

Genetics of developmental psychiatric disorders: pathways to discovery

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Genetics has captured the imagination of the public, the interest of the media and a large place in the sciences. Since the discovery of the structure of DNA by Watson and Crick, the double helix has epitomized the main dogma of genetics: everything from the tiniest details of the human body to the most complex of behaviours is encoded in the genes. This belief has been strengthened by the tremendous success that has been achieved in cloning more than 1000 genes that cause simple Mendelian disorders. However, for complex disorders, particularly psychiatric conditions, the search for genes has been frustrating and has not yielded definitive results, although claims of gene discoveries are made regularly. In this article, we discuss the possible causes for these difficulties, along with some directions that may help in reducing these problems. We also consider the implications of psychiatric genetic research for individual and public health.

La génétique captive l'imagination du public et l'intérêt des médias, et occupe une place importante en sciences. Depuis la découverte de la structure de l'ADN par Watson et Crick, la double hélice incarne le principal dogme de la génétique : les gènes codent tout, du détail le plus minuscule du corps humain jusqu'au plus complexe des comportements. La réussite énorme que représente le clonage de plus de 1000 gènes qui causent de simples troubles mendéliens a renforcé cette croyance. Dans le cas des troubles complexes, toutefois, et en particulier des problèmes psychiatriques, la recherche génétique s'est révélée frustrante et n'a pas produit de résultats définitifs, même si l'on affirme régulièrement avoir découvert des gènes. Dans cet article, nous discutons des causes possibles de ces difficultés, ainsi que d'orientations qui peuvent aider à atténuer ces problèmes. Nous tenons aussi compte des répercussions de la

Introduction

It has now been well established that genetic factors play an important role in increasing susceptibility to and modulating the onset and outcome of most developmental psychiatric disorders. Genetic epidemiologic studies indicate that there is usually 40%–90% heritability for disorders such as schizophrenia,¹ autism² and attention deficit hyperactivity disorder (ADHD).³ This conclusion contrasts drastically with the failure of molecular genetic studies to identify specific genes that can be implicated beyond doubt in any of these disorders. For example, in the case of schizophrenia, in spite of some consistency reported in recent meta-analyses of genome-wide

linkage studies^{4,5} and enthusiasm for recent associations of positional candidate genes (i.e., genes mapping to linked loci) with schizophrenia,^{6,7} replication of these results has proven problematic. To cite only one gene that has attracted much attention in the past few years, 2 recent meta-analyses failed to identify any effect of the catechol-*O*-methyl transferase gene in increasing the risk for schizophrenia.^{8,9} Other examples of positional candidate genes for schizophrenia include neuregulin (*NRG1*, 8p),¹⁰ dysbindin (*DTNBP1*, 6p),¹¹ *G72/G30* (13q),¹² *RGS4* (1q),¹³ *Nogo* (2p),¹⁴ calcineurin (8p)¹⁵ and *CAPON* (1q22)¹⁶ (for reviews, see O'Donovan et al¹⁷ and Harrison and Weinberger⁷). Although some of these genes have gained widespread acceptance and have been cited as examples of the re-

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Medical subject headings: genetics; complex disorders; schizophrenia; attention deficit disorder with hyperactivity; autistic disorder; models, animal; endophenotype.

Submitted Apr. 25, 2005; Revised July 19, 2005; Accepted July 21, 2005

markable success of identifying genes in complex disorders in humans,¹⁸ the current literature is far from conclusive. For ADHD, linkage studies have not identified major loci,^{19,20} and genetic association studies have implicated several genes encoding components of the dopamine pathway. Here again, the results have been difficult to replicate.²¹

These difficulties give rise to several questions. First, why is it so difficult to identify genes implicated in these disorders? Second, are these difficulties specific to psychiatric disorders, or are they common to the study of all complex diseases in humans? Third, should the approach used to identify genes implicated in psychiatric disorders be adjusted? Fourth, should expectations of the outcome of genetic research and its potential ramifications for personal and public health be modified? In this paper we briefly address these questions.

Why has it been so difficult to identify genes implicated in developmental psychiatric disorders?

The ultimate goal of genetic research is to map the genome onto the "phenome" and vice versa. Over the past 2 decades, tremendous strides have been made in deciphering the human genome, a process that culminated with the sequencing of the entire genome. One of the most surprising findings of this project was that humans have a much smaller number of genes than previous estimates had indicated. Indeed, in spite of their complex and highly organized nervous systems and behavioural repertoires, humans have a relatively modest number of genes compared with "simple" model organisms like the worm *Caenorhabditis elegans* or the fruit fly *Drosophila melanogaster*. Although this may be considered good news for "gene hunters," it may also indicate that much of the complexity that humans display is embodied at systems levels that are more or less remote from genes (genomic, epigenetic, proteomic and neuropsychologic systems, metabolic and neural networks) and that the path from genes to behaviours may be much more difficult to navigate than was previously anticipated.

One of the other difficulties facing the genetic research community is that, in contrast to genes, which are more or less segmented, discrete entities, and genetic variations, which are amenable to unambiguous identification, behavioural phenotypes are neither segmented nor discrete, and they entail a substantial amount of subjectivity in their definition and unreliability in their assessments. It is difficult, therefore, to know what would be a relevant phenotype from a gene identification perspective. Indeed, most of the behavioural phenotypes that are extensively used have earned their validity on grounds that are not genetically pertinent. For example, the most characteristic symptoms of schizophrenia, i.e., Schneider's first-rank symptoms, have been reported not to be heritable at all²² or to have at most a lower heritability than the schizophrenia syndrome.²³ Similarly, intrafamilial correlations for schizophrenia dimensions (positive, negative and disorganization) are not significant.²⁴ In fact, conceptions of mental disorders are modelled on somatic diseases, with

the assumption that the clustering of symptoms within the same individual refers to one or a few causes. This assumption is probably too simplistic in the case of mental and behavioural disorders. Indeed, behaviours and behavioural disorders may represent end points for various physiologic and pathological processes, which obey complex, nonlinear dynamics and developmental trajectories. This diversity of pathways leading to behavioural disorders is often referred to as "heterogeneity," a concept used to explain away difficulties encountered in replicating genetic results. It is interesting to note that the meaning of the term "heterogeneity" is defined by its use in Mendelian genetics and as such it refers to allelic and interlocus heterogeneity. In this context, there may be attempts to reduce heterogeneity, using clinical (e.g., early or late age at onset) or genetic (e.g., recessive or dominant mode of transmission) criteria, which often results in the re-establishment of linearity in the relation between a gene and a given phenotype. "Complex heterogeneity" may be a better term to characterize the heterogeneity observed in behavioural disorders because the gene-phenotype relation may not be amenable to linearity, given that it depends on a large number of interacting events, both environmental and genetic, that punctuate the developmental trajectory of the affected subject. In any case, appreciation of the extent of the heterogeneity of behavioural disorders is limited for now. The worst-case scenario would be that each individual patient (or a relatively small number of patients) develops a given behavioural disorder because of a specific combination of genetic and environmental risk factors. Under such a scenario, the heterogeneity will be high, and it will be difficult to identify the genes implicated in these disorders. The best-case scenario would be one of "Mendelian heterogeneity" such as observed in Alzheimer's disease, although the chances that this scenario applies to most psychiatric disorders are becoming slimmer.

Are these difficulties specific to psychiatric disorders?

In fact, these difficulties are not restricted to psychiatric disorders. Most multifactorial human disorders with late onset pose the same challenging question of how to prove beyond any doubt whether or not a given gene is implicated in pathogenesis. Type 2 diabetes,²⁵ high blood pressure²⁶ and nonsyndromic obesity²⁷ are examples of common complex disorders in which the identification of susceptibility genes has been and still is challenging. Even skin pigmentation, a physical trait that is much simpler than behavioural traits, has been difficult to resolve from a genetic standpoint in spite of the fact that it is developmentally stable and not subject to strong environmental influences.²⁸ In fact, Ioannidis et al²⁹ have shown that the odds ratio associated with genetic variants explored in the context of several somatic disorders converges on 1 as sample sizes increase. Thus, the difficulty of identifying genes is not restricted to complex psychiatric disorders, although the problem may be compounded by the relative complexity of the phenotype compared with somatic complex disorders or traits.

How should approaches to identifying the genes implicated in psychiatric disorders be adjusted?

Notwithstanding the fact that each developmental psychiatric disorder has its particularities and may need a specifically tailored approach, we³⁰ and others³¹ believe that a better understanding of the genetic makeup of these disorders requires that they be broken down into simple traits, behavioural or otherwise, that are considered more basic manifestations of the disorders. For example, in schizophrenia, a deficit in gating, representing a deficiency in the capacity of the brain to filter out irrelevant internal and external stimuli, appears to be a relatively simple trait that may explain important aspects of the disorder.³² Other examples include deficits in executive function, thought to be fundamental to both schizophrenia³³ and ADHD,^{34,35} and aversion-to-delay, which is postulated to be important for ADHD.³⁶ Although these traits are often qualified as “simple,” they are in fact quite complex, appearing simple only in relation to the more complex disorders to which they may contribute. These traits may be signs and symptoms that are observed clinically (e.g., motor hyperactivity, impulsivity or inattention in the case of ADHD) or they may be other phenotypes that require laboratory measurement but that are possibly further upstream along the chain of pathological events linking genetic determinants to the clinical syndrome (e.g., gating deficits or abnormal event-related potentials in the case of schizophrenia). Thus, these distinct measures may occur at different biobehavioural integrative levels along the chain of events linking genes to the clinical syndrome, starting from the most elementary levels (molecular, cellular) and progressing to more complex levels (neurophysiologic, neuropsychologic, behavioural). It may be assumed that the more elementary the measure of interest, the closer it is to the genetic determinants and the less specific it is to the syndrome. In contrast, measures reflecting more complex integrative levels would be more specific to the syndrome under investigation but further from the genetic determinants of the syndrome. Thus, it may be important to study traits from different integrative levels, those with a close phenomenologic relation to the clinical syndrome (exophenotypes) and those with a close relation to the genetic determinants (endophenotypes).

A recent review of the genetic basis of quantitative traits points to the difficulties of, as well as exciting new developments in the methods for, identifying the genetic determinants of these traits.³⁷ Thus, improved understanding of the genetics of developmental psychiatric disorders will depend on the answers to the following questions:

- What are the simple traits that are pertinent for developmental psychiatric disorders, and how do they combine to lead to the clinical expression of these disorders?
- What are the genes (in isolation or in various combinations) modulating these simple traits?
- How do these genes (in isolation or in various combinations) relate to psychiatric disorders?

To borrow an image from the science of chemistry, the “Mendeleev periodic table” of behaviours relevant for de-

velopmental psychiatric disorders must be constructed to help understand the “atomic structure” underlying these complex behavioural disorders. This “Mendeleev table” can then be used to understand the “molecules” or different sub-syndromes representing the spectrum of behavioural manifestations related to a given psychiatric disorder. Only then will it be possible to understand the “macromolecular” structure or syndromic nature of developmental psychiatric disorders. Although this parallel may partially capture the reality of the pathogenesis of developmental psychiatric disorders, researchers are still far from discovering the genes implicated in these disorders. Thus, much more work aimed at identifying the genetic determinants of simple behavioural traits, both in humans (with and without mental disorders) and in animal models will be needed before the genetic puzzle of these disorders can be pieced together.

Although a full-fledged demonstration of this approach has yet to be realized, it is notable that many investigators have included, at least partially, quantitative traits in their quest for the genes increasing the risk for developmental psychiatric disorders.^{38–41} In most cases, the application of this approach has not been integrated a priori in research designs but rather has been applied post hoc. Nevertheless, the integration of quantitative traits in linkage analyses has usually been reported to result in better genetic signals, although these findings remain to be replicated and confirmed. One recent example⁴² may be illustrative of the approach that we are advocating. In this example, the authors undertook a search for genes implicated in IQ (intelligence quotient), a highly heritable quantitative trait, in healthy children. The authors found that the most significant signal originated from locus 2q24.1–31.1, which largely overlaps with locus 2q21–33 and which has yielded suggestive linkage to autism in at least 4 independent genomic screens. Given that IQ is often low and shows important variability in children with autism, it may be that the 2q21–33 linkage signal observed in autism is “specific” to this particular trait.

Success with this trait-oriented, quantitative genetic approach also requires a paradigm shift from the model of simple linear causality used for Mendelian disorders (whereby the gene leads directly to the phenotype). Indeed, in most instances, the psychologic and behavioural constructs that are being used in behavioural (including psychiatric) research derive their validity from correlation analyses, which assume that correlated behaviours reflect common neurobiologic determinants.⁴³ In a recent paper, Flint⁴⁴ proposed that genetic analyses could help to validate these psychologic and behavioural constructs by showing that the same gene affects a multitude of traits in a theoretically predictable fashion. In other words, showing that a gene has a pleiotropic effect on several traits that are part of the same construct will contribute significantly to validation of the construct. Conversely, fine-tuning the definition of the traits that are part of the construct under investigation in a way that optimizes the gene–trait relationship will also increase the validity of the construct. Hence, it may be argued that it will be the joint refinement of both behaviours and their genetic correlates, but not refinement of each one in isolation from the other, that

will help to better define valid behavioural constructs. This represents an epistemic leap from the tradition of Mendelian genetics, where a phenotype showing Mendelian segregation is quasi-synonymous with the presence of a gene mutation that merely awaits identification.

Another source of validation of psychologic and behavioural constructs that is widely used in psychiatry is psychopharmacology. In fact, many of the current theories on the pathophysiology of psychiatric disorders have been inferred from the therapeutic effects of the drugs that are used to treat those disorders. Although in clinical practice certain therapeutic approaches are considered appropriate for certain syndromes, the effects of the drugs are often limited and affect only specific traits within a given syndrome. For each trait (T) of relevance to a psychiatric disorder, the response (r) of the trait to a pharmacologic agent (d) can be defined as rTd . Both T and rTd can be studied with respect to a gene (G). We are using this pharmacobehavioural genetic approach to study the genetics of ADHD. This approach differs from classical pharmacogenetics because in this context drug responsiveness is used to dissect behaviours, not to predict therapeutic response or the side effects of medication. Given the wealth of information on the molecular mechanisms of action of drugs, this approach facilitates the selection of candidate genes to be studied for a selected behaviour. For example, in the context of ADHD, motor hyperactivity (MA), a trait highly relevant to the disorder, and the response of MA (rMA) to methylphenidate may be studied jointly in relation to variations in the dopamine transporter gene (*SLC6A3*). The choice of the dopamine transporter gene is guided by the fact that methylphenidate acts mainly by increasing synaptic levels of dopamine, which is in turn accomplished by blocking the dopamine transporter. This pharmacobehavioural genetic analysis embodies the concepts described in this paper: studying a simple trait relevant for a psychiatric disorder (in this example, MA) in conjunction with the response of that trait (rMA) to a pharmacologic agent (methylphenidate) in relation to a pharmacologic candidate gene (*SLC6A3*) selected on the basis of what is known about the mechanisms of action of the drug. Furthermore, it is possible to measure the MA of a subject in different contexts (at home, as assessed by parents, or at school, as assessed by teachers), as well as to define and measure MA in alternate, yet clinically pertinent ways. In doing so, it may be possible to get closer to a pertinent definition of MA from the perspective of its genetic determinants (and more specifically, from the perspective of the dopamine transporter gene) by optimizing the effects of the gene on MA and rMA as measured in various contexts and by different methods. This example illustrates how genetic analyses can contribute to the validation of behavioural constructs and vice versa.

Finally, in addition to reducing complex genetic behavioural disorders to simpler and genetically more tractable traits, other approaches have been advocated to circumvent the difficulties encountered in identifying susceptibility genes. For example, many authors have advocated the study of the epigenetic determinants (DNA and chromatin modifications that play a critical role in the regulation of

various genomic functions) of psychiatric disorders⁴⁵ while others have emphasized the role of gene–environment interactions.⁴⁶ However, it is important to note that the main premise of genetic research in developmental psychiatric disorders is that a significant part of the variance in these disorders is attributable to genetic factors, that is, DNA sequence variations. Nongenetic factors have always been estimated as less important than genetic factors, and the sources of nongenetic variation are still unclear. Although it is often assumed that this nongenetic variation may be due to differences in the environment at different stages of development, several studies indicate that at least part of this variation may be related to a “third component,”⁴⁷ the nature of which has yet to be identified. Some authors have suggested that this “third component” may be embodied by epigenetics,⁴⁸ although it is difficult to rule out other mechanisms such as developmental noise or stochastic factors.⁴⁹ In addition, for most of the developmental psychiatric disorders, there is little information on specific environmental factors, in part because of the difficulty of retrospectively measuring environmental adversity, which renders the study of gene–environment interactions arduous to say the least. Because of these and other considerations, the identification of sequence variations, which is the most important source of variation in the expression of developmental psychiatric phenotypes, remains a primary objective, although specific experimental designs aimed at controlling for environmental or other sources of variance may be useful.

Should expectations of the outcomes of genetic research be modified?

When the first disease-causing gene was mapped 20 years ago⁵⁰ and cloned 10 years later,⁵¹ it was hoped that the methods used to achieve these landmark discoveries in human genetics would help to uncover genes for all kinds of human heritable diseases. This expectation has been fulfilled to a certain extent as more than a thousand mutated genes have been assigned to human disorders. However, the majority of these mapped disorders are Mendelian diseases, in which the probability of having the disease when the mutation is present, $P(D/m)$, is very high (about 1). In contrast, for psychiatric developmental disorders, any given susceptibility gene is most likely associated with a modest $P(D/m)$. This has important implications both for the health of individuals (in terms of diagnosis, prevention and genetic counselling) and for the health of populations.

For an individual, the genetic information encapsulated in a specific gene may be meaningless for determining the risk of the disorder occurring. Thus, it cannot be used for diagnosis, prevention or genetic counselling. However, if many susceptibility genes are identified, the importance of the aggregate genetic effect, $P(D/m_1, m_2, m_3, m_4, \dots)$, may be substantial and of clinical value. However, the ability to calculate such a conditional probability for a given individual may be complicated if the effects of the genes are themselves dependent on past environmental events that are difficult to reconstruct.

From a population health point of view, the effect of a sin-

gle gene could be important, as the attributable fraction of a disease depends both on the gene effect and the frequency of that variant in the general population. A genetic variant that has only a modest effect but that is highly prevalent in the population may account for a substantial fraction of the attributable risk. However, genetic variants are not malleable risk factors that can be directly controlled. This limitation may call into question the utility of understanding the genetic basis of complex psychiatric disorders.

In our view, genetic research on psychiatric disorders in general and developmental disorders in particular may be important only if genetic risk factors can lead to a better understanding of the biology of these disorders and how environmental and genetic risk factors interact to increase susceptibility to the disorder. A better understanding of the biology will increase the ability to design medications to treat the disorders, and a better understanding of how genetic risk factors interact with environmental risk factors will allow the design of population interventions to reduce the population load of these disorders (if these environmental risk factors turn out to be malleable, which is often the case). Seen from this perspective, the genetics of developmental psychiatric disorders is still in its infancy but holds great potential to contribute to the understanding and treatment of these disorders.

Conclusions

"They all talked at once, their voices insistent and contradictory and impatient, making of unreality a possibility, then a probability, then an incontrovertible fact, as people will when their desires become words." Weiss and Terwilliger⁵² used this wonderful quotation from W. Faulkner (*The Sound and the Fury*, 1929) to introduce a thoughtful and critical paper published a few years ago on the promise of genetic research in the management of complex disorders. It appears as if psychiatric genetics may be at risk of enacting this elegant quotation, when one considers the many claims and counterclaims in the field and the state of inflated societal expectations from genetics. Having a reasonable view of where research in this field is currently situated and where it is headed may help in this regard.

Competing interests: None declared.

Contributors: All authors contributed substantially to drafting and revising the article, and each gave final approval for the article to be published.

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July 9-13, 2006

Lakeside Center at McCormick Place

The 29th Annual Meeting of the CCNP will take place in Chicago from July 9 to 13, 2006. This meeting will be held jointly with the Collegium Internationale Neuro-Psychopharmacologicum (CINP), and will be an excellent opportunity to highlight Canadian neuropsychopharmacology research to our colleagues from around the world. The CCNP will present four symposia and our prestigious Award lectures as part of the meeting program.

For further information, please contact

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