Dear Families,

We would like to thank you for your support of our research efforts. Our clinical team has remained busy throughout the year seeing children and families and many more Irish families who were previously recruited have been included in the genetic studies.

**Important Research Findings**

**Genome-Wide Association Studies in Autism**

Over the last year 12-months we have published findings from our genome-wide association study of autism. A genome-wide association study or GWAS is a study that looks at hundreds of thousands of common differences (or sign-posts) in our DNA to see if some of these are more likely to be inherited in individuals with autism than we would expect by chance alone. We have looked at over 1 million sign-posts across all chromosomes in nearly 3000 families. We found that these do not by themselves explain or cause autism. By themselves they have a very small effect. However, we calculated that they are still important, as we have shown that in combination they do explain part of the genetic risk. This is important as it provides evidence of which research strategies we should pursue.

To be sure of which of these differences are important we need to look at many thousands of individuals. In collaboration with colleagues around the world, we are directly involved in Ireland at combining GWAS data from our studies and those of others to perform the largest global GWAS of autism on data from nearly 7000 families. This large study is identifying some interesting genes and we are double checking and confirming our findings before we hopefully publish them in the coming months.

This is not the end of the research, as noted above we now know that sign-posts explains some of the genetic risk to autism, and we calculate that by performing GWAS in at least another 13000 families we will identify many genes important in this risk.

We are encouraged by recent success of GWAS in schizophrenia. In a study of over 25000 people with schizophrenia more than 60 regions of the genome that we are confident are important in schizophrenia. This is probably the single greatest advance in schizophrenia genetics and scientists all over the world are developing experiments to assess how variation in these genes impacts individuals and how this information can be used to help diagnose and predict clinical outcomes.

Hopefully in the coming years we have a similar story in relation to autism – we are not there yet - but we are encouraged and confident that we will get there. It is your help in giving your time and support that is enabling these studies to be performed and we cannot thank you enough.

**DNA Sequencing Studies in Autism**

In addition to looking at common sign-posts, we have begun to look for rare and private (to a family) differences. To do this we are reading the DNA sequence to find rare or unique differences.

Our genome is made up of DNA which contains the code for genes, which are read and decoded to produce the proteins. Think of your genome as a library and genes as the books. Occasionally when the books are re-written we make spelling mistakes. Reading of these books suggests that on average our cells make a typo about once every 100 million letters. Most of these typos are silent, some offer an advantage and some can be detrimental. With exceptional advances in our ability to read DNA, we and other have begun reading the DNA of parents and their children. We are looking for new typo events, identifying which genes they are in and what they are likely to do to the protein. By reading the code of these genes (or books) we can predict if typos alter the meaning of the book. Typos can by change, add or delete words in a sentence, they can tell us to skip a paragraph or a chapter, or most importantly they can tell us to stop reading the book which prevents a full protein being made.

Identifying which genes contain the most damaging new typos in individuals with autism, we hope to learn more about the biology of autism. In the last 12-months, using this approach we have identified the genes **CDH8, KATNAL2, GRIN2B, LAMC3, SCN1A and SCN2A** as possibly important in autism. We must now see how common typos are in these genes in the wider community and see if individuals with typos show similarities in their autism and their outcomes.

**Molecular Genetics Study**

We are looking for participants to take part in our Molecular Genetic study. If you are interested in taking part in this study and would like more information please contact us by email: autism@tcd.ie or tel. 01-896 2144

**Investigating rates of autism in 1st generation Irish children**

This study looked at a population of children attending a paediatric developmental service in the Adelaide and Meath Hospital incorporating the National Children's Hospital in Tallaght. It highlights an observation of increased rates of ASD among a migrant population derived particularly from children born to parents originating in Sub-Saharan African. It shows a more severely affected African cohort of children with ASD. The children in the African group were also more likely to have a positive family history with more first degree family members affected. Follow up investigations to this study will include interrogation of the Growing Up in Ireland
(GUI) Longitudinal Cohort data, a longitudinal cohort of children aged 9 months and 9 years. The research funds were donated by the National Children's Foundation, Tallaght.

**Stem cells program**

TCD Collaborates with NUI Galway on Stem Cell Research

The 2012 Nobel Prize in Physiology/Medicine was awarded jointly to Sir John B. Gurdon and Shinya Yamanaka "for the discovery that mature cells can be reprogrammed to become pluripotent". The discoveries made it possible to turn skin cells into Induced pluripotent stem (iPS) cells using four transcription factors. The iPS cells can then become cells needed by patients. This has raised the possibility of treating patients with their own somatic cell-derived stem cells.

Ireland is developing a programme in the generation of induced pluripotent stem cells. Professor Sanbing Shen is leading an iPS cell research group at the Regenerative Medicine Institute in NUI Galway. REMEDI is a strategic research cluster funded by Science Foundation Ireland which also supports Professor Shen’s research programme. Together with Professor Tim O’Brien and Frank Barry, they have made the first Irish iPS cell lines from human skin biopsy using Yamanaka’s technology.

Professor Louise Gallagher at TCD is collaborating with the REMEDI team to advance stem cell research on autism spectrum disorders. They are currently recruiting autism patients and healthy donors to participate in the study. This research project aims to discover at the cellular level what goes wrong in neurons generated from iPS cells from patients with autism. In addition, the collaborative research project will aim to discover drugs which may help to reverse the disease pathology. Patients and controls are currently being sought for this research programme. If you are interested to participate, please contact sanbing.shen@nuigalway.ie.

**Neuroimaging studies**

**TRACT neuroimaging project (Jane McGrath)**

I am delighted to finally send out information about the TRACT project in this newsletter! Once again, many thanks to everyone who took part in the TRACT study. Some of you may not have heard anything about this study since the first scanning back in 2009, and I apologies for the lack of contact.

Scanning for the first phase of the study finished in 2011, and a considerable amount of data was collected for every person. We are able to investigate how brain structure influences brain activity, connectivity and behaviour. The excellent quality of the data is a credit to all those who were so patient and stayed very still for long periods in the scanner. I am delighted to say that the first paper from this work was published a couple of weeks ago (link is: http://www.ncbi.nlm.nih.gov/pubmed/ 22865697). In it we describe how the participants with an ASD show a relative advantage over controls in mental rotation (imagining a 3D shape rotated into a different orientation in space). The brain activity and connectivity results are very interesting; in brief, they suggest that the participants with ASD in this study process visual-spatial information in a different, possibly more efficient, way than controls. We have used the information from the DTI scan (the long noisy one!) to investigate whether there are any differences in the structure of brain white matter (the main connecting fibres) that could explain the differences in brain activity and connectivity. So far, we have seen that some of the important long white matter fibres are slightly more complex in participants with ASD compared with controls. This increased complexity might mean that the ASD group find it slightly harder to integrate information in the brain, and that they have developed enhanced visual perceptual functioning to compensate for this difficulty.

We were very pleased to be awarded a grant to continue this work and Jackie Fitzgerald has already started working on the new phase of the TRACT study. As part of this work, we will be in touch with everyone who participated in the study, and we will be recruiting new people to the study.

**Social Reward and Autism (Sonja Delmonte)**

We would like to thank all of those who took part in the MRI study on social reward in ASD. The data have now been analysed and the results indicate that people with ASD show reduced activity in the striatum (a part of the brain that is important for processing rewards) when they receive social rewards. This may explain some of the difficulties with social interaction in ASD. The results have been submitted for publication and further data analysis is being carried out to examine whether these differences in brain activation are due to underlying differences in brain structure and connectivity.

**Upcoming studies**

**IDEAs: Improving Diagnosis of Anxiety in autism spectrum disorders (Codruta Sudrijan)**

There is substantial evidence that people with ASDs are at high risk of associated psychiatric disorders, particularly depression and anxiety (>55%). This research project aims to establish the clinical features of anxiety in ASD and the key components of anxiety in ASD using multi-informant reports and physiological parameters.

**Research Team Contact Information**

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