Available online at www.sciencedirect.com
SCIENCE DIRECT®
European Journal of Pharmacology 480 (2003) 177–184
www.elsevier.com/locate/ejphar

The genetics of schizophrenia: glutamate not dopamine?

David A. Collier[a,b,*], Tao Li[a,c]

[a] Section of Molecular Genetics, P82, Division of Psychological Medicine, The Institute of Psychiatry, De Crespigny Park, Denmark Hill, London SE5 8AF, UK
[b] Social, Genetic and Developmental Psychiatry Research Centre, The Institute of Psychiatry, De Crespigny Park, Denmark Hill, London SE5 8AF, UK
[c] Department of Psychiatry, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, PR China

Accepted 25 August 2003

Abstract

The major targets of current drugs used in mental health, such as neurotransmitter receptors and transporters, are based on serendipitous findings from several decades ago, and there is currently a severe drought of new drug targets. There is a pressing need for novel drugs, and much hope has been placed on the use of molecular genetics to help define them. However, despite evidence for a genetic basis to schizophrenia stretching back for over a century, and a heritability of about 80%, the identification of susceptibility genes has been an uphill struggle. Candidate gene studies, which have generally focussed on obvious candidates from the dopamine and serotonin systems, as well as genes involved in brain development, have not generally been successful, although meta-analysis indicates that the dopamine D3 receptor gene (DRD3) and the serotonin receptor gene type 2A (HTR2A) may have a very small influence on risk. Linkage analysis has provided robust evidence of genetic loci, for example, on chromosomes 8p, 13q and 22q, and also implies shared genetic aetiology with bipolar disorder. The identification of these loci together with advances in genetic technology, especially the characterisation of polymorphisms, the understanding of haplotypes and the development of statistical methods, has lead to the identification of several plausible susceptibility genes, including neuregulin 1, proline dehydrogenase and dysbindin. Interestingly, these genes point more towards a role for the glutamate pathway rather than the dopamine pathway in schizophrenia. We have attempted to replicate some of these findings in schizophrenic patients from SW China, and we find significant association with a novel neuregulin 1 haplotype, with proline dehydrogenase polymorphisms, but not with catechol-*O*-methyltransferase (COMT). The replication of neuregulin 1 association on chromosome 8p by several investigators is the most convincing to date, and the presence of a syndrome similar to dementia praecox of 8p linked families, and the lack of linkage of bipolar disorder to this region is a testament to the ideas of Kraepelin more than 100 years ago.

Keywords: Psychosis; Linkage; Association; Genetic; 5-HT (5-hydroxytryptmamine, serotonin); Proline; Neuregulin

1. Introduction

Schizophrenia is a debilitating brain disease, which affects up to 1% of the population worldwide. There is no cure, and treatments, which are mainly based on antagonism of dopamine, serotonin and other neurotransmitter receptors in the brain, are only partially effective. There is a severe drought of drug targets in schizophrenia and other disorders, with the majority of drug targets having been discovered serendipitously over the past 50 years, and their corresponding genes have not been shown to play anything other than a minor role in disease aetiology (Hyman and Fenton, 2003). The reasons underlying this drought involve many factors including a lack of understanding of the pathophysiology of schizophrenia and the effect of diagnostic boundaries which may not reflect the natural boundaries of disease. Genetics has the promise to change this process by identifying new drug targets and biochemical pathways, which can be manipulated. In addition, the delineation of schizophrenia into components of symptom complexes and the development of targets for these narrower clinical measures has been proposed (Hyman and Fenton, 2003). The ability to achieve this will require an understanding of genetic and environmental effects in schizophrenia, as well as their interaction.

A variety of environmental risk factor have been identified, including pregnancy and delivery complications, delayed developmental milestones, lower IQ, urban upbringing, being offspring of immigrants, having older

* Corresponding author. Section of Molecular Genetics, P82, Division of Psychological Medicine, The Institute of Psychiatry, De Crespigny Park, Denmark Hill, London SE5 8AF, UK. Tel.: +44-20-7848-0631; fax: +44-20-7848-0295.
E-mail address: d.collier@iop.kcl.ac.uk (D.A. Collier).

0014-2999/$ - see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejphar.2003.08.105

fathers, cannabis smoking and childhood viral infections (Van Os and Marcelis, 1998). There are also prodromal factors associated with later development of the illness (Niemi et al., 2003), including thought disorder and negative symptoms in children (Ott et al., 2002) and abnormal suspiciousness, sensitivity and relationship difficulties (Bearden et al., 2000). In particular, a cluster of early features—including cognitive, academic, and social impairments, along with odd/disorganized behaviours—appear to anticipate positive symptoms and may constitute a core risk profile (Cornblatt, 2002). These factor, combined with the apparent absence of neuropathological changes in the disease (Weinberger and McClure, 2002), support the neurodevelopment hypothesis of schizophrenia (see McGrath et al., 2003), whereby schizophrenia results from neurodevelopmental impairment early in life (2nd/third trimester), based on neuropsychological abnormalities, high frequency of obstetric complications, viral infections and abnormalities of cell formation in hippocampus, cingulate gyrus, prefrontal cortex and temporal lobe. This could involve environmental and genetic aberrations in brain development, and is most likely the result of gene–environment interaction (Van Os and Marcelis, 1998).

The diathesis-stress model (Hanson et al., 1976) hypothesises that schizophrenia arises from the impact of the environment on the genetically vulnerable. This probably involves a multifactorial polygenic model (Gottesman and Shields, 1967), with schizophrenia arising from a pool of genetic and environmental factors at a critical threshold. At lower thresholds, other disorders or traits are expressed (e.g. schizotypy, neuropsychological impairment).

However, the relative risks associated with environmental risk factors are small compared to having a first degree relative, with lambda S (the sibling recurrent risk) being about 10. Schizophrenia is a highly familial disorder, and although the aetiology of schizophrenia is not well understood, there is longstanding evidence that this familiarity results from a genetic component. Recent twin studies place the heritability of schizophrenia at more than 80% (Cardno and Gottesman, 2000).

Despite this high heritability, numerous candidate gene association studies have failed to clearly identify susceptibility genes because of lack of consistent replication, leading to the perception that false positive findings are common (Lohmueller et al., 2003). Indeed, the low prior probability of a gene being a true risk factor means that modestly significant P values more likely arise by chance than through true association. In addition to false positive findings, false negative findings or true variability between populations could also explain this inconsistency. There are also a variety of reasons for this failure related to the probable pathophysiology of the disease, including, the existence of substantial locus and aetiological heterogeneity, characterised by numerous genes of small effect, the involvement of several biological pathways, lack of information to help with the selection of candidate genes, and methodological difficulties related to study design, statistical power and diagnostic validity and reliability (Tabor et al., 2000).

Most obvious candidate genes, such as genes in the serotonin and dopamine systems, have been examined with negative results, leading to the conclusion of that genes for schizophrenia novel unknown proteins or unexpected candidates. However, recent approaches based on meta-analyses of published data which take account of publication bias indicate that some favoured candidate genes for schizophrenia (the dopamine D3 receptor gene, DRD3 and the serotonin receptor gene type 2A, HTR2A) may have a small effect on risk, with odds ratios of about 1.1 (Lohmueller et al., 2003). Other genes which have been associated with schizophrenia in the past such as the dopamine D2 receptor gene and catechol-*O*-methyltransferase gene (COMT) did not provide evidence for association from meta-analysis.

2. Linkage analysis

Linkage analysis has been more successful, with good evidence for genetic loci identified on chromosomes 8p, 22q, 13q and several other locations in the genome, findings which are strengthened by meta-analysis of published data (Badner and Gershon, 2002; Lewis et al., 2003). These linkage findings have led to systematic genetic mapping efforts and positional candidate gene analysis of these loci, which appears at last to be leading to the unequivocal identification of susceptibility genes.

An interesting feature of linkage analysis in psychosis is that some loci are positive for linkage to both bipolar disorder and schizophrenia, since the two disorders are typically thought to be distinct with different clinical characteristics, aetiologies, and treatment regimens. (Berrettini, 2000; Badner and Gershon, 2002). This will not surprise many clinical psychiatrists as, anecdotally, psychotic patients often have both diagnoses in their notes. Indeed, similarities between the two disorders include age at onset, lifetime risk, course of illness, worldwide distribution, risk for suicide, equal gender risk and similar genetic susceptibility and multiple family studies are consistent with greater overlap than previously acknowledged. This indicates that our nosology will require substantial revision in the light of molecular genetic findings (Berrettini, 2000).

A number of investigators have published evidence implicating specific genes as risk factors for schizophrenia (Cloninger, 2002). These emerging genetic findings are described below.

3. Neuregulin 1

In a recent publication by Stefansson et al. (2002), linkage to chromosome 8p followed by haplotype mapping with microsatellites and single nucleotide polymorphisms

(SNPs) identified at-risk neuregulin 1 haplotypes for schizophrenia in patients from Iceland. Three microsatellite at-risk haplotypes, each individually in excess in patients, were found to have the same single nucleotide polymorphism core haplotype upstream of the first 5′ exon of NRG1. This finding has now been replicated in two large case control studies from Scotland (Stefansson et al., 2003) and the UK (Williams et al., 2003). The haplotype frequencies in Scottish and Icelandic patients and in Scottish and Icelandic controls, respectively, are very similar. A second replication study in a UK population found a small excess of the same neuregulin 1 risk haplotype, particularly when patients with a family history were analysed. In a Chinese sample, this haplotype was not found but a potential at-risk haplotype mapping to the same location in the gene was significant by both family-based and case control association methods (Li et al., submitted for publication) and a combination of three single nucleotide polymorphisms was also significant in an independent sample from Eastern China (Yang et al., 2003). Thus, evidence is accumulating that neuregulin 1 may be a genuine risk gene for schizophrenia. However, association is restricted to haplotypes, and the underlying functional variant(s) that give rise to disease risk have not yet been identified.

Neuregulin 1 is a plausible candidate gene for schizophrenia. It has multiple functions in a variety of tissues (Buonanno and Fischbach, 2001), including acting as a glial growth factor (an alternative name for NRG1 is glial growth factor 2) and migration of cerebellar and cerebral cortical neurons along radial glia is dependent on NRG1. In addition, it regulates neurotransmitter receptor expression, including the NMDA 2c receptor, GABA receptor β2 subunit, and neural nicotininc acid receptors (acetylcholine receptors) α5 and α7. NRG1 signalling contributes to long-term potentiation/synaptic plasticity through fyn kinase phosphorylation of NMDA2a at CA1 synapses, so a role in both the development of neurodevelopmental and neurotransmitter receptor abnormalities is plausible. However, it is not known how this effect is mediated.

The haplotypic association is not strong enough to account for the magnitude of linkage on chromosome 8p; there are two explanations for this, either that the underlying functional variants bear a stronger relationship to the disease, or that there is a second locus for schizophrenia on chromosome 8p such as the calcineurin gamma subunit proposed by Gerber et al., 2003 (see *other genes* below).

4. Catechol-*O*-methyltransferase

Catechol-*O*-methyltransferase (COMT) is one of the major degradative enzymes of the catecholamine transmitters. It catalyses the transfer of a methyl group from *S*-adenosylmethionine to catecholamines, including the neurotransmitters dopamine, epinephrine, and norepinephrine. COMT has long been a candidate for aetiological involvement in schizophrenia, because of its role in dopamine metabolism and association with the velocardiofacial syndrome. Both linkage and association studies have implied that chromosome 22q11 is a locus for schizophrenia (Karayiorgou and Gogos, 1997). Microdeletions of 22q11 are associated with velocardiofacial syndrome, a contiguous gene syndrome that includes a variety of congenital abnormalities, learning difficulties, and psychosis in up to one third of patients (Golding-Kushner et al., 1985). The deletion is also 80-fold more common in patients with psychosis compared to the normal population (Sugama et al., 1999). Haploinsufficiency for at least one gene from the 1.5-Mb 'psychosis critical region' at 22q11, defined by deletion analysis of a schizophrenic patient (Karayiorgou et al., 1995), is causally implicated in psychosis. From this region, two genes proline dehydrogenase gene (PRODH) and COMT were identified as a potential candidate for schizophrenia.

There have been many conflicting reports of association, which culminated in a recent meta-analysis of data, indicating that the COMT activity polymorphism, Met158Val, in which the met allele causes instability of the enzyme and a low activity phenotype, is not associated with schizophrenia (Lohmueller et al., 2003). However, further investigation of the role of this polymorphism using the Wisconsin card sorting test, a neuropsychological test of frontal lobe function, indicates that the valine allele is associated with poorer performance and may be a contributor to the neuropsychological impairment seen in schizophrenia (Egan et al., 2001).

However, it is still possible that other polymorphisms in COMT confer risk to schizophrenia. We previously identified an association between a COMT *haplotype* consisting of multiple markers around the gene, and schizophrenia (Li et al., 2001). We genotyped five single nucleotide polymorphisms from the COMT gene and two from the ARVCF gene, which abuts the 3′ end of COMT, and haplotype construction in family trios with schizophrenia from SW China. In this study, we found a five-marker haplotype that was transmitted to schizophrenic offspring more often than expected by chance ($P = 6 \times 10^{-4}$). Shifman et al. (2003) also identified a highly significant association between a COMT haplotype and schizophrenia. Although the haplotypic association finding of Shifman et al. (2003) appears to confirm our earlier finding of haplotypic association, of the seven polymorphic markers used by Shifman et al., only two (Rs4633, previously denoted COMT 186C/T; and Rs165688, the functional activity polymorphism also denoted COMT Val158Met) were used in our earlier study, making the two results difficult to compare directly. A recent analysis of the effect of the Shifman et al. haplotype on expression of COMT indicated that the 'risk' haplotype is associated with lower expression of the protein (Bray et al., 2003).

In order to attempt to replicate our original finding in the same geographic population, we have genotyped an independent sample of 136 sib-pair families (289 affected

siblings) collected from the same region of SW China. families in which two or more siblings met DSM-IV schizophrenia diagnosis criteria were recruited from Sichuan Province, Southwest China. We used the pedigree disequilibrium test (PDT; PDTPHASE; http://www.hgmp.mrc.ac.uk/Menu/Help/unphased) in the family sample and the same set of six markers, we analysed in our initial study with family trios. This time, none of the individual polymorphisms were significant when analysed alone, if corrected for multiple testing, including the Val158 polymorphism, which was significantly over-transmitted at the $P=0.01$ level (uncorrected) in the initial study (Li et al., 2001) and was not significant in the replication sample ($P=0.43$). We also did not find significant haplotypic association with haplotypes of [186C/T-472G/A] and [472G/A-900ins/delC], which were previously reported as positive in our first sample.

5. Proline dehydrogenase

As discussed above, PRODH is one of two candidate genes for schizophrenia from the 22q11 region deleted in VCFS. Analysis of PRODH-deficient mice revealed a deficit in prepulse inhibition, a sensorineuronal gating deficit functionally relevant to schizophrenia, making PRODH a strong functional and positional candidate gene (Gogos et al., 1999).

Liu et al. (2002) examined a single nucleotide polymorphism in the PRODH gene, PRODH2*1945, and demonstrated association between allele 2 by both TDT and case control analysis. Subsequent analysis of further single nucleotide polymorphisms and 'moving window' haplotype analysis revealed a two-marker haplotype, PRODH2*1945/1766, which was more significantly associated than either single nucleotide polymorphisms alone in three independent samples. A three marker haplotype including the marker PRODH2*2026 was also significant in some samples. In addition, the PRODH gene has a nearby pseudogene-like structural variant that may generate mutations through a gene-conversion mechanism, especially in early onset cases.

We have attempted to replicate their findings of association between a haplotype in the PRODH2 gene in a sample of family trios from SW China. We performed a system screening of the promoter regions and coding regions in PRODH gene for potentially functional polymorphisms using human genome sequence, single nucleotide polymorphism databases and polymorphism screening. Six single nucleotide polymorphisms (PRODH1945G/A, PRODH1852G/A, PRODH1766C/T, PRODH1483A/G, PRODH1482C/T and PRODH1195G/A) have been identified; within them, PRODH1852G/A and PRODH1483A/G were first reported in our study. Individual genotyping of these six single nucleotide polymorphisms was performed on 500 nuclear families with at least one offspring with schizophrenia, all from SW China. Transmission distortion test (TDT) for individual single nucleotide polymorphisms and haplotypes of paired markers were performed using program UNPHASED. PRODH1852G/A showed significant allelic transmission distortion ($P=0.02$), and two flanking single nucleotide polymorphisms (PRODH1945G/A and PRODH1766C/T) also showed a trend of allelic transmission distortion ($P=0.08$ for PRODH1945G/A and $P=0.07$ for PRODH1766C/T). Haplotypic analysis of paired markers supported the association between a haplotype of PRODH1945G/A-PRODH1852G/A and schizophrenia (Global $P=0.0006$), and PRODH1852G/A and PRODH1766C/T and schizophrenia (Global $P=0.01$) before correction for multiple testing.

6. Other genes: dysbindin, G72, DAOO and PPP3CC

Chromosome 6p was one of the first regions of strong linkage detested for schizophrenia. Straub et al. (2002) used a family-based haplotype mapping approach to examine this locus in Irish families to identify complex association between a cluster of single nucleotide polymorphisms at the human dystrobrevin binding protein 1 locus (DTNBP1) locus, implicating this gene as a potential risk gene for schizophrenia. One replication study has also found association here but with a common rather than a rare allele. A follow up study in the same families reanalysed the data and used two novel single nucleotide polymorphisms. A single 30-kb high-risk haplotype was identified that showed a significant association with schizophrenia and explained the pattern of significant findings in the analyses with individual markers (Van den Oord et al., 2003).

Chumakov et al. (2002) created a map of single nucleotide polymorphisms across a 5-Mb segment from chromosome 13q34 that has been genetically linked to schizophrenia using a sample of Canadian families. Association data pointed to a novel, primate specific gene (termed G72) encoding a 153-aa protein. Yeast two-hybrid experiments with the G72 protein identified interaction with the enzyme D-amino acid oxidase (DAAO), a potent activator of *N*-methyl-D-aspartate type glutamate receptor in the human brain. Four single nucleotide polymorphism markers from DAAO were found to be associated with schizophrenia in the Canadian samples, and furthermore, genetic interaction between the two genes was found.

Gerber et al. (2003) analysed a subset of calcineurin-related genes as candidates for schizophrenia based on their role in downstream regulation of dopaminergic signal transduction and NMDA-dependent synaptic plasticity. Genes from this family were prioritised based on their location within loci implicated in psychosis by linkage analysis such as chromosome 8p. The authors found association between polymorphisms in the PPP3CC gene which encodes the calcineurin gamma catalytic subunit gene. This is biologically plausible as mice with a forebrain specific calcineurin 1 knockout display schizophrenia related behavioural ab-

normalities. This association finding is near to the neuregulin 1 gene identified in an Icelandic sample (Stefansson et al., 2002) as being associated with schizophrenia. It is possible that both findings are correct, and the reason linkage between schizophrenia and chromosome 8p appears to be relatively strong is the presence of two susceptibility genes in this region. On the other hand, the association with neuregulin 1 appears statistically robust and the discovery of the underlying causative polymorphisms in this gene may be sufficient to explain all linkage and association in this region.

7. Symptom dimensions and the influence of individual genes

One possible way to overcome the limitations on gene mapping imposed by these factors is to refine the phenotype so that each individual susceptibility gene has a more direct relationship with a measurable characteristic, such as a quantitative score for a symptom dimension or an endophenotype such as an electrophysiological measurement (Leboyer et al., 1998). This will work conversely as well, as the influence of a given susceptibility gene on symptoms can be evaluated by examining patients with the risk alleles versus patients without. The importance of this process may lie in the delineation of schizophrenia and related mental disorders into component symptom complexes so that drug therapy can be aimed at these narrower clinical complexes which cut across diagnostic boundaries rather than as monotherapies ineffective in many patients within a heterogeneous disorder.

For the use of symptom dimensions to be successful in genetic analysis, there must have a heritable genetic basis, which can be estimated from family, twin studies and adoption studies. Family studies cannot estimate the extent of heritability, but interfamilial correlation between siblings or other relatives implies that a trait is influenced either by genes or shared environment. The latter is not thought to be important in schizophrenia (Cardno and Gottesman, 2000).

Although the underlying nosology of schizophrenia remains controversial, it is generally accepted that psychosis can be divided into clusters of related symptoms. Several studies have found five clusters of negative symptoms, cognitive symptoms, positive symptoms, hostile excitement/mania, and finally depression (von Knorring and Lindstrom, 1995; Van Os et al., 1999; Mass et al., 2000). Similar dimensions were found by Wickham et al. (2001) consisting of two affective dimensions (depressive and manic), and three schizophrenic dimensions (reality distortion, disorganisation and psychomotor poverty). But do these symptoms have an individual heritable origin and show familiality or do they vary randomly between patients? A series of studies have attempted either to predict the occurrence of the disease or its spectrum disorders in the relatives of probands based on epidemiological measures, or using family history data. In two studies, probands' scores on positive or negative dimensions did not predict schizophrenia in relatives (Kendler et al., 1994; Cardno et al., 1997) although in a broader study of functional psychosis, negative scores did (Van Os et al., 1997). However, dimensions related to disorganisation (positive formal thought disorder and/or inappropriate affect/bizarre behaviour) were predictive (Cardno et al., 1997; Van Os et al., 1997).

Five studies have examined within-family correlations of symptom dimensions in sibling pairs or families. Burke et al. (1996) found modest correlation for positive, negative and disorganisation dimensions, Kendler et al. (1997) found correlation for positive and negative symptoms but did not examine disorganisation, and Loftus et al. (1998) and Cardno et al., (1999) found highest correlation for disorganisation. Wickham et al. (2001) found that psychomotor poverty, disorganisation and mania were familial.

Several studies have examined familiality of clinical characteristics, with course and severity consistently being shown as correlated between affected relatives (Slater, 1953; Bleuler, 1978; Burke et al., 1996; Kendler et al., 1997; Wickham et al., 2002) and modest familiality being found for age at onset (Gottesman and Shields, 1972; Crow and Done, 1986; Kendler et al., 1987; Kendler and Mclean, 1990; Wickham et al., 2002). Of three studies investigating pre-morbid functioning (DeLisi et al., 1987; Cardno et al., 1999), two showed significant familiality. Two studies investigated the familiality of mode at onset (Cardno et al., 1999; Wickham et al., 2002).

The reverse of this approach was attempted by Kendler et al. (2000), who examined the 'Major Symptoms of Schizophrenia Scale' in families showing linkage to chromosome 8p. This scale has 10 key variables, plus outcome: hallucinations, delusions, Schneiderian delusions, positive thought disorder, catatonic symptoms, affective deterioration, negative thought disorder, depression, mania and chronicity. The 8p linked families showed evidence of a symptom cluster of positive thought disorder, affective deterioration, depression and poor outcome, akin to the core dementia-praecox syndrome described by Kraepelin more than 100 years ago (Adityanjee et al., 1999). This definition was the first division of manic depressive psychosis from the previous single psychosis, and it is poetic that molecular genetics can confirm this notion over 100 years later.

8. Discussion

Despite evidence for heritability of schizophrenia stretching back for over a century, and a genetic contribution to aetiology of about 80%, the identification of genetic susceptibility factors has been an uphill struggle, presumably because of factors related to biological and genetic hetero-

geneity, complex inheritance, diagnostic definition, etc. Classically, the neurochemical theories of schizophrenia have focussed mainly on the dopamine, and more recently, the serotonin system. The failure to identify anything but weak association with genes of the dopamine and serotonin system implies that there is not major *direct* involvement of these pathways in pathophysiology. Instead evidence from linkage analysis and positional mapping using haplotypes appears to indirectly implicate the glutamate system, in addition to evidence from other data (Tsai and Coyle, 2002). As outlined by Harrison and Owen (2003), many of the genes above are involved in the glutamate system, including neuregulin 1 (regulation of NMDA receptor gene expression/presence in glutamatergic synaptic vesicles) G72 and DAOO (metabolism of D-serine, a glutamate receptor modulator), and the calcineurin gamma catalytic subunit gene downstream, involved in regulation of dopaminergic signal transduction and NMDA-dependent synaptic plasticity. In fact, the regulation of and interaction between the dopamine and glutamate systems may be the important feature of pathophysiology in schizophrenia. Of course, it is also equally plausible that there is no central underlying neurochemical pathophysiology in schizophrenia, but instead a series of biologically diverse neurodevelopmental abnormalities which are clustered together by the similarity of their clinical outcome.

Either way, this developing new understanding of basic pathophysiology important implications for schizophrenia has the potential to (i) guide development of new pharmaceuticals through the identification of novel drug targets, (ii) identify the highest risk individuals (such as schizophrenic family members, or those with prodromal symptoms most likely to convert to schizophrenia) for early intervention, (iii) guide treatment selection according to genotype (pharmacogenetics) and (iv) improve nosological classification, which has implications for treatment and for clinical and biological research by reducing heterogeneity of study populations. This process will involve the amalgamation of aetiological genetics, pharmacogenetics, nosology, symptomatology and environmental risk factor analysis into a cohesive multidisciplinary field.

References

Adityanjee, Aderibigbe, Y.A., Theodoridis, D., Vieweg, V.R., 1999. Dementia praecox to schizophrenia: the first 100 years. Psychiatr. Clin. Neurosci. 53, 437–448.

Badner, J.A., Gershon, E.S., 2002. Meta-analysis of whole-genome linkage scans of bipolar disorder and schizophrenia. Mol. Psychiatry 7, 405–411.

Bearden, C.E., Rosso, I.M., Hollister, J.M., Sanchez, L.E., Hadley, T., Cannon, T.D., 2000. A prospective cohort study of childhood behavioural deviance and language abnormalities as predictors of adult schizophrenia. Schizophr. Bull. 26, 395–410.

Berrettini, W.H., 2000. Are schizophrenic and bipolar disorders related? A review of family and molecular studies. Biol. Psychiatry 48, 531–538.

Bleuler, M., 1978. The Schizophrenic Disorders: Long-Term Patients and Family Studies. Yale Univ. Press, New Haven, CT.

Bray, N.J., Buckland, P.R., Williams, N.M., Williams, H.J., Norton, N., Owen, M.J., O'Donovan, M.C., 2003. A haplotype implicated in schizophrenia susceptibility is associated with reduced COMT expression in human brain. Am. J. Hum. Genet. 73, 152–161.

Buonanno, A., Fischbach, G.A., 2001. Neuregulin and ErbB receptor signaling pathways in the nervous system. Curr. Opin. Neurobiol. 11, 287–296.

Burke, J.G., Murphy, B.M., Bray, J.C., Walsh, D., Kendler, K.S., 1996. Clinical similarities in siblings with schizophrenia. Am. J. Med. Genet. 67, 239–243.

Cardno, A.G., Holmans, P.A., Harvey, I., Williams, M.B., Owen, M.J., McGuffin, P., 1997. Factor-derived subsyndromes of schizophrenia and familial morbid risks. Schizophr. Res. 23, 231–238.

Cardno, A.G., Jones, L.A., Murphy, K.C., Sanders, R.D., Asherson, P., Owen, M.J., McGuffin, P., 1999. Dimensions of psychosis in affected sibling pairs. Schizophr. Bull. 25, 841–850.

Cardno, A.G., Gottesman, I.I., 2000. Twin studies of schizophrenia: from bow-and-arrow concordances to Star Wars Mx and functional genomics. Am. J. Med. Genet. 97, 12–17.

Chumakov, M., Blumenfeld, O., Guerassimenko O., Cavarec, L., Palicio, M., Abderrahim, H., Bougueleret, L., Barry, C., Tanaka, H., La Rosa, P., Puech, A., Tahri, N., Cohen-Akenine, A., Delabrosse, S., Lissarrague, S., Picard, F.P., Maurice, K., Essioux, L., Millasseau, P., Grel, P., Debailleul, V., Simon, A.M., Caterina, D., Dufaure, I., Malekzadeh, K., Belova, M., Luan, J.J., Bouillot, M., Sambucy, J.L., Primas, G., Saumier, M., Boubkiri, N., Martin-Saumier, S., Nasroune, M., Peixoto, H., Delaye, A., Pinchot, V., Bastucci, M., Guillou, S., Chevillon, M., Sainz-Fuertes, R., Meguenni, S., Aurich-Costa, J., Cherif, D., Gimalac, A., Van Duijn, C., Gauvreau, D., Ouellette, G., Fortier, I., Raelson, J., Sherbatich, T., Riazanskaia, N., Rogaev, E., Raeymaekers, P., Aerssens, J., Konings, F., Luyten, W., Macciardi, F., Sham, P.C., Straub, R.E., Weinberger, D.R., Cohen, N., Cohen, D., Ouelette, G., Realson, J., 2002. Genetic and physiological data implicating the new human gene G72 and the gene for D-amino acid oxidase in schizophrenia. Proc. Natl. Acad. Sci. U. S. A. 99, 13675–13680.

Cloninger, C.R., 2002. The discovery of susceptibility genes for mental disorders. Proc. Natl. Acad. Sci. U. S. A. 99, 13365–13367.

Cornblatt, B.A., 2002. The New York high risk project to the Hillside recognition and prevention (RAP) program. Am. J. Med. Genet. 114, 956–966.

Crow, T.J., Done, D.J., 1986. Age of onset of schizophrenia in siblings: a test of the contagion hypothesis. Psychiatr. Resid. 18, 107–117.

DeLisi, L.E., Goldin, L.R., Maxwell, M.E., Kazuba, D.M., Gershon, E.S., 1987. Clinical features of illness in siblings with schizophrenia or schizoaffective disorder. Arch. Gen. Psychiatry 44, 891–896.

Egan, M.F., Goldberg, T.E., Kolachana, B.S., Callicott, J.H., Mazzanti, C.M., Straub, R.E., Goldman, D., Weinberger, D.R., 2001. Effect of COMT Val108/158Met genotype on frontal lobe function and risk for schizophrenia. Proc. Natl. Acad. Sci. U. S. A. 98, 6917–6922.

Gogos, J.A., Santha, M., Takacs, Z., Beck, K.D., Luine, V., Lucas, L.R., Nadler, J.V., Karayiorgou, M., 1999. The gene encoding proline dehydrogenase modulates sensorimotor gating in mice. Nat. Genet. 21, 434–439.

Gottesman, I.I., Shields, J., 1967. A polygenic theory of schizophrenia. Proc. Natl. Acad. Sci. U. S. A. 58, 199–205.

Hanson, D.R., Gottesman, I.I., Heston, L.L., 1976. Some possible childhood indicators of adult schizophrenia inferred from children of schizophrenics. Br. J. Psychiatry 129, 142–154.

Harrison, P.J., Owen, M.J., 2003. Genes for schizophrenia? Recent findings and their pathophysiological implications. Lancet 361, 417–419.

Gerber, D.J., Hall, D., Miyakawa, T., Demars, S., Gogos, J.A., Karayiorgou, M., Tonegawa, S., 2003. Evidence for association of schizophrenia with genetic variation in the 8p21.3 gene, PPP3CC, encoding the calcineurin gamma subunit. Proc. Natl. Acad. Sci. U. S. A. 100, 8993–8998.

Golding-Kushner, K.J., Weller, K.J.G., Shprintzen, R.J., 1985. Velo-cardio-facial syndrome: language and psychological profiles. J. Craniofac. Genet. Dev. Biol. 5, 259–266.

Gottesman, I.I., Shields, J., 1972. Schizophrenia and Genetics: A Twin Study. Academic Press, Vantage Point, New York.

Hyman, S.E., Fenton, W.S., 2003. Medicine. What are the right targets for psychopharmacology? Science 299, 350–351.

Karayiorgou, M., Gogos, J.A., 1997. Dissecting the genetic complexity of schizophrenia. Mol. Psychiatry 2, 211–223.

Karayiorgou, M., Morris, M.A., Morrow, B., Shprintzen, R.J., Goldberg, R., Borrow, J., Gos, A., Nestadt, G., Wolyniec, P.S., Lasseter, V.K., 1995. Schizophrenia susceptibility associated with interstitial deletions of chromosome 22q11. Proc. Natl. Acad. Sci. U. S. A. 92, 7612–7616.

Kendler, K.S., Mclean, C.J., 1990. Estimating familial effects on age of onset and liability to schizophrenia: 1. Results of a large sample family study. Genet. Epidemiol. 7, 409–417.

Kendler, K.S., Tsuang, M.T., Haps, P., 1987. Age at onset in schizophrenia: a familial perspective. Arch. Gen. Psychiatry 44, 881–890.

Kendler, K.S., McGuire, M., Gruenberg, A.M., Walsh, D., 1994. Clinical heterogeneity in schizophrenia and the pattern of psychopathology in relatives: results from an epidemiologically based family study. Acta Psychiatr. Scand. 89, 294–300.

Kendler, K.S., Karkowski-Shuman, L., O'Neill, F.A., Straub, R.E., MacLean, C.J., Walsh, D., 1997. Resemblance of psychotic symptoms and syndromes in affected sibling pairs from the Irish Study of High-Density Schizophrenia Families: evidence for possible etiologic heterogeneity. Am. J. Psychiatr. 154, 191–198.

Kendler, K.S., Myers, J.M., O'Neill, F.A., Martin, R., Murphy, B., MacLean, C.J., Walsh, D., Straub, R.E., 2000. Clinical features of schizophrenia and linkage to chromosomes 5q, 6p, 8p, and 10p in the Irish Study of High-Density Schizophrenia Families. Am. J. Psychiatr. 157, 402–408.

Leboyer, M., Bellivier, F., Nosten-Bertrand, M., Jouvent, R., Pauls, D., Mallet, J., 1998. Psychiatric genetics: search for phenotypes. Trends Neurosci. 21, 102–105.

Lewis, C.M., Levinson, D.F., Wise, L.H., DeLisi, L.E., Straub, R.E., Hovatta, I., Williams, N.M., Schwab, S.G., Pulver, A.E., Faraone, S.V., Brzustowicz, L.M., Kaufmann, C.A., Garver, D.L., Gurling, H.M., Lindholm, E., Coon, H., Moises, H.W., Byerley, W., Shaw, S.H., Mesen, A., Sherrington, R., O'Neill, F.A., Walsh, D., Kendler, K.S., Ekelund, J., Paunio, T., Lonnqvist, J., Peltonen, L., O'Donovan, M.C., Owen, M.J., Wildenauer, D.B., Maier, W., Nestadt, G., Blouin, J.L., Antonarakis, S.E., Mowry, B.J., Silverman, J.M., Crowe, R.R., Cloninger, C.R., Tsuang, M.T., Malaspina, D., Harkavy-Friedman, J.M., Svrakic, D.M., Bassett, A.S., Holcomb, J., Kalsi, G., McQuillin, A., Brynjolfson, J., Sigmundsson, T., Petursson, H., Jazin, E., Zoega, T., Helgason, T., 2003. Genome scan meta-analysis of schizophrenia and bipolar disorder: Part II. schizophrenia. Am. J. Hum. Genet. 73, 34–48.

Li, T., Ball, D., Zhao, J., Murray, R.M., Liu, X., Sham, P.C., Collier, D.A., 2001. Family-based linkage disequilibrium mapping using single nucleotide polymorphism marker haplotypes: application to a potential locus for schizophrenia at chromosome 22q11. Mol. Psychiatry 54, 77–84.

Liu, H., Heath, S.C., Sobin, C., Roos, J.L., Galke, B.L., Blundell, M.L., Lenane, M., Robertson, B., Wijsman, E.M., Rapoport, J.L., Gogos, J.A., Karayiorgou, M., 2002. Genetic variation at the 22q11 PRODH2/DGCR6 locus presents an unusual pattern and increases susceptibility to schizophrenia. Proc. Natl. Acad. Sci. U. S. A. 99, 3717–3722.

Loftus, J., DeLisi, L.E., Crow, T.J., 1998. Familial associations of subsyndromes of psychosis in affected sibling pairs with schizophrenia and schizoaffective disorder. Psychiatry Res. 80, 101–111.

Lohmueller, K.E., Pearce, C.L., Pike, M., Lander, E.S., Hirschhorn, J.N., 2003. Meta-analysis of genetic association studies supports a contribution of common variants to susceptibility to common disease. Nat. Genet. 33, 177–182.

Mass, R., Schoemig, T., Hitschfeld, K., Wall, E., Haasen, C., 2000. Psychopathological syndromes of schizophrenia: evaluation of the dimensional structure of the positive and negative syndrome scale. Schizophr. Bull. 26, 167–177.

McGrath, J.J., Feron, F.P., Burne, T.H., Mackay-Sim, A., Eyles, D.W., 2003. The neurodevelopmental hypothesis of schizophrenia: a review of recent developments. Ann. Med. 35, 86–93.

Niemi, L.T., Suvisaari, J.M., Tuulio-Henriksson, A., Lonnqvist, J.K., 2003. Childhood developmental abnormalities in schizophrenia: evidence from high-risk studies. Schizophr. Res. 60, 239–258.

Ott, S.L., Roberts, S., Rock, D., Allen, J., Erlenmeyer-Kimling, L., 2002. Positive and negative thought disorder and psychopathology in childhood among subjects with adulthood schizophrenia. Schizophr. Res. 58, 231–239.

Shifman, S., Bronstein, M., Sternfeld, M., Pisante-Shalom, A., Lev-Lehman, E., Weizman, A., Reznik, I., Spivak, B., Grisaru, N., Karp, L., Schiffer, R., Kotler, M., Strous, R.D., Swartz-Vanetik, M., Knobler, H.Y., Shinar, E., Beckmann, J.S., Yakir, B., Risch, N., Zak, N.B., Darvasi, A., 2003. A highly significant association between a COMT haplotype and schizophrenia. Am. J. Hum. Genet. 71, 1296–1302.

Slater, E., 1953. Psychotic and Neurotic Illnesses in Twins. Her Majesty's Stationery Office, HMSO, Norwich, UK.

Stefansson, H., Sigurdsson, E., Steinthorsdottir, V., Bjornsdottir, S., Sigmundsson, T., Ghosh, S., Brynjolfsson, J., Gunnarsdottir, S., Ivarsson, O., Chou, T.T., Hjaltason, O., Birgisdottir, B., Jonsson, H., Gudnadottir, V.G., Gudmundsdottir, E., Bjornsson, A., Ingvarsson, B., Ingason, A., Sigfusson, S., Hardardottir, H., Harvey, R.P., Lai, D., Zhou, M., Brunner, D., Mutel, V., Gonzalo, A., Lemke, G., Sainz, J., Johannesson, G., Andresson, T., Gudbjartsson, D., Manolescu, A., Frigge, M.L., Gurney, M.E., Kong, A., Gulcher, J.R., Petursson, H., Stefansson, K., 2002. Neuregulin 1 and susceptibility to schizophrenia. Am. J. Hum. Genet. 71, 877–892.

Stefansson, H., Sarginson, J., Kong, A., Yates, P., Steinthorsdottir, V., Gudfinnsson, E., Gunnarsdottir, S., Walker, N., Petursson, H., Crombie, C., Ingason, A., Gulcher, J.R., Stefansson, K., St. Clair, D., 2003. Association of neuregulin 1 with schizophrenia confirmed in a Scottish population. Am. J. Hum. Genet. 72, 83–87.

Straub, R.E., Jiang, Y., MacLean, C.J., Ma, Y., Webb, B.T., Myakishev, M.V., Harris-Kerr, C., Wormley, B., Sadek, H., Kadambi, B., Cesare, A.J., Gibberman, A., Wang, X., O'Neill, F.A., Walsh, D., Kendler, K.S., 2002. Genetic variation in the 6p22.3 gene DTNBP1, the human ortholog of the mouse dysbindin gene, is associated with schizophrenia. Am. J. Hum. Genet. 71, 337–348 (Published erratum appears in Am. J. Hum. Genet. 2002, 71, 1007).

Sugama, S., Namihira, T., Matsuoka, R., Taira, N., Eto, Y., Maekawa, K., 1999. Psychiatric inpatients and chromosome deletions within 22q11.2. J. Neurol. Neurosurg. Psychiatry 67, 803–806.

Tabor, H.K., Risch, N.J., Myers, R.M., 2000. Opinion: candidate-gene approaches for studying complex genetic traits: practical considerations. Nat. Rev., Genet. 3, 391–397.

Tsai, G.C., Coyle, J.T., 2002. Glutamatergic mechanisms in schizophrenia. Annu. Rev. Pharmacol. Toxicol. 42, 165–179.

Van Os, J., Marcelis, M., 1998. The ecogenetics of schizophrenia: a review. Schizophr. Res. 27, 127–135.

Van Os, J., Marcelis, M., Sham, P., Jones, P., Gilvarry, K., Murray, R.M., 1997. Psychopathological syndromes and familial morbid risk of psychosis. Br. J. Psychiatry 170, 241–246.

Van Os, J., Gilvarry, C., Bale, R., Van Horn, E., Tattan, T., White, I., Murray, R.M., 1999. A comparison of the utility of dimensional and categorical representations of psychosis. UK700 Group. Psychol. Med. 29, 595–606.

van den Oord, E.J., Sullivan, P.F., Jiang, Y., Walsh, D., O'Neill, F.A., Kendler, K.S., Riley, B.P., 2003. Identification of a high-risk haplotype for the dystrobrevin binding protein 1 (DTNBP1) gene in the Irish study of high-density schizophrenia families. Mol. Psychiatry 8, 499–510.

von Knorring, L., Lindstrom, E., 1995. Principal components and further possibilities with the PANSS. Acta Psychiatr. Scand., Suppl. 388, 5–10.

Weinberger, D.R., McClure, R.K., 2002. Neurotoxicity, neuroplasticity, and magnetic resonance imaging morphometry: what is happening in the schizophrenic brain? Arch. Gen. Psychiatry 59 (6), 553–558.

Wickham, H., Walsh, C., Asherson, P., Taylor, C., Sigmundson, T., Gill, M., Owen, M.J., McGuffin, P., Murray, R.M., Sham, P., 2001. Fami-

liality of symptom dimensions in schizophrenia. Schizophr. Res. 47, 223–232.

Wickham, H., Walsh, C., Asherson, P., Gill, M., Owen, M.J., McGuffin, P., Murray, R.M., Sham, P., 2002. Familiality of clinical characteristics in schizophrenia. J. Psychiatr. Res. 36, 325–329.

Williams, N.M., Preece, A., Spurlock, G., Norton, N., Williams, H.J., Zammit, S., O'Donovan, M.C., Owen, M.J., 2003. Support for genetic variation in neuregulin 1 and susceptibility to schizophrenia. Mol. Psychiatry 5, 485–487.

Yang, J.Z., Si, T.M., Ruan, Y., Ling, Y.S., Han, Y.H., Wang, X.L., Zhou, M., Zhang, H.Y., Kong, Q.M., Liu, C., Zhang, D.R., Yu, Y.Q., Liu, S.Z., Ju, G.Z., Shu, L., Ma, D.L., Zhang, D., 2003. Association study of neuregulin 1 gene with schizophrenia. Mol. Psychiatry 8, 706–709.