21
Chapter Two – RNA Expression Profiling in Multiple Sclerosis.....	23
Introduction .....	25
Publication One.....	27
Co-author Statement .....	28
Altered expression of the plasminogen activation pathway in peripheral blood mononuclear cells in multiple sclerosis: possible pathomechanism of matrix metalloproteinase activation.....	29
Publication Two.....	45
Co-author statement .....	46
MicroRNAs miR-17 and mir-20a inhibit T cell activation genes and are under-expressed in MS whole blood .....	47
Chapter Three - Candidate Gene SNP Association Studies in Multiple Sclerosis .....	65

Introduction .....	67
Publication Three .....	69
Co-author statement .....	70
Common genetic variants in the plasminogen activation pathway are not associated with multiple sclerosis .....	71
Publication Four .....	77
Co-author statement .....	78
Potential association of vitamin D receptor polymorphism Taq1 with multiple sclerosis. ....	79
Chapter Four - Discussion .....	95
Discussion.....	97
Gene expression.....	97
miRNA expression .....	99
Vitamin D Receptor.....	101
Plasminogen Activation Pathway.....	102
Conclusion.....	103
Future Directions .....	103
Bibliography .....	105
Appendices.....	117
Appendix One: Supplementary material for Publication One .....	119
Altered expression of the plasminogen activation pathway in peripheral blood mononuclear cells in multiple sclerosis: possible pathomechanism of matrix metalloproteinase activation.....	119
Appendix Two: Supplementary material for Publication Two.....	125
MicroRNAs miR-17 miR-20a Inhibit T Cell activation Genes and Are Under-Expressed in MS Whole Blood.....	125
Appendix Three: Supplementary material for Publication Three.....	157
Common genetic variants in the plasminogen activation pathway are not associated with multiple sclerosis .....	157



## **Abstract**

Multiple sclerosis (MS) is an autoimmune disorder directed against the central nervous system (CNS). While it is known that lymphocytes can cross the blood brain barrier from the periphery, resulting in inflammatory lesions in the brain and spinal cord, the underlying aetiology of MS remains unknown. Current evidence suggests that the risk of developing MS is a result of both genetic and environmental factors. At least 57 genetic loci have been confirmed to be associated with MS, with DRB1\*1501 showing the strongest effect. Alone these associated genes do not explain all of the predicted genetic contribution that underlies MS. Environmental factors, including low levels of vitamin D and smoking, have also been associated with an increased risk of developing MS, and together with genetic risk factors are thought to contribute significantly to the likelihood of developing disease.

The aim of this study was to investigate variation in the transcriptome and genome of MS patients, to identify genes, and pathways that interact with environmental factors that could potentially explain the risk of developing MS.

In this thesis, several levels of genetic investigation were undertaken which were then correlated with potential factors that interact with the environment. Initially a whole-genome gene expression study comparing MS cases against healthy controls was undertaken which revealed a predominance of genes involved in the immune system. Interestingly, four of the dysregulated genes form part of the plasminogen activation pathway, including *MMP9*, which is thought to be involved in the break-down of the blood brain barrier.

To investigate potential causes of this dysregulation in the plasminogen activation pathway, I performed a candidate gene SNP association study, investigating 17 common variants within these four genes, in over 4500 samples. There was no association of any variant investigated and MS risk, nor did genotype correlate with gene expression.

The role of miRNA and its association with gene expression in MS was undertaken where I identified an expression profile, unique to MS compared to healthy controls. Two of the miRNAs, miR-17 and miR-20a which were significantly under-expressed in MS were further investigated, and found to target genes involved in T cell activation. It appears from this study that the dysregulation of miRNAs observed in this study may result in increased T cell activation, as seen in MS.