Genetic factors contribute to schizophrenia and bipolar disorder, and linkage and association studies have been successful in identifying several candidate genes. However, these genes explain only a very small part of the total population risk and the psychoses appear to be very heterogeneous with several models of genetic inheritance relevant to different groups of patients, including some cases caused by multiple common genetic variants, while others are single gene disorders. Studying chromosomal abnormalities is a useful strategy for identifying genes in illness, and patients with both mental retardation and psychosis form a special group where large chromosomal abnormalities detected by routine cytogenetic analysis are more prevalent than in patients with schizophrenia or bipolar disorder alone, or in the general population. Studying these patients provides valuable opportunities to identify genes contributing to psychoses. This review of the literature on large chromosomal rearrangements in patients with mental retardation and psychotic illness illustrates how schizophrenia and bipolar phenotypes are associated with a large number of different chromosomal disruptions. Recent genome wide association studies have identified an excess of small chromosomal deletions and duplications in schizophrenia, adding further support to the importance of chromosomal structural variation in psychotic illness. The genes GRIK4 and NPAS3, each associated with psychosis in patients with mental retardation are discussed to illustrate the value of rare cytogenetic events as a means to signpost neurobiological pathways of general importance for illness in the wider population.

Keywords: Mental Retardation; Schizophrenia; Bipolar disorder; Chromosomes; Cytogenetics; Genes

INTRODUCTION

Despite convincing evidence that genetic factors have a major role in schizophrenia and bipolar disorder, progress towards identification of individual genes has been slow. Family linkage studies have identified a number of chromosomal locations thought likely to harbour genes contributing to symptoms, but only a few linkage "hotspots" have been widely replicated by independent studies or highlighted in meta analyses (Badner and Gershon, 2002; Segurado et al., 2003; McQueen et al., 2005). Case control association studies of candidate genes have identified several genes likely to contribute to schizophrenia or bipolar disorder (Harrison and
Weinberger, 2005; Ross et al., 2006) and recently genome wide association studies (GWAS) using up to one million single nucleotide polymorphisms (SNPs) in large cohorts of several thousand patients have identified novel genetic variants and confirmed previously known risk factors in bipolar disorder and schizophrenia (Wellcome Trust Case Control Consortium, 2007; Baum et al., 2008; Sklar et al., 2008; Stefansson et al., 2008; Stone et al., 2008). These studies suggest that many rare, highly penetrant genetic variants, including small chromosomal deletions and duplications described as Copy Number Variants, contribute to the psychoses which apparently have a high degree of locus heterogeneity. This can explain the lack of power and poor history of replications of association studies, because if illness can be caused by any one of a large number of highly penetrant rare genetic variants each of which has a very small effect in the total population, these genes are likely to show only weak association with illness in studies involving a few thousand cases.

DISC1 is an example of a highly penetrant rare gene defect in psychiatric illness. Disruption of this gene by a reciprocal balanced chromosomal translocation is associated with a near 50-fold increased risk of major mental illness in members of one particular family (Blackwood et al., 2001). Variation in another gene, PDE4B, may also be a rare highly penetrant cause of schizophrenia because this gene was disrupted by a chromosomal translocation breakpoint in a patient with schizophrenia. Subsequent work demonstrated that DISC1 and PDE4B directly interact to modulate neuronal cAMP levels, pointing to a cell signalling pathway of possible relevance to illness (Millar et al., 2005). Recent case-control analyses have revealed significant associations between variation in PDE4B and psychiatric disorder in the general population (Pickard et al., 2007; Numata et al., 2008).

Mental Retardation Co-Morbid with Psychosis

Patients with mental retardation who develop psychotic illness in adolescence or adulthood are an important group to study in the search for rare highly penetrant genetic variants in schizophrenia and bipolar disorder. Intellectual disability affects at least 2 to 3% of the population in developed countries and it has long been established that the prevalence of schizophrenia in intellectual disability is higher than the general population, and more recently it has been shown to be associated with an increase in the familial risk of schizophrenia (Doody et al., 1998). Prevalence is estimated to be 2-6% in institutions and 3% in the community compared to 1% of the general population (Vitiello and Behar, 1992). The most recent community study using DSM IV criteria estimated the point prevalence of schizophrenia in learning disability to be 3.4% and 2-year incidence to be 1.2% (Cooper et al., 2007; Smiley et al., 2007).

The reasons for the increase of schizophrenia (and also bipolar disorder) in people with mental retardation are unclear but there are several hypotheses: (a) psychosis with mental retardation represents a very severe and early onset form of the mental illness, and mental retardation and psychosis arise from a common cause; (b) the specific cognitive deficits within intellectual disability increase vulnerability to developing psychotic symptoms; (c) the findings are coincidental. Brain MRI studies give strong support to the first of these explanations because these patients have a pattern of structural deficits in the amygdala and hippocampus as found in schizophrenia, but dissimilar from the pattern of changes in patients with mental retardation who do not have psychotic illness. Subjects with MR and schizophrenia show reductions in the volumes of the whole brain, temporal lobes and amygdalo-hippocampal complex, with enlargement of the lateral ventricles (Moorhead et al., 2005). A series of studies compared the following four groups of subjects:

1. schizophrenia with mental retardation,
2. mental retardation alone,
3. patients with schizophrenia, and
4. controls with normal IQ.

MRI brain images showed close resemblances between the schizophrenic subjects and the group with mental retardation and psychosis, while the group with learning disability alone more resembled controls. Those with mental retardation and psychosis had the smallest total brain volume and the smallest volume of the amygdalo-hippocampal complex (Sanderson et al., 1999; 2001). These findings were replicated using voxel-based morphometry demonstrating similar grey matter reduction in the comorbid and schizophrenia group com-