HEADLINES
SCHIZOPHRENIA RESEARCH INSTITUTE FEB 2008

MicroRNA: a new chief suspect?

Dr Murray Cairns, M.C. Ainsworth Research Fellow, led the University of Newcastle team in this important genetic study.

It is now widely understood from countless news items and 'forensic detective' stories, that Deoxy ribonucleic acid (DNA) contains the genetic instructions (genes) used in the development and functioning of all living organisms. Less well known is Ribonucleic acid (RNA), which is just as important as DNA for building and maintaining living bodies.

The main types of RNA translate the DNA 'code' to construct the protein building blocks of cells. The more recently discovered microRNA regulate the degree to which specific genes are expressed, and can even switch genes on and off. It is this ability to alter the expression of many genes at once that makes microRNA of special interest to medical researchers seeking better treatments for illnesses involving genetic predispositions.

Researchers estimate there could be between 200 to 1,000 types of microRNA, and little is known about them. In the short five years since the discovery of these tiny molecules, dozens of studies have been published on the roles they may play in plant, animal and human biology.

MicroRNA in brain development

In the case of schizophrenia, many recent research studies have supported the neurodevelopmental hypothesis, which suggests that genetic factors are involved in producing abnormalities in brain plasticity and connectivity during development from infancy to adulthood, leading to onset of the illness, usually in early adulthood. However, rather than a single target gene, there appear to be many genes involved in the development of schizophrenia. As microRNA is known to play a major role in coordinating gene expression during development, and can regulate dozens of genes at once, it presents an exciting new target for schizophrenia researchers.

The Institute team based at the University of Newcastle used post-mortem tissue from the superior temporal gyrus (STG) brain areas of 21 schizophrenia donors and 21 controls to investigate whether their microRNA levels differed. The STG area was chosen because it contains the auditory cortex thought to be involved in generating the 'hearing voices' symptom in schizophrenia.

Results from the study have indicated that the schizophrenia STG contains elevated levels of microRNA. Significantly, average levels of one type of microRNA, miR-181b, was shown to be 1.5 times higher in the schizophrenia brain tissue. Further tests revealed that these high miR-181b levels could down-regulate a number of genes already known to be implicated in schizophrenia - by as much as 67 per cent.

These results suggest that genes which are normally fully expressed during brain development are suppressed by abnormally high levels of a particular microRNA molecule, and that this may contribute to some of the biological brain abnormalities associated with schizophrenia.

This important finding provides a potential link between the many genes implicated in schizophrenia, opening the door to further advances in knowledge about the genetic mechanisms of the illness, and possibly to finding a means of prevention.

*Beveridge NJ, Tooney PA, Carroll AP, Gardiner E, Bowden N, Scott RJ, Tran N, Dedova I, Cairns MJ. Dysregulation of miRNA 181b expression in the temporal cortex in schizophrenia. *Human Molecular Genetics*. In press.

Helen Connealy joins the Central Office team..

Please welcome Helen Connealy

Our new Fundraising and Partnerships Director

With over eighteen years of business management, marketing, journalism and public relations experience, gained in London, Hong Kong and Sydney, Helen joins the Institute from The Children's Hospital at Westmead.

In her previous role as Head of Public Relations, Helen was responsible for special events such as the Teddy Bears' Picnic and Bandaged Bear Day, the major merchandise fundraising campaign for the Hospital.

Helen began her career in publishing and worked in journalism and public relations before moving to the not-for-profit sector. She brings new business development experience to the Institute and aims to develop a comprehensive fundraising strategy to expand support and assist in the Institute's future growth.

INSIDE: Coast to Coast Research ◆ Ultra-High Risk Factors ◆ Focus on the Genetic Suspect

The 'Bank': Coast to Coast Research

Launched in April last year, the Australian Schizophrenia Research Bank (ASRB) has already attracted the interest of 2,300 volunteers, and 200 of these have completed the assessment process. The 'Bank' is now well on its way towards the national recruitment target of 2,000 people with schizophrenia and 2,000 controls.

Expanding the Sydney team to help process volunteers, Siobhan Quinn and Carollyne Youssef have joined Yen Lim at the Prince of Wales Medical Research Institute. Clinical Assessment Officers (CAOs) in other centres are as captioned.

The ASRB's five-year project aims to obtain brain scans, genetic profiles and detailed individual information from all volunteers, and to cross reference all data creating the world's biggest schizophrenia research database of its type.

The logistical problems of processing information on each volunteer, and scheduling appointments for them at clinical centres in six Australian cities are daunting. The Institute congratulates all CAOs on doing an heroic job, and looks forward to the establishment of the ASRB as a truly valuable worldwide resource.

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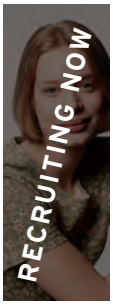


PERTH

Newcastle Office (L-R): Dr Carmel Loughland, Janette Howell, Jaci Richards, Michelle Poole. Melbourne Office (L-R): Rebecca Wilson, Antonia Stuart. Sydney Office(L-R): Siobhan Quinn, Yen Lim, Carollyne Youssef. Brisbane Office: Dr Kelly Mouat. Perth Office: CAO being recruited.

The TV and press campaign donated by Singleton Ogilvy & Mather, Plush Films, Black Dog Photography, and with a voiceover by Russell Crowe, is due for a further airing on all channels nationwide this year.

The TV appeal and more information about the ASRB research program is available for viewing at the Institute's website - and please consider signing up as a volunteer.

For full details on joining the ASRB, just call 1800 639 295.
Or see more information at:
www.schizophreniaresearch.org.au

Ultra-High Risk Factors

A new proposal aims to chart the course of the descent into psychosis

Research discoveries over recent decades have defined many differences between people with schizophrenia and those without: structural, functional and genetic differences in the brain, as well as cognitive/perceptual differences.

Professors Ulli Schall and Pat Michie of the University of Newcastle are leading a collaborative group of the SRI Cognition and Connectivity Panel to apply the knowledge from these discoveries in a multi-centre study aiming to define the factors involved in schizophrenia onset.

The study will recruit young people (12-25 years) from clinical centres in Newcastle, Orange and Sydney. Of the many young people presenting at these centres each year, up to 130 are deemed to be at ultra-high risk (UHR) of developing a psychotic disorder such as schizophrenia. Records show that 30-50 percent of such patients develop psychosis within 12 months.

Mismatch negativity traces show similar auditory processing abnormalities between high-risk (red) and schizophrenia (blue) subjects compared to healthy controls (black).

Each UHR individual will be age/sex matched with a healthy control, and both will receive a sequence of tests devised from recent discoveries. These include MRI brain scans to measure cortical differences; DNA profiling to detect changes in gene expression; mismatch negativity tests to detect auditory cognitive abnormalities - as well as a number of cognitive/perceptual tests.

The 5-year study aims to compare results from the UHR participants who develop schizophrenia with those that do not, and with matched controls, to closely map the transition from high-risk to psychosis. The study has received funding from the Hunter Medical Research Institute, and the University of Newcastle Priority Centre for Brain and Mental Health Research & Research Grants Committee.

Focus on the Neuregulin Gene

Six SRI research teams investigate the genetics of brain development

Many studies have now confirmed that abnormalities in the Neuregulin-1 (NRG1) gene are found in people with schizophrenia, and researchers are looking closely at this gene as both a possible 'marker' of schizophrenia risk and a source of new treatment. The Institute's Developmental Neuro--biology Panel has combined forces to further define the links between NRG1, brain development and schizophrenia.

NRG1 is one of the largest genes in the human genome, sprawling over some 1,125,000 units of DNA, and it is expressed widely throughout the brain. What attracts the attention of so many schizophrenia researchers is that NRG1 seems to regulate key neurodevelopmental processes in the brain during puberty, a time which is particularly relevant to the development and onset of schizophrenia.

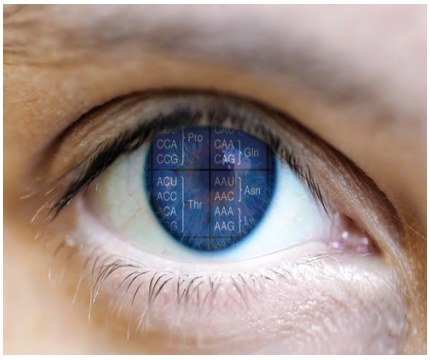
Members of the Institute's Developmental Neurobiology Panel are initiating a large scale collaborative project in which six SRI schizophrenia research centres will use their on-site expertise and research techniques to examine a specific component of NRG1's role in brain development and schizophrenia. To support this research two research resources are being developed: post mortem human brain tissue from a large number of individuals with schizophrenia and matched controls, and brain tissue from mice with reduced levels of Neuregulin-1. Once obtained, this tissue will be distributed to the various centres, for multi-faceted investigations, which will encompass a formidable range of research techniques and expertise including:

1. Dr Katerina Zavitsanou's group at the **Australian Nuclear Science and Technology Organisation** will investigate NRG1-related protein expression in the human brain.

2. At the **Garvan Institute**, Dr Tim Karl's team will investigate how NRG1 depletion and exposure to cannabis influences behaviour (see below).

3. Prof. Cyndi Shannon Weickert's team at the **Schizophrenia Research Laboratory** aim to determine how the reduction of NRG1 expression in mice affects their viability as models for schizophrenia.

4. Dr Jan Fullerton and Dr John Kwok at the **Prince of Wales Medical Research Institute** will map specific variants in the NRG1 gene that are associated with schizophrenia.



In the 'Nature V Nurture' debate concerning schizophrenia risk factors, expert opinion now agrees that genetic susceptibility is the chief cause.

5. Dr Murray Cairns and Dr Paul Tooney at the **University of Newcastle** plan to investigate the role of microRNA in modulating NRG1 gene expression in the human brain tissue.

6. Prof. Xu-Feng Huang's team at the **University of Wollongong** will use human tissue and 'knockout' mice to investigate the relationship between NRG1 and a range of receptors.

This multi-centre research approach will provide a comprehensive understanding and characterisation of NRG1, how it affects brain development and its role in schizophrenia from multiple perspectives. It will also develop the infrastructure necessary for the Developmental Neurobiology Panel to investigate other potential 'markers' for the illness in the future.

$437,125 for Mice and Cannabis

Further to his 2007 investigations into the effects of cannabis on schizophrenia risk, Dr Tim Karl has teamed up with Dr Jonathan Arnold and Prof. Iain McGregor at the University of Sydney, and Prof. Xu Feng Huang at the University of Wollongong to devise a broader study. The team's proposal has been awarded a National Health and Medical Research Council (NHMRC) Project Grant of $437,125. In the highly competitive environment of NHMRC funding, this is a major win for schizophrenia research.

The new study will seek to answer the question of why some adolescent cannabis users develop schizophrenia while others do not. Does the risk depend upon a genetic vulnerability?

In the earlier study, Dr Karl used genetically modified 'knockout' mice in which the NRG1 gene expression had been reduced. When dosed with THC (the psychotropic agent in cannabis), these mice were shown to be more sensitive to its behavioural effects compared to unaltered 'wild-type' mice. However, as the earlier study used a one-off dose of THC, and susceptibility to schizophrenia is associated with long-term cannabis usage, a further study was indicated in which repeated doses of THC and cannabidiol (another component of cannabis) would be applied to adolescent as well as to mature mice. The new study will accomplish this, and also measure how such dosage affects schizophrenia-related receptors (e.g. cannabinoid, glutamate, dopamine) in the brains of both the 'knockout' and 'wild-type' mice.

Dr Tim Karl - with some of the most valuable mice in the world.

The results of this study will provide an extensively characterised animal model of how genetic vulnerability to schizophrenia interacts with the effects of cannabis, thereby helping to clarify the complex relationship between the drug and schizophrenia.

Dr Karl was also awarded the inaugural SRI 'Early Career Researcher Award' of $10,000 to help fund his work.

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CONGRATULATIONS

To Dr Carmel Loughland, Manager of ASRB. Carmel is the first scientist to reach 10 years employment with the Institute.

To Daren Draganic, Director of Operations. Daren has run a close second to Carmel in the 10 Year Stakes.

To SRI Board member Prof. Pat Michie, who has been appointed Pro Vice Chancellor for Research at the University of Newcastle.

And to Alan Tunbridge, Communications Director. Following Australia wide distribution, Alan's poster has been translated into Urdu and distributed throughout Pakistan.

Please help by completing and mailing this form to Schizophrenia Research Institute, 384 Victoria Street, Darlinghurst, NSW 2010, or fax to (02) 9295 8415, or simply call (02) 9295 8407.

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