



From Professor Nick Martin:

The aim of QIMR's numerous genetic projects is to understand what causes differences between people in their behaviour, habits, and risk of disease. We specifically want to know how important genes and environment are for these differences.

This interest is not just academic. If we can show that a characteristic is largely caused by environmental factors, there is a greater chance that we can identify which aspects of the environment (diet, sun exposure, infections) can be changed to improve it.

If, on the other hand, we show that genes are more important than environment, we have a realistic chance of finding the particular genes involved because of recent breakthroughs in molecular biology. Ultimately this may lead to new and better drug treatments and more effective screening tests.

One very nice thing about working in Australia is that so many people are happy to give their time freely and willingly to help medical research. Receipt of this newsletter indicates that you are one of these and we are grateful.

In trying to cover all projects in so little space, coverage is necessarily brief. If you would like more details, I encourage you to look at our website, where you will find links to all our research publications.

# Research Update: Genes & Health

Twin & Family Studies at the  
Queensland Institute of Medical Research

# 2008

<http://genepi.qimr.edu.au>

**FRECALL 1800 257 179**

## Queensland Twin Registry



The Queensland Twin Registry was established by Professor Nick Martin, the head of the Genetic Epidemiology Unit at QIMR. Q Twin is a population based registry of identical and non-identical twins of all ages.

All adult & child twins, born in or currently living in Queensland are eligible to register. Triplets & other multiples are also eligible to register. Membership of the registry is **FREE**.

Twins Helping  
Medical Research

You can register by filling in a Q Twin Registration form and mailing or faxing it back to us. You can also register online at [www.qtwin.org.au](http://www.qtwin.org.au)

Queensland  
Twin Registry

You can be involved in current research projects looking in to:

Twin parents and their children, twin adolescent studies, twinning in families, genetics of brain ageing, inattention, substance misuse & mental health, eating disorders, human behaviour and health outcomes, breast feeding study and genetics in decision making.

Registering with Q Twin does not mean you are obliged to participate in any particular study. We will contact you about each new study that is proposed and invite you to consider participating.

For more information, phone 1800 257179 (Free Call), or email [info@qtwin.org.au](mailto:info@qtwin.org.au)

## New Studies at the Unit

### Money in your Genes?

Identifying the sources of behavioural variation has long been the predominant goal of researchers. Why do some people take risks with their investments while others play it cautiously? Why do some contribute to charities while others do not? Why do some people join large public-interest groups while others do not?

Money in Your Genes, a new study being conducted jointly by Virginia Commonwealth University and QIMR, is a study of money, rationality, politics and risk. At QIMR we will be inviting participants, aged 19-30 years old, from the Twin Moles and MAPS studies to complete a series of online economic games.

Participants will be asked to decide how to divide or invest sums of money and answer questions about their opinions and attitudes on various economic, political and social matters.

### Older Australian Twins Study (OATS)

Age affects us all in different ways, but it is still unclear why some people age better, with good mental and physical abilities, and others not so well, with reduced thinking and physical functions. What influences the process and rate of ageing? Is it our genes? Is it our lifestyle, diet, or medical conditions?

The Older Australian Twins Study (OATS) aims to find out what influences memory and thinking as we age, and in order to do this we need to study twins, both identical and non-identical, and their brothers and sisters aged 65 years or older. With few exceptions, we invite everyone to participate, regardless of whether or not you have memory or health problems. We hope that the results from our study will lead to approaches that could slow the ageing process and prevent age-related decline in function and age-related diseases such as Alzheimer's disease.

This study is being conducted in New South Wales, Victoria, and Queensland, with an NHMRC/Ageing Well Ageing Productively grant. The Principal investigator of the study is Prof. Perminder Sachdev from the University of New South Wales, and the Queensland component of the study is conducted by Dr. Margie Wright, Prof. Nick Martin and colleagues from the Genetic Epidemiology Unit at the Queensland Institute of Medical Research.

Participation involves a visit to the Queensland Institute of Medical Research (next to Royal Children's Hospital) at Herston, for an assessment of your memory and thinking, and general health and well being. If you are a twin or the sibling of a twin aged 65 or older, and are interested in learning more about this research please contact us on 1800 81 TWIN (1800 81 8946). All enquiries are confidential.

# What Have We Found So Far?

To read more about our work  
and obtain research papers visit  
our website:  
<http://genepi.qimr.edu.au>

## Anxiety & Depression

From questionnaires completed by twins and their siblings we have found that about ~20% of people experience major depression (MD) sometime in their life. This estimate is very much in line with other studies of populations, but is much higher than the ~3% of people requiring treatment at a hospital psychiatric clinic. Our surveys have confirmed that there is a genetic component to major depression as the prevalence of MD is higher in siblings of individuals with MD than in those without. About 50% of people with MD suffer from anxiety disorders, and this type of depression has a greater tendency to run in families. We have conducted a number of studies designed to identify genetic variants with increase risk to MD. No genetic variants of large effect have

been identified. The general picture that emerges is that we expect there to be many, many genetic variants each contributing a small increased risk to MD. In order to identify these variants with certainty, extremely large study samples are required, of the order of 10,000 cases and 10,000 controls. To achieve study samples of this size, groups around the world have joined forces in a Psychiatric Genetics Consortium funded by the US National Institute of Health. The questionnaires completed by our study participants are going to prove extremely valuable in the next stage of this research because the many questions probe subtle differences in the types of anxiety and depression symptoms individuals may experience.

## Endometriosis

Endometriosis is a common condition with severe consequences for many women. Our program aims to understand pathways that cause this disease. Around 4000 women with surgically confirmed endometriosis have participated in our study. Adding parents and other family members brings the total to around 10,000 individuals across Australia. We identified a region on chromosome 10 that contains a gene or genes that may lead to increased risk of the disease and are currently conducting a detailed study to find these genes.

We also contribute to an international consortium known as the International Endogene Consortium. Recent advances in human genetics have made it possible to find genes contributing to many complex diseases. As part of the consortium we are using these methods to search all chromosomes to find the genes that contribute to risk of endometriosis.

### How do you find genes?



By producing genotyping data from purified DNA we look for genetic linkages between a condition/disease and one or more regions of a chromosome.

When a genetic link is found, the next step is finding the exact gene responsible. This is done by using a range of molecular biology techniques including looking directly at the composition of the DNA. This process is time consuming, highly skilled, and very expensive - but we could do nothing at all without your DNA.

Incidentally, identical twins are vital to the earlier stages of our research but when it comes to actually finding the genes, it is non-identical twins and their brothers and sisters who are crucial to our success.

## Twinning in Families

Why do some families have lots of twins in their family tree? Female relatives of mothers with non-identical twins are more likely to have non-identical twins themselves. Our research is focused on finding out why this happens to some women. The increased frequency of twins is partly due to a tendency for increased multiple ovulation (releasing two or more eggs in some cycles). We have shown that a small number of families carry variants in a gene expressed in developing eggs that contribute to increased twinning. We are currently searching for gene variations that contribute to increased twinning in other families.



## Migraine

Since our previous update we have replicated a number of chromosomal regions implicated in our genome-wide searches for migraine susceptibility genes, resulting in numerous high profile journal articles. We are also principal partners in a large international consortium of leading migraine researchers working together to identify migraine genes. In September of this year, we received our first batch of 610,000 single nucleotide polymorphisms (SNPs) genotyped in 993 migraine sufferers from our Australian twin families (over 605 million genotypes!). This is a very exciting stage of our migraine research as these SNPs will help us identify the specific genes underlying migraine susceptibility.

## To see or not to see?

Individuals who have trouble seeing distant objects have myopia (short-sightedness). This condition can have a large impact on an individual's quality of life, is expensive for society as a whole and the incidence is increasing. Axial length is a specific measurement from the front to back of the eye; this distance is longer than normal when a person is short-sighted. In a recent study, 893 individuals had the axial length in each eye measured. We found that genetic factors explained approximately 80% of the axial length values.

A genome scan performed on 318 individuals suggested that chromosome 5 (specifically the 5q region) is involved in the inheritance of axial length. Improving our knowledge of the heritability of various eye components can help us better understand eyesight problems and may lead to advanced screening, preventative, and treatment options.



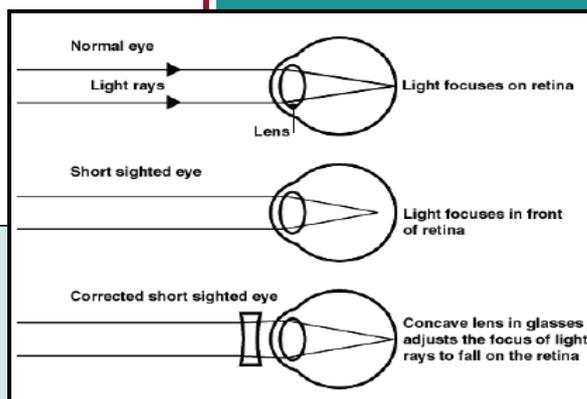
## Why do some of us have blue eyes?

Our group at QIMR has solved the age-old problem of why some of us have blue eyes. Together with Dr Rick Sturm at the University of Queensland, we found a single change in a gene on chromosome 15 called HERC2. One version of this allows binding of a factor that allows reading of the gene next door called OCA2 and leads to brown eye colour. But the other version does not allow binding, so OCA2 is not able to be read, so there is no brown pigment and the eyes are blue. This discovery will enable accurate prediction of eye colour of suspects in forensic investigations. Perhaps more importantly, these genes seem to be involved in melanoma risk and further investigation will allow us to predict those most vulnerable to melanoma so they can take preventative actions.

## 19UP

QIMR, in conjunction with the Brain and Mind Research Institute (BMRI) in Sydney, is conducting a new study for participants aged 19 years and older. Over 75% of mental disorders commence before age 25. The onset of many mental disorders during the critical period of adolescence or early adult life coincides with the later stages of frontal lobe maturation. There is widespread concern that adverse impacts during this critical developmental period may have life-long behavioural, cognitive and social consequences. The brain changes that occur with concomitant changes in social and neuropsychological function prior to the onset of mental disorders need to be explored. The extent of such effects, however, may be dependent on other genetic factors which mediate structural brain changes or risk to mental disorders.

Large twin studies examining genotypes are ideal to explore these changes and the use of relevant new technologies, such as MRI, can help to disentangle the potential determinants of changes in brain structure and function.



## Height: the long and the short of it

The genetics of height has been studied for over a century, because it shows a strong resemblance between relatives and has a typical bell-shaped distribution in the population. Height has also been associated with a number of diseases. We have shown in a number of studies that use twins and their siblings that the heritability of height is very high, about 80 to 90%. This means that of all variation between people in height, about 80 to 90% is because of genetic difference between these people. We found that self-reported height is almost as accurate as clinically measured height, which is re-assuring and evidence that participating twin families take care when filling in questionnaires or answering questions on the phone.

Most people shrink a bit when they get older but forget about this when self-reporting height. Quite understandable - presumably everyone remembers their height from measurements when they were young or simply report the measure as given in their passport. We are now conducting research in finding genes that can explain some of the variation in height between people. Worldwide, a total of about 50 such genes have now reported, and we hope to add to this list in the near future.

## Melanoma

Melanoma, the deadliest form of skin cancer, has long been known to be caused by sun exposure, but some people are more likely to develop melanoma than others. We have undertaken a large study aiming to better understand the genetic basis of melanoma. In the initial stages of our study, we focused on people affected by melanoma from Queensland, with people from across Australia included in the later stages.

We published a major finding in July 2008 (*Nature Genetics*, 40(7):838-40), in which we found genetic variants on chromosome 20 to be important determinants of melanoma risk. Such variants are carried by one in six people in Queensland, with carriers at almost a two-fold increased risk of developing the disease.

This work is important because the 5-year survival rate is dramatically higher for patients diagnosed in the early rather than late stages of the disease. Despite decades of research, metastatic melanoma remains an incurable disease and early detection is perhaps our best hope. An understanding of the genetic factors influencing risk of developing melanoma is crucial to the identification of at-risk individuals and could greatly increase early-detection of the disease.

## Cannabis

QIMR is currently undertaking a unique, large-scale twin study on Cannabis use and Mental Health across Australia. There is a growing recognition that cannabis is widely used in the community yet little is known about the side effects of marijuana and the genetic and environmental factors that lead to the increased use of this drug. QIMR, in collaboration with Washington University USA, is collecting information from twins and their siblings on their use of cannabis and other illicit drugs, and their mental health in order to address these and other important questions about this drug.

We have interviewed approximately 3,000 twins and siblings and aim to interview another 3,000 more. We have found that some lifetime experience with cannabis is common in this cohort: 72% of men and 67% of women report lifetime cannabis use. While many reporting lifetime cannabis use had used the drug only infrequently, 14% of men and 7% of women reported using cannabis on a daily basis at some time in their lives. Results are only preliminary, but the data appears to suggest a genetic variation in a person's initiation to using cannabis and the effects that cannabis has on a person.

## PACER

The PACER project (Parents and their Children Environmental Risk) is one of many family studies conducted at QIMR. Data is currently being collected from over 2,000 twin parents and their children in an attempt to disentangle the genetic and environmental components of drinking, smoking and health-related behaviours.

This longitudinal project will compare children of twins over time to identify specific high risk exposures and environments that can lead to particular child outcomes, such as Attention Deficit and Hyperactivity Disorder (ADHD), Conduct Disorder, smoking and drinking behaviours, depression, and anxiety.

The project has recently shifted from the initial parent interview stage onto phase 2, the child interview phase. Preliminary analysis indicates that there appears to be a genetic risk for externalising behaviours such as ADHD and Conduct Disorder. The study will continue to run for the next 5 years.

## Genetics of Brain Structure and Function (Twin Imaging Study)

We are conducting an exciting new study that investigates, using Magnetic Resonance Imaging (MRI), the different roles of genes and the environment in shaping brain structure and function. This work has the potential not only to advance our understanding of normal brain development, but to provide greater knowledge of developmental disorders and diseases that affect the brain.

The study is funded by The National Institutes of Health, United States, and we are conducting it with Dr. Greig de Zubicaray and Dr. Katie McMahon from the Centre for Magnetic Resonance (CMR) at the University of Queensland, and Dr Paul Thompson and Professor Arthur Toga from the University Of California Los Angeles School Of Medicine.

Participation involves an MRI examination lasting 1 hour, which will take place in the MRI suite at the Wesley Hospital (Brisbane). At completion, in appreciation of your time and willingness to take part in the study, you will receive a Coles Myer voucher to the value of \$100.

## MATCH—Twin Mothers And Their Children

We are currently in year 9 of this project. Recent analyses have focused on the relationship between maternal smoking during pregnancy and child conduct problems, both with and without maternal alcoholism. Compared to control families where neither mother nor her twin sister has a history of alcohol use disorder, rates of problems are significantly elevated if there is a maternal history of alcohol dependence or alcohol

abuse, but also for children of a non-alcoholic mother with an MZ twin sister who has a history of alcohol abuse or dependence. Controlling for maternal genetic risk of alcohol use disorder, maternal smoking during pregnancy beyond the 1st trimester and maternal heavy smoking beyond the 1st trimester (more than 15 cigarettes per day) remain strong predictors of risk of child conduct problems.

An area of increasing emphasis is the domain of environmental risk exposures associated with parental marital separation and divorce. There is a striking three-way interaction of parental alcoholism, parental marital separation and offspring gender – separation from an alcoholic parent is indeed associated with a reduced risk of both early onset alcohol use, and of alcohol dependence, but only in male offspring.

**Acknowledgement ~ This edition of the Genetic Epidemiology Newsletter was made possible due to the generous donation from the Maxwell Drake Estate.**



**Twins Lisa and Jess from “The Veronicas” also participated in our MRI project.**

**If you have changed address or phone number please let us know:**

Queensland Twin Registry  
Genetic Epidemiology Unit  
Queensland Institute of  
Medical Research  
Post Office, Royal Brisbane Hospital  
HERSTON, QLD 4029



**Phone: 1800 257179 (Free Call)**