Investigating the molecular and cellular consequences of Disrupted in Schizophrenia 1 in patient-derived neural stem cells

Schizophrenia Research Fund & Mental Health Research UK Joint Award

John Grace QC PhD Scholarship 2012, University of Edinburgh, RC Institute of Genetics and Molecular Medicine

Supervisors: Professor David Porteous and Professor Andrew McIntosh

Research Student: Daniel McCartney

Start date: September 2012

Description

Schizophrenia, bipolar disorder and recurrent major depression are devastating conditions for which current treatments are only partially effective. Lack of access to human neural tissue is a major limitation to developing more effective and better tolerated treatments. To address this, we will harness the exciting potential of stem cell technology in which the University of Edinburgh is one of the world's leading centres: human fibroblasts are routinely obtained through biopsy, cultured to become stem cells, then reprogrammed to become neurons, enabling us to study living human neural tissue. Critically, we also have access to the unique Scottish t(1;11) family carrying a causative disruption of the DISC1 gene: members have provided skin biopsies from which stem cells and neurons have already been obtained in two cases. This PhD project will characterise these cells at the molecular, cellular and pharmacological level. Using tools and techniques established in our laboratory, the student will profile these patient-derived stem cells as they form neurons and compare these profiles to normal cells. We will use the profiles to tell us what neural processes are perturbed in schizophrenia, and test how these respond to treatment with antipsychotics.

Daniel McCartney the successful MHRUK/Schizophrenia Research Fund Scholar said:

"I'm very pleased to have been awarded this studentship by MHRUK and the Schizophrenia Research Fund. I'm looking forward to beginning work with Professors Porteous and McIntosh at the Centre for Molecular Medicine and hope to contribute to shedding light on the molecular and cellular basis of mental illness. In spite of the fact that mental illness is such a common occurrence, I believe mental health research is not as well publicised as other fields of research. I hope that the research I will undertake, along with the work of other scientists, will give mental health research and its funding bodies the publicity they deserve."

Daniel's Final Report

I submitted my PhD thesis entitled “Investigating Genome-wide Methylomic and Transcriptomic Consequences of a Balanced t(1;11) Translocation Linked to Major Mental Illness” in September 2016 and successfully defended in February 2017.

My project was focused on a large Scottish family with a chromosomal mutation linked to schizophrenia, bipolar disorder and depression. Using three types of biological samples from this family (blood-derived immortalised cell lines, whole blood and stem cell-derived brain cells), I examined global gene expression levels and a process called DNA methylation. Methylation is an alteration to DNA that can be caused by environmental influences (e.g. smoking, stress) and has been shown to be altered in numerous diseases including psychiatric disorders. Examination of blood-derived DNA from 41 family members revealed strong differences in DNA methylation at the genomic regions in which the above-mentioned chromosomal mutation occurred. This finding presented a potential biological mechanism for illness in the family members carrying this mutation. Towards the latter part of my PhD I was investigating DNA methylation in stem cell-derived neuronal material from six family members : three with the mutation and three without. Some differences were observed in individuals carrying the mutation but the effects were not as strong as those seen in blood. A reason for this may have been the small number of individuals profiled. To address this issue, work is ongoing to generate additional stem cell-derived neuronal samples from the family. Work is also ongoing to examine gene expression levels in these samples with an additional aim to investigate the relationship between DNA methylation and gene expression in the family. The output of my PhD is a first author paper [1] and a second in preparation, relating to the blood-based study of DNA methylation. The published paper describes a method to increase the reliability of data generated from a widely-used product for the detection of DNA methylation in various traits and disorders. The goal of this paper is to provide a useful resource to the research community.

As of October 2016 I have been working for an Edinburgh-based Genomics company, providing analytical services to commercial and academic groups. This has allowed me to apply the experience gained during my studies, assisting in multiple research projects related to a broad range of disorders.

Altered DNA methylation associated with a translocation linked to major mental illness

https://www.nature.com/articles/s41537-018-0047-7

2015 Report

My PhD project is focused on investigating psychiatric illness among a family with a high incidence of schizophrenia, recurrent major depressive disorder and related illnesses. In this family, psychiatric illness has been found to be co-inherited with a chromosomal rearrangement. We know that psychiatric illness is caused by a combination of inherited (genetic) factors, and environmental factors, such as stress, and the interaction between the two. These factors may influence gene expression (i.e. switch certain genes on or off),

which may play a role in illness. I am comparing DNA samples from carriers of the above mutation to those from non-carrying relatives with an aim to identify such factors and interactions which may be contributing to illness in these individuals. A major part of my project over the past year has involved looking at a process called DNA methylation. This process can be altered by the environment (e.g. stress, smoking status) and is linked to gene expression. Recent studies have also reported abnormal DNA methylation levels in psychiatric illness. I have been examining DNA methylation levels in blood-derived DNA from the family to identify genes with altered methylation levels between carriers of the chromosomal rearrangement and their non-carrying relatives. Although still ongoing, I have given poster presentations on the progress so far at the World Congress of Psychiatric Genetics in Copenhagen as well as several local meetings here in Edinburgh. More recently, I have also been looking for a relationship between DNA methylation and various psychiatric diagnoses in these individuals. Additionally, I am attempting to identify any effects of variation in the genetic codes of these individuals on DNA methylation. The final stages of my PhD will involve similar studies on different material: induced pluripotent stem cells (iPSCs). Here, I will be examining methylation and any related gene expression changes in brain-like cells generated from skin biopsies from the family. We hope that these will provide a better model for the brain. We have recently started growing and harvesting this material with an aim to begin experiments in the coming months. I am hoping these results will identify brain-related pathways showing disrupted methylation patterns in ill individuals which can then be followed up by looking for changes in gene expression.

2016 Report

My PhD project is focused on investigating psychiatric illness among a family with a high incidence of schizophrenia, recurrent major depressive disorder and related illnesses. In this family, psychiatric illness has been found to be co-inherited with a chromosomal rearrangement. We know that psychiatric illness is caused by a combination of inherited (genetic) factors, and environmental factors, such as stress, and the interaction between the two. These factors may influence gene expression (i.e. switch certain genes on or off), which may play a role in illness. I am comparing DNA samples from carriers of the above mutation to those from relatives who do not carry it, with an aim to identify such factors and interactions which may be contributing to illness in these individuals. I am now in the final months of my PhD, finalising my analyses and writing my thesis, with submission due by the end of August.

A major part of my project over the past year has involved looking at a process called DNA methylation. This chemical modification of the DNA we inherit can be influenced by the environment (e.g. infection, stress, smoking) and is linked to altered gene expression. Recent studies have also reported abnormal profiles and levels of DNA methylation in psychiatric illness. I had previously been examining DNA methylation levels in blood-derived DNA from the family to identify genes with altered methylation levels between carriers of

the chromosomal rearrangement and their non-carrying relatives. Additionally, I have been examining the effects of variation in the genetic codes of these individuals on DNA methylation. I found the strongest differences in DNA methylation occurred within the regions of the chromosomal rearrangement in these individuals. A paper describing this work is currently in preparation.

My original PhD proposal was to exploit the power of IPSC technology to model the brain in a dish. IPSC stands for induced pluripotent stem cell. Briefly, by taking skin biopsies from patients, culturing the skin cells (fibroblasts) then exposing them to a cocktail of factors can induce a change for the differentiated fibroblast state to an earlier, undifferentiated, or stem cell state. These pluripotent stem cells can then be induced to follow an alternative pathway of differentiation, in our case to neurons. These derived neurons can then be cultured in the laboratory, hence 'brain-in-a-dish'. The last year has involved growth and preparation of a set of these samples derived from carriers of the chromosomal rearrangement and non-carriers, in which DNA methylation has been measured on a genome-wide scale. DNA methylation studies require extensive quality control measures to generate reliable data. Illumina, a leading vendor in this research area, recently launched a new 'chip' used to capture methylation data. As a first step, I examined this 'chip' for variants that could be prone to false results due to underlying genetic variation. I am first author on a paper that describes these findings and which is likely to be a valuable guide to all those starting to use this new 'chip' for genome-wide DNA methylation analysis. This procedure is anticipated to be applied to many future studies by others assessing the relationship between DNA methylation and various traits and conditions, including psychiatric disorders.

I am currently performing various analyses on these data comparing differences between carriers of the rearrangement to non-carriers, as well comparing DNA methylation between blood and brain within these individuals. This will complete my thesis studies.

Reference to published paper:
McCartney, D. L., Walker, R.M., Morris, S.W., McIntosh, A.M., Porteous, D.J., & Evans, K.L. (2016). Identification of polymorphic and off-target probe binding sites on the Illumina Infinium MethylationEPIC BeadChip. Genomics Data, 9, 22-24. doi:10.1016/j.gdata.2016.05.012.