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.

From Professor Nick Martin:

The Australian Twin Migraine Study

Migraine is a frequent, debilitating and painful disorder that normally affects people during their most productive years. Although migraine is highly prevalent in our society (affecting 25% of females and 7.5% of males), its aetiology remains obscure. Our laboratory has recently completed a study in which at least one novel gene was implicated. Importantly, our results indicate the presence of additional genes contributing towards migraine susceptibility.

We also recently reported that genetic influences explain the co-occurrence of migraine and endometriosis (another trait our research is leading the world in) within women. Our research is making a substantial contribution to understanding the underlying genetic architecture and biological pathways of migraine and endometriosis.

New Study Social Attitudes, Economics and Emotion

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 (even though their participation will not make a difference in the achievement of group goals) while others do not?

Identifying the sources of behavioural variation has long been the predominant goal of the social sciences. This is a new study looking at how people form attitudes, read emotions, and make decisions about the way they invest money. The study includes questions about politics, attitudes, religious and moral views. The core theory is that these important variations will be partially accounted for by genetics. The study aims to explain why behaviour varies by systematically measuring variation in behaviours, assessing what proportion of that variation is inheritable, and identifying the specific genes correlated with that behaviour. The central aim of this project is to examine the extent to which economically relevant attitudes and dispositions are influenced by the environment (e.g. parental influences, particular formative events, specific career tracks, education experiences, cultural or institutional norms etc.) and by genetic predispositions. Medical research has recently found connections between social behaviour and positive health outcomes. However, the exact nature of these relationships remains unclear. This study will help to provide important insights into social decision making processes which can help produce better public policies and healthier citizens.

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.

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 …(CONT)
Healthy breathing is a capacity that most of us take for granted. However, for the 1 in 10 Australians that suffer from asthma, there are days when their airways have narrowed so much that breathing is not only difficult, but potentially life-threatening.

Every year, asthma attacks are responsible for 1 million work days lost, 36,000 hospital admissions and 402 deaths, not to mention over $600 million a year in direct costs. Back in the late 1990’s, Prof Nick Martin and Dr David Duffy started a study at QIMR to try to understand why some people get asthma and others don’t; specifically, the aim was to identify the genes that contribute to the risk of developing asthma. As part of that study, we tested and collected DNA from over 3,000 twins and their relatives from families having at least one asthmatic twin. The analysis of these data suggested to us that an asthma gene is located at the end of chromosome 20, a finding that we reported in a scientific journal back in 2005 (American Journal of Human Genetics 77: 1075-1085). Since then, the technology to analyse genetic data has improved dramatically and it is now possible to conduct genetic studies with much greater resolution and with many thousands of participants. Last year, Dr Manuel Ferreira established a collaboration between our group and investigators in Melbourne, Perth and Sydney to precisely perform such a study, which constitutes the largest study of asthma genetics conducted to date in Australia and will likely identify more accurately which genes influence asthma. For more information on this study, named the Australian Asthma Genomics Consortium, please visit the website http://genepi.qimr.edu.au/aagc/.

Cannabis

QIMR is currently finalising a unique, large-scale twin study on cannabis use and mental health across Australia. Cannabis is the most widely used illicit drug worldwide, yet little is known about the side effects of marijuana and the genetic and environmental factors that lead to cannabis use. QIMR, in collaboration with Washington University USA, has collected 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 almost 4000 twins and siblings between the age of 27 and 49. We found that a high percentage of men (64%) and women (60%) have used cannabis at least once in their lifetime. On average, people start using marijuana when they are about 18 years old. While many reporting life-time 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. It is already known that the reason that some people use drugs while others do not is partly because of their genetic differences. At the moment, we are trying to find which genes play a role in cannabis use.

Previous research has shown that people with common mental health problems such as depression, anxiety or psychosis have subtle changes in brain structure and function.

These changes may be causing the illness or be a result of the condition, and are associated with problems of everyday cognitive skills such as concentration and memory, social skills and ability to work or study. At this stage, it is not known when these brain changes start to happen and how they progress over time. Additionally, it is not known whether medical or psychological treatments reverse these changes.

QIMR, in conjunction with the Brain and Mind Research Institute (BMRI), is conducting the 19 Up Study for participants aged 19 years and older. It aims to examine the relationship between critical frontal-temporal structures in the brain and the onset of affective (depression, anxiety) symptoms. It will assess whether pre-existing structural liabilities, known to be related to affective disorders, are a consequence of an early onset of illness. The central aim of this study is to map brain changes, to determine whether brain changes are related to cognitive, social and work functioning.

Our new model of classifying different stages of illness will allow us to develop a better understanding of the relationship between the illness stage and progressive brain changes. This may assist health professionals in offering different forms of treatment at different stages of illness. This should help, in turn, to reduce the amount of cognitive, social and work or study related disability.
Age affects us all in different ways, but it is 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) is the most comprehensive ageing study involving twins ever undertaken in Australia. We invite identical and non-identical twins aged 65 years or older to participate in this research which aims to investigate what influences memory and thinking as we age. We hope that 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.

The study is being conducted in New South Wales, Victoria and Queensland. The principal investigator 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.

Twins Kevin (L) and Bevan (R) participating in the Older Australian Twins Study at QIMR

Eye Studies (These studies are discussed in more detail on pages 5 to 7 >>>)

Researchers at QIMR have found two genes that influence blinding eye diseases. Working in collaboration with Professor David Mackey’s research team from the Centre for Eye Research Australia, over 1000 sets of twins were examined in Brisbane and Tasmania as part of an international collaboration. One gene, known as ATOH7, has been discovered to alter development of the optic nerve, which transmits visual signals from the eye to the brain. The initial discovery was made by studying a large cohort of twins. This gene is associated with optic nerve hypoplasia, one of the causes of blindness in children. This discovery may lead to a genetic test in utero to determine the chances of the child having optic nerve hypoplasia. ATOH7 has been studied in Drosophila fruit flies and mice and is involved in embryonic eye development.

In a related study, the Genetic Epidemiology team have also identified the gene (ZNF469) involved in the thickness of the cornea, the clear outer covering of the eye. Decreased corneal thickness is a known risk factor for glaucoma, the second leading cause of irreversible blindness. It is estimated that by 2010, approximately 60 million people will be affected by glaucoma globally. The gene is involved in brittle cornea syndrome, a rare condition that results in extremely thin corneas. But now we know that this gene also influences the corneal thickness in the general population. Through genetic testing, we may be able to determine who might be at high risk of developing glaucoma, and they can be examined for early signs and treatment to lower pressure in the eye started before significant damage to vision occurs.

Elevated rates of childhood trauma, particularly childhood sexual abuse and physical abuse, have been reported in studies assessing adults and adolescents receiving treatment for alcoholism or drug dependence. Trauma survivors in treatment have increased rates of alcohol and drug dependence and other negative outcomes. However, establishing the causal role of trauma to alcohol and drug use has proved difficult.

The MARC 7 project is a study that looks at identifying factors which may influence a person’s experience with alcohol and investigates the relationship between early childhood experiences, such as important events and relationships, and alcohol use. By examining these factors we hope to obtain a better understanding of the development and course of alcohol use. The study population will include 3607 individuals of European ancestry who have recently participated in genetic studies of nicotine and alcohol dependence.
The adolescent twin study has been running since 1992 and is producing important results on many fronts. At ages 12 and 14, twins and their siblings come to QIMR and have their moles counted and other melanoma risk factors assessed. The twins then return at 16 to take part in the Memory, Attention and Problem Solving (MAPS) study to help discover genes that may influence brain functioning. Since its inception we have seen over 2100 pairs of twins and 800 siblings in the Mole study and have tested over 1000 sets of twins for MAPS, along with more than 300 of their siblings.

During their visit, twins and their families provide a small blood sample and a cheek swab. Using a new and powerful technique called genome-wide association scanning, we have typed 610,000 gene variants on the DNA collected from twins and their other family members and so far have found three new genes that influence mole count and melanoma risk. At present, early detection of melanoma is our best hope and an understanding of the genetic factors influencing risk of developing melanoma is crucial to identify at-risk individuals and could greatly increase early-detection of the disease.

At each of the visits we also collect other measures to help us understand more about melanoma and brain function. We have found new genes for eye colour and hair colour which indirectly influence the risk of melanoma. Our group was one of the first to find the major determinant of blue-brown eye colour. And recently, we have found the major gene determining whether a person has straight or curly hair, and have been inundated with emails from people wanting us to develop a pill for straight hair (we are not!).

Twins who visit us at 14 participate in a binocular rivalry task. We have shown that the binocular rivalry task, which measures the rate at which attention switches between the left and right hemispheres of the brain and is a predictor of risk for bipolar disorder (‘manic depression’), is strongly genetically determined. We now hope to find some of the genes responsible and thereby help those at risk of bipolar disorder.

Most recently, we have invited twins who are now young adults (21-30yrs), to come back again for a brain scan at the Wesley hospital – over 500 of you have been scanned so far. This study is producing fascinating results as we map genetic influences on brain structure and function. We are now leading an international team to take a systematic approach to mapping genetic influences on the brain.

Thus, our Brisbane twin volunteers (and their parents and siblings) are helping us make fundamental breakthroughs both in melanoma research and in the field of mental health.

### PACER

The PACER project (Parents and their Children - Environmental Risk) is a longitudinal family study that looks at the behaviours of children over time to identify what leads to behavioural problems in adolescence and adulthood. By collecting data on the environments of children and comparing their outcomes over time, investigators are hoping to reveal specific factors that can cause disorders such as Attention Deficit and Hyperactivity Disorder (ADHD), Conduct Disorder, smoking and drinking addiction, depression, and anxiety. We have collected data from 700 twins and their children, and aim to collect 400 more parents over the next few years. 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 few years.

### Endometriosis

Endometriosis is a common condition with severe consequences for many women. Our program aims to understand pathways that cause this disease, and around 4000 women and 6000 family members have participated in our study. We previously identified a region on chromosome 10 that appears to increase risk for the disease and we are studying several related genes that may be accountable for this risk. We are also founding members of the International Endogene Consortium. We recently completed a large new study that included our endometriosis families and identified a region on chromosome 7 that contributes particularly to the risk of severe endometriosis. We are currently searching for the mechanisms responsible.

### Twinning in Families

Why do some families have many twins in their family tree? Female relatives of mothers with non-identical twins are more likely to have non-identical twins themselves. We have previously shown that rare genetic variants in a gene called **GDF9** expressed in developing eggs contributes to increased twinning in a small number of families. This year we published a study including over 500 of our families that revealed several chromosomal locations that may contain more genes for twinning. It is now clear that many genes are likely to be responsible for increased non-identical twinning and the search for their identity continues.
Can you tell if twins are identical or not by looking at their eyes?

We found out that by looking at the back of the eye, specialist eye doctors could correctly identify if twins were identical or not almost 90% of the time. (Ref Hewitt et al Invest Ophthalmol Vis Sci. 2007;48:2469-75.)

How good is your eye anatomy?

These are some of the parts of the eye that we are measuring in healthy people. We hope to discover genes that influence the measurements and find out whether these genes can lead to eye diseases like glaucoma and myopia (short sightedness).

Since 2001 over 1,000 sets of twins and nearly 200 of their other brothers and sisters have been involved in the Twins Eye Study (TEST). (We saw some of the brothers and sisters to check that the twins had similar eye measurements to singletons and most of the time they do.) About half the twins were in Tasmania (TEST) and half in Brisbane (BATS) and a few from the other states and Norfolk Island. We saw all ages but most were teenagers or young adults. (Ref Mackey et al Twin Res Hum Genet. 2009;12:441-54.)

Some of the things we measured were:

- Visual acuity (how well you read the chart)
- Eye movements and 3D vision
- UV damage to the front of the eye
- Refraction (strength of glasses needed)
- Corneal thickness
- Axial length of the eye
- Intra-ocular pressure
- Optic nerve and vessels (using 3D photographs of the optic nerve).
Early in the study we found that identical (MZ) twins (on the left) had more similar corneal thickness than the non-identical (DZ) twins (on the right). Indeed there was a 95% heritability so we were confident that we would find some genes affecting the thickness of the cornea, which is an important measure in glaucoma and for determining whether people are candidates for laser surgery for myopia. (Ref Toh et al. Invest Ophthalmol Vis Sci. 2005;46:3718-22)

We did find some genes called ZNF469 and FOXO1. The markers are shown on the graph below; when they rise above 7 (in dark red) we can be confident that they are really affecting the corneal measurement. There are still some more genes to find.

We also found a gene region on chromosome 5 (the 5th largest chromosome) that is associated with the axial length of the eye. This is an important measure for the risk of becoming myopic. (Ref Zhu et al. Ophthalmol. 2008;115:1053-7)

(Ref Lu et al. PLoS Genet. 2010;6:e1000947)

Below: Photos of the optic nerves of identical twins - that tells us that genes are at work there!

We measured the size of the optic nerves using a 3D computer to map out the edges.

The optic cup is yellow and the optic rim is blue. The combined area is the disc size.

With these measurements on everyone in the TEST we then compared over half a million DNA markers called SNPs and found one was frequently associated with larger optic nerve size. This was near a gene called ATOH7, which researchers had found was related to the optic nerve development in the mouse. (Ref MacGregor et al. Hum Mol Genet. 2010;19:2716-24.)

The blue shows where the ATOH7 gene is expressed in the mouse eye – right in the middle of the optic nerve as we expected. These developing nerve fibres find their way back to the brain and transmit signals from the eye. Glaucoma is the most common disease to affect the optic nerve and we hope that this gene will help us understand more about glaucoma and other optic nerve diseases.

There were some other genes that looked like they might affect the optic nerve but we need to study a lot more people to prove this. Often we find other research, like the UK Twins Eye Study led by Professor Chris Hammond, and by combining our data using a method called meta-analysis we are able to find more genes.

The statistic experts at QIMR are among the best in the world for this.
Some of the Brisbane Twin Eye Team: Byoung-Sun, Bob, Colleen, David and Lisa

Professor David Mackey and his team will be making a few weekend visits to Brisbane in mid 2011. If you would be interested in participating in the 2-hour eye exam please let us know (email D.Mackey@utas.edu.au) and we can confirm the dates. Anyone living in Perth, Melbourne or Tasmania can also be seen in those locations. If you know your twin missed out, there is an opportunity now for a thorough eye examination.

DO THE MEASUREMENTS CHANGE AS WE GET OLDER AND WHAT INFLUENCES THESE CHANGES?

We hope to do a 10-year follow-up of the Twins Eye Study in Tasmania and Brisbane starting in 2013. So keep in touch!

If you have any questions relating to your eye exam with us, or your own eye care provider would like a copy of the photos or measurements, please let us know or contact Professor Mackey on the email above.

You can log on to the eye study web site and the links there will take you to the journal articles if you would like to read them.

Photos (above) converted to map (right) by 3D mapping of the disc photos. We have been working with some other American researchers who can turn our stereo photos into 3D maps of the eye. (Ref Xu et al Opt Express. 2010;18:11347-50.)

Is everything genetic?

We are also looking at environmental factors that influence the eye.

In the Tasmanian Twins, we found that if the mother smoked during pregnancy then there was an increased risk that the twins would have a turn in their eye (strabismus) and poor 3D vision (10% of people have poor 3D/ stereo vision and therefore don’t get the full effect of 3D movies like Avatar; Ref Ponsonby et al. Ophthalmic Epidemiol. 2007;14:351-9.) We also found that smaller birth size was associated with narrower blood vessels in the eye (Ref Sun et al Hypertension. 2009;53:487-93.)
Are you a twin? Do you know other twins? Would you like to help medical research?

QTWIN NEEDS YOU!

QTwin is a population based registry of identical and non-identical twins (including boy-girl twins) of all ages. All adult & child twins, born in or currently living in Queensland, are eligible to register. Triplets & other multiples are also encouraged to join. Twins under 18 need a parent’s signature on the registration form.

Registering with QTwin 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. Membership is free, and you may be eligible to receive monetary reimbursements (from $25-$100) for your participation.

Register online now to be involved in current research projects looking in to:
Twinning in families; the genetics of brain ageing; substance misuse and mental health; eating disorders; human behaviour and health outcomes; the genetics of decision making; and many more!

Visit our website at www.qtwin.org.au to register online or download a Q Twin registration form and mail or fax it back to us.

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Q Twin observes the National Privacy Principles (Privacy Act 1988) and the code of conduct set out in the National Statement of Ethical Conduct in Human Research.