

# GENE DISCOVERY IN SCHIZOPHRENIA AND BIPOLAR DISORDER

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Over the past few years there have been encouraging advances identifying genetic risk factors in schizophrenia and bipolar disorder and these may be the first steps towards understanding the biology of the disorders leading to novel treatment and preventative strategies. Recently the pace of discovery has increased as new microarray and DNA sequencing technologies now make it possible to survey very large cohorts of patients using many DNA markers to identify some of the many common and rare genetic variants contributing to the disorders. Douglas Blackwood, professor of psychiatric genetics at the University of Edinburgh has been working with Dr Muhammad Ayub, carrying out genetic linkage studies with families from Pakistan with bipolar disorder and depression.

## INTRODUCTION

A remarkable series of recent studies, described as genome-wide association studies (GWAS), representing some of the largest collaborations so far undertaken in bipolar disorder and schizophrenia may at last be providing clues about the nature of the genetic risk factors and are giving direction to discovering the underlying neurobiology to these heterogeneous disorders<sup>1-7</sup>. Genome wide association studies (GWAS) are designed to detect genetic association between an illness and genetic markers, usually single nucleotide polymorphisms (SNPs), distributed across all chromosomes. Many genetic association studies in schizophrenia and bipolar disorder have been carried out over the past two decades and candidate genes identified but recent developments in microarrays have provided the technology to genotype individuals from large cohorts of cases and controls using many markers giving power to detect genes that make only small contributions to genetic risk (odds ratio <1.5). Recently published GWAS involving cohorts of several thousand cases and controls brought together in large international collaborations, using over 1 million SNP markers have identified novel genes, highlighted the involvement of some previously identified candidate genes and delivered unexpected findings on the role in disease of rare micro deletions and duplications, termed copy number variants (CNVs). These discoveries signpost the functional pathways involved in the pathogenesis of illness. GWAS promises to be an important step towards an eventual understanding of

the neurobiology of disease by identifying some of the genes involved and providing initial indications of the total number and classes of genes contributing to these complex heterogeneous disorders. Further developments are now likely in several directions: the discovery of individual genes will be followed by pathway analysis to uncover functional links between candidate genes and to identify the underlying biological changes in neurons and glia cells. This in turn will direct the search for novel drug targets and new treatment and preventative strategies. Secondly an understanding of genetics may form the basis for a biological classification of the psychoses which at present relies on patients' reports of symptoms. Thirdly, there is now need for careful debate about how novel genetic discoveries can best be applied for the benefit of individuals and their families affected by illness. Predictive testing and accurate assessment of risk in a clinical context is not currently feasible but cannot be entirely ruled out in the future raising important ethical issues. Genetic markers could also have a future role identifying sub groups of patients responsive to particular treatments and interventions permitting more targeted treatments.

## The Inheritance of Schizophrenia and Bipolar Disorder

Schizophrenia and bipolar disorder often run in families and the classical studies of twins showing greater concordance in identical compared with non identical twins have confirmed that genetic factors are responsible with an estimated heritability of around 80%. These findings from population genetics underpinned the substantial investment made by many research groups into genetic linkage and association studies in schizophrenia and bipolar disorder over the past two decades. The discovery of different types of genetic markers coupled with improved genotyping technologies made these approaches possible on an increasingly large scale. Many chromosomal locations strongly implicated in schizophrenia and bipolar disorder were

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detected and in a few cases including *DISC1* and *NRG1* evidence was accumulated supporting the involvement of specific genes. However there is still much uncertainty about the nature of the genetic risk factors in psychoses, the number of genes involved and the neurobiological pathways disrupted. While it is clear that the genetic risks for schizophrenia and bipolar disorder cannot be explained by the actions of one or a few major genes a genetic model that adequately accounts for the diversity of genetic findings in these disorders has not been defined. As with other complex disorders such as diabetes and inflammatory bowel disease it seems likely that a large proportion of the genetic risk factors in the psychoses are common genetic variants present in a large proportion of the population. Common variants each contribute only a very small risk of illness to an individual (odds ratios <1.5) but their contribution to the prevalence of illness in the population (population attributable risk) becomes substantial. Illness is presumed to develop in an individual who has inherited multiple risk factors just as a person's height is determined by the interaction of many contributing factors none of which has a major affect by itself. However common risk factors do not explain several things we know about the genetics of psychoses. It is clear that in some individuals and families the disruption of a single gene is accompanied by a high risk of illness. For example the gene *DISC1* when disrupted in some individuals was found to increase the risk of major mental illness about 50 fold<sup>8</sup>. In individuals who inherit the microdeletion on chromosome 22 associated with the velo-cardio-facial syndrome (VCFS) , about 30% will develop psychotic illness<sup>9</sup>. The recent discovery of the important role of rare copy number variants (CNVs) in schizophrenia confirm an important role in schizophrenia of genes whose disruption is a major, or indeed the main cause of illness in some individuals<sup>3,6</sup>. A model of genetic risk in schizophrenia and bipolar disorder is only complete when it includes the influence of environment on genes. How and at what stage of development gene- environment interactions are most influential are questions remaining largely unanswered.

### **The contribution of genome wide association studies**

Genetic association studies, designed to compare the frequencies of genetic markers in groups of cases and controls are simple in concept. When a genetic marker lying within or near a gene is observed significantly more often in cases than controls the gene is assumed likely to have some role in disease. Many significant associations between genetic markers and schizophrenia or bipolar disorder have been published from studies involving relatively small numbers of markers and several hundreds of patients and controls. However these studies have had limited power to detect common risk factors (OR<1.5) and are very unlikely to detect rare variants. The increased marker density avail-

able on microarrays containing over 1 million SNPs and greatly expanded cohorts of several thousand cases and controls established by pooling clinical resources in international collaborations has now made it possible to identify some of these important risk variants.

### **Recent genome wide association studies in bipolar disorder**

GWAS studies recently reported<sup>1,5,7</sup> a combined analysis of over four thousand bipolar cases and six thousand controls all of European ancestry where two novel genes were identified showing significant association with bipolar disorder, Ankyrin-3 gene (*ANK3*) on chromosome 10 and a calcium channel gene *CACNA1C* on chromosome 12<sup>2</sup>. This analysis clearly demonstrated the importance of assembling large data sets since neither of the genes *ANK3* or *CACNA1C* had reached levels of genome wide significance in the individual smaller studies making up the larger set. These two genes are also of interest for understanding the biology of bipolar disorder as Ankyrin-3 belongs to a family of membrane proteins that have roles in many cellular functions and are part of the structure of voltage gated sodium channels. It is interesting that both *ANK3* and *CACNA1C* proteins are a part of ion channels, supporting further studies of synaptic proteins in bipolar disorder. However this study of three thousand cases and six thousand controls still has limited power to detect other genes contributing small genetic risks and much larger case control cohorts in bipolar disorder are required. Progress is now likely in two main directions: future association studies will involve even larger cohorts and secondly by pathway analysis using data from very large numbers of SNPs in thousands of cases it may be possible to identify groups of related genes and link their roles to particular biological processes creating a picture of the brain processes disrupted in illness.

### **Genome wide associations in schizophrenia**

Data analysis from genome wide association studies involving large cohorts of patients with schizophrenia and controls has recently highlighted the important role of a type of variation detected in genes called copy number variation (CNV) which are small chromosomal deletions and duplications<sup>3,6</sup>. The best described example connected with schizophrenia is in patients with velo-cardio-facial syndrome (VCFS) who have a deletion approximately 1.5Mb in length, across a region of chromosome 22 where the disruption of a number of genes causes dysmorphic features and psychosis will develop in about 30% of cases. Recent studies have also identified large rare CNVs on chromosome 15 and chromosome 1 causing schizophrenia in a small but significant number of cases. Across the genome small CNVs are also present, many in the size range of

1-500kb and these may be related to disease when the function of particular genes is disrupted. CNVs found within genes are common in all individuals but are significantly more frequent in patients with schizophrenia and further studies are expected to identify more of these variants. A major aim of genetic research is to catalogue these novel sources of genetic variation and to describe the clinical phenotypes associated with the disruption of genes harbouring CNVs.

## CONCLUSIONS AND FUTURE DIRECTIONS

Initial discoveries from GWAS even with relatively small cohorts of patients and controls, have produced a rich harvest of novel findings and we can expect further gene discoveries when combined analyses are performed on increasingly large sets of data. A start has been made in finding common and rare variations in bipolar disorder and schizophrenia and some broad conclusions are emerging: 1) a variety of different types of genetic variation including rare and common variants, large and small chromosomal deletions and duplications are contributing to the genetic risk in these disorders and there is more diversity and heterogeneity than previously known; 2) Individual genes have been identified in schizophrenia and bipolar disorder and we can begin to study the biological pathways linking these genes. 3) There is much overlap in genetic factors contributing to schizophrenia and bipolar disorder and the identification of further genes may provide the tools to develop biologically based classifications of the psychoses. Genetic discoveries may also have a future role in the design of treatment studies by identifying sub populations of these highly heterogeneous disorders. 4) Most studies published to date are on patients of European ancestry. It is likely that some rare variants will be population specific and the role of common variants may differ between different ethnic groups. Large cohort studies in a variety of ethnic groups are required to find population specific risk factors and environmental interactions. Genome wide association studies have very limited power to detect rare variations causing illness because the sample sizes required are unrealistically large. There is a strong case for continued family studies and studies of rare chromosomal rearrangements associated with unusual phenotypes in families as these offer a powerful route to discovering rare genes. The population and family structure in Pakistan is suited to these studies aimed at detecting major genes some of which may be population specific and cause illness in relatively few individuals but which nevertheless can provide crucial new insights into the pathology of these illnesses<sup>10,11</sup>.

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