Genetics of schizophrenia: from animal models to clinical studies

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Genetic epidemiological studies strongly suggest that additive and interactive genes, each with small effects, mediate the genetic vulnerability for schizophrenia. With the human genome working draft at hand, candidate gene (and ultimately large-scale genome-wide) association studies are gaining renewed interest in the effort to unravel the complex genetics of schizophrenia. In the absence of an unequivocally established biological theory for schizophrenia, identifying candidate genes to be tested in an association paradigm remains a challenging task. We maintain that it is possible to use animal models to map genes or loci involved in behavioural traits that are relevant to schizophrenia. The human genes (or syntenic loci) homologous to those identified in mice can subsequently be tested in patients with schizophrenia who have been carefully phenotyped for traits "isomorphic" to the ones modelled in mice. If confirmed in humans, these genes may be further analyzed in the animal model to identify their role and the biological network they are involved in. To tackle the complex and intimidating problem of the genetics of schizophrenia, it may be necessary to go from animal models to human studies and vice versa; this strategy has been proven to be efficient in less complicated, though complex, human diseases.

Des études d'épidémiologie génétique indiquent fortement que des gènes additifs et interactifs, dont chacun a des effets minimes, interviennent dans la vulnérabilité génétique à la schizophrénie. Comme on dispose d'une copie de travail du génome humain, les études d'association de gènes candidats (qui deviendront éventuellement des études à grande échelle sur le génome au complet) suscitent un intérêt renouvelé à l'égard de l'effort déployé pour dénouer la génétique complexe de la schizophrénie. Comme il n'y a pas de théorie biologique sans équivoque sur la schizophrénie, l'identification de gènes candidats à analyser dans le contexte d'un paradigme d'association demeure un grand défi. Nous soutenons qu'il est possible d'utiliser des modèles animaux pour cartographier des gènes ou des lieux impliqués dans les caractéristiques comportementales pertinentes à la schizophrénie. Les gènes humains (ou lieux synténiques) homologues à ceux qu'on a identifiés dans les souris peuvent par la suite être analysés chez des patients atteints de schizophrénie dont on a établi avec soin le phénotype de traits «isomorphes» par rapport à ceux qui

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ont été modélisés chez la souris. S'ils sont confirmés chez les êtres humains, on pourra analyser plus à fond ces gènes dans le modèle animal pour déterminer leur rôle et le réseau biologique où ils interviennent. Pour s'attaquer aux problèmes complexes et intimidants que pose la génétique de la schizophrénie, il peut être nécessaire de passer des modèles animaux aux études humaines et vice versa. Cette stratégie s'est révélée efficace dans le cas de maladies humaines moins compliquées mais tout de même complexes.

Introduction

Family,[1] twin[2] and adoption studies[3,4] provide overwhelming evidence for a significant genetic role in the pathogenesis of schizophrenia, yet no specific genes implicated in increasing the risk for this disorder have been identified. Although the recent sequencing of the human genome, combined with the development of high throughput technology, provides more potential for scientific advancement in this field,[5] new approaches to the problem of gene discovery in schizophrenia may be needed. In this paper, we present an approach that combines animal models to identify candidate genes relevant for schizophrenia with human association studies to test the human homologues of the genes identified in those animal models. We hope that this approach to the complex genetics of schizophrenia will help to identify the elusive genes that increase the susceptibility to this disorder.

Although genetic linkage studies have been heavily advocated and used to identify susceptibility genes in the last 2 decades, results of genetic epidemiology studies indicate that it would be very difficult to identify genes for schizophrenia using linkage approaches. First, the observed familial clustering of schizophrenia can not be explained by the transmission of 1 (or a few) major gene(s).[6–8] On the contrary, the pattern of distribution of the risk for schizophrenia in relatives of patients with schizophrenia is consistent with an oligogenic[9] or multifactorial polygenic[2,10,11] mode of transmission. Second, it has been elegantly demonstrated that people carrying genes predisposing to schizophrenia do not necessarily express the disease, indicating that predisposing genes are not sufficient to induce a full-blown disorder.[12] Furthermore, carriers of genetic risk factors (e.g., nonaffected relatives of those with schizophrenia and, particularly, obligate carriers) may express a myriad of abnormal behaviours and psychobiological traits, indicating that the dichotomous phenotypic outcome (schizophrenia v. no schizophrenia) typically used in linkage studies is but a very gross phenotypic reflection of the genotypic structure of schizophrenia. These traits include schizotypal personality traits, eye-tracking abnormalities, sensorimotor-gating deficits and other characteristics that are mainly quantitative in nature and would better be analyzed with quantitative genetic trait approaches. Third, despite tremendous efforts to identify clinical subsyndromes that are transmitted according to a mendelian pattern (that "breed true") within the constellation of schizophrenia, this line of research has not yielded satisfactory answers.[7]

These well-replicated observations suggest that the genetic susceptibility to schizophrenia may be displayed as a wide spectrum of phenotypic expressions ranging from an apparently normal phenotype (incomplete penetrance), to subtle behavioural or neurophysiological deviances (variable expressivity), to fully expressed schizophrenia. This contrasts with the much simpler one-to-one relation between genes and phenotypes that characterizes mendelian disorders. Hence, it is not surprising that efforts aimed at identifying susceptibility genes for schizophrenia using methods designed to identify genes with major effects (i.e., mendelian disorders) have not been successful. Indeed, a number of linkage studies in schizophrenia, including genome-wide screens,[13,14] have yielded negative or inconclusive results.[15] Although some of these results are promising[16,17] (see also review by Riley and McGuffin[18]), replicating them and narrowing the linked chromosomal regions to small intervals suitable for positional cloning of the mutated gene(s) remain challenging tasks.[19]

The chain of events linking the causative factors (genetic or environmental) implicated in schizophrenia and the final pathologic state of the brain is relatively unknown. Here, our understanding is limited to a few hypotheses that have been suggested mainly through the so-called pharmacological bridge (i.e., the assumption that the brain neurotransmitter pathways affected by drugs effective in reducing symptoms of schizophrenia may be implicated in the pathogenesis of the disease). Although this approach has been productive for some disorders (e.g., dopa-sensitive dystonia[20]), lessons from other disorders such as Parkinson's disease indicate that the therapeutic pathway and the

genetic causative pathway may be distinct.[21,22] The most researched hypothesis based on the pharmacological bridge in schizophrenia is the dopamine (DA) hypothesis. On the basis of the fact that DA antagonists, particularly DA receptor 2 blockers, reduce psychotic symptoms in most patients affected with schizophrenia,[23] it was postulated that DA dysregulation may play a role in the pathogenesis of schizophrenia. However, although this and other observations[24,25] support the DA hypothesis of schizophrenia, other findings, including the fact that negative symptoms are not alleviated by DA antagonists, suggest that DA dysregulation is only a part of a more complex network of brain dysfunction. In particular, it remains unclear whether DA dysregulation is a necessary and sufficient event for the development of schizophrenia or whether it is only one of the potential routes of neurochemical alterations associated with some, but not all, of the phenomenological aspects of schizophrenia.

The consequence of this poor understanding of the pathophysiology of schizophrenia is that it is difficult to select highly relevant candidate genes for the purpose of candidate gene testing. Indeed, without strong a priori knowledge of the involvement of a specific biological pathway in the pathogenesis of a disease, the selection of candidate genes remains a "fishing expedition." Previous research involving candidate genes reflects these difficulties. Most association studies conducted in the past 15 years have focused primarily on genes coding for proteins involved in brain DA or serotonin neurotransmission. Overall, the results emerging from this literature are difficult to interpret because of several limitations, both methodologic (e.g., small sample sizes, different clinical characteristics of the samples and lack of matching between cases and controls with regard to ethnicity) and conceptual ones (e.g., absence of strong implication of these genes in the pathogenesis of schizophrenia). For example, the genes for DA receptor 3[26–43] and for serotonin receptor 2A (5-HT_{2A})[44–50] were very widely investigated in association studies, but their roles in producing schizophrenia or in modifying its phenotype are unclear.

Despite these difficulties, leading genetic statisticians argue that association studies are the method of choice to detect genes with small effects in complex disorders, in general,[51–53] and in psychiatric disorders, in particular.[54] This is especially true given the wealth of genetic information available from the recently completed human genome sequence[55,56] and the ever-growing information on its variations.[56,57] The promise of this approach in deciphering the genetics of complex diseases has been buttressed with a flurry of new statistical techniques aimed at correcting or circumventing several of the problems associated with classical case–control association studies.

However, to facilitate the identification of susceptibility genes using association approaches in schizophrenia, several questions and considerations need to be addressed.

First, what priority should be given to the genes to be tested? There are at least 2 answers to this question. It is possible to use "brute force" to do high throughput genome-wide linkage disequilibrium mapping in a large sample of patients with schizophrenia. Although this approach has proven to be effective for some other complex disorders,[58,59] it may represent a difficult task in schizophrenia research because of the prohibitive number of cases and controls (i.e., parents or unrelated subjects) that need to be collected. This comprehensive approach may be the ideal aim in the long run, but more attainable objectives may be achieved by focusing on highly relevant candidate genes for schizophrenia. However, given our limited knowledge of the pathogenesis of schizophrenia, we need to develop new experimental approaches to achieve this aim. We maintain that it is possible to use animal models to identify highly relevant candidate genes for schizophrenia and will illustrate this approach using prepulse inhibition (PPI) of startle as a behaviour, which has been reported to be deficient in patients with schizophrenia, their nonaffected relatives and patients with schizotypal personality disorder.[60,61] Loci or genes involved in the modulation of this behaviour can be identified in mouse models, and the human homologues of these genes tested in patients with schizophrenia.

Second, even with highly relevant and trait-targeted candidate genes at hand, confirming (or refuting) their role in schizophrenia may be a daunting task. This is because schizophrenia is believed to be a heterogeneous condition at both the clinical and genetic levels. Clinical approaches aimed at reducing this heterogeneity may well be a cornerstone in the strategy of identifying susceptibility genes in schizophrenia. We will argue that phenotyping patients with schizophrenia with regard to marker traits that are isomorphic to traits modelled in animals for the purpose of identifying candidate genes may help to decipher the genetic basis of these traits and, thus, the genetics of schizophrenia.

The third question is of wider scope but highly significant for genetic research in schizophrenia and mental disorders in general. The fact that there is a strong genetic contribution to schizophrenia is now beyond doubt. The fact that no major genes are involved in schizophrenia is becoming more widely accepted, though a few exceptions might exist that remain to be identified.[16,62] It is therefore possible that most cases of schizophrenia will be secondary to a multitude of additive or a few interacting genes. This raises the issue of whether the identification of these genes will have profound implications on the way we diagnose, treat and prevent schizophrenia. In other words, what would change in the clinic after our gene hunting (on "small prey," some skeptics would say) is finished? Here again, in contrast to simple mendelian disorders, the relative importance of genetic variants in the pathogenesis of the disorder may be very difficult to elucidate for the same reasons that render linkage studies difficult in schizophrenia (i.e., low penetrance, variable expressivity). We believe that starting from animal models for targeted traits and using a system that allows the study of individual genes, one by one, in these animal models may give us tremendous leverage to further study the effects of the genes (identified in animals and confirmed in humans) on different brain systems, at different developmental stages and in different combinations, as allowed by breeding and introgression techniques (as well as gene manipulation techniques).

Identifying candidate genes or loci in animal models

Genetic tools: the quantitative trait locus approach

It is now well recognized that tremendous advances in mouse genetics, combined with well-developed tools of behavioural analyses, offer unprecedented opportunities to dissect the genes underlying complex neuronal systems and the behaviours that are mediated by these systems. The 2 major approaches used to study how genes modulate behaviour are distinguished by whether the starting point of the analysis is genes or behavioural phenotypes (for review, see Tecott and Wehner[63]). Those starting with gene manipulation (knock-out and knock-in technologies) seek to determine the behavioural changes induced by the modified expression of a target gene. Those that begin with the behaviour currently include 2 major methods. The first involves random mutagenesis and identifying the deviant behavioural phenotypes and subsequent positional cloning of the mutation responsible for the behavioural deviations. The second is identifying the genetic loci and genes responsible for a natural variation in a given behavioural phenotype, a method referred to as quantitative trait locus (QTL) analysis. Although these different approaches are complementary and may shed light on different aspects of the genetics of traits relevant for schizophrenia, in this paper, we focus on the latter approach, which we elected to use in an attempt to dissect the genetic complexity of schizophrenia.

In contrast to simple mendelian dichotomous disorders caused by rare and highly penetrant mutated genes, complex behavioural disorders are more likely to be caused by multiple, weakly penetrant and highly prevalent genetic variants, which lead to a cluster of clinical manifestations often grouped in syndromes. Some of the manifestations of these complex disorders may be quantitative traits and represent extremes of a normal distribution. The method aimed at identifying the genetic underpinnings of these quantitative traits, quantitative trait locus (QTL) mapping, was developed mainly in plants and livestock to enhance some of their economically important characteristics. The basic idea in QTL mapping is that, if 2 parental strains of animals differ with respect to a trait, it is possible to map the genes involved in this trait by correlating the phenotypes and the genotypes in the progeny derived from different crosses of these parental lines. This is possible because alleles that differ between the 2 parental lines will be surrounded by different segments of DNA identical by descent.[64] In our studies, we are using recombinant congenic lines (RCLs) of mice derived from 2 parental lines (i.e., A/J and C57BL/6J) and developed by Skamene et al as a tool to dissect the genetics of complex disorders.[65] These lines have proven successful in linkage mapping of many complex traits, including infectious diseases[66] and cancers.[67,68] RCLs are obtained by first crossing a donor inbred parent to a recurrent inbred line to form a hybrid first-generation F1. The resulting offspring are then back-crossed to the recurrent parent for several generations (usually 2 generations for mouse RCLs). Animals are then repeatedly sib-mated (for at least 20 generations) to form the final recombinant inbred line. After this breeding scheme, a panel of congenic inbred lines with a small proportion of the donor parent genome introduced on the recurrent parental genome is generated. Each of these

inbred lines contains 1 or more small regions of DNA from a donor parent in an otherwise standard background of a recurrent parent (e.g., A/J donor on C57BL/6J recurrent parent or C57BL/6J donor on A/J recurrent parent). The RCL system transforms a multigenic trait into a series of single gene traits, where each gene contributing to the multigenic control of the trait can be mapped and studied separately. Most importantly, RCLs are a unique resource for correlative phenotypic studies because they represent inbred "immortalized" replicas of the appropriate chromosomal recombinations that led to the informative phenotypes. Hence, they are an ideal system to identify the molecular and cellular underpinnings of target behavioural traits across the lifespan of the animals.[69]

Deficit in prepulse inhibition: a relevant behavioural trait for schizophrenia

Of critical importance to the concept of using animal models to search for genes predisposing to schizophrenia is the choice of phenotype to be used in the animal model and its relevance to schizophrenia. The goal is certainly not to model schizophrenia in its entirety, a formidable and likely impossible task. Rather, the goal is to model a discrete physiological or neurochemical mechanism that has relevance to the pathophysiology of schizophrenia, has cross-species validity from human to the animal and can be objectively and reliably measured in the animal model (for review see Swerdlow et al[70]). Several traits that have been studied in patients with schizophrenia and in animals may fulfill some of these criteria. In our studies, we have been using prepulse inhibition of acoustic startle as such a model. This model has been extensively studied[71–76] and has face, predictive and construct validity.[77]

The acoustic startle response consists of a strong activation of antagonistic muscle groups throughout the body in response to a sudden, relatively intense acoustic stimulus. Prepulse inhibition (PPI) refers to an inhibition of the startle response when a low-intensity stimulus, the prepulse, precedes the startling stimulus (by 30–500 ms). PPI is a form of sensorimotor gating that is widely conserved across mammalian species and carries the advantage that it can be measured under nearly identical conditions in humans and experimental animals.[75] Deficits in sensorimotor gating in schizophrenia have been demonstrated in several paradigms including studies of habituation,[73] gating of P50 event-related potentials[78] and numerous independent studies of PPI of startle.[73,75,78–84] Convergence of results from these studies support sensorimotor gating theories of schizophrenia, which suggest that impaired sensory gating leads to sensory overload and cognitive fragmentation in schizophrenia.

The relevance of PPI deficits to the clinical syndrome of schizophrenia is supported by recent studies demonstrating that PPI deficits in patients with schizophrenia are associated with core cognitive symptoms such as thought disorder and distractibility,[85,86] with neuropsychological measures of perseveration in the Wisconsin Card Sorting Test[87] and with measures of illness severity (e.g., number of admissions to hospital, chlorpromazine equivalents[80,84,88] and age at onset[82]). Given these correlations, it has been hypothesized either that deficits in PPI contribute directly and mechanistically to clinical symptoms in schizophrenia or that abnormalities in the same neural circuitry are responsible for deficits in PPI and clinical symptoms of schizophrenia. Importantly, PPI does not appear to be a secondary consequence of gross behavioural impairment accompanying the schizophrenia phenotype; PPI deficits are also observed in nonmedicated persons with schizotypal personality disorder[60,61] as well as in nonaffected relatives of patients with schizophrenia.[61]

Extensive animal studies, particularly in rats, have delineated that the neural circuitry involved in the modulation of PPI includes limbic cortical regions such as the medial prefrontal cortex and hippocampus, the nucleus accumbens (ventral striatum) and globus pallidus (reviewed in Swerdlow and Geyer[75]). These regions have been implicated in the pathophysiology of schizophrenia in morphological and in structural and functional imaging studies. As well, neurotransmitter systems that modulate PPI (e.g., DA, glutamate, serotonin) are also potent modulators of psychotic symptoms.[75] Thus, PPI may be a valuable mechanism to probe neural substrates of schizophrenia and possibly other mental disorders where it has been shown that PPI is deficient.[89–91]

Some illustrative results

Detailed results of the initial step of mapping of QTLs involved in the modulation of the acoustic startle and PPI, using RCLs from A/J and C57BL/6J parental lines, are now in press.[92] Here, we report some illustrative results and discuss them from the general perspec-

tive of integrating results of animal and human studies to understand the genetics of schizophrenia.

The A/J and C57BL/6J parental lines showed significant ($p < 0.05$) differences in PPI magnitude at several prepulse intensities. All RCLs with A/J background, whose PPI was significantly different from that of the parental A/J line, showed an increase in this trait, irrespective of the intensity of the prepulse used. Conversely, almost all the lines with C57BL/6J background, whose PPI deviated significantly from their parental phenotype, showed a decrease in this trait. These observations suggest that alleles responsible for increased PPI in the C57BL/6J parental line (compared with the A/J line) segregated in some RCLs with A/J background to increase their PPI compared with the parental phenotype; conversely, alleles responsible for decreased PPI in the A/J inbred line segregated in some of the lines with the C57BL/6J background to decrease their PPI. No strain differed dramatically from the others, suggesting that no genes with major effects segregated in any of the lines. These results also suggest that genes with major effects are unlikely to be involved in the control of PPI and that genetic control of this trait resides, instead, at a number of QTLs.

Our provisional mapping of QTLs indicates that there are at least 7 loci involved in the modulation of PPI across a wide range of prepulse intensities. Of these QTLs, 4 (on chromosome [chr] 2, 3, 7 and the proximal QTL on chr 16) appear to be associated with a decrease in PPI in animals with the C57BL/6J genetic background, 1 (on chr 11) with an increase in PPI in animals with the C57BL/6J background and 2 (on chr 5 and distal chr 16) with an increase in PPI in animals with the A/J background. Other QTLs (on chr 6, 14, 15, 18) were found to have effects on PPI restricted to midrange prepulse intensities.

These data provide valuable information on homologous candidate genes and loci in humans. For this purpose, we used the Mouse Genome Database (www.informatics.jax.org/searches/linkmap_form.shtml) to generate a mouse–human comparative map at the loci identified in the mouse PPI experiments. Our aim was to use this information along with other published literature on the genetics of schizophrenia to generate testable hypotheses. We therefore selected candidate genes in human loci syntenic (i.e., loci with conserved genomic structure between 2 species) to the QTLs mapped in mice according to 2 criteria. First, the mouse gene had to be homologous (or orthologous) to a human gene present in a locus previously linked to schizophrenia (either a relatively high lod score or modest lod scores but replicated in at least 2 independent studies) or the mouse gene had to be a homologue to a human gene that has been reported to be associated with schizophrenia in more than 3 independent studies. Second, the mouse gene, its human homologue or both had to have been implicated in sensory gating regulation. Doing so, we maximize the probability of the selected gene being a good candidate gene for schizophrenia by bringing together 3 sources of information: mapping in mice, functional relevance to PPI and mapping in patients with schizophrenia.

We provide, here, 2 examples of genes, identified during our preliminary homology map analyses, meeting these criteria. The first is the adrenergic receptor kinase beta 2 (*Adrbk2*) gene. Also known as G-protein coupled receptor kinase 3, this kinase mediates agonist-dependent phosphorylation and desensitization of β-adrenergic and several other G-protein coupled receptors (e.g., α_2-adrenergic, muscarinic cholinergic, kappa opioid, neurokinin I, corticotropin releasing factor and cannabinoid I receptors). *Adrbk2* maps within 2 cM (centimorgan) of marker D5Mit338, which was associated with increased PPI on the A/J genetic background. The human homologue of this mouse gene, *ADRBK2*, maps to band 22q11, a locus associated with schizophrenia on the basis of linkage and other sources of information.[93–97] In addition, an important body of literature indicates that adrenergic receptors may modulate PPI in rodents.[98–100] Furthermore, the fact that tyrosine kinases are involved in modifying the sensitivity of the receptor to its binding molecule as a function of its previous activation (neural plasticity at the molecular level) makes this gene a very attractive candidate to be studied as a modulator of PPI, a behavioural trait responsive to neuronal plasticity. The convergence of this evidence makes this gene very interesting for further investigation in schizophrenia.

The second example is the 5-HT_{2A} receptor gene. The mouse 5-HT_{2A} receptor gene maps to chr 14, 2.5 cM distal to marker D14Mit114, which is highly associated with a decreased PPI on the C57BL/6J background. This is one of the few genes that have been consistently associated with schizophrenia in several studies[46,48] as well as in a large meta-analysis.[45] In our own studies,[50] we found that this gene is associated only with the severe forms of schizophrenia refractory to neuroleptic medication, forms known to present greater PPI deficits. Finally, several studies indicate that this gene

is implicated in the modulation of PPI. It is possible that the association observed between the 5-HT_{2A} receptor and schizophrenia may be mediated through the role that this receptor plays in the modulation of PPI. These observations generate a testable hypothesis stipulating that schizophrenia with PPI deficits may be the form of schizophrenia associated with genetic variants of the 5-HT_{2A} receptor. Hypotheses suggesting that a gene is associated with a particular subtype or characteristic of schizophrenia, rather than with the disorder in its entirety, are becoming increasingly prominent in the study of the genetics of schizophrenia.

Critical role of phenotyping

Even with plausible candidate genes at hand, the confirmation of their involvement in schizophrenia remains a complex task. This is mainly because of the phenotypic heterogeneity of schizophrenia and the lack of objective definition of the disorder.

Several approaches to reduce this phenotypic heterogeneity have been proposed. Among these, the stratification of patients according to neurophysiological or neuropsychological dimensions associated with the clinical phenotype of schizophrenia has attracted increasing interest. For example, it has been shown recently that a functional polymorphism in the catechol *O*-methyltransferase (COMT) gene, $Val^{108/158}$ Met, modulates performance on the Wisconsin Card Sorting Test in normal controls, patients with schizophrenia and their first-degree relatives.[101,102] Other studies have investigated the association between specific candidate genes and specific traits such as event-related potentials[103] and eye-tracking abnormalities.[104] These approaches represent a very promising avenue of research because they investigate phenotypes that are possibly closer, along the causal chain of events, to the susceptibility genes, and because the genetics of these traits may be accessible to study in animal models.

Another line of research, which can be broadly referred to as the "pharmacogenetics approach," is based on the hypothesis that patients with schizophrenia who respond to neuroleptics and those who do not may represent 2 groups of patients with at least partially distinct pathogenesis.[105–130] Candidate genes tested within this paradigm have been mainly selected on the basis of the so-called pharmacological bridge (i.e., the assumption that neurochemical pathways involved in mediating the therapeutic activity of a medication may also be involved in the pathogenesis of the disorder); this is particularly so in the subgroup of patients who respond to a specific pharmacological intervention.

In the last few years, we have recruited, according to a priori defined criteria, and comprehensively evaluated 2 subgroups of patients with schizophrenia: those who responded very well to neuroleptic medication and had a very good long-term outcome (R, $n = 43$) and those who did not respond and had very poor long-term outcome (NR, $n = 65$). NR patients were significantly younger at the onset of the first psychotic symptoms and had poorer premorbid functioning than R patients. NR patients were also more frequently diagnosed with disorganized or undifferentiated schizophrenia and spent much longer periods of their lives as inpatients.[131] First-degree relatives of NR patients were at higher risk for schizophrenia spectrum disorders (morbid risk [MR] 8.84) than relatives of control subjects (MR 1.52, $p < 0.001$) and relatives of R patients (MR 2.45, $p = 0.013$).[132] In addition, when compared with R patients, NR patients with schizophrenia performed significantly worse in all neuropsychological domains that we assessed.[133] Our molecular genetic studies strongly suggest that distinguishing these 2 types of patients may be critical to identifying genes associated with schizophrenia. Indeed, we have tested for association between schizophrenia and several candidate genes that we selected according to literature suggesting their potential role in schizophrenia and found that some reported positive associations are, in fact, more pronounced in the group of nonresponding patients[50,134,135] and that others are specific to responding patients.[136,137] Of particular interest to the approach combining animal models and human studies, a modest but significant excess of allele 2 of the 5-HT_{2A} receptor gene[50] was identified in the group of NR but not in the group of R patients.[137] Given the mapping of the 5-HT_{2A} receptor gene to a region that we linked to decreased PPI in C57BL/6J mice and the fact that the gene is an important player in the modulation of PPI,[138–140] it is possible that this association reflects a disturbance of PPI in the patients who do not respond to neuroleptic treatment. One of our future objectives is to test this hypothesis by comparing patients with and without PPI deficits with regard to polymorphisms in the 5-HT_{2A} receptor gene.

Conclusion

After the flamboyant success of linkage analysis in

mapping the gene for Huntington's disease and then subsequently cloning it, an enthusiasm for linkage analysis infiltrated the scientific community working in the field of genetics of complex human disorders, in general, and of schizophrenia, in particular. However, experience accumulated in the last 18 years suggests that trying to decipher the genetic underpinnings of schizophrenia using linkage analysis may result in an echo of the grim adage from the field of neuropathology, that "schizophrenia is the graveyard of the pathologist." Indeed, it is becoming clear that, as in the field of neuropathology, where a gross neuropathological signature of schizophrenia does not exist, major genes causing schizophrenia do not exist. In addition to classic factors of complexity related to the non-mendelian mode of inheritance of schizophrenia, the lack of a phenotypic definition based on objective, reliable and reproducible measurements is one of the major obstacles in the way of gene discovery. Similarly, because of the lack of a clear understanding of the pathogenesis of schizophrenia and the biological pathways that may be disturbed in this disorder, genetic association studies have not yet contributed substantially to our understanding of the genetics of schizophrenia.

Using animal models to identify genes involved in phenotypic traits considered to be relevant for schizophrenia may be critical to paving the way for identifying genes that increase the susceptibility to schizophrenia. This approach can improve the selection of candidate genes on the basis of their involvement in specific and refined traits that can also be measured in patients. Combined with the recent explosive increase in genomic information, such methods may herald the turning of the tables for genetic research in schizophrenia.

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2001 Award Winners

Heinz Lehmann Award

Dr. Franco Vaccarino is the recipient of the 2001 Canadian College of Neuropsychopharmacology (CCNP) Heinz Lehmann Award. Dr. Vaccarino is currently a professor in the Departments of Psychiatry and Psychology at the University of Toronto and vice president of research at the Centre for Addiction and Mental Health. This award is designed to recognize outstanding research achievements by Canadian scientists in the field of neuropsychopharmacology. The award, donated by Hoffmann-La Roche Limited, consists of $5000 and an engraved plaque. Congratulations to Dr. Vaccarino!

Presentation: CCK modulation of mesolimbic DA function: a model for the opposing effects of stress on motivated behaviour

Jock Cleghorn Award

Mr. Steven Szabo is the recipient of the 2001 CCNP Jock Cleghorn Prize. Mr. Szabo is doing research training in the Department of Psychiatry, University of Florida in Gainsville, Fla. This award is designed to recognize the best poster presentation by a research trainee at the CCNP Annual Meeting. The award, donated by the CCNP, consists of $500. Congratulations to Mr. Szabo!

Presentation: Serotonin receptor effects on norephinephrine neuron firing are mediated through excitatory amino acid and GABA-A receptors

Innovations in Neuropsychopharmacology Award

Dr. Harold A. Robertson is the recipient of the 2001 CCNP Innovations in Neuropsychopharmacology Award. Dr. Robertson is currently professor and head of the Department of Pharmacology, Faculty of Medicine, Dalhousie University in Halifax. This award is designed to recognize outstanding research innovations in the basic or clinical fields of neuropsychopharmacology. The award, donated by Pfizer Canada Inc., consists of $5000 and an engraved plaque. Congratulations to Dr. Robertson!

Presentation: The genome and the brain: towards a neurobiology of psychiatric disorders

Young Investigator Award

Dr. Ridha Joober is the recipient of the 2001 CCNP Young Investigator Award. Dr. Joober is currently an assistant professor in the Department of Psychiatry and associate member in the Department of Neurology and Neurosurgery at McGill University. The award, donated by Bristol-Myers Squibb Company, consists of a $2500 bursary plus a $2000 research grant and an engraved plaque. Congratulations to Dr. Joober!

Presentation: Genetics of schizophrenia: combining animal models and clinical studies