Autism Research Newsletter  
January 2014  

Autism Research Group  
Trinity College Dublin  

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 families who have taken part in various studies.

Important Research Findings

Autism Spectrum Disorder Genetics Studies

Over the last year we have been continuing our efforts to understand how genes are important in ASD. We want to know to what extent genes play in ASD, which genes or groups of genes and whether we can identify specific differences in our genes that can be used to help diagnose individuals or inform on clinical management.

Differences in our DNA influence the likelihood of developing ASD. Previous work on understanding the genetics of ASD relied upon studying twins and calculating the rate at which identical and non-identical twins shared ASD. Using state-of-the-art approaches we can look at many millions of differences in your DNA and calculate how these differences between an individual’s DNA influences ASD. This means we can look at populations and not just twins. Over the last year, this is where your DNA was examined; published in the prestigious scientific journals *Nature Genetics* and *Molecular Autism*, we and others confirmed that ASD is highly heritable and that up to 80% of this was influenced by the common DNA differences.

Which genes are important? Now this is the tricky question that we continue to investigate. For common DNA differences we are continuing to examine many thousands of individuals DNA to better identify these genes. Dr Richard Anney, an Assistant Professor of Neurodevelopmental Molecular Genetics in our team is leading these large international efforts. In October he presented the latest work from this working group at the World Congress of Psychiatric Genetics in Boston, USA. In a study of nearly 7000 families we are identifying new genes and strengthening evidence from previously identified genes in ASD. To make the science better and improve our confidence in the statistics we are moving forward with much larger studies called the PsychChip and announced work on a project to look at the DNA of a further 100,000 people, 18,000 of whom have ASD. This is an exciting project, one that will deliver important information to help develop diagnostic tests and provide the fundamental information required to investigate how differences in our genes impact on your ASD.

For some families it is not the common DNA differences described above but rare or even private DNA differences that look to be the most important for their ASD. We continue to explore these types of DNA variation too. As part of our work leading the Autism Genome Project, Professors Gallagher, Anney and Dr Alison Merikangas have looked at a phenomenon called copy number variation. This is when your usual 2-copies of a gene or part of a chromosome is changed by deletion or duplication. Everyone has copy number variation in our DNA but sometimes they occur at genes and alter how that gene works. Sometimes these CNVs are de novo (that means that mom and dad do not have them but their child does – an example of one of these
Copy Number Variation (CNV) Clinical Outcome Studies (Alison Merikangas)
Using data from the Autism Genome Project we did a study to see if the clinical presentation was different between people who had structural changes in their DNA (copy number variants: CNVs) impacting specific genes that were either 1/ brain expressed (BE); or 2) previously implicated in Autism/Intellectual disability (ASD/ID). Clinical features we investigated were ASD features, adaptive function, IQ, developmental delay, family characteristics and parental age at birth. We found that some changes in were associated with language and communication and adaptive function. De novo changes (not inherited) were associated with language and presence of seizures and in some cases with simplex family type (only one case of autism in the family). Finally, increased paternal age predicted deletions in brain expressed genes . This work was presented at a number of international conferences, and has been written up for publication. Alison is now working on another international autism data set from the Simon’s Simplex Collection in order to replicate the findings from her work with the AGP data.

Migration and Risk of Autism (Dr. Suzanne Bolton)
Environmental risk factors for autism spectrum disorders may well represent a critical component of risk and etiology for the condition. However, such factors have been difficult to identify and quantify. In a report published 2 October in the European Journal of Pediatrics, we describe how, in Ireland, children born to women who have emigrated from certain African countries are more likely to be diagnosed with autism, and to have more severe symptoms of the disorder, than their peers.

Other studies have also found this, e.g. in immigrants from Somalia in Sweden and second-generation Afro-Caribbean people in the U.K. In the U.S., however, some
immigrant groups, such as Mexicans, are reported to have lower levels of autism than others. Here in Ireland we had an increase in immigrations from the mid-1990s to the mid-2000s. Anecdotally we and others observed that there was an apparent rise in the number of children with autism born to mothers who had immigrated to the country. We investigated this in a clinic sample attending the neurodevelopmental clinic in Tallaght Hospital in Dublin, Ireland. We found that children in immigrant groups presented for diagnosis about 4.5 months later, on average, than the Irish group. This may reflect their barriers to accessing diagnostic services. Of children diagnosed with autism we found that 71 percent were Irish, 18 percent African and 11 ‘other.’ Birth statistics for the period indicate that approximately 3-5% of all births are to mothers from Africa indicating that we were observing higher rates of autism in our clinic sample. We also observed that children born to African mothers were likely to have greater severity of autism symptoms and intellectual impairment, were later born and were more likely to have a sibling with autism. It is plausible that the greater severity and familial loading in the African group reflects ascertainment bias — that is, that parents may seek health services for more severe cases, and less severe cases go undetected. We are investigating this theory using population-based data from the Growing Up in Ireland Study. Our findings fit with reports in other countries of higher rates of autism among immigrants, particularly those from Sub-Saharan Africa in Sweden and a Somali group in Minnesota. Further investigations of this phenomenon may help to identify environmental factors or gene-environment interactions that are contributing to increased rates in people who have immigrated to Ireland.

**Neuroimaging Studies**

Our work using neuroimaging (MRI) techniques to investigate ASD continues to produce some very interesting and novel findings. Since our newsletter last year, more work from the first phase of the TRACT study completed by Dr. Jane McGrath and Dr. Sonja Delmonte’s research regarding social reward in ASD have been reviewed and published in prominent scientific journals.

Dr. McGrath’s research has found that there were significant differences in some of the main white matter tracts (connecting brain fibres) in people with ASD and that these differences were associated with visuospatial processing. In another paper recently published by Dr. McGrath, she found that atypical structural connectivity (how the brain is wired) is linked to atypical brain function. Dr. Sonja Delmonte has published her work in Molecular Autism journal describing how reduced activity in the striatum (where rewards are processed in the brain) was found in individuals with ASD. Following on from this, Dr. Delmonte’s research found that there was an over-connectivity in specific brain circuits believed to be responsible for deficits in social interaction and restricted repetitive behaviours in ASD. Both Dr. McGrath and Dr. Delmonte’s research suggests that the core difficulties experienced by individuals with ASD may be due to a disruption in how various parts of the brain are connected.

The second phase of the TRACT study, which is being conducted by Jackie Fitzgerald is well underway. Recruitment is ongoing and MRI scans have been carried out over the past year. The recruitment phase of the project will be coming to an end shortly in early 2014 and finalised data analysis will begin. To date this research has found that individuals with ASD use different brain regions to typically developing individuals to perform direct attention. This may suggest that people with ASD have the ability to develop compensatory mechanisms to improve behaviour. We have submitted this work for publication and it is currently under review.

The group has also just begun an MRI project investigating ‘Theory of Mind’ in ASD. Theory of mind is the name given to the idea that individuals understand that people hold different beliefs, opinions and ideas, which differ from our own. This project has been set up in collaboration with Dr. Joshua Balsters at ETH in Zurich and is currently being carried out by Ms. Rea Lehner. Recruitment is ongoing for this project and we are always looking for people to take part in our research studies so if you, any family members or friends might be interested, please do let us know.

**A Consultation Concerning the Establishment of a National Autism and Related Neurodevelopmental Disorders Registry and Biobank**

This is a consultation process that is being undertaken by three partner organizations, namely the National University of Ireland, Galway (NUIG), The Autism and Related Neurodevelopmental Disorders Research Group, Trinity College Dublin (TCD) and Autism Speaks. The aim of the consultation is to engage with stakeholders affected by or involved in service provision to people with autism or other related neurodevelopmental disorders. Specifically we would like to learn more about the needs of the community and what kind of information is most helpful to record in a clinical registry. Additionally we would like community feedback on the development of a Biobank to support biomedical research. At the end of this process we plan to produce a report that will be provided to the stakeholders summarizing the outcomes and recommendations for next steps.
What is a clinical registry?
Clinical registries gather clinical information and other data on patients to inform the development of clinical practice, services and future research. Some of the best-known examples of registries are those that exist in Scandinavain countries where there are well-established patient registries for a variety of physical and mental illnesses and disabilities. These well-organised registries provide critical data that are useful for the development of services and to identify critical research questions to be further investigated.

The development of a registry can address a range of research topics that may include:

- The scale of autism in Ireland across the lifespan
- The behavioral health and the medical needs of the Irish autism community
- The impact of early intervention on later outcomes
- Factors that influence successful school placement
- Factors that influence improved quality of life among adolescents and adults with autism
- Planning for transitions in service delivery, e.g. from pre-school to school, from school to adult services

What is a Biobank?
A Biobank is a type of repository that stores biological materials, such as blood or saliva that can be used in research. Biobanks have become a key resource to support medical research particularly in the fields of genetics and personalized medicine and for the development of biomarkers for various human conditions. Biobanks typically include samples from people affected by the same condition. In the future is it hoped that by combining genetic information (e.g. DNA or RNA) with other information e.g. regarding physical symptoms or environmental factors, it will be possible to better understand how genes and environment interact to cause autism and to find ways to prevent and treat the condition.

We launched this consultation process at the 2nd conference on autism and related neurodevelopmental disorders at NUIG in June 2013, where we had a roundtable discussion and conducted a pilot survey. The next phase of the consultation process involved engagement with the community through town hall meetings, meeting with service providers and policy makers and an online survey. The scheduled dates and locations of townhall meetings are as follows:

- January 14th – Dublin (Trinity Biomedical Sciences Institute) 7pm
- January 28th – Galway (NUIG) 7pm
- February 4th – Cork (UCC or location TBD) 7pm
- February 13th – Sligo (IT or location TBD) 7pm

In addition we will launch an online survey to the autism and related neurodevelopmental disorders community in early 2014. Please check our Facebook page for further information and for the link to the survey once launched.

Upcoming Studies
We are planning several other studies and these are regularly updated on our website and Facebook page.

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