Newsletter Issue #5

minds for minds
Unlocking Autism Together

Contents

Contact Us

www.mindsforminds.org.nz

Research inquries: inquiries@ARNNZ.org

Charitable Trust inquiries: info@mindsforminds.org.nz

Also find us on facebook and twitter (@mindsforminds)

Updates from our Minds for Minds Researchers

Genetics: Jessie Jacobsen, Russell Snell, Rosamund Hill and Klaus Lehnert

We are continuing to sequence, analyse and find answers for more cases in the genetics part of our project. In collaboration with Dr Javier Virues-Ortega we have also undertaken a full analysis of the high-level demographics of the individual information on the Minds for Minds database. The results of this work are being prepared for publication. Some of the key points to come out of this analysis are listed below:

- We observe the well-reported male to female gender bias (4:1)
- The population distribution reflects New Zealand's latest census
- Anxiety disorders, depression and epilepsy were highly prevalent amongst individuals with ASD and their families
- 48.5% reported at least one other co-occurring condition
    - The most common co-occurring condition in those under 7 is ADHD, then in decreasing frequency dyspraxia, followed by depression and anxiety
    - The most common condition in those aged 8 to 17 was depression and anxiety, then in decreasing frequency ADHD, followed by dyspraxia
    - The most common condition in those over the age of 18 was depression and anxiety, then in decreasing frequency gastrointestinal symptoms, followed by ADHD
- The number of co-occurring conditions increased with age
- 91.2% of individuals reported one or more condition among first-degree relatives
- The most common conditions occurring in relatives were ADHD, depression and anxiety, ASD/ Asperger syndrome, dyspraxia, and obsessive compulsive disorder

There is evidence to suggest that individuals with high functioning ASD are more likely to present with depression and anxiety (Strang et al., 2012). In a large epidemiological survey using a US-based registry of 4343 children, Rosenberg Kaufmann, Law, and Law (2011) reported that a diagnosis of ASD was also associated with a higher prevalence of depression, anxiety disorders, ADHD, and overall psychopathology.

Strang, J. F., Kenworthy, L., Daniolos, P., Case, L., Wills, M. C., Martin, A., & Wallace, G. L. (2012). Depression and anxiety symptoms in children and adolescents with autism spectrum disorders without intellectual disability. Research in Autism Spectrum Disorder, 6, 406-412. doi:10.1016/j.rasd.2011.06.015

Rosenberg, R. E., Kaufmann, W. E., Law, J. K., & Law, P. A. (2011). Parent report of community psychiatric comorbid diagnoses in autism spectrum disorders. Autism Research and Treatment. doi:10.1155/2011/405849

We will let you know when the article is published.

In regards to sequencing to identify potentially causative variants, we are continuing to consent new registrands and progressively sequence those already formally consented as funding permits. We are observing just how varied and complex the genetics of ASD can be. The results of some of those we have sequenced to date has meant more accurate redefined syndromic diagnoses (e.g. Rett syndrome, Bainbridge-Ropers syndrome), and some have revealed causative copy number variations (e.g. 15q13.3 microduplication syndrome), while others show a combination of genetic variations.

In collaboration with our Massachusetts General Hospital and Harvard Medical School colleagues we are also investigating extraordinarily complex genetic rearrangements, involving several different regions of a person's DNA including multiple chromosomes. We were incredibly fortunate to host two of these collaborators in New Zealand recently, Professors Jim Gusella and Marcy MacDonald. More about their trip is summarised on page 9.

The genetics group has published two papers on rare neurodevelopmental disorders recently. A short summary of both is included below:

Whole Exome Sequencing Reveals Compound Heterozygosity for Ethnically Distinct PEX7 Mutations Responsible for Rhizomelic Chondrodysplasia Punctata, Type 1

Two siblings presented with a rare, developmental disorder, which affected their brain and bones. One child died at 19 years of age without a unifying diagnosis. We used the latest DNA sequencing technologies to interpret their genetic information to find a diagnosis for the family. We identified two changes in their DNA (inherited from Mum and Dad), disrupting the function of a protein critical for nervous system function, PEX7. The inheritance of these two genetic changes together has not been described before. These specific genetic variations cause a condition called Rhizomelic Chondrodysplasia Punctata type 1, providing a diagnostic scaffold for the interpretation of their clinical histories. This delivered a diagnosis for the family 26 years after the birth of their first child, and facilitated an improved clinical management strategy for the surviving child.

http://www.hindawi.com/journals/crig/2015/454526/

Brain dopamine-serotonin vesicular transport disease presenting as a severe infantile hypotonic parkinsonian disorder

We utilized DNA sequencing methodology to identify the underlying genetic cause for two brothers who presented in the clinic with severe movement disorder and developmental delay. The younger sibling had passed away from respiratory failure. Investigation of their genetic material identified a brand new DNA variation present in both siblings, which is predicted to disrupt the transport of key chemicals that communicate information in the brain. Variations in the DNA, making up the *SLC18A2 gene*, cause Brain Dopamine-Serotonin Transport Disease. There has only been one other family described in the world with this condition. This diagnosis has led to the specific use of a treatment to replace one of these important brain chemicals, which resulted in improvement in the surviving child's alertness and communication. This diagnosis and subsequent treatment strategy significantly improved the quality of life for this family and highlights the importance of DNA sequencing in the diagnosis of children with undiagnosed neurodevelopmental disorders.

http://link.springer.com/article/10.1007%2Fs10545-015-9897-6

Research Participation Opportunities

Psychology study lead by Dr Javier Virues-Ortega

This study aims to explore the brain activity patterns of children and adolescents with Autism Spectrum Disorder as a function of their history of health and educational services. We will be using functional magnetic resonance imaging (fMRI) to measure the participant's brain activity while they are resting. In order to compare the fMRI results to each participant's service history, a research assistant will interview the clients' parents about their child's diagnoses, education, and professional services they have received over the years.

The total time commitment would be about 5 hours over two or three appointments. Families will be reimbursed for their transportation expenses within Auckland. The fMRI session will take place at the Centre for Advanced MRI at Auckland CBD.

Interested families should contact Jessica McCormack jmcc146@aucklanduni.ac.nz or Dr. Javier Virues-Ortega j.virues-ortega@auckland.ac.nz This pioneering study will help us learn about how various evidence-based interventions contribute to brain development.

News from our Charitable Trust

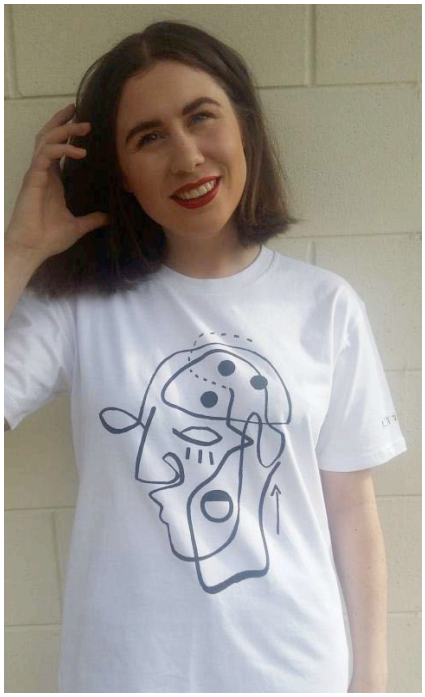
Minds for Minds Charitable Trust Chairman, Len Ward, reports that the Trust is actively looking at ways to raise funds, in addition to selling the fantastic Tee Shirts designed specifically for us by Ken Griffen. He says that his Board is considering events such as a charity golf tournament and a charity dinner/auction but these things take time to organise. In the meantime we are also looking to attract a number of 'regular givers' by way of monthly automatic payments into the Trusts bank account. "For the price of a cup of coffee a week, or better yet a bottle of wine, our supporters can make a huge difference to our ability to support our amazing scientists in their quest to unlock autism" Len said. Anyone wanting our automatic payment form can get one by emailing him at len@tusklegal.co.nz and he will be glad to provide one for you (and one more for you to give to a friend).

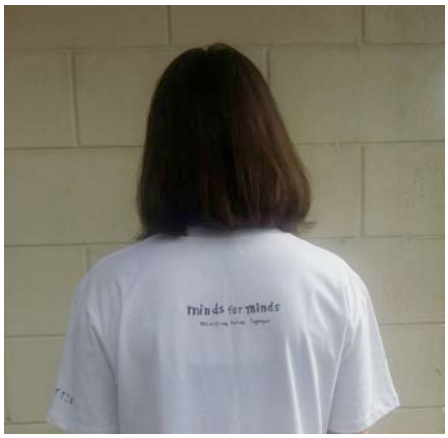
Fundraising is much harder in New Zealand than many think. "There are nearly 30,000 charities registered here and nearly all of them are raising funds from the public in one way or another" Len says. "Every dollar we collect goes direct to the Minds for Minds team and helps in their work and for all New Zealand tax payers their donation is deductible for tax purposes and is received by the Trust tax free, so it is a very efficient way for us to increase funding".

If you want to help by making a one off donation you can do that by visiting the website at www.mindsforminds.org.nz and hitting the 'donate' button.

Our charitable trust still has limited edition T-shirts for sale, designed by Ken Griffen. Ken is a young New Zealand artist, based internationally, who exhibited at the Allpress Gallery in Auckland and the show was a complete "smash" and sold out. Before moving to Europe Ken was Senior Graphic

Designer and Creative Director for the Huffer Brand. He has created an exclusive image for Minds for Minds for a limited edition of signed T Shirts to raise funds for the project. There are only 250 available. The signature is on the sleeve. Please email info@mindsforminds.org.nz if you are interested.





Our Minds for Minds website is currently undergoing a revamp – check back soon for up to date content and international research news!

International genetics+microbiology research news

Latest Centers for Disease Control and Prevention (CDC) report indicates prevalence estimates may be levelling off

Following an extended period in which reported ASD prevalence estimates continued to rise, the most recent release from the CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network has shown a potential leveling off of prevalence estimates. This current study has estimated the rate of ASD in the United States to be 1 in 68 for 2012, no change from the rate in 2010. Although it is too early to say whether or not the prevalence has stabilised, this is an indication that changing diagnostic criteria and public attitudes towards ASD mean that the majority of cases are now being identified, where in the past they could have remained undiagnosed. A summary of the study and a link to the full paper can be found at: http://www.cdc.gov/features/new-autism-data/index.html

Simons Simplex Collection ASD whole exome sequence data release

The Simons Simplex Collection is a unique scientific resource for the Simons Foundation Autism Research Initiative (SFARI), with genetic samples from a cohort of 2,600 simplex ASD families (families with one affected child, and unaffected parents and siblings). In a huge step towards open source research, SFARI in partnership with WuXi NextCODE have released the whole exome sequence data for these families for researchers to analyse and perform their own research. This is big news not only for researchers with an interest in ASD, but also shows a movement towards greater data sharing and transparency for genetic research. For more information or apply for access to the WuXi NextCODE SSC portal visit: https://goo.gl/g3cVQm

iHART aim to make 10,000 ASD whole genome sequences available by 2017

The Hartwell Autism Research and Technology Initiative (iHART) have teamed up with Illumina to build the largest and most comprehensive collection of genomic and clinical information on children with autism to-date. The collection currently contains over 5,000 sequences, and aims to grow to nearly 10,000 by 2017. Researchers from UCLA, Cold Spring Harbor, UCSF, the New York Genome Center, and the Simons Foundation are collaborating with iHART to empower the global scientific research community with open access to this phenomally powerful dataset. The data is hosted on Basespace, a summary of the project and access can be found via http://www.ihart.org/

A good webinar by Brian O'Roak discussing autism genetics is available on the 'Spectrum' website:

https://spectrumnews.org/features/webinars/webinar-brian-oroak/

Paper summary of Choi *et al.* (2016) The maternal interleukin-17a pathway in mice promotes autism-like phenotypes in offspring. *Science* 351: 933-939

Increasing evidence suggests that viral infection of a woman during pregnancy may be correlated with an increased incidence of autism spectrum disorder (ASD) **. Indeed, this is the very method by which "autism-like characteristics" can be induced in juvenile mice, in the so-called maternal immune activation (MIA) model. In this model, pregnant mice injected with a virus or viral mimic may give birth to offspring with increased anxiety, reduced communication and increased repetitive behaviours. While some may question the value of using mouse models to study such a complex human condition as ASD, such models do offer the opportunity to experimentally investigate possible causes in a way that is neither appropriate nor possible with humans.

The MIA model has been around for a while, and a particularly notable 2013 study by US researchers utilised MIA mice to show that a probiotic bacterium could reverse some of the autism-like symptoms. However, only now, in a recent paper by Choi and colleagues, has the MIA immune pathway become well understood. This is important for two reasons: (1) it leads to a better understanding of the MIA model, which should facilitate future ASD research using these mice; (2) by identifying a key signal molecule involved in the MIA immune pathway, it opens the door to development of potential therapies to prevent ASD due to maternal infection.

The paper by Choi and colleagues built upon previous MIA research which has implicated cytokines. Cytokines are signalling molecules made by the immune system as a response to infection, and as such they are crucial to our wellbeing. However, they can also play other, less desirable, roles within the body, and some cytokines have been implicated in inflammatory and autoimmune disorders such as inflammatory bowel disease and asthma. Various cytokines are known to increase in both the brains and blood of MIA mice, leading to altered brain development in affected offspring.

So, if all this was known before, then what is the key advance of the Choi *et al.* (2016) paper? In a nutshell, they demonstrated for the first time that a particular cytokine (interleukin-17, IL-17), secreted by immune cells in the mother's blood in response to infection, can cross the placenta and lead to abnormalities in the developing foetal brain. Fascinatingly, blocking of the IL-17-generating immune pathway reversed these abnormalities and ameliorated ASD-like behaviours in the offspring. Targeting this pathway might therefore one day prove to be an effective therapy to prevent the development of ASD in the offspring of susceptible mothers. However, as with many aspects of this complex condition, development of such therapeutic options will be a complicated process, as cytokines have multiple roles within the body and simply knocking them out may well have other, unforeseen consequences. Nonetheless, those of us with personal and/or professional interests in ASD should watch this area of research with great interest.

** Please note: it is important to realise that, of those mothers who experience an infection during pregnancy, only a minor fraction of these will give birth to a child with ASD.

http://science.sciencemag.org/content/early/2016/01/28/science.aad0314

Focus On:
Russell Snell

Professor Snell works in the School of Biological Sciences and Centre for Brain Research in the University of Auckland. His initial educational background was in physics (BSc, MSc), which lead towards his PhD in genetics at Cardiff University. Russell's PhD identified the gene for Huntington's disease, which was found as part of a large star-studded international collaboration. This finding was groundbreaking for the field of human genetics. Since then Russell has been part of several successful research teams, also identifying genes for Myotonic Dystrophy and Tuberous Sclerosis. His research has been cited more than 10,000 times, and he has a wide research team consisting of 20+ students, research fellows and technicians.

Russell's primary research drive is to discover underpinning mechanisms in biology using genetics. All of his research projects have had a focus of gene and mutation discovery followed by investigation of the associated biological system. Professor Snell's wider research group works on a range of topics including the development of sheep models of disease (Huntington's and Alzheimer's), worm models, finding cow and goat genes for the dairy industry and new genes for human conditions. One of his most successful projects is his Huntington's disease sheep model, which is being used for research into disease mechanisms and therapeutic testing as part of a large international collaboration. You can read more about this project in this NZ Herald article:

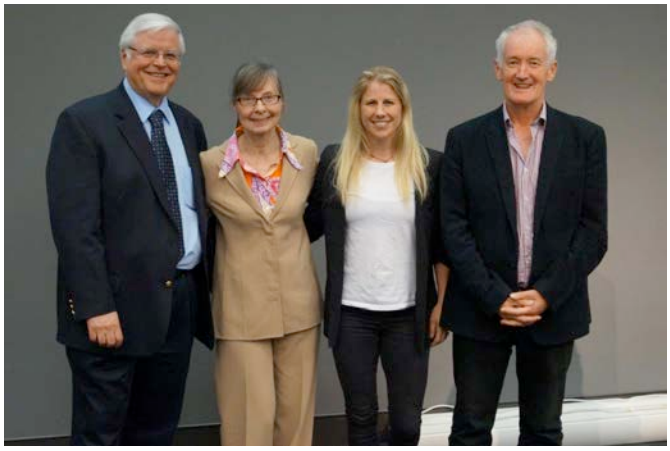
http://www.nzherald.co.nz/nz/news/article.cfm?c_id=1&objectid=11125578

In 2013, together with Dr Jessie Jacobsen and Dr Rosamund Hill he helped establish the Minds for Minds research network in an effort to identify the genes that underlie autism in New Zealand. This network has grown to include over 50 New Zealand researchers and clinicians. An update on their collaborative research project can be found on page 2 of this newsletter. We are very fortunate to have someone of Russell's caliber in the Minds for Minds team.

More information about Russell can be found on the University of Auckland website:

https://unidirectory.auckland.ac.nz/profile/r-snell.

Visit from Freemasons Travelling Scholars Professors James Gusella and Marcy MacDonald



Professors James Gusella, Marcy MacDonald with Dr Jessie Jacobsen and Professor Russell Snell

Two renowned genetic scientists from the Center for Human Genetic Research at Massachusetts General Hospital and Harvard Medical School visited Auckland as Freemasons Travelling Scholars in March. They presented their latest research into the role of genetics in the development of human conditions such as Huntington's disease and Autism Spectrum Disorder. They were here at the invitation of the University's Centre for Brain Research (CBR) and Minds for Minds.

Professors Marcy MacDonald and James Gusella are preeminent human geneticists who have had very significant success in uncovering the causes of many human disorders. Their contributions to medicine through their research have provided insight into many conditions, which has had direct positive benefits for patients and families.

The two visiting professors were part of an international collaboration (which included Russell Snell) which in 1993 discovered the gene mutation which causes Huntington's disease. While Huntington's disease is primarily caused by one gene, Autism Spectrum Disorder is caused by a large number of different genes.

Professor MacDonald discussed their latest research into Huntington's disease and the success they have had at finding genetic modifiers of the age of onset of the disorder. Professor Gusella discussed their research into autism spectrum disorder, including some of the most complex cases they have been studying. These cases have been shedding light on some key biology, including genes that are invovled in interaction and communication between the surfaces of nerve cells in the brain. Some of this work was published in 2012 in one of the world's top journals, Cell. This research offers hope of defining shared bioloical pathways that lead to individual features of the autism spectrum.

Professor James Gusella presenting his research at a public seminar at The University of Auckland

We were honoured to have Jim and Marcy with us for the week and hope they return again soon.

News from some of our Community Groups

Autism New Zealand (www.autismnz.org.nz)

Autism Conference 2016 one not to be missed!

Autism New Zealand brings two renowned Keynotes for its 2016 conference and looks to raise the bar on discussion of diagnosis and research findings within Autism in infancy.

The 2016 Autism NZ conference runs the theme empowering those living with Autism.

The keynotes bring to the conference enriched research and insight into ASD at prenatal stage and an approach to empowering people with Autism from as early as 1 years old.

Minds for Minds researchers Dr Jessie Jacobsen and Professor Russell Snell will be presenting their latest research

Two Directors from the leading University of California, San Diego (UCSD) Autism Center of Excellence headline what will be a game changing conference. Dr. Karen Pierce and Eric Courchesne have been confirmed as the Keynotes for the Autism NZ conference.

Dr Pierce has been studying autism for the past 20 years and is a leading expert on the neural and clinical phenotype of ASD. Her research spans a range of topics from early screening and detection to eye tracking and functional magnetic resonance imaging (fMRI). Her early detection approach, called the 1-Year Well-Baby Check-Up Approach, has identified several hundred ASD toddlers around the 1st birthday and has resulted in rapid treatment access.

Eric Courchesne is internationally recognised for his research on the developmental neurobiology of ASD, including genomic, molecular, cellular, anatomical and functional abnormalities associated with the disorder. His research has elucidated the early developmental neural and genomic bases of ASD as well as identified biomarkers for earlier diagnosis that enable earlier treatment referral.

The conference also provides workshops covering the core areas of empowerment, empowering People with Autism, Empowering Parents and Family/Whanau and Empowering Professionals. The workshops hope to engage in setting up a greater platform for the vision of Autism NZ “empowering people living with Autism”.

The Autism New Zealand website http://www.autismnz.org.nz/conference-2016/home provides a full overview of the conference, venues, ticketing as well as full synopsis of the keynotes. Registration opens May 12th 2016 and Early Bird registration ends on 7 July 2016.

Children's Autism Foundation (www.autism.org.nz)

The Children's Autism Foundation provide direct support to families of children affected by autism. Our programmes are best practice, multi-cultural and evidence based.

Autism Intervention Trust (www.autisminterventiontrust.org.nz)

The Autism Intervention Trust is run by parents and supports children with autism and their families in the Wellington region. Their mission is to support other families affected by autism in practical and positive ways.

Altogether Autism (www.altogetherautism.org.nz)

Altogether Autism is an information, advisory and support service for people with ASD, their families, professionals and service providers. A team of trained information officers put together credible evidence based information tailored to specific needs. They also have access to a consultant clinical psychologist and a team of professionals with experience and expertise in ASD.

Tuberous Sclerosis Complex New Zealand (www.tsc.org.nz)

Tuberous Sclerosis Complex (TSC or TS) is a genetic disorder that affects people in many different ways and is associated with a range of behavioural, cognitive and physical difficulties including autism spectrum disorder, intellectual disability and epilepsy. TSCNZ is a registered charity and the only organization dedicated to TSC in New Zealand.