Genes:

Multigene Families,

Control of Gene Expression,

Genetic contributions to Human Diseases,
including
Chromosomal Fragile Sites and
'Dynamic' and 'Non-self' Mutations

by

Robert Ian Richards,

BSc(Hons)(Adelaide)

PhD(Adelaide)

Submitted for the degree of

Doctor of Science

The University of Adelaide

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Declaration

Statement of Authorship

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name 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. In those cases where the publications include work that also forms part of the thesis work of a student, this is clearly indicated by the student's name being ***printed in italics, bold and underlined***. The work carried out in the Publications was carried out by me or under my immediate supervision except where indicated under the Explanations re Joint Authorship and in the Acknowledgements to each publication. Post-graduate students under my (direct or joint) supervision were Anthony J. Mason, Catherine C. Drinkwater, Adrian K. West, Ian Lyons, William M. Clouston, Mario Congiu, Matthew Digby, Sui Yu, Yang Shen, Naras Lapsys, Julie K. Nancarrow, Lesley Ades, Kathryn Friend, Catherine McLeod, Amanda Lumsden, Alex Colella, Tanya Henshall, Clare van Eyk, Ben Tucker, Kynan Lawlor, Saumya Samaraweera, Amanda Choo, Cheng Shoou Lee and Andrew Scott. Manuscripts where these colleagues are co-authors will have formed or will form part of their post-graduate (PhD or Masters) theses.

In addition, I certify that no part of this work will, in the future, be used in a submission in my name for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint award of this degree.

The author acknowledges that copyright of published works contained within this thesis resides with the copyright holder(s) of those works.

I give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

Acknowledgements

I give thanks to John Shine and John Pateman for providing resources necessary to undertake those studies carried out at the Department of Genetics, Research School of Biological Sciences, Australian National University; John Baxter for support at the University of California, San Francisco Medical Centre; Hugh Niall, John Coghlan and Geoff Tregear for providing resources necessary to undertake studies at the Howard Florey Institute of Experimental Physiology and Medicine, University of Melbourne; Grant Sutherland for providing resources necessary for undertaking those studies at the Department of Cytogenetics and Molecular Genetics, Women's and Children's Hospital, Adelaide, Peter Rathjen, Graham Mayrhofer, Richard Ivell and David Adelson for providing resources necessary for undertaking those studies at School of Molecular and Biomedical Sciences, The Univeristy of Adelaide and Rob Saint for providing resources necessary for undertaking those studies at the ARC Special Research Centre for the Molecular Genetics of Development, The University of Adelaide. I also acknowledge Grant Sutherland for encouragement to submit these published works for this thesis.

While the direct outcomes of this kindness appear elsewhere (in my PhD thesis) I am particularly grateful to Bill Rutter and Axel Ullrich for their goodwill and kindness in finding me lab space and accommodation in San Francisco during six months of my PhD – a period of time that changed my life and gave me the desire and confidence to pursue a career in research. I am sincerely grateful to Michael Karin, David Schlessinger, Denis Le Paslier, Daniel Kastner, Norman Doggett, Chris Jones, Marshall Horwitz, Deon Venter, Cath Suter, John Hopwood and Michael Lardelli for their trust in collaborating with me.

I am deeply indebted to the students and post-doctoral fellows that I have had the good fortune to supervise - in particular Tony Mason, Barbara Van Leeuwen, Adrian West, Cathy Drinkwater, Bill Clouston, Matthew Digby, Ian Lyons, Mario Congiu, Sui Yu, Eric Kremer, Yang Shen, Lesley Ades, Naras Lapsys, Julie Nancarrow, Marie Mangelsdorf , Kathie Friend, Duncan Hewett, Oliva Handt, Karin Ried, Louise O'Keefe, Amanda Lumsden, Catherine McLeod, Yinghong Liu, Alex Colella, Donna Crack, Tanya Henshall, Clare van Eyk, Ben Tucker, Kynan Lawlor, Saumya Samaraweera, Amanda Choo and Cheng Shoou Lee.

I have also had the great fortune to be able to direct the research work of some highly skilled and dedicated research assistants including Ailsa Chambers, Kerry Fowler, Kathy Holman, Kathie Friend, Marie Mangelsdorf, Lynne Hobson, Sonia Dayan, Merran Finnis and Alison Perkins. Thanks also go to Helli Meinecke and Evi Guidolin for turning the administrative experiences of running a Centre and a Research Network into something of a dream (rather than a nightmare). Helli in particular was not only an amazing zeitgeber but her commitment, dedication and professionalism have been an inspiration. I also thank Allen Roses and Brian Brophy for their timely advice and expert intervention respectively.

I am also thankful to Misha, Peer, Juni and Shelley Richards variously for their support, encouragement, inspiration and love at times and their great expectations at others. I would also like to thank my mother and my brother for their care, support and concern. Friends and colleagues have also been a vital source of support and inspiration – particularly Norman Eberhardt and Werner Muller-Esterl (both for decades), and my great fishing amigos John Mackrill, George Rogers and Garry Penney. I have been moved by the courage and spirit that Ada Delver, Sonia Elts and Michael Roberts have shown in confronting their illnesses.

I am particularly grateful to Sarah Robertson for enabling me to feel love again and for her unshakable faith in me.

Dedication

I would like to dedicate this work to those friends, colleagues and mentors whose lives have positively influenced mine but are no longer here to personally thank – Bill Clouston, Ada Delver, Bill Elliott, Pam Harris, Michael Roberts, Allen Roses, David Rowe, Bob Symons and Julian Wells.

Abstract

The early work in this thesis utilizes the general approach of comparative analysis. In order to find out the relationship between entities (either functional or genetic) my colleagues and I have attempted to identify the important elements by detecting similarity between those entities that act in a similar manner. The philosophy behind this approach is simply that when two distinct objects perform a similar process then the requirements essential for that process will be revealed as similarities between those objects above a noise of difference between them. The use of comparative analysis in biological systems is an attempt to identify natural order from apparent chaos.

This work includes but is not limited to :-

1. discovery of the family of kallikrein genes and exploration of their roles in biology,
2. identification of the DNA sequence elements required for hormonal and heavy metal control of metallothionein gene expression
3. discovery of at least some of the necessary and sufficient conditions for the appearance of fragile sites on chromosomes, and their consequent contributions to disease,
4. the molecular properties of repeat DNA sequence expansion that lead to *dynamic mutation* and consequent fragile site expression and / or disease pathogenesis.

In a sense the use of genetic animal models in order to study gene function and pathogenesis follows similar logic of comparative analysis – the mutation of a single endogenous gene or the expression of a single introduced mutated gene in a (presumed) constant genetic background to enable the biological consequences of the genetic mutation or aberrant gene expression by comparing animals from the 'wild-type' or parent line with those that now carry the mutation or altered gene. This approach has been utilized in the most recent work contained herein as a means to determine gene function and / or to model human genetic disease pathogenesis, specifically pathogenic mechanisms of the protein WWOX in cancer and expanded repeat RNAs in neurodegenerative diseases.

The culmination of this recent work is the development of an hypothesis –

4. that expanded repeat double-stranded RNA leads to neurodegeneration through its recognition by the RNA-binding pattern recognition receptors as a 'non-self' or foreign nucleic acid due to a paucity of RNA modification.

The resultant pathogenic mechanism is therefore autoinflammatory disease. Given the wide range and variety of evidence of inflammatory activation in neurodegenerative diseases in general, this mechanism is therefore hypothesized to be the general causal mechanism for most (or all) of these diseases.

A specific *Introduction* - highlighting the **nature** and **significance** of the work, and a *Conclusion* – of how this work has **contributed to knowledge**, are given at the start of each chapter, while the *impact* of the various components of this work is indicated by the **number of citations** for each of the included publications. *Authorship contributions* to each of the included publications in this work are also indicated with each specific reference.

The Submission

Section I Gene Families:

Chapter 1. *Kallikrein* gene family and the *Angiotensinogen* gene: Candidate genes for hypertension and prohormaone processing

Citations 1,228

*This project began in 1980 when I identified a cDNA clone from a mouse salivary gland cDNA library that showed 57% sequence homology to pig pancreatic kallikrein (**ref #1**). This finding was my first experience at how useful computer analysis could be in biology and preceded by many years the discipline now known as 'bioinformatics'. Dr Adrian Gibbs at the Research School of Biological Sciences at ANU had developed a program (which he called 'SEQ') for searching for strings of homology – this was a precursor to the now widely used 'BLAST' algorithm. I used the SEQ program to search the Dayhoff database collection of known (at the time) protein sequences and found 57% sequence identity between the amino acid sequence predicted by an open reading frame of one of the mouse salivary gland cDNA clones with the amino acid sequence of pig pancreatic kallikrein. This finding also initiated an interest in genes that might have roles in important biological functions – such as blood pressure regulation. I was fortunately able to take this project with me when I left the ANU in Canberra and took up a position at the Howard Florey Institute of Experimental Physiology and Medicine in Melbourne. This project included the efforts of the PhD students Tony Mason, Catherine Drinkwater, Ian Lyons, Matthew Digby, Bill Cloustin, Mario Congiu and the post-doctoral fellows Bronwyn Evans and Barbara van Leeuwen – all of whom I supervised.*

*This work resulted in publications in the journals Nature (**ref 2**), J. Biol. Chem. (**refs #4, 5, 10**), Biochemistry (**refs #7, 9**), EMBO Journal (refs #3, 6) and Trends in Biochemistry (**ref #15**) as well as invitations to speak at Gordon Research Conferences and specialist international Kallikrein-Kinin conferences.*

*Bill Clouston initiated, and Mario Congiu completed, a series of genetic studies on the mouse angiotensinogen gene and its regulation (**refs #16-20**).*

A) *KALLIKREIN* GENES:

1. Mouse glandular kallikrein genes : Nucleotide sequence of cloned cDNA coding for a member of the kallikrein-arginyl esteropeptidase group of serine proteases.
Journal of Biological Chemistry (1982) 257: 2758-2761.
Richards, R.I., Catanzaro, D.F., ***Mason, A.J.,*** Morris, B., Baxter, J.D., Shine, J.

This project arose out of attempts to find a different gene (that encoding renin) and the serendipitous finding enabled me to develop a project specifically analysing kallikrein genes. I was therefore in the fortunate position of being able to pursue and oversee this project independently of other projects being conducted in my post-doctoral supervisors' (Drs Shine and Baxter) laboratories. I conducted the majority of the experimental work, analysed and interpreted the data and wrote the manuscript. ***Citations 67***

2. Structure of the mouse glandular kallikrein gene family suggests a role in the processing of biologically active peptides.
Nature (1983) 303: 300-307.
Mason, A.J., Evans, B.A., Cox, D., Shine, J., **Richards, R.I.**

This work was a key part of Tony Mason's PhD thesis. I oversaw the entire project. I established the collaboration with David Cox. I conducted some of the experimental work, supervised the project, analysed and interpreted the data, conceived of the overall content of the paper and wrote the manuscript. ***Citations 271***

3. Genes for the alpha & gamma subunits of mouse nerve growth factor are contiguous.
EMBO Journal (1985) 4: 133-138.
Evans, B.A., **Richards, R.I.**

I oversaw the entire project. I conducted some of the experimental work, supervised the project, analysed and interpreted the data, conceived of the overall content of the paper and co-wrote the manuscript. ***Citations 77***

4. Mouse glandular kallikrein genes : Identification, structure and expression of the renal kallikrein gene.
Journal of Biological Chemistry (1986) 261: 5529-5535.
Van Leeuwen, B.H., Evans, B.A., Tregear, G.W., **Richards, R.I.**

I oversaw the entire project. I supervised the experimental work, analysed and interpreted the data, conceived of the overall content of the paper and co-wrote the manuscript. ***Citations 104***

5. Mouse glandular kallikrein genes : Structure and partial sequence analysis of the kallikrein gene locus.
Journal of Biological Chemistry (1987) 262: 8027-8034.
Evans, B.A., ***Drinkwater, C.C.,*** **Richards, R.I.**

I oversaw the entire project. I supervised the experimental work, analysed and interpreted the data, conceived of the overall content of the paper and co-wrote the manuscript. ***Citations 174***

6. Cellular basis for the differential response of mouse kallikrein genes to hormonal induction.
EMBO Journal (1987) 6: 1705-1713.
van Leeuwen, B.H., Penschow, J.D., Coghlan, J.P., **Richards, R.I.**

I oversaw the entire project. I co-supervised the experimental work, analysed and interpreted the data, conceived overall content of the paper and co-wrote the manuscript. ***Citations 44***

7. Mouse glandular kallikrein genes : Identification and characterization of the genes encoding the EGF-binding protein(s).
Biochemistry (1987) 26: 6750-6756.
Drinkwater, C.C., Evans, B.A., **Richards, R.I.**

This work was a key part of Cathy Drinkwater's PhD thesis. I oversaw the entire project. I supervised the experimental work, analysed and interpreted the data, conceived of the overall content of the paper and co-wrote the manuscript. ***Citations 67***

8. Sequence of the mouse glandular kallikrein gene, mGK-5.
Nucleic Acids Research (1987) 15: 10052.
Drinkwater, C.C., **Richards, R.I.**

I oversaw the entire project. I supervised the experimental work and interpreted the data and the manuscript is purely descriptive. ***Citations 8***

9. Structure and chromosomal localization of the human renal kallikrein gene.
Biochemistry (1988) 27: 3124-3129.
Evans, B.A., Zhang, X-Y, Close, J.A., Tregear, G.W., Kitamura, N., Nakanishi, S., Callen, D.F., Baker, E., Hyland, V.J., Sutherland, G.R., **Richards, R.I.**

I oversaw the majority of the project and negotiated the collaborations with Grant Sutherland and Shigetada Nakanishi. I supervised and conducted much of the experimental work, analysed and interpreted the data, conceived of the overall content of the paper and wrote the manuscript. ***Citations 160***

10. Sequence and expression of mouse gamma-renin.
Journal of Biological Chemistry (1988) 263: 8565-8569.
Drinkwater, C.C., Evans, B.A., **Richards, R.I.**

This work was a key part of Cathy Drinkwater's PhD thesis. I oversaw the project. I supervised the experimental and interpreted the data, conceived of the overall content of the paper and co-wrote the manuscript. ***Citations 17***

11. Human prostate specific antigen is a member of the glandular kallikrein gene family at 19q13.
Cytogenetics and Cell Genetics (1988) 48: 205-207.
Sutherland, G.R., Baker, E., Hyland, V.J., Callen, D.F., Close, J.A., Tregear, G.W., Evans, B.A., **Richards, R.I.**

I oversaw the majority of the project and negotiated the collaboration with Grant Sutherland. I supervised part of the experimental work, supervised the project, analysed and interpreted the data, conceived of the overall content of the paper and co-wrote the manuscript. ***Citations 42***

12. Nucleotide sequence of the mouse glandular kallikrein gene mGK-11.
Nucleic Acids Research (1988) 16: 10918.
Drinkwater, C.C., **Richards, R.I.**

I oversaw the project. I supervised the experimental work, analysed and interpreted the data, and the manuscript is purely descriptive. ***Citations 5***

Differential binding of thyroid hormone receptors to mouse glandular kallikrein gene promoters: Evidence for multiple binding sites in the mGK-6 gene.
Journal of Molecular Endocrinology (1989) 3: 79-84.
Barlow, J.W., Raggat, L.E., ***Drinkwater, C.C., Lyons, I.G.,*** **Richards, R.I.**

13. Human prostate specific antigen (PSA) gene: Structure and linkage to the kallikrein-like gene hGK-1
Nucleic Acids Research (1989) 17: 2137.
Digby, M., Zhang, X-Y, **Richards, R.I.**

This work was a key part of Matthew Digby's PhD thesis. I oversaw the project. I supervised the experimental work, analysed and interpreted the data, and the manuscript is purely descriptive. . ***Citations 41***

Thyroid hormone receptors from IM-9 cells but not HeLa cells bind to promoters of T3-responsive genes.
Molecular and Cellular Endocrinology (1990). 69: 129-134.
Barlow, J.M., Raggatt, L.E., ***Drinkwater, C.C.,*** **Richards, R.I.** .

14. Human glandular kallikrein genes : Genetic and physical mapping of the KLK1 locus using a highly polymorphic microsatellite marker.
Genomics (1991) 11: 77-82.
Richards, R.I., Holman, K., ***Shen, Y.,*** Harley, H., Brook, D., Shaw, D.

I oversaw the project and negotiated the collaboration with Helen Harley and Duncan Shaw. I conducted the majority of the experimental work, analysed and interpreted the data, and wrote the manuscript. ***Citations 40***

The kallikrein multigene family : Specific processing of biologically active peptides.
Cold Spring Harbor Symposia on Quantitative Biology 48: Molecular Neurobiology 419-426 (1983). Shine, J., ***Mason, A.J.,*** Evans, B.A., **Richards, R.I.**

15. Kallikreins, kinins and growth factor biosynthesis.
Trends in Biochemical Sciences 13: 169-172 (1988).
Drinkwater, C.C., Evans, B.A., **Richards, R.I.**

I conceived of the review and lead the writing of the manuscript. ***Citations 51***

Molecular biology of the glandular kallikrein genes of mouse and man.
in: *'The Kallikrein-Kinin System in Health and Disease'* (Fritz, H., Schmidt, I., Dietze, G. eds.) Limbach-Verlag Braunschweig, (1989) pp.215-225.
Richards, R.I., Coghlan, J.P., ***Digby, M.,*** ***Drinkwater, C.C.,*** Lloyd, C., ***Lyons, I.,*** Zhang, X-Y.

B) *ANGIOTENSINOGEN* GENE:

16. Molecular cloning of the mouse angiotensinogen gene.
Genomics (1988) 2: 240-248.
Clouston, W.M., Evans, B.A., Haralambidis, J., **Richards, R.I.**

This work was a key part of Bill Clouston's PhD thesis. I initiated and oversaw the project. I supervised the experimental work, contributed to the analysis and interpretation of the data, conceived of the overall content of the paper and made a minor contribution to the writing of the manuscript. ***Citations 66***

An alleic polymorphism of the angiotensinogen gene in mice.
Nucleic Acids Research (1989) 17: 822.
Clouston, W.M., **Richards, R.I.**

17. Tissue-specific hormonal control of angiotensinogen minigenes in transgenic mice.
EMBO Journal (1989) 8: 3337-3344.
Clouston, W.M., Lyons, I.G., **Richards, R.I.**

This work was a key part of Bill Clouston's PhD thesis. I oversaw the project. I supervised the experimental work, contributed to the analysis and interpretation of the data, conceived of the overall content of the paper and made a minor contribution to the writing of the manuscript. ***Citations 39***

18. The angiotensinogen gene is located on mouse chromosome 8.
FEBS Letters (1989) 255: 419-422.
Clouston, W.M., Fournier, R.E.K., **Richards, R.I.**

This work was a key part of Bill Clouston's PhD thesis. I supervised part of the experimental work, Bill Clouston wrote the first draft and I had a minor role in the writing of the manuscript.
Citations 15

19. Inducible antisense RNA for angiotensinogen in stably-transformed hepatoma cells.
Journal of Molecular Endocrinology (1990) 4: 107-117.
Clouston, W.M., Lloyd, C.J., **Richards, R.I.**

This work was a key part of Bill Clouston's PhD thesis. I oversaw the project. I supervised the experimental work, contributed to the analysis and interpretation of the data, conceived of the overall content of the paper and Bill Clouston wrote the manuscript. ***Citations 7***

20. The functions of conserved elements in the promoter of the mouse angiotensinogen gene.
Journal of Molecular Endocrinology (1992) 9: 19-30.
Congiu, M., Clouston, W.M., Fernley, R.T., **Richards, R.I.**
This work was a key part of Mario Congiu's PhD thesis. I co-supervised the experimental work, co-supervised the project and I had minor role in writing the manuscript.
Citations 4

LIBRARY NOTE:

The following Chapter 1 publications have been removed due to copyright.

Chapter 2. Regulation of gene expression and the *Metallothionein* gene family

Citations 2,532

*This work began from my interest in the hormonal regulation of gene expression. I was a post-doctoral fellow in the laboratories of Dr John Shine (ANU, Canberra) and Dr John Baxter (University of California, San Francisco) primarily working on the structure and regulation of the growth hormone gene. I made a minor contribution to this area (**ref #21**), however I was able to initiate a collaboration with a fellow post-doc, Dr Michael Karin, which spanned 10 years and produced an extensive characterisation of the structure of the human metallothionein gene family and the regulation of these genes by glucocorticoid hormones and heavy metals (**refs #22-28**). Subsequently an additional study, looking at negative regulation by glucocorticoids, was undertaken as collaborative project (ref Medcalf et al., 1986). Ironically it has turned out that the negative regulation of gene expression by glucocorticoids has a more important role to play in biology than the positive regulation however this served as an important paradigm for the general mechanism by which steroids regulate gene expression. It would be fair to say that Michael Karin was the main driver in the metallothionein project and that it was both a pleasure and an inspiration to try to keep up with him!*

This work produced several publications in the journals Nature and Cell. It also resulted in the first ever identification and DNA sequence motif of a DNA regulatory element for a steroid receptor (the Glucocorticoid Regulatory Element).

A) *GROWTH HORMONE* GENE

21. Primary structure and evolution of rat growth hormone gene.
Proceedings of the National Academy of Sciences USA (1981) 78: 4867-4871.
Barta, A., **Richards, R.I.**, Baxter, J.D., Shine, J.

I contributed to the experimental work, analysed and interpreted much of the data and I had minor role in writing the manuscript. ***Citations 300***

Expression and hormonal regulation of rat growth hormone gene in transfected mouse L cells.
DNA (1984) 3: 147-155.
Karin, M., Eberhardt, N.L., Mellon, S.H., Malich, N., **Richards, R.I.**, Slater, E.P., Barta, A., Martial, J.A., Baxter, J.D., Cathala, G.

B) HUMAN *METALLOTHIONEIN* GENES AND THEIR REGULATION:

22. Human metallothionein genes: Molecular cloning & sequence analysis of the mRNA.
Nucleic Acids Research (1982) 10: 3165-3173.
Karin, M., **Richards, R.I.**

This project was a collaboration between Michael Karin and myself, initiated when we were both post-doctoral fellows in Dr John Baxter's laboratory at UCSF. I contributed to the experimental work, analysis and interpretation of the data and I co-wrote the manuscript.
Citations 114

23. Human metallothionein genes : Primary structure of the metallothionein-II gene and a related processed gene.
Nature (1982) 299: 797-802.
Karin, M., **Richards, R.I.**

This project was part of a collaboration. I contributed to the experimental work, analysis and interpretation of the data and I co-wrote the manuscript. ***Citations 491***

24. Structural and functional analysis of the human metallothionein-Ia gene: Differential induction of metallothionein genes by metal ions and glucocorticoid hormones.
Cell (1984) 37: 263-272.
Richards, R.I., Heguy, A., Karin, M.

This project was part of a collaboration. I contributed to the molecular experimental work, analysis and interpretation of the data, and I co-wrote the manuscript. ***Citations 321***

25. Characterization of the heavy metal ion and glucocorticoid hormone responsive elements of the human metallothionein-IIa gene.
Nature (1984) 308: 513-519.
Karin, M, Haslinger, A, Holtgreve, H, **Richards, R.I.**, Krauter, P., Westphal, HM., Beato,M.

This project was part of a collaboration. I made a significant contribution to the interpretation of the experimental work (I identified the consensus Glucocorticoid Receptor DNA binding sequence) and had a minor role in writing the manuscript ***Citations 902***

26. Structure and tissue specific expression of the human metallothionein Ib gene.
Molecular and Cellular Biology (1986) 6: 2149-2157.
Heguy, A., ***West, A.K.,*** **Richards, R.I.**, Karin, M.

This project was part of a collaboration. This work was a part of Adrian West's PhD thesis. I supervised part of the molecular experimental work and I had minor role in writing the manuscript ***Citations 223***

Suppression of urokinase-type plasminogen activator mRNA levels in human fibrosarcoma and synovial fibroblasts by anti-inflammatory glucocorticoids.
EMBO Journal (1986) 5: 2217-2222.
Medcalf, R.L., **Richards, R.I.**, Crawford, R.J., Hamilton, J.A.

5' Flanking region of the human metallothionein, MT-IIa, gene identifies two moderately frequent RFLP's.
Nucleic Acids Research (1987) 15: 1350.
Hyland, V.J., Grist, S., ***West, A.K.,*** **Richards, R.I.**, Sutherland, G.R.

27. Human metallothionein genes : Structure of the functional gene locus at chromosome 16q13.
Genomics (1990) 8: 513-518.
West, A.K., Stallings, R., Hildebrand, C.E., Chiu, R., Karin, M., **Richards, R.I.**

This work was a key part of Adrian West's PhD thesis. This project was part of a collaboration. I supervised part of the experimental work, analysis and interpretation of some of the data, and I had minor role in writing the manuscript. ***Citations 108***

REVIEW

28. The human metallothionein gene family: Structure and expression
In: *Environmental Health Perspectives* 54: 111-115 (1984).
Karin, M., **Richards, R.I.**

I had the minor role in writing the manuscript. This review contains several references to unpublished work that formed the basis of the 'Nature' and 'Cell' papers of 1984 (above)
Citations 73

LIBRARY NOTE:

The following Chapter 2 publications have been removed due to copyright.

Section II Genetic Contributions to Human Disease

Chapter 3. Genetic Markers and Disease Gene Identification:
Application to studies on Human Chromosome 16 - including -
The genes causing Familial Mediterranean Fever and Pseudoxanthoma Elasticum

Citations 1,763

*In 1989 I moved from the Howard Florey Institute in Melbourne to the Department of Cytogenetics and Molecular Genetics at what was then known as the Adelaide Children's Hospital. One of the attractions to move to this department was the opportunity to work on various aspects of what was then the fledgling 'Human Genome Project'. A major contribution of the department to the Human Genome Project was the construction of a physical and genetic map of human chromosome 16. My role on this project was to supervise the isolation of genetic markers from human chromosome 16 and to implement their use in both the construction of these maps and in the positional cloning of disease genes on this chromosome. In practice this meant a variety of contributions to numerous projects. I was able to make a commitment to the positional cloning of the gene for FMF as part of a consortium of laboratories with this common interest. This collaboration led to the successful identification of the pyrin gene as the cause of FMF. Yang Shen was a PhD student working with me from 1991-1994 and a number of the publications (**refs #30, 31**) will therefore have appeared in her PhD thesis. Other students (H. Kozman, S. Apostolou and J. Balow) were supervised by collaborators. The identification of the FMF gene was published in the journal Cell and is the subject of a patent on which I am a co-inventor. Another of these collaborations, for Pseudoxanthoma Elasticum, was successful in characterising the spectrum of mutations that give rise to the disease.*

A) HUMAN CHROMOSOME 16 : PHYSICAL AND GENETIC MAP

29. Human Chromosome 16 Physical Map : Mapping of Somatic Cell Hybrids Using Multiplex PCR Deletion Analysis of Sequence-Tagged Sites.
Genomics (1991) 10: 1047-1052.
Richards, R.I., Holman, K., Lane, S., Sutherland, G., Callen, D.F.

A major contribution of the Adelaide Children's Hospital to the international Human Genome Project was the construction of a physical and genetic map of human chromosome 16. I was responsible for the Molecular Genetic component of this project – others were responsible for the Cytogenetics and Linkage Mapping. In the work described in this manuscript I conducted the majority of the experimental work, analysed and interpreted the data and wrote the manuscript ***Citations 10***

30. Isolation and characterisation of (AC)n microsatellite genetic markers from human chromosome 16.
Genomics (1992) 13: 402-408
Thompson, AD, ***Shen, Y.,*** Holman, K., Sutherland, GR, Callen, D.F, **Richards, R.I.**

I supervised the experimental work, supervised the project, analysed and interpreted the data, conceived of the overall content of the paper and co-wrote the manuscript ***Citations 112***

Four dinucleotide repeat polymorphisms on human chromosome 16 at D16S289, D16S318, D16S319 and D16S320. *Human Molecular Genetics* (1992) 1: 773.
Shen, Y., Thompson, AD., Holman, K., Callen, DF., Sutherland, GR., **Richards, R.I.**

Five dinucleotide repeat polymorphisms on human chromosome 16q24.2-q24.3.
Human Molecular Genetics (1993) 2: 1504.
Shen, Y., Holman, K., Doggett, N.A., Callen, D.F., Sutherland, G.R., **Richards, R.I.**

Six dinucleotide repeat polymorphisms on human chromosome 16q12.1-q24.1.
Human Molecular Genetics (1993) 2: 1505.
Shen, Y., Holman, K., Doggett, N.A., Callen, D.F., Sutherland, G.R., **Richards, R.I.**

Three dinucleotide repeat polymorphisms on human chromosome 16p13.11- p13.3.
Human Molecular Genetics (1993) 2: 1506.
Shen, Y., Holman, K., Doggett, N.A., Callen, D.F., Sutherland, G.R., **Richards, R.I.**

Four dinucleotide repeat polymorphisms on human chromosome 16.
Human Molecular Genetics (1993) 2: 1745.
Shen, Y., Holman, K., Doggett, N.A., Callen, D.F., Sutherland, G.R., **Richards, R.I.**

Dinucleotide repeat polymorphisms D16S525, D16S359, D16S531 and D16S522
Human Molecular Genetics (1994) 3: 210.
Shen, Y., Holman, K., Doggett, N.A., Callen, D.F., Sutherland, G.R., **Richards, R.I.**

31. A PCR-based genetic linkage map of human chromosome 16.
Genomics (1994) 22: 68-76.
Shen, Y., Kozman, H., Thompson, A., Phillips, H.A., Holman, K., Nancarrow, J., Lane, S., Chen, L.-Z., ***Apostolou, S.,*** Doggett, N., Callen, D.F., Mulley, J.C., Sutherland, G.R., **Richards, R.I.**

This work was a key part of Yang Shen's PhD thesis. I supervised the experimental work, supervised the project, analysed and interpreted the data, conceived of the overall content of the paper and lead the *writing of the manuscript* ***Citations 33***

B) POSITIONAL CLONING and MUTATION CHARACTERISATION: Familial Mediterranean Fever and Pseudoxanthoma Elasticum

A third Wilms' tumour locus on chromosome 16q.
Cancer Research (1992) 52: 3094-3098.
Maw, M.A., Grundy, P.E., Millow, L.J., Eccles, M.R., Dunn, R.S., Smith, P.J., Feinberg, A.P., Law, D.J., Paterson, M.C., Telzerow, P.E., Callen, D.F., Thompson, A.D., **Richards, R.I.**, Reeve, A.E.

Fine genetic mapping of the Batten disease locus (CLN3) by haplotype analysis and demonstration of allelic association with chromosome 16p microsatellite loci.
Genomics (1993) 16: 455-460.
Mitchison, H.M., Thompson, A.D., Mulley, J.C., ***Kozman, H.M.,*** **Richards, R.I.**, Callen, DF, Stallings, RL, Doggett, NA, Attwood, J, McKay, TR, Sutherland, G.R., Gardiner, R.M.

32. Refined mapping of the gene causing familial Mediterranean fever by linkage and homozygosity studies.
American Journal of Human Genetics (1993) 53: 451-461.
Aksentijevich, I., Pras, E., Gruberg, L., ***Shen, Y.,*** Holman, K., Helling, S., Prosen, L., Sutherland, GR., **Richards, R.I.**, Ramsburg, M., Dean, M, Pras, M, Amos, CI, Kastner, DL

I participated in consortium planning meetings and I supervised our lab's contribution to the experimental work and I had minor role in writing the manuscript. ***Citations 38***

33. Familial Mediterranean fever in Moroccan Jews : Demonstration of a founder effect by extended haplotype analysis.
American Journal of Human Genetics (1993) 53: 644-651.
Aksentijevich, I., Pras, E., Gruberg, L., ***Shen, Y.,*** Holman, K., Helling, S., Prosen, L., Sutherland, G.R., **Richards, R.I.**, Dean, M., Pras, M., Kastner, D.L.

I participated in consortium planning meetings and I supervised our lab's contribution to the experimental work and I had minor role in writing the manuscript. ***Citations 35***

34. Linkage disequilibrium mapping places the gene causing Familial Mediterranean Fever close to *D16S246*.
American Journal of Human Genetics (1996) 58: 523-534.
Levy, E.N., ***Shen, Y.,*** Kupelian, A., Krugliak, L., Aksentijevich, I., Pras, E., ***Balow, J.E.,*** Linzer, B, Pras, M, Shohat, M., Rotter, J.I., Fischel-Ghodsian, N., **Richards, R.I.**, Kastner, D.L.

I participated in consortium planning meetings and I supervised our lab's contribution to the experimental work and I had minor role in writing the manuscript. ***Citations 26***

35. Construction of a 1Mb restriction-mapped cosmid contig containing the candidate region for Familial Mediterranean Fever (*MEFV*) on 16p13.3.
Genomics (1997) 42:83-95.
Sood, R., Blake, T., Aksentijevich, I., Wood, G., Chen, X., Gardner, D., Shelton, D.A., Mangelsdorf, M., Orsborn,A., Pras, E., ***Balow, J.E.,*** Centola, M., Deng, Z., Zaks, N., Chen, X., Richards, N., Fischel-Ghodsian, N., Rotter, J.I., Pras, M., Shohat, M., Deaven, L.L., Gumucio, DL, Callen, DF, **Richards, R.I.**, Collins, F.S., Liu, PP, Kastner, D.L., Doggett, N.A.

I participated in consortium planning meetings and I supervised our lab's contribution to the experimental work and I had minor role in writing the manuscript. ***Citations 26***

36. A high-resolution genetic map of the Familial Mediterranean Fever candidate region allows identification of haplotype-sharing among ethnic groups.
Genomics (1997) 44:280-291.
Balow J.E., Shelton, D.A., Orsborn, A., Mangelsdorf, M., Aksentijevich, I., Blake, T., Sood, R., Gardner, D., Liu, R., Pras, E., Levy, E., Centola, M., Deng, Z., Zaks, N., Wood, G., Chen, X., Richards, N., Shohat, M., Livneh, A., Pras, M., Doggett, N.A., Collins, F.S., Liu, P.P., Rotter, J.I., Fischel-Ghodsian, N., Gumucio, D., **Richards, R.I.**, Kastner, D.L.

I participated in consortium planning meetings and I supervised our lab's contribution to the experimental work and I had minor role in writing the manuscript. ***Citations 48***

37. Ancient Missense Mutations in a New Member of the *RoRet* gene Family Are Likely to Cause Familial Mediterranean Fever.
Cell (1997) 90:797-807. The International FMF Consortium (labs numbered) -
I Aksentijevich, I., Centola, M., Deng, Z., Sood, R., ***Balow J.E.,*** Wood, G., Zaks, N., Mansfield, E., Raben, N., Eisenberg, S., Pras, E., Pras, M., Kastner, D.L.;
II Blake, T., Braxevanis, A., Collins, F.S., Liu, P.P.;
III Chen, X., Shohat, M., Rotter, J.I., Fischel-Ghodsian, N.;
IV Richards, N., Shelton, D.A., Gumucio, D.;
V Yokoyama, Y., Mangelsdorf, M., Orsborn, A., **Richards, R.I.**;
VI Ricke, D.O., Buckingham, J.M., Moyzis, R.K., Deaven, L.L., Doggett, N.A.

I participated in consortium planning meetings and I supervised our lab's contribution to the experimental work and I had minor role in writing the manuscript. ***Citations 1022***

38. Construction of a 700 kb transcript map around the Familial Mediterranean Fever locus on Human chromosome 16p13.3.
Genome Research (1998) 8: 1172-1191.
Centola, M., Chen, X., Sood, R., Deng, Z., Aksentijevitch, I., Blake, T., Ricke, D.O., Chen, X., Wood, G., Zaks, N., Richards, N., Krizman, D., Mansfield, E., Apostolou, S., Liu, J., Shafran, N., Vedula, A., Gumucio, D., Callen, D.F., **Richards, R.I.**, Doggett, N, Moyzis, R, Collins, F.S., Liu, P.P., Fischel-Ghodsian, N., Kastner, D.L.

I participated in consortium planning meetings and I supervised our lab's contribution to the experimental work and I had minor role in writing the manuscript. ***Citations 12***

39. A 500 Kb Region on chr 16p13.1 Contains the Pseudoxanthoma Elasticum Locus: High Resolution Mapping and Genomic Structure
Journal of Molecular Medicine (2000) 78: 36-46.
Cai, L., Struk, B., Adams, M.D., Ji, W., Haaf, T., Kang, H-L., Dho, S.H., Xu, X., Ringpfeil, F., Nancarrow, J., Züch, S., Schaen, L., Niu, T., Chung, J., Lunze, K., Verrecchia, B., Goldsmith, L.A., Viljoen, D., Figuera, L.E., Fuchs, W., Lebwoh, M., Uitto, J., **Richards, R.I.,** Hohl, D., Ramesar, R., Callen, D.F., Kim, U-J., Doggett, N.A., Neldner K.H. and Lindpaintner, K.

I participated in collaboration planning meetings and I supervised our lab's contribution to the experimental work and I had minor role in writing the manuscript. ***Citations 78***

40. Mutations in the Gene Encoding the Transmembrane Transporter Protein, ABC-C6, Cause Pseudoxanthoma Elasticum
Journal of Molecular Medicine (2000) 78: 282-286.
Struk, B., Cai, L., Zach, S., Ji, W., Chung, J., Lumsden, A., Stumm, M., Schaen, L., Kim, C-A. Goldsmith, L.A., Viljoen, D., Figuera, L.E., Fuchs, W., Ramesar, R., Hohl, D., **Richards, R.I.,** Neldner K.H. and Lindpaintner, K.

I supervised our lab's contribution to the experimental work and I had minor role in writing the manuscript. ***Citations 135***

41. A novel mutation exists the Transmembrane Transporter Protein, ABC-C6 and its pseudogene – Implications for mutation analysis in Pseudoxanthoma Elasticum
Journal of Molecular Medicine (2001) 79: 536-546.
Cai, L., Lumsden, A. L., Guenther, U.P., Neldner S.A., Zuch, S., Ramesar, R., Hohl, D., Callen, DF., Neldner KH., Lindpaintner, K., **Richards, R.I.,** and Struk, B.

I supervised part of the experimental work and I had substantial role in writing and re-writing the manuscript. ***Citations 53***

42. Molecular Genetics of Pseudoxanthoma Elasticum : Types and Frequencies of Mutation in *ABCC6*
Human Mutation (2005) 26: 235-248.
Miksch, S., Lumsden, A. L., Guenther, U.P., Foernzler, , D., Christen-Zäch, S., Daugherty , C., Ramesar, R., Lebwohl, M., Thierfelder, L., Hohl, D., Neldner K.H., Lindpaintner, K., **Richards, R.I.,** and Struk, B.
I supervised part of the experimental work, analysed and interpreted the data, and I had substantial role in writing and re-writing the manuscript ***Citations 96***

REVIEW

43. DNA Repeats: A treasury of human variation.
New England Journal of Medicine (1994) 331: 191-193.
Sutherland, G.R., **Richards, R.I.**
I co-authored the manuscript and corrected the extensively edited proofs. ***Citations 39***

LIBRARY NOTE:

The following Chapter 3 publications have been removed due to copyright.

Chapter 4. Common Chromosomal Fragile Sites: DNA Instability and Functional Contribution to Cancer

Citations 1,052

*Based on a correlation between the location of various common fragile sites on chromosomes and known DNA instability and / or 'cancer genes', Yunis and Soreng (1984, Science, **226**, 1199-1204) proposed that common chromosomal fragile sites were predisposed to DNA instability in cancer and that the genes perturbed by this instability contributed in some way to cancer cell biology. Experiments at the most readily inducible common fragile site, FRA3B, appeared to support this hypothesis in identifying both the region as one of frequent instability in cancer and also the FHIT gene spanning the fragile site as one with affected gene expression and a functional contribution to cancer. Despite these findings there was much scepticism by both the field in general and by my immediate colleagues as to the generality of such a relationship at its contribution (if any) to cancer cell biology. Therefore, in order to assess whether these features were common to other chromosomal fragile site loci I initiated studies at the second most readily induced common chromosomal fragile site, FRA16D. This work identified the region of as one where various forms of DNA instability did occur in cancer and a gene (FOR or WWOX) that spanned the region and appears to contribute to cancer cell biology (**refs #45, 46**). I established collaborations with Drs Venter and Chenevix-Trench, principally in order to obtain tumour samples and cancer cell lines. The crucial cytogenetics experiments were conducted, interpreted and supervised by Elizabeth Baker and her colleagues in the Cytogenetics Unit, WCH.*

*In addition to identifying the FOR (WWOX) gene, our lab addressed several key aspects of the mutation mechanism that gives rise to homozygous deletion at the FRA16D fragile site in cancer cells. First, the timing of the deletion event in the neoplastic process, as it is assumed that early events are more likely to be causal rather than consequential. Secondly, the relationship between FRA16D associated deletion and another form of deletion (loss-of-heterozygosity, LOH) known to occur at high frequency in certain cancers in the 16q23.2 region. Thirdly, the nature of the deletion endpoints and any identifiable characteristics of the sequences at or near these deletion endpoints. Fourthly, the extent of 'genome-wide' instability that occurs in FRA16D deleted cell lines. Finally, the effect of FRA16D associated deletions on the cytogenetic expression of the FRA16D fragile site. This work was published in the journal Human Molecular Genetics (**ref #48**) with a figure appearing on the issue cover.*

*We have since used a combination of Drosophila genetics and biochemical approaches to discover the normal function of the Wwox gene. Our initial efforts were thwarted by difficult to detect background mutations (**refs #47, 49**), We have subsequently found that a significant proportion of Drosophila Wwox interactors identified by proteomics and microarray analyses have roles in aerobic metabolism. Functional relationships between Wwox and either CG6439/isocitrate dehydrogenase (Idh) or Cu–Zn superoxide dismutase (Sod) were confirmed by genetic interactions. In addition, altered levels of Wwox resulted in altered levels of endogenous reactive oxygen species. Wwox (like FHIT) contributes to pathways involving aerobic metabolism and oxidative stress, providing an explanation for the 'non-classical tumour suppressor' behaviour of WWOX. Fragile sites, and the genes that span them, are therefore part of a protective response mechanism to oxidative stress and likely contributors to the differences seen in aerobic glycolysis (Warburg effect) in cancer cells. This work was also published in the journal Human Molecular Genetics (**ref #50**).*

*Our most recent experiments with Wwox demonstrate an interrelationship with metabolism – Wwox is both a regulator of metabolism and is regulated by metabolism (**ref #51**). An insight in to the contribution Wwox plays in cancer was revealed by competition experiments that showed a role for Wwox in the elimination of tumourigenic cells (**ref #52**). Furthermore Wwox acts to moderate the mitochondrial respiratory – a likely contribution to the Warburg effect (**ref #53**).*

44. Fragile sites at 16q22 are not at chromosomal rearrangement breakpoint in AMMoL
Science (1987) 236: 92-94.
Simmers, R.N., Sutherland, G.R., ***West, A.K.,*** **Richards, R.I.**

I negotiated the collaboration and I had a minor role in writing the manuscript ***Citations 55***

45. Chromosomal Fragile Site *FRA16D* and DNA Instability in Cancer.
Cancer Research (2000) 60: 1683-1689.
Mangelsdorf, M., Ried, K., Woollatt, E., Dayan, S., Eyre, H., Finnis, M., Hobson, L., Nancarrow, J., Venter, D., Baker, E., **Richards, R.I.**

I supervised the experimental work, analysed and interpreted the data and oversaw the molecular components of the project and I wrote the draft and revised versions of the manuscript ***Citations 139***

46. Common chromosomal fragile site *FRA16D* DNA sequence: Identification of the *FOR* gene spanning *FRA16D* and homozygous deletions and translocation breakpoints in cancer cells.
Human Molecular Genetics (2000) 9: 1651-1663.
Ried, K., Finnis, M., Hobson, L., Mangelsdorf, M., Dayan, S., Nancarrow, J., Woollatt, E., Kremmidiotis, G., Gardner, A., Venter, D., Baker, E., **Richards, R.I.**

I supervised the experimental work, analysed and interpreted the data and oversaw the molecular components of the project and I wrote the draft and revised versions of the manuscript. ***Citations 296***

47. *FRA16D* common chromosomal fragile site oxido-reductase (FOR/WWOX) acts in a protective manner against the effects of ionising radiation in *Drosophila*
Oncogene (2005) 24: 6590-6596 *Corrigendum*: *Oncogene* (2006) 25: 7662.
O'Keefe, L.V., Liu, Y-H., Perkins, A., Dayan, S., Saint, R.B., and **Richards, R.I.**

These functional studies were a collaboration with Rob Saint. The Drosophila work was overseen by Louise O'Keefe. I supervised the molecular genetic experimental work and the analysis and *interpretation of the data, oversaw the project overall and I had a substantial role in writing of both the primary manuscript and the corrigendum. The corrigendum was agreed to by the journal after it was found that the basis for the observed phenotype was background mutation. This finding was important to the field as evident from the complete publication of its description and resolution in Trends in Genetics (**Ref #49**).* ***Citations 27***

48. Common chromosomal fragile site *FRA16D* mutation in cancer cells.
Human Molecular Genetics, (2005) 14: 1341-1349.
Finnis, M., Dayan, S., Handt, O., Hobson, L., Chenevix-Trench, G., Friend, K., Ried, K., Venter, D., Woollatt, E., Baker, E., and **Richards, R.I.**

I supervised the experimental work, analysed and interpreted the data, I oversaw the project and I wrote the draft and revised versions of the manuscript. ***Citations 84***

49. Know thy fly
Trends in Genetics (2007) 23: 238-242.
O'Keefe, L.V, ***Smibert, P,*** ***Colella, A,*** Chataway, TK, Saint R. and **Richards, R.I.**

The Drosophila work was overseen by Louise O'Keefe. Tim Chataway supervised the proteomic work. I contributed to the analysis and *interpretation of the data, I oversaw the project overall and I had a substantial role in writing of the manuscript including negotiating its content with the editor.* ***Citations 22***

50. *Drosophila* orthologue of WWOX, the chromosomal fragile site *FRA16D* tumour suppressor gene, functions in aerobic metabolism and regulates reactive oxygen species
Human Molecular Genetics (2011) 20: 497–509.
O'Keefe, L.V., ***Colella, A.,*** Dayan, S., Chen, Q., ***Choo, A.,*** Jacob, R., Price, G., Venter' D. and **Richards, R.I**

This manuscript evolved over a lengthy period starting off with drafts based on Alex Colella's PhD thesis then added to substantially with additional data, its interpretation and discussion from Louise O'Keefe and Sonia Dayan. I oversaw the assemblage of the manuscript and its multiple revisions. ***Citations 38***

51. Common Chromosomal Fragile Site *FRA16D* Tumour Suppressor *WWOX* Gene Expression and Metabolic Reprogramming in Cells.
Genes, Chromosomes and Cancer (2013) 52: 823-831.
Dayan, S., O'Keefe, L.V., ***Choo, A.,*** and **Richards, R.I**

Sonia Dayan conducted a broad range of human cell line studies into the regulation and role of WWOX expression in relation with metabolism. These relationships were verified in the Drosophila model by Amanda Choo and Louise O'Keefe. I contributed to the experimental designs and co-wrote the first and final drafts. ***Citations 18***

52. Tumor suppressor WWOX contributes to the elimination of tumorigenic cells.
PLOS One (2015) 10(8):e0136356. doi: 10.1371
O'Keefe, L.V., ***Lee, C.S., Choo, A.,*** and **Richards, R.I.**

Louise O'Keefe conceived of the experimental design and conducted the majority of Drosophila experiments. I contributed to the interpretation of the experimental data and to the writing of the manuscript. ***Citations 11***

53. Tumour suppressor *WWOX* moderates the mitochondrial respiratory complex.
Genes, Chromosomes and Cancer (2015) 54, 745-761. doi: 10.1002/gcc.22286.
Choo, A., O'Keefe, L.V., ***Lee, C.S.,*** Gregory, S.L., Shaukat, Z., Colella, A. Lee, K., Denton, D. and **Richards, R.I.**

This work was the major component of Amanda Choo's PhD thesis. I co-supervised the research with Louise O'Keefe. Others contributed supportive experiments and / or essential components. Amanda wrote the manuscript and I contributed to the interpretation of the data and the final draft.

Citations 14

REVIEWS

54. Fragile and unstable chromosomes in cancer: causes and consequences
Trends in Genetics (2001) 17: 339-345.
Richards, R.I.

I wrote this review article ***Citations 240***

55. Common Chromosomal Fragile Sites and Cancer: Focus on *FRA16D*
Cancer Letters (2006) 232: 37–47.
O'Keefe, L.V. and **Richards, R.I.**

Louise O'Keefe took the lead role and I made a substantial contribution to the writing of this review article. ***Citations 93***

Richards, R.I. (2006) "Chromosomal Fragile Sites: Mechanisms of Cytogenetic Expression and Pathogenic Consequences" *In Genetic Instabilities and Hereditary Neurological Diseases, Volume 2, R. Wells and T. Ashizawa eds. Chapter 12, pages 195 – 207* ***Textbook***

56. Richards, R.I., Choo, A., Lee, C.S., Dayan, S. and O'Keefe, L.V. (2015) *WWOX,* the Chromosomal Fragile Site *FRA16D* Spanning Gene: its role in metabolism and contribution to cancer. *Experimental Biology & Medicine* 240(3): 338-344.

I wrote this review article in substantial consultation with the co-authors. ***Citations 15***

LIBRARY NOTE:

The following Chapter 4 publications have been removed due to copyright.

Chapter 5. 'Dynamic' Mutations:
Rare Chromosomal Fragile Sites, Mechanism of Repeat Expansion

Citations 6,138

*In addition to contributing to the Human Genome Project another reason why I was attracted to working at the Adelaide Children's Hospital was because of the work that Grant Sutherland and Liz Baker had previously done on Fragile X Syndrome. This project involved the positional cloning of the mutation causing this disease based on its physical location on a chromosome (rather than its genetic position). I was responsible for oversight and conduct of the Molecular Genetics component of this mainly 'internal' collaboration. Liz Baker and her colleagues in the Cytogenetics Unit conducted the cytogenetics (fluorescence in situ hybridisation) component of the project. In 1991 this research resulted in the identification of an expanded CGG repeat as the mutation causing of Fragile X Syndrome. This work was the subject of two publications in the journal Science (**refs #58, 60**). Subsequently a series of publications ensued reporting the various properties of the unstable repeat and how they account for the unusual genetics of this disease (**refs #63 – 67**). Coupled with similar findings for other diseases caused by expanded repeats, I coined the term 'Dynamic Mutation' in order to distinguish this form of mutation from other (static) mutations (**refs #84, 86, 91, 95**). This term is now in wide usage in Genetics, including in textbooks and an encyclopedia.*

*I then conducted a comparative analysis of different chromosomal fragile sites in order to identify their common and distinguishing features and relate these to their biological properties. Folate sensitive rare fragile sites were found to all be due to expanded CGG repeats (irrespective of whether they were located on the X-chromosome) and were not normal sites of DNA imprinting. The work by PhD student Julie Nancarrow on FRA16A was published in the journal Science (**ref #68**). Work on the FRA11B folate sensitive fragile site was a collaboration with Chris Jones and colleagues in the UK and succeeded in demonstrating for the first time that chromosomes could break in vivo at fragile site loci and that this breakage could be responsible for a proportion of cases of a chromosomal breakage disorder – in this case Jacobsen Syndrome. This work was published in the journal Nature (**ref #72**). Other non-folate sensitive rare chromosomal fragile sites FRA10B and FRA16B were found to be also due to expanded DNA repeats, but of considerably greater length and AT-rich composition (possibly accounting for their distinct induction chemistry). This work was published in the journals Molecular Cell and Cell, respectively (**refs #74, 76**).*

*While the identification of expanded repeats has lead to definitive diagnostic tests for their respective diseases, there has been a low uptake of such tests by at-risk, pre-symptomatic individuals in affected families for certain of these diseases (e.g. Huntington's Disease) because nothing can be done for individuals with a positive test result. For this reason, I moved MY lab to the University of Adelaide in 2001 for the specific purpose of utilizing the model organisms Drosophila and zebrafish to both model and genetically dissect the molecular pathways from the expanded repeat mutation to the clinical symptoms of these diseases. These studies have enabled the testing of various hypotheses including the role of RNA in the pathogenic process for the dominantly inherited neurodegenerative diseases. They have also enabled the analysis of the normal function of the genes responsible for these diseases with a view to understanding how the perturbation of these normal roles might contribute to pathogenesis (**see Chapter 6**)*

57. Fragile X Syndrome : Diagnosis Using Highly Polymorphic Microsatellite Markers.
American Journal of Human Genetics (1991) 48: 1051-1057.
Richards, R.I., ***Shen, Y.,*** Holman, K., Kozman, H., Hyland, V, Mulley, J., Sutherland, G.

I oversaw the Molecular Genetic component of this project. I conducted the majority of the experimental work, analysed and interpreted the data and wrote the draft and revised versions of the manuscript.

Citations 45

58. The fragile X genotype is characterized by an unstable region of DNA.
Science (1991) 252: 1179-1182.
Yu, S., Kremer, E., Pritchard, M., Lynch, M., Nancarrow, J., Baker, E., Holman, K., Mulley, J.C., Warren, S.T., Schlessinger, D., Sutherland, G.R., **Richards, R.I.**

This work was a 'team effort' but was also a key part of Sui Yu's PhD thesis. I supervised the experimental work, I oversaw the Molecular Genetic component of this project, contributed to the analysis and interpretation of the data, conceived of the overall content of the paper and wrote the draft and revised versions of the manuscript. ***Citations 875***

59. DNA instability at the fragile X maps to a trinucleotide repeat sequence p(CCG)n.
Science (1991) 252: 1711-1714.
Kremer, E., Pritchard, M., Lynch, M., ***Yu, S.,*** Holman, K., Warren, S.T., Schlessinger, D., Sutherland, G.R., **Richards, R.I.**

This work was a 'team effort' but was also a key part of Sui Yu's PhD thesis. I supervised the experimental work, I oversaw the Molecular Genetic component of this project, contributed to the analysis and interpretation of the data, conceived of the overall content of the paper and wrote the draft and revised versions of the manuscript. ***Citations 963***

60. Isolation of a human DNA sequence which spans the fragile X.
American Journal of Human Genetics (1991) 49: 656-661.
Kremer, E.J., ***Yu, S.,*** Pritchard, M., Nagaraja, R., Heitz, D., Lynch, M., Baker E., Hyland, V.J., Little, R.D., Wada, M., Toniolo, D., Vincent, A., Rousseau, F., Schlessinger, D., Sutherland, G.R., **Richards, R.I.**

This work was a key part of Sui Yu's PhD thesis. I supervised the experimental work, I oversaw the Molecular Genetic component of this project, contributed to the analysis and interpretation of the data, conceived of the overall content of the paper and co-wrote the manuscript ***Citations 56***

61. Hereditary unstable DNA : A new explanation for some old genetic problems?
Lancet (1991) 338: 289-292.
Sutherland, G, Haan, E., Kremer, E., Lynch, M., Pritchard, M., ***Yu, S.,*** **Richards, R.I.**

Grant Sutherland conceived of the overall content of the paper and I co-wrote the manuscript, edited the final version and amended the proofs. ***Citations 83***

62. Prenatal diagnosis of fragile X syndrome by direct detection of the characteristic unstable DNA sequence.
New England Journal of Medicine (1991) 325: 1720-1722.
Sutherland, G.R., ***Gedeon, A.,*** Kornman, L., Donnelly, A., Byard, R.W., Mulley, J.C., Kremer, E., Lynch, M., Pritchard, M., ***Yu, S.,*** **Richards, R.I.**

Grant Sutherland conceived of the overall content of the paper and I had a minor role in writing the manuscript. ***Citations 117***

63. Fragile X syndrome : Genetic localization by linkage mapping of two microsatellite repeats *FRAXAC1* and *FRAXAC2* which immediately flank the fragile site.
Journal of Medical Genetics (1991) 28: 818-823.
Richards, R.I., Holman, K., Kremer, E., Lynch, M., Pritchard, M., ***Yu, S.,*** Mulley, J., ***Kozman, H.,*** Sutherland, G.R.

I conducted the majority of the experimental work, analysed and interpreted the data and wrote the manuscript. ***Citations 148***

64. Fragile X syndrome : Unique genetics of the heritable unstable element.
American Journal Human Genetics (1992) 50: 968-980.
Yu, S., Mulley, J., Loesch, D., Turner, G., ***Gedeon, A., Donnelly, A.,*** Kremer, E., Lynch, M., Pritchard, M., Sutherland, G.R., **Richards, R.I.**

This work was a key part of Sui Yu's PhD thesis. It was Sui who first saw that the properties of the unstable repeat explained the Sherman Paradox. I supervised the experimental work, analysed and interpreted the data together with Sui Yu, and I wrote the manuscript (3 times - as this manuscript was rejected by 'Nature', then by 'Cell'). ***Citations 235***

65. Evidence of founder chromosomes in fragile X syndrome.
Nature Genetics (1992) 1: 257-260.
Richards, R.I., Holman, K., Friend, K., Kremer, E., Hillen, D., Staples A., Brown, W.T., Goonewardena, P., Tarleton, J., Schwartz, C., Sutherland, G.R.

I proposed the hypothesis that this work tested. I established the collaborations necessary to obtain sufficient material to replicate my initial findings, in multiple fragile X populations. I conducted the majority of the experimental work, analysed and interpreted the data and wrote the manuscript. ***Citations 196***

66. Fragile X syndrome unstable element, p(CCG)n, and other simple tandem repeat sequences are binding sites for specific nuclear proteins.
Human Molecular Genetics (1993) 2: 1429-1435.
Richards, R.I., Holman, K., ***Yu, S.,*** Sutherland, G.R.

I conceived the project and conducted and / or supervised the experimental work, analysed and interpreted the data and wrote the manuscript. ***Citations 149***

67. Haplotype analysis at the *FRAXA* locus in the Japanese population.
American Journal of Medical Genetics (1994) 51: 412-416.
Richards, R.I., Kondo, I., Holman, K., Yamauchi, M., Seki, N., Kishi, K., Staples, A., Sutherland, G.R., Hori, T.

I conducted and / or supervised the experimental work, analysed and interpreted the data and wrote the draft and revised versions of the manuscript. ***Citations 38***

68. Implications of *FRA16A* structure for the mechanism of chromosomal fragile site genesis.
Science (1994) 264: 1938-1941.
Nancarrow, J.K., Kremer, E., Holman, K., Eyre, H., Doggett, N., Le Paslier, D., Callen, D.F., Sutherland, G.R., **Richards, R.I.**

This work was a key part of Julie Nancarrow's PhD thesis. I supervised the experimental work, contributed to the analysis and interpretation of the data and wrote the draft and revised versions of the manuscript. ***Citations 153***

69. *FRAXAC2* instability.
Nature Genetics (1994) 7: 122-123.
Richards, R.I., Holman, K., Friend, K., Staples, A., Sutherland, G.R., Oudet, C., Biancalana, V., Mandel J.-L.

I wrote this letter in response to a manuscript that appeared to contradict our earlier findings (i.e. in reference #71). ***Citations 9***

70. Physical linkage of the fragile site *FRA11B* and a Jacobsen syndrome chromosome deletion breakpoint in 11q23.3.
Human Molecular Genetics (1994) 3: 2123-2130.
Jones, C., Slijepcevic, P, Marsh, S., Baker, E., Langdon, W.Y., **Richards, R.I.**, Tunnacliffe, A.

I established this collaboration with Alan Tunnacliffe and Chris Jones. I supervised part of the experimental work, analysed and interpreted some of the data and I had a significant role in writing the manuscript. ***Citations 98***

71. Molecular basis of p(CCG)n repeat instability at the *FRA16A* fragile site locus.
Human Molecular Genetics (1995) 4: 367-372.
Nancarrow, J.K., Holman, K., Mangelsdorf, M., Hori, T., Denton, M., Sutherland, G.R., **Richards, R.I.**

This work was a key part of Julie Nancarrow's PhD thesis. I supervised the experimental work, contributed to the analysis and interpretation of the data and wrote the draft and revised versions of the manuscript. ***Citations 47***

72. Association of a chromosome deletion syndrome with a fragile site within the proto-oncogene *CBL2*
Nature (1995) 376: 145-149.
Jones, C., Penny, L., Mattina, T., ***Yu, S.,*** Baker, E., Voullaire, L., Langdon, W.Y., Sutherland, G.R., **Richards, R.I.**, Tunnacliffe, A.

I established this collaboration with Alan Tunnacliffe and Chris Jones. I supervised part of the experimental work, analysed and interpreted some of the data and I had a significant role in writing (several versions of) the manuscript – one of which was rejected by 'Science'.
Citations 219

73. Dynamic Mutation Loci: Allele distributions in different populations.
Annals of Human Genetics (1996) 60: 391-400.
Richards, R.I., Crawford, J., Narahara, K., Friend, K., Mangelsdorf, M., Staples, A., Denton, M., Easteal, S., Hori, T-A., Kondo, I., Jenkins, T., Goldman, A., Panich, V., Ferakova, E., Sutherland, G.R.

I established the collaborations needed to assemble the DNA samples from various populations. I conducted and / or supervised the experimental work, analysed and interpreted the data and wrote the draft and revised versions of the manuscript. ***Citations 29***

74. Human chromosomal fragile site *FRA16B* is an amplified AT-rich minisatellite repeat
Cell (1997) 88: 367-374.
Yu, S., Mangelsdorf, M., Hewett,D., Hobson, L., Baker, E., Eyre, H., ***Lapsys, N.,*** Le Paslier, D., Doggett, N., Sutherland, G.R., **Richards, R.I.**

Part of this work was a component of Naras Lapsys's PhD thesis. Sui Yu had returned to our lab as a post-doctoral fellow. I established the crucial collaboration with Denis LePaslier (CEPH) to enable isolation of YACs spanning the fragile site. I supervised the experimental work, contributed to the analysis and interpretation of the data and wrote the draft and revised versions of the manuscript. ***Citations 199***

75. Genetic Heterogeneity in Familial Myelogenous Leukemia: Evidence for a Second Locus on Chromosome 16q21-23.2.
American Journal of Human Genetics (1997) 61: 873-881.
Horwitz, M., Benson, K.F., Li, F-Q., Wolff, J., Leppert, M.F., Hobson, L., Mangelsdorf, M., ***Yu, S.,*** Hewett, D., **Richards, R.I.**, Raskind, W.H.

I established the collaboration with Marshall Horwitz. I supervised part of the experimental work analysed and interpreted some of the data and I had a minor role in writing the manuscript. ***Citations 44***

76. *FRA10B* Structure Reveals Common Elements in Repeat Expansion and Chromosomal Fragile Genesis.
Molecular Cell (1998) 1: 773-781.
Hewett, D.R, Handt ,O., Mangelsdorf, M., Hobson, L., Eyre, H., Baker, E., Sutherland, G.R., Schuffenhauer, S., Mao, J., **Richards, R.I.**

I established the crucial collaborations with Drs Schuffenhauer and Mao. I supervised the experimental work, analysed and interpreted the data and wrote the draft and revised versions of the manuscript ***Citations 101***

77. CAG repeat expansion in autosomal dominant familial spastic paraparesis: novel expansion in a subset of patients.
Human Molecular Genetics (1998) 7: 1779-1786.
Benson, K.F., Horwitz, M., Wolff, J., Friend, K., Thompson, E., White, S., **Richards, R.I.**, Raskind, W.H., Bird, T.D.

I supervised part of the experimental work and I had a minor role in writing the manuscript ***Citations 31***

78. Detection of a novel missense mutation and second recurrent mutation in the *CACNA1A* gene in individuals with EA-2 and FHM
Human Genetics (1999) 105: 261-265.
Friend, K., Crimmins, D., Phan, T.G., Sue, C.M., Colley, A., Fung, V.S.C., Morris, J.G.L., Sutherland, G.R., **Richards, R.I**

This work forms the core of Kathryn Friend's PhD thesis. I supervised the experimental work and I had a minor role in writing the manuscript. ***Citations 87***

79. Analysis of replication timing at the *FRA10B* and *FRA16B* Fragile Site loci.
Chromosome Research (2000) 8: 677-688.
Handt, O., Baker, E., Dayan, S., Gartler, S., Woollatt, E., **Richards, R.I.**, Hansen, R.S.

I established this collaboration with Drs Hansen and Gartler, supervised part of the experimental work, analysis and interpretation of data, and I had a minor role in writing the manuscript. ***Citations 45***

Expression of three zebrafish orthologs of human FMR-1-related genes and their phylogenetic relationships
Developmental Genetics and Evolution (2004) 214: 567-574.
Tucker, B., **Richards, R.I.,** and Lardelli, M

80. Autosomal dominant congenital non-progressive ataxia overlaps with the *SCA15* locus.
Neurology (2004) 63: 2288-2292.
Dudding, T.E., ***Friend, K.,*** Schofield, P., Lee,S, Wilkinson, I.A., and **Richards, R.I.**

This work was a key part of Kathie Friend's PhD thesis. I supervised part of the project and had a minor role in writing of the manuscript. ***Citations 79***

REVIEWS

81. Fragile X Syndrome : The molecular picture comes into focus.
Trends in Genetics (1992) 8: 249-255.
Richards, R.I., Sutherland, G.R.

I led the writing of this review article ***Citations 61***

82. Heritable unstable DNA sequences.
Nature Genetics (1992) 1: 7-9.
Richards, R.I., Sutherland, G.R.

I led the writing of this article. ***Citations 152***

83. Invited Editorial : Anticipation Legitimized : Unstable DNA to the Rescue.
American Journal of Human Genetics (1992) 51: 7-9.
Sutherland, G.R., **Richards, R.I.**

I had a minor role in the writing of this review article. ***Citations 36***

84. Dynamic Mutations : A new class of mutations causing human disease.
Cell (1992) 70: 709-712.
Richards, R.I., Sutherland, G.R.

I coined the term 'Dynamic Mutation' and I led the writing of this article. ***Citations 383***

85. Fragile X Syndrome : The most common cause of familial intellectual handicap.
Medical Journal of Australia (1993) 158: 482-485.
Sutherland, G.R., Mulley, J.C., **Richards, R.I.**

I had a minor role in the writing of this review article. ***Citations 15***

Fragile sites and unstable elements.
Chromosomes Today (1993) 11: 215-226.
Richards, R.I., Sutherland, G.R.

86. Dynamic mutations on the move.
Journal of Medical Genetics (1993) 30: 978-981.
Sutherland, G.R., **Richards, R.I.**

I had a major role in the writing of this review article. ***Citations 27***

Dynamic mutation.
American Scientist (1994) 82: 157-163.
Sutherland, G.R., **Richards, R.I.**

87. Simple repeat DNA is not replicated simply.
Nature Genetics (1994) 6: 114-116.
Richards, R.I., Sutherland, G.R.

I led the writing of this article.

Citations 365

88. Simple tandem DNA repeats and human genetic disease.
Proceedings of the National Academy of Science USA (1995) 92: 3636-3641.
Sutherland, G.R., **Richards, R.I.**

I made a significant contribution to the writing of this review article. ***Citations 401***

89. The molecular basis of fragile sites in human chromosomes.
Current Opinion in Genetics and Development (1995) 5: 323-327.
Sutherland, G.R., **Richards, R.I.**

I made a significant contribution to the writing of this review article. ***Citations 114***

Fragile sites *in* 'Encyclopedia of Molecular Biology' volume II, 313-318. (1996)
Sutherland, G.R., Baker, E., **Richards, R.I.**

90. Repeat Offenders: Simple Repeat Sequences and Complex Genetic Problems.
Human Mutation (1996) 8: 1-7.
Richards, R.I., Sutherland, G.R.

I led the writing of this article. ***Citations 20***

Fragile sites, repeat instability and cancer.
Todays' Life Science (1996) 8: 14-18.
Richards, R.I., ***Yu, S.***

91. Dynamic Mutation: Possible Mechanism and Significance in Human Disease
Trends in Biochemical Sciences (1997) 22: 432-436.
Richards, R.I., Sutherland, G.R.

I led the writing of this article. ***Citations 107***

92. Fragile Sites Still Breaking
Trends in Genetics (1998) 14: 501-506.
Sutherland, G.R., Baker, E., **Richards, R.I.**

I made a significant contribution to the writing of this review article. ***Citations 191***

93. Fragile sites - cytogenetic similarity with molecular diversity
American Journal of Human Genetics (1999) 64: 354-359.
Sutherland, G.R. and **Richards, R.I.**

I made a significant contribution to the writing of this review article. ***Citations 47***

Okazaki fragments in dynamic mutation
Trends in Genetics (1999) 15: 10.
Sutherland, G.R., Baker, E., **Richards, R.I.**

94. Fragile sites and minisatellite repeat instability
Molecular Genetics and Metabolism (2000) 70: 99-105.
Handt, O., Sutherland, G.R. and **Richards, R.I.**

Oliva Handt and I co-wrote this review ***Citations 40***

95. Dynamic Mutations: a decade of unstable expanded repeats
Human Molecular Genetics (2001) 10: 2187-2194.
Richards, R.I.

I wrote this article. ***Citations 133***

Dynamic Mutations *in 'Encyclopedia of Genetics'* (2001) pp 593-597.
Richards, R.I. and Sutherland, G.R.

Fragile X Syndrome *in 'Encyclopedia of Genetics'* (2001) pp 726-728.
Sutherland, G.R. and **Richards, R.I.**

Polyglutamine repeats *in 'Encyclopedia of Molecular Medicine'* John Wiley, (2002)
Richards, R.I. and ***Friend, K.***

Dynamic Mutations on the Move in Banff *Nature Genetics,* (2004) 36: 667-670.
La Spada, A.R., **Richards, R.I.** and Wieringa, B.

RNA-Mediated Neurodegeneration Caused by the Fragile X Premutation rCGG Repeats in *Drosophila Chem. Tracts* (2005) 18: 153 – 158.
Richards, R.I. and ***McLeod, C.***

Chromosomal Fragile Sites: Molecular Basis and Pathogenic Consequences *in Genetic Instabilities and Hereditary Neurological Diseases, Volume 2, R. Wells and T. Ashizawa eds. Chapter 12, pages 195 – 207* (2006)
Richards, R.I.

LIBRARY NOTE:

The following Chapter 5 publications have been removed due to copyright.

Chapter 6. Pathogenic pathways from expanded repeat mutation to disease: 'Non-self' Mutations and the autoinflammatory mechanism of neurodegenerative diseases

Citations 488

*These manuscripts detail our efforts to model expanded repeat diseases in Drosophila and zebrafish. The overall aim was to utilize these models to discover the responsible pathogenic pathways and thereby identify targets for therapeutic invention in the human diseases. Experiments in zebrafish were able to assess the consequences on development of reduced protein levels of either FMRP (**ref #97**) or huntingtin (**refs #98, 99**).*

*In the Drosophila model we tested the idea that expanded repeat RNA in one form or other might by the common proximal pathogenic agent in the dominantly inherited expanded repeat diseases that exhibit the common pathology of neurodegeneration (**refs #96, 100-102, 104, 105**). This idea was based on the observation that all expanded repeat loci are transcribed (typically off both strands) but not all expanded repeats encoded proteins – or even when aberrantly translated the resultant polypeptides were unrelated. The experimental data led to the hypothesis that the dominantly inherited expanded repeat diseases are due to an autoinflammatory disease mechanism whereby the expanded repeat encoded double-stranded RNA synthesized from bi-directional transcription, is no longer correctly modified and is therefore recognized as 'non-self' even when it is produced endogenously (**refs #106-108**). This recognition elicits the anti-viral RNA pathway that typically recognizes long double strand viral RNA and includes cell death as a normal containment strategy for exogenous RNA (such as that from viruses) but leads to pathology for endogenously expressed 'non-self' RNA (**ref #105).***

96. The pathogenic agent in *Drosophila* models of 'polyglutamine' diseases.
Human Molecular Genetics (2005) 14: 1041-1048.
McLeod, C., O'Keefe, L. and **Richards, R.I.**

This work forms the core of Catherine McLeod's PhD thesis. I proposed the hypothesis that was being tested, I supervised the project, analysed and interpreted the data and had a minor role in writing of the manuscript. ***Citations 41***

97. Contribution of mGluR and Fmr1 Functional Pathways to Neurite Morphogenesis, Craniofacial Development and Fragile X Syndrome.
Human Molecular Genetics (2006) 15: 3446-3458.
Tucker, B., **Richards, R.I.,** and Lardelli, M.

This work forms the core of Ben Tucker's PhD thesis. I jointly supervised Ben with Michael Lardelli. Ben wrote the first draft of the manuscript and subsequent revisions with my and Michael's input. While I instigated the project Ben took up the challenge to make it work experimentally and it is Ben's model in this paper that also graces the cover of the journal issue in which it was published. ***Citations 115***

98. Huntingtin deficient zebrafish exhibit defects in iron utilization and development.
Human Molecular Genetics (2007) 16: 1905-1920
Lumsden, A.L., Henshall, T., Dayan, S., Lardelli, M., and **Richards, R.I.**

This work forms the core of Amanda Lumsden's PhD thesis. I was Amanda's major supervisor and instigated this project. Amanda identified and experimentally validated the significant role of huntingtin in iron metabolism. Amanda wrote the first draft and subsequent revisions after input from myself and the other co-authors. ***Citations 134***

99. Selective neuronal requirement for Huntingtin in the developing zebrafish.
Human Molecular Genetics (2009) 18: 4830-4842.
Henshall, T.L., Tucker, B., Lumsden, A.L., Nornes, S., Lardelli, M.T and **Richards, R.I**

This work forms the core of Tanya Henshall's PhD thesis. I was Tanya's major supervisor and instigated this project. Tanya identified and experimentally validated the significant role of huntingtin in early nervous system development. Tanya wrote the first draft and subsequent revisions after input from myself and the other co-authors. ***Citations 41***

100. Perturbation of the Akt/Gsk3-β signalling pathway is common to Drosophila expressing expanded untranslated CAG, CUG and AUUCU repeat RNAs.
Human Molecular Genetics **(**2011) 20: 2783-2794.
van Eyk, C.L., O'Keefe, L.V., Lawlor, K.T., Samaraweera, S.E., McLeod, C.J., Price, G.R., Venter, D.J., and. **Richards R.I.**

This work forms the core of Clare van Eyk's PhD thesis. I was Clare's major supervisor and instigated this project and the collaboration, with Deon Venter, required to complete it. Clare wrote the first draft and subsequent revisions after input from myself and the other co-authors. ***Citations 29***

101. Double stranded RNA is pathogenic in *Drosophila* models of expanded repeat neurodegenerative diseases
Human Molecular Genetics (2011) 20: 3757–3768.
Lawlor, K.T., O'Keefe, L.V., ***Samaraweera, S.,*** van Eyk, C., McLeod, C.J., Maloney, C., Dang, T., Suter C. and **Richards, R.I.**

This work contains key components of the PhD theses of Kynan Lawlor and Saumya Samaweera. Along with Louise O'Keefe I was supervisor for both and instigated this project. and the collaboration, with Cath Suter, required to complete it. I wrote the first draft and subsequent revisions after input from the other co-authors. ***Citations 48***

102. Ubiquitous Expression of CUG or CAG Trinucleotide Repeat RNA Causes Common Morphological Defects in a Drosophila Model of RNA-Mediated Pathology.
PLoS ONE (2012) 7(6): e38516. doi:10.1371/journal.pone.0038516
Lawlor, K.T., O'Keefe, L.V., ***Samaraweera, S.E.,*** van Eyk, C.L., **Richards, R.I.**

This work contains key components of the PhD thesis of Kynan Lawlor. Along with Louise O'Keefe I was supervisor and instigated this project. Kynan Lawlor wrote the first draft and I rewrote subsequent revisions after input from the other co-authors.
Citations 10

103. Comparative Toxicity of Polyglutamine, Polyalanine and Polyleucine Tracts in Drosophila Models of expanded repeat disease
Human Molecular Genetics (2012) 21: 536-547.
van Eyk, C.L., McLeod, C.J., O'Keefe, L.V., and **Richards, R.I.**

Clare van Eyk undertook these studies as a post-doctoral fellow under my and Louise O'Keefe's supervision. Clare wrote the first draft and I rewrote subsequent revisions after input from the other co-authors. ***Citations 17***

104. Distinct roles for Toll and autophagy pathways in double-stranded RNA toxicity in a Drosophila model of expanded repeat neurodegenerative diseases.
Human Molecular Genetics (2013) 22: 2811-2819. PMID: 23719916
Samaraweera, S.E., O'Keefe, L.V., Price, G.R., Venter D.J. and **Richards, R. I.**

This work contains the major components of the PhD theses of Saumya Samaweera. Along with Louise O'Keefe I was supervisor and instigated this project. Saumya and I wrote the first draft and I rewrote subsequent revisions after input from the other co-authors. ***Citations 16***

105. Non-self Mutation: Double-stranded RNA elicits antiviral cell death response in a Drosophila model of expanded CAG repeat neurodegenerative diseases
Human Molecular Genetics (2019) *doi/10.1093/hmg/ddz096/5487598*
van Eyk, C.L., ***Samaraweera, S.E., Scott, A.,*** Webber, D.L., Harvey, D.P., O'Keefe, L.V., Cropley, J.E., Young, P., Ho, J., Suter C., and **Richards R.I.**

This work contains the major components of the PhD theses of Andrew Scott and Saumya Samaweera. Along with Louise O'Keefe I was supervisor and instigated this project. I wrote the first draft and I rewrote subsequent revisions after input from the other co-authors.

REVIEWS and HYPOTHESES

Dynamic mutations: where are they now?
Chapter in 'Tandem Repeats and Dynamic Mutations Leading to Neurological Disorders' (A, Hannan, ed) Adv Exp Med Biol. 2012; ***769****: 55-77.*
van Eyk, C.L. and ***Richards, R.I.*** *(2012)*

Modeling and Analysis of Repeat RNA Toxicity in Drosophila
Methods Mol Biol.(2013) **1017**: 173-192. doi: 10.1007/978-1-62703-438-8_13.
Samaraweera, S.E., O'Keefe, L.V., van Eyk, C.L., Lawlor, K.T., Humphreys D.T., Suter, C.M. and **Richards, R.I.**

106. RNA pathogenesis via Toll-like receptor-activated inflammation in expanded repeat neurodegenerative diseases
Frontiers in Molecular Neuroscience (2013) 6: 25 doi: 10.3389/fnmol.2013.00025.
Richards, R.I., Samaraweera, S.E., van Eyk, C.L., O'Keefe, L.V., Suter C.M.

I wrote this manuscript with numerous consultations with my colleagues. I wrote the revised and resubmitted version. ***Citations 10***

"Dynamic Mutations (Revised)" *In Brenner's Online Encyclopedia of Genetics 3e* (2016)
Richards, R.I. ***Encyclopedia***

107. ***The Enemy Within: Innate Surveillance-mediated Cell Death, the common mechanism of neurodegenerative disease.***
Front. Neurosci. (2016) *Doi: 10.3389/fnins.2016.00193*
Richards, R.I., Robertson, S.A., O'Keefe, L.V., Fornarino, D., Scott, A., Lardelli, M, Baune, BT

I formulated the central hypothesis put forward. I wrote this manuscript after numerous consultations with my colleagues. I wrote the revised and resubmitted version. ***Citations 24***

Guidelines for the Use and Interpretation of Assays for Monitoring Autophagy (3rd edition) Autophagy, (2016) ***12****(1): 1-222.*
Klionsky, D.J. and >2,000 co-authors including ***Richards, R.I.***

108. Neurodegenerative diseases have genetic hallmarks of autoinflammatory disease
Human Molecular Genetics (2018) 27(R2):R108-R118. doi: 10.1093/hmg/ddy139.
Richards, R.I., Robertson, S.A., Kastner, D.L.

I formulated the central hypothesis put forward. I wrote this manuscript after numerous consultations with my colleagues. I wrote the revised and resubmitted version. ***Citations 3***

LIBRARY NOTE:

The following Chapter 6 publications have been removed due to copyright.