The genetics of mental illness: implications for practice

Steven E. Hyman[1]

Many of the comfortable and relatively simple models of the nature of mental disorders, their causes and their neural substrates now appear quite frayed. Gone is the idea that symptom clusters, course of illness, family history and treatment response would coalesce in a simple way to yield valid diagnoses. Also too simple was the concept, born of early pharmacological successes, that abnormal levels of one or more neurotransmitters would satisfactorily explain the pathogenesis of depression or schizophrenia. Gone is the notion that there is a single gene that causes any mental disorder or determines any behavioural variant. The concept of the causative gene has been replaced by that of genetic complexity, in which multiple genes act in concert with non-genetic factors to produce a risk of mental disorder. Discoveries in genetics and neuroscience can be expected to lead to better models that provide improved representation of the complexity of the brain and behaviour and the development of both. There are likely to be profound implications for clinical practice. The complex genetics of risk should reinvigorate research on the epidemiology and classification of mental disorders and explain the complex patterns of disease transmission within families. Knowledge of the timing of the expression of risk genes during brain development and of their function should not only contribute to an understanding of gene action and the pathophysiology of disease but should also help to direct the search for modifiable environmental risk factors that convert risk into illness. The function of risk genes can only become comprehensible in the context of advances at the molecular, cellular and systems levels in neuroscience and the behavioural sciences. Genetics should yield new therapies aimed not just at symptoms but also at pathogenic processes, thus permitting the targeting of specific therapies to individual patients.

Keywords: mental disorders, genetics; neurosciences; mental disorders, drug therapy; genetic predisposition to disease; antipsychotic agents, therapeutic use.

Voir page 460 le résumé en français. En la página 461 figura un resumen en español.

Background

It is worth considering the complexity of the human brain so as to put in perspective what is required of genetic tools. The brain is the most complex object of investigation in the history of biological science. Its development depends on complex, often non-linear, gene–gene and gene-environment interactions, as well as on stochastic processes associated with the interconnection of 100 000 million or more neurons. As we are beginning to understand, the complexity of the brain and the combinatorial interactions of many genes and non-genetic signals involved in building it are consistent with the richness of our mental lives and behaviour. This complexity, however, has made progress in the neuroscience and genetics of mental illness exceedingly difficult. Each neuron in the brain makes thousands of connections or synapses with neighbouring and distant neurons; there are probably more than 100 trillion such connections, and across them each neuron may utilize several of more than 100 chemical neurotransmitters. Signals encoded by each neurotransmitter are decoded by the receiving cell, using one or several of the many receptor subtypes that exist for each neurotransmitter. For example, the neurotransmitter serotonin has at least 14 different known subtypes of receptors. Neurotransmitter receptors initiate complex signalling cascades within nerve cells. These cascades process information, produce immediate outputs, such as a decision to fire, and, at the same time, initiate long-term, activity-dependent changes in the receiving cells which may eventually lead to synaptic plasticity. Each synapse is embedded in one or more neural circuits that can be recruited or engaged with exquisite specificity. In the basal ganglia, for example, a given neuron might fire in conjunction with a particular movement made as part of a specific behavioural task, but not with the same movement when in a different behavioural situation (*1*).

The crowning complexity of the brain, however, is that it is not static. Every time something new is learnt, whether a new name, a new skill or a new emotional reaction, the active neurons alter the synaptic architecture of the circuit in which the learning has occurred. This process is termed plasticity; new synapses may be formed and old ones may be pruned; existing synapses may be strengthened or weakened. As a result, information is processed differently. Ultimately, in ways not yet understood, our mental lives and behaviour are

[1] Director, National Institute of Mental Health, 6001 Executive Boulevard, Room 8235, MSC 9669, Bethesda, MD 20892-9669, USA.

Ref. No. **00-0642**

emergent properties of the firing patterns of neurons within the parallel, distributed and potentially plastic circuits of our brains.

Diseases of the brain, whatever their pathophysiological basis, ultimately affect behaviour by altering the function of brain circuits. For example, stroke is an illness in which neurons die because of a lack of oxygen. This event may create gaps in circuits that traverse the damaged area or kill cells that give rise to neural projections. The precise functional deficit depends on the circuits that have been disrupted and on the location. In most individuals, for example, information processing and important outputs required for the production of fluent speech come together in Broca's area of the left hemisphere of the cerebral cortex. Stroke in this region often causes a motor aphasia, but damage to other regions of speech circuitry may produce related aphasic symptoms. Despite the ability of the brain to adapt, brain diseases remind us that natural processes of plasticity are finite. In adults, only partial recovery from a Broca's aphasia is the rule. In some situations, such as in chronic neuropathic pain resulting from nerve damage (*2*), the processes underlying plasticity can be subverted by illness or injury so as to produce serious symptoms. Indeed, the pathogenesis of addictive disorders (*3*) and post-traumatic stress disorder (*4*) may represent the usurpation of normal learning processes in reward and fear circuits respectively.

Just as specific neural circuitry underlies primary sensory processes (e.g. vision or touch) and motor control, it is now recognized that specific identifiable circuits underlie different aspects of cognition (*5*) and emotion (*6*, *7*). Ultimately, understanding the biological underpinnings of a disease like schizophrenia will be not simply a matter of finding several genes associated with the phenotype, measuring neurotransmitter levels, or identifying a spot on a magnetic resonance imager. Rather, we must understand how a disease process disrupts the parallel distributed processing that underlies relevant aspects of thinking, emotion and motivation (*8*). This will require that function be understood at the molecular, cellular and systems levels and at the level of behavioural neuroscience. Eventually, however, it should be possible to ask how one version of a given gene (allele) contributes to the risk of depression or schizophrenia while another, probably only a slightly different version, does not. It should also be possible to ask when, in development, alleles that confer a risk of autism or schizophrenia are active, thus giving clues about the time of action of environmental factors and information about when interventions might best take place. It may be that an allele producing a risk of manic depressive illness, in combination with certain alleles occurring at other loci in the genome, is neutral or even advantageous in other combinations. Although we are still far from such achievements, it is already possible to chart some important clinical implications of genetic studies.

Genetics of behaviour and mental illness

Genetic factors contribute to almost every human disease by conferring susceptibility or resistance, and, if disease occurs, by influencing severity and progression. Because genes encode the building blocks of cells, i.e. proteins, they should prove to be extremely powerful tools for research on mental disorders. Gene discovery should have a transforming influence on clinical practice. However, the genetics of behavioural variation and of mental illness has proved enormously complex. This is consistent with the intricate wiring of the brain and the wide range of human behaviour, but means that the benefits of genetics for practice remain some years in the future.

It is well established that the risk of mental illness runs in families. Family, twin and adoption studies have shown that, for schizophrenia, autism, manic depressive illness, major depression, attention deficit hyperactivity disorder, panic disorder and other mental illnesses, the transmission of risk is due to heredity (*9*–*13*). How might this come about? DNA transmits information contained in the sequential order of its four nucleotide bases across generations and is the information repository that, in interaction with environmental signals, controls the development of an organism and the cells and organs within it. In cells, the information contained in DNA is transferred to proteins via other molecules including structural RNA and messenger RNA. Messenger RNA is translated to produce proteins, which, for example, control the shapes of cells, regulate their chemical reactions and form neurotransmitter receptors and ion channels. With respect to neural development, proteins form guidance cues or control their synthesis; these direct the migration of neurons to their correct places in the brain, leading to the establishment of appropriate connections. Other proteins are required if the brain is to adapt in response to environmental inputs associated, for example, with drugs, injury or disease. Genes and their protein products are not the only factors involved in establishing and consolidating the synaptic structure of the brain; the activity of synapses themselves, partly resulting from experience, also plays a vital role. Nonetheless, genes are critical to the development of the overall circuit maps and function of the brain. Variations in the DNA sequence of genes may lead to the expression of an altered protein with loss of function or with a new function that might be adaptive, neutral or toxic to cells. Variations in DNA sequences that regulate gene expression might alter the timing, cell type or spatial location in which a protein is expressed. Variations in either protein coding regions or regulatory regions of DNA might also result in a complete failure to express a protein. Sequence variants that affect behaviour, including the risk of mental illness, must affect neurons in such a way as to change the architecture, function or adaptability of neural circuits in the brain.

The goal of molecular genetic studies of mental disorders is to identify and clone genes that contribute to the risk of such disorders, influence their course or promote resilience. However, the risk of mental disorders is genetically complex (*14*, *15*). Genetic complexity means that a trait such as vulnerability to a mental illness results not from a single genetic defect but from the interaction of multiple genes. These gene–gene interactions need not be simply additive; the function of one gene may be dependent on the prior function of one or more other genes, a phenomenon known as epistasis (*16*). Moreover, even in combination, genes do not appear to fully determine the occurrence of a mental illness but must interact with non-genetic factors. Indeed, studies of monozygotic twins, i.e. who have 100% of their DNA in common, performed in relation to schizophrenia and manic depressive illness (*17*), confirm the requirement for non-genetic factors to convert vulnerability into illness. In no mental illness is there 100% concordance for the illness within monozygotic twin pairs. Complexity may not end with the need for multiple alleles at multiple loci in the genome or with the need for non-genetic factors: it is possible that there is no single required allele for any mental disorder, i.e. different combinations of alleles may influence vulnerability in different families.

Diseases due to a single major genetic locus, whether dominant or recessive, are often called Mendelian disorders, Gregor Mendel having initially described the inheritance of traits due to the operation of single genes. In the human population in general, deleterious mutations contributing to Mendelian disorders are rare. Indeed, the genetics of the most common human disorders tend to be complex, and include, in addition to mental disorders, coronary artery disease, diabetes mellitus types I and II, and hypertension. It is likely that the alleles contributing to common complex disorders do not represent deleterious mutations, e.g. changes in DNA nucleotide sequence that would markedly damage a protein, but that they are genetic variants that in some combinations are neutral or even advantageous (thus explaining their high population frequency), only producing a disease risk in certain unfortunate combinations. There are rare Mendelian disorders with mental symptoms, e.g. Rett syndrome, in which symptoms resembling those of autism coexist with mental retardation (*18*), and there are rare Mendelian forms of early-onset familial Alzheimer disease (*19*). The identification of such Mendelian forms, even though they may be responsible for only a small percentage of cases within a population, e.g. of Alzheimer disease, is potentially very important as a research tool. No rare Mendelian forms of the common mental disorders have yet been detected.

It is far easier to identify a genetic locus that contributes very large effects on phenotype than to identify multiple loci where each contributes a small effect (*20*). For almost all the important Mendelian disorders, such as cystic fibrosis and Huntington disease, genes have been identified and cloned. In addition to the technical difficulties of finding the multiple alleles of small effect that characterize genetically complex disorders there are difficulties in defining phenotypes. For mental disorders this, indeed, may be the most difficult problem of all. There are useful tools for communication (*21*, *22*) but it would be wrong to imagine that their criteria map on to the genome. These diagnostic systems describe a large number of putative disorders with widely varying levels of validation. The refinement of phenotypes and gene discovery may have to go hand-in-hand (*23*, *24*). In the case of familial Alzheimer disease, genotypes have helped to clarify phenotypes and vice versa.

Strategies for progress

Given the difficulties described above, how can risk genes for mental disorders be identified? How can we move beyond the current situation in which there have been no fully convincing replications of genetic linkages in mental disorders? There is widespread agreement that progress in gene discovery requires the collection and analysis of one or more of the following types of data sets:

- large numbers of pedigrees from outbred populations containing multiple individuals affected with a given mental disorder;
- pedigrees from genetically isolated populations;
- large numbers of affected individuals and control samples.

In outbred populations, large numbers of pedigrees are needed to provide sufficient statistical power to detect the small effects of the multiple genes that produce the risk of mental disorders. In isolated human populations a significant fraction of affected individuals inherits a disease risk allele from a common ancestor. In addition to the benefit of reduced genetic heterogeneity, all affected individuals may be treated as distant relatives. Considerable genetic information can be obtained by considering not only the generation of probands (identified affected individuals) but also all family relationships in the history of a population. A third data set for gene discovery is based on the collection of genetic material from large numbers of affected individuals and their parents or other suitable controls. These data may be used to evaluate so-called candidate genes that are thought to play a role in gene pathophysiology. Given the complexity of the brain and the current state of knowledge it is not surprising that the number of compelling candidate genes is quite small. As a result of advances in technology, such as high-throughput analytical and molecular methods, it should be possible to test every human gene as a possible candidate gene for the production of risk of mental disorders, or, indeed, any other phenotype of interest.

The National Institute of Mental Health, Bethesda, is funding large collaborative projects in China, the Eastern Mediterranean, Europe, Latin America, and the USA, as well as studies of isolated populations in the Azores, Micronesia, the Russian Federation, and South Africa. An important aspect of the Institute's approach to human genetics research is that investigators should eventually place their DNA samples and phenotypes in the public domain. In this way, as new ideas become available, it should be possible to test them rapidly. Thus the data sets should be available for future studies as the technologies for genotyping and the statistical analysis of complex data sets (*25*) mature (see http://www-grb.nimh.nih.gov/gi.html). Developing statistical and molecular approaches for efficient genome-wide studies of gene variants should greatly benefit from the availability of such archived materials. A similar effort is now under way in the United Kingdom to develop collections of well-characterized DNA samples of genetically complex disorders having a significant impact on public health (see http://www.mrc.ac.uk/welcome.htm).

The critical technological platforms for facilitating gene discovery are the completion of the international Human Genome Project and parallel projects within industry, revealing the sequence of the human genome, and multiple international projects aimed at identifying variation in all human genes. The variations that are the focus of most current large-scale efforts are DNA sequence variations in which a single nucleotide base is altered, i.e. single-nucleotide polymorphisms (*26*). These represent the most common polymorphisms in the human genome. Because of their abundance and wide distribution across the genome, as well as their potential for large-scale automated sequence analysis (genotyping) using DNA microarrays (DNA chips) or mass spectrometry, single-nucleotide polymorphisms are likely to prove extremely useful for genetic studies of complex diseases. New mathematical methods are being developed to analyse genotypes at many loci in whole-genome studies, whereby associations may be detected between single-nucleotide polymorphism variants and the presence of a trait such as a mental disorder (*27*). The availability of large DNA and phenotype collections, catalogues of human genetic variation, and mature genotyping and analytic technologies should eventually permit the identification of genes that produce risk for mental disorders.

Clinical implications of genetics

Epidemiology

Since the beginning of the modern era of psychiatric diagnosis it was hoped that symptom clusters defining syndromes, courses of illness, family history and perhaps treatment response would coalesce into valid disease entities. This simple picture has proved invalid in the light of present knowledge of the complexity of risk of mental disorders. Thus there is substantial comorbidity between depression and certain anxiety disorders and there is comorbidity between tic disorders and obsessive–compulsive disorder. Moreover, some clinically important disease variants, such as rapid cycling bipolar disorder, do not breed true within families. This picture is consistent with the complexity of genetic risk. It may be that what maps on to the genome will prove to be simpler clusters of symptom complexes than those in the current diagnostic manuals, or perhaps risk that can be converted into depression, an anxiety disorder or both, depending on the presence of modifier genes or of certain life experiences. It is also possible that what maps best on the genome is not symptom clusters but underlying neurobiological differences, sometimes referred to as endophenotypes. Such phenotypes currently being used in genetic studies include abnormalities in eye movements which are associated with schizophrenia (*28*). However, as advances in cognitive neuroscience and neuroimaging take place, phenotypes based on patterns of brain activity or neurochemical differences may emerge. The discovery of disease vulnerability genes should be an important step in helping to resolve the boundaries of some disease entities and to understand the precise nature of risk transmitted within families. Interestingly, these discoveries may not yield diagnostic tests that are generally useful in screening diverse populations. Depending on the number of loci required for a particular mental illness phenotype and the degree to which there is heterogeneity among the loci contributing to illness in different families, tests may be cumbersome, requiring multiple family members and genotypes at multiple loci. Given the importance of non-genetic factors in disease expression, the predictive value of genetic tests may also prove to be poor. Because of the difficulty and imprecision of predictive genetic screens, their value in high-risk families may only outweigh the problems after effective preventive interventions are developed.

Impact of genetics on the development of treatment

The concept of a drug target, i.e. a molecular target against which compounds can be tested for inhibitory or facilitative activity, is central to modern processes of drug development. In psychiatry, the identification of effective drug treatments began with a series of serendipitous discoveries, firstly of lithium (*29*) and later of chlorpromazine, the first antipsychotic drug, and imipramine and the monoamine oxidase inhibitors, the first antidepressant compounds.

As was the rule during the 1950s, the actual molecular targets of antipsychotic and antidepressant drugs became known only after the drugs were found to be efficacious. The precise molecular target of lithium remains a matter of debate, although there are at least two highly compelling candidates. The D2 dopamine receptor family and the serotonin 2a

(5-HT2a) receptor were identified as molecular targets for antipsychotic drug development on the basis of the efficacy of existing antipsychotic drugs and the properties of clozapine respectively. In the case of antidepressant drugs, the monoamine reuptake transporters, most notably the norepinephrine and serotonin reuptake transporters, were identified as drug targets. More recently a host of other synaptic proteins within noradrenergic, serotonergic and dopaminergic synapses have been identified as potential targets for the development of antidepressant drugs. As a result of the exploitation of these molecular targets by the pharmaceutical industry, antipsychotic drugs have been developed which may have enhanced efficacy, and new antipsychotic and antidepressant drugs are available that have milder side-effects than older compounds. These treatments represent real advances but there is a great need for fundamentally new treatments directed at the actual pathophysiology of mental disorders and perhaps capable of preventing the onset or progression of disease or of effecting cures. Thus the goal for the development of treatment is to move from drug targets derived from the action of existing treatments to targets related to pathophysiological processes. This is perhaps the greatest promise of genetics and neuroscience. Consider, for example, genetic discoveries that may lead to new treatments for Alzheimer disease. Success is not certain but there are some very promising leads that illustrate the power of neuroscience and genetics to identify drug targets involved in the fundamental disease process. The result could be treatments that would slow or halt progression of the disease.

Much research in biochemistry, genetics and neurobiology has suggested that a small fragment of the β-amyloid precursor protein (a specific form of the so-called Aβ fragment) may be one of the causes of cell death in Alzheimer disease. A large amount of biochemical research led to the identification of this fragment but the major breakthroughs came from genetics. The common varieties of Alzheimer disease appear to be genetically complex, i.e. resulting from multiple genes (including the ApoE locus) and non-genetic factors. However, a small percentage of familial Alzheimer disease of early onset results from Mendelian transmission, i.e. in these cases the dominant inheritance of a single locus is sufficient to produce illness. Genetic linkage studies in early-onset families identified multiple mutations in three different genes: the β-amyloid precursor itself and genes encoding the previously unknown proteins presenilin 1 and presenilin 2.

It appears that the β-amyloid precursor protein can be cleaved in three positions to produce different smaller fragments that are then released into the extracellular space, where, under normal circumstances, they may be involved in cellular growth and maintenance. However, one fragment, the Aβ peptide, has a tendency to precipitate out and form pathogenic amyloid deposits. Each cleavage site involves a different protease, and since the fragments are ultimately secreted these protein-cleaving enzymes are referred to as the α-, β- and γ-secretases. If the β-amyloid precursor is cleaved by the α-secretase, the resulting fragment is not pathogenic. The action of the β- and γ-secretases, together releasing the Aβ fragment, may lead to amyloid deposition. The little understood γ-secretase may be presenilin 1 or closely associated with it. The mutations that produce early-onset familial Alzheimer disease bias these processes toward the production of pathogenic Aβ fragments. It now appears likely that other genetic variants that have been implicated in late-onset Alzheimer disease, such as ApoE4 and certain α_2-macroglobulin alleles, may affect the metabolism of β-amyloid and its cleavage products. This has led to an intense race among pharmaceutical companies to produce inhibitors of the β- and γ-secretases.

Although the β-amyloid story has yet to be confirmed, these two secretase molecules have become important drug targets whose inhibition, very significantly, would interrupt the pathogenesis of Alzheimer disease. Should the story prove correct, and should safe and effective inhibitors be found, powerful new weapons would be available for altering the course of or even preventing Alzheimer disease.

The genetics of the most common mental disorders appears more complex than that characterizing early-onset Alzheimer disease families, which led to the breakthroughs outlined above. Nonetheless, through the discovery of vulnerability genes it is conceivable that indications will be obtained of pathogenic pathways where direct intervention in those processes becomes possible. Improved timing of interventions should be achievable if it proves possible to determine when, in development, these genes are active.

Genetics also offers the prospect of individualized treatments by predicting which patients might give a good response to a drug, or, more probably, which might experience serious side-effects. Pharmacogenetics focuses on genes that affect the actions of many drugs used to treat clinical disease. Mutations in a given gene lead to variations in the amount of a protein that is synthesized, its properties and its final destination. Such genetic mutations may produce a variant protein that can cause an altered drug response. One early clinical application would be in genetic testing to determine a person's cytochrome *P*-450 enzyme genotypes. Different versions of these enzymes that are critical to drug metabolism in the liver would influence dosing with or tolerance of different drugs. Ultimately, one of the greatest benefits from genetic research may come from understanding the genetic contributions to individual-specific drug action.

Conclusion

Through the integration of information coming from genes, molecules and cells with that flowing from the

environment and experience to the brain's neuronal circuits, neuroscience can be expected to revolutionize clinical practice. In the immediate future it is necessary to obtain genetic resources from well-defined pedigrees that are readily accessible to all investigators, while building the technological platform needed to transform these resources into cloned risk-conferring genes. Major steps can be expected to hinge on the imminent availability of a reference human genome sequence, at least in draft form, and on an extensive catalogue of genetic variation in the form of single-nucleotide polymorphisms, both produced by international public and private efforts. The eventual identification of risk-conferring genotypes at certain loci should provide informative independent variables capable of revolutionizing the ability to classify mental disorders. By combining a knowledge of gene function with the search for modifiable environmental risk factors, it should be possible to contribute towards a refocusing of psychiatric epidemiology from counting individuals with syndromes defined by the International Classification of Diseases or the American Psychiatric Association Diagnostic and Statistical Manual to the investigation of disease risk. This would lead to benefits for primary, secondary and tertiary prevention and for the timing of treatment. Breakthroughs in preventive and treatment interventions should come from progress in genetics research and neuroscience. Information on how variations in the DNA nucleotide sequence of genes can alter not only the function, but also the timing, cell type or spatial location in which gene products are expressed, and, in turn, how neural circuits are built, should provide critical tools for understanding how the particular architecture or adaptability of specific neural circuits may affect behaviour. Although the identification, cloning and characterization of the functions of disease vulnerability genes have proved more difficult than was once envisaged, strategies for fulfilling these tasks are emerging, with potentially rich benefits for clinical practice. ■

Acknowledgements

The author thanks Paul Sirovatka, Steven Moldin and Hemin Chin for invaluable help with the manuscript.

Résumé

Génétique et maladie mentale : incidences sur la pratique

La génétique moléculaire et, plus particulièrement, l'identification des gènes responsables de la vulnérabilité à la maladie mentale, renferme un énorme potentiel, qu'il s'agisse de comprendre la physiopathologie des troubles mentaux, d'élaborer une nouvelle épidémiologie des troubles mentaux axée sur le risque ou de découvrir des traitements pour guérir, et même prévenir, ces maladies incapacitantes, souvent mortelles. Cependant, si l'on veut tirer pleinement parti de la génétique, il faut au minimum se fixer pour but l'identification, le clonage et la caractérisation fonctionnelle des gènes de vulnérabilité à la maladie. Cette tâche s'est révélée plus difficile qu'on ne le pensait communément il y a dix ans. Aucun variant génétiquement simple, c'est-à-dire de type mendélien, des principales maladies mentales n'a été mis en évidence. Les études sur les jumeaux et les études cherchant à établir un lien entre le risque de maladie et leur localisation chromosomique révèlent la complexité génétique des maladies mentales. Aussi, contrairement à la chorée de Huntington ou aux rares formes familiales de la maladie d'Alzheimer, aucun gène n'est à l'origine à lui seul des troubles de l'humeur, de l'anxiété ou de la schizophrénie. Ces maladies semblent en fait résulter de l'interaction entre des locus nombreux agissant ensemble et des facteurs non génétiques.

Cette difficulté est accrue du fait de l'hétérogénéité sous-jacente des phénotypes qui pourraient être identifiés d'après les critères de la Classification internationale des maladies ou du manuel diagnostique et statistique des troubles mentaux (DSM) de l'American Psychiatric Association. Identifier des variants génétiques multiples situés dans des locus distincts du génome, dont chacun augmenterait un peu le risque ou même interagirait non linéairement, serait beaucoup plus difficile que de découvrir les causes des maladies monogéniques. C'est la raison pour laquelle le National Institute of Mental Health des Etats-Unis d'Amérique a énormément investi dans ce domaine, comme l'ont fait le Medical Research Council au Royaume-Uni et d'autres organismes. L'un des objectifs du National Institute of Mental Health est de constituer de très nombreuses collections d'ADN et de recueillir les données correspondantes sur le phénotype, tout en assurant la protection appropriée des sujets humains, collections que tous les chercheurs pourront utiliser une fois prêt le support technique permettant l'analyse des troubles complexes. Ce support inclut le projet international sur le génome humain et les initiatives privées déployées en parallèle pour établir le séquençage de tout le génome humain. Elle comprend également les initiatives publiques et privées qui visent à dresser des catalogues utiles des variantes des séquences humaines ; s'y ajoutent les tentatives faites pour mettre au point, pour la recherche des gênes de risque, des méthodes de génotypage à haut rendement et peu coûteuses et des méthodes d'analyse statistique appliquées à la génétique sensiblement améliorées.

Pour comprendre comment les gènes interagissent avec les facteurs non génétiques (facteurs de développement stochastiques et facteurs environnementaux spécifiques) pour construire le cerveau et déboucher sur un risque de différentes maladies mentales, des recherches sont nécessaires à divers niveaux des neurosciences cognitives – molécules, cellules et système – ainsi qu'au niveau des sciences du comportement. En raison de la complexité des problèmes que pose l'architecture génétique du comportement, les modèles algoristiques et l'informatique sont également mis à

contribution. Vu qu'il faut faire appel à plusieurs disciplines pour élucider la complexité structurelle et fonctionnelle du cerveau, son développement, sa plasticité et à sa capacité à évoluer au cours de la vie, on peut s'attendre à ce que la génétique devienne un outil de recherche de plus en plus puissant. Il devrait en résulter des changements profonds dans la pratique clinique.

La complexité évidente au niveau génétique fait ressortir un aspect que les cliniciens connaissent depuis longtemps : l'extraordinaire hétérogénéité des entités diagnostiques présumées de nos manuels diagnostiques actuels. Si l'on pouvait connaître le génotype de certains locus et le considérer comme une variable indépendante, la classification des maladies mentales serait facilitée. En associant la connaissance de la fonction des gènes et la recherche de facteurs de risque environnementaux modifiables, il devrait être possible d'aider à recentrer l'épidémiologie psychiatrique sur le risque, et donc sur la possibilité de prévenir l'apparition et l'évolution de la maladie ou de l'incapacité.

Les progrès continus de la recherche génétique devraient déboucher sur des avancées thérapeutiques importantes. Les chercheurs sont de plus en plus conscients de l'influence de l'ADN sur la structure et le fonctionnement des cellules et de leurs principaux outils, les protéines, et de la façon dont celles-ci dirigent ou influencent à leur tour le développement du système nerveux qui conduit à la constitution des circuits complexes du cerveau. Sachant que la variation des séquences nucléotidiques de l'ADN peut non seulement modifier la fonction mais également agir sur l'expression d'une protéine – moment, type cellulaire et localisation de la production – les chercheurs peuvent entrevoir comment les variants des séquences qui influent sur l'architecture ou l'adaptabilité des neurocircuits peuvent influer sur le comportement.

L'une des principales applications de la génétique moléculaire à la mise au point du traitement des maladies mentales est la capacité d'identifier des produits géniques susceptibles de servir de cibles moléculaires aux médicaments ou aux autres interventions visant directement certains processus physiopathologiques. Les recherches sur la maladie d'Alzheimer illustrent la tâche à venir. Après avoir identifié plusieurs gènes de risque sur un sous-type mendélien de la maladie, dit forme familiale précoce de la maladie d'Alzheimer, les chercheurs ont découvert que certaines enzymes de clivage des protéines, ou protéases, semblaient capables de produire des fragments toxiques du produit, par ailleurs bénin, des gènes de risque, à savoir le précurseur de la protéine bêta-amyloïde. Cette découverte a suscité un déploiement intensif d'activités pour mettre au point des inhibiteurs des protéases dangereuses. Si la génétique des troubles mentaux est beaucoup plus complexe que celle de la forme familiale précoce de la maladie d'Alzheimer, les stratégies de la génétique moléculaire sont également applicables à la recherche d'une approche directe de la physiopathologie des troubles mentaux, de leur traitement, de leur guérison et de leur prévention.

Resumen

Genética de las enfermedades mentales: implicaciones prácticas

La genética molecular, y más concretamente la identificación de genes causantes de vulnerabilidad a las enfermedades mentales, abre grandes posibilidades de entender la fisiopatología de las enfermedades mentales, diseñar una nueva epidemiología de esas enfermedades centrada en el riesgo y conseguir tratamientos que permitan curar o incluso prevenir estas dolencias discapacitantes y a menudo mortales. Sin embargo, para lograr el máximo beneficio de la genética, el objetivo debería ser como mínimo identificar, clonar y caracterizar funcionalmente los genes que determinan la vulnerabilidad a las enfermedades. La tarea ha resultado más ardua de lo que muchos creían hace una década. No se ha hallado ninguna variante genéticamente simple, es decir, mendeliana, de los trastornos mentales más graves. Los resultados de los estudios realizados con gemelos y de los trabajos de asociación del riesgo de enfermedad a determinadas regiones cromosómicas muestran que las enfermedades mentales son genéticamente complejas. Ello significa que, a diferencia de la enfermedad de Huntington o de raras variantes familiares de la enfermedad de Alzheimer, no hay ningún gen que por sí solo cause trastornos del estado de ánimo o de ansiedad o esquizofrenia. Antes bien, estas enfermedades parecen ser el resultado de la interacción de muchos loci genéticos con factores no genéticos.

Esa dificultad se ve agravada por la heterogeneidad de los fenotipos que podrían identificarse con arreglo a los criterios de la Clasificación Internacional de Enfermedades o del Manual Diagnóstico y Estadístico de las Enfermedades Mentales de la Asociación Americana de Psiquiatría. La identificación de múltiples variantes genéticas en distintos loci del genoma, que puedan contribuir a incrementar ligeramente el riesgo, cuando no interaccionen de manera no lineal, resultará mucho más difícil que descubrir las causas de trastornos monogénicos. En consecuencia, el Instituto Nacional de Salud Mental de los Estados Unidos ha hecho inversiones considerables en ese terreno, al igual que el Consejo de Investigaciones Médicas del Reino Unido y otros organismos. Uno de los objetivos del Instituto Nacional de Salud Mental es crear un gran repertorio de secuencias de ADN y de la información fenotípica correspondiente – observando siempre los sistemas de protección establecidos para los trabajos con sujetos humanos – al que puedan acceder todos los científicos, para cuando se ultime la plataforma tecnológica que ha de permitir determinar el origen de trastornos complejos. Dicha plataforma incluye el Proyecto Genoma Humano, de ámbito internacional, y actividades privadas paralelas que persiguen la secuenciación completa de los genes humanos. Incluye también las actividades públicas y privadas emprendidas para crear catálogos de utilidad de

las variaciones de esas secuencias, proyectos de desarrollo de métodos de genotipificación de bajo costo y alto rendimiento, y métodos genéticos estadísticos muy mejorados para la detección de genes de riesgo.

Para entender cómo interaccionan los genes con factores no genéticos (incluidos aquí tanto factores estocásticos que actúan durante el desarrollo como factores ambientales específicos) para configurar el cerebro y crear predisposición a diferentes enfermedades mentales, es necesario realizar investigaciones a distintos niveles, por ejemplo a nivel molecular, celular y de sistemas en el campo de las neurociencias cognitivas, y a nivel de las ciencias del comportamiento. Debido a la complejidad de los problemas que plantea la arquitectura genética del comportamiento, entran también en juego la informática y los modelos computacionales. Dada la multiplicidad de disciplinas implicadas en la elucidación de la complejidad estructural y funcional del cerebro, de su desarrollo y de su plasticidad o capacidad para evolucionar a lo largo de la vida, cabe prever que la genética se convertirá en un arma de investigación cada vez más poderosa, y ello transformará profundamente la práctica clínica.

La notoria complejidad observada a nivel genético abunda en algo que los investigadores clínicos constataron ya hace tiempo, a saber, la enorme heterogeneidad de las posibles entidades diagnósticas presentadas en los manuales diagnósticos. El hecho de poder disponer por fin de genotipos de determinados loci como variables independientes debería permitirnos clasificar mejor las enfermedades mentales. La combinación del conocimiento de la función de los genes y la búsqueda de factores de riesgo ambientales modificables habrá de contribuir a reorientar la epidemiología psiquiátrica hacia el concepto de riesgo y, por consiguiente, hacia la posibilidad de prevenir la aparición o el agravamiento de las enfermedades o las discapacidades conexas.

Los continuos avances de las investigaciones genéticas deberían conducir a importantes innovaciones terapéuticas. Los investigadores son cada vez más conscientes de la influencia del ADN en la estructura y función de las células y de sus principales herramientas, las proteínas, y de cómo, a su vez, las proteínas dirigen o influencian los procesos de desarrollo neural que determinan los complejos circuitos cerebrales. Sabiendo que las variaciones de la secuencia nucleotídica de los genes pueden influir no sólo en su función sino también en el momento, el tipo de célula o el lugar del organismo en que esa función se exprese, los investigadores pueden empezar a desentrañar de qué manera pueden incidir en el comportamiento esas variantes que afectan a la arquitectura o la adaptabilidad de los neurocircuitos.

Una aplicación clave de la genética molecular para el desarrollo de tratamientos contra las enfermedades mentales consiste en la posibilidad de identificar productos de los genes que puedan utilizarse como dianas de medicamentos u otras intervenciones dirigidas a procesos fisiopatológicos específicos. Las investigaciones sobre la enfermedad de Alzheimer ilustran la tarea que nos espera. Después de identificar varios genes de riesgo en un subtipo mendeliano de la enfermedad, el denominado Alzheimer familiar de aparición precoz, diversos investigadores descubrieron que algunas enzimas de escisión de proteínas, o proteasas, podían al parecer producir fragmentos tóxicos del producto normalmente benigno de los genes de riesgo, esto es, la proteína precursora del beta-amiloide. Este descubrimiento ha dado lugar a una intensa actividad para desarrollar inhibidores de esas peligrosas proteasas. Aunque la genética de los trastornos mentales comunes es mucho más compleja que la de la enfermedad de Alzheimer familiar de aparición precoz, las estrategias de genética molecular se pueden aplicar igualmente a la búsqueda de un punto de intervención directa en la fisiopatología de las enfermedades mentales, así como en su tratamiento, curación y prevención.

References

1. **Kimura M et al.** Activity of primate putamen neurons is selective to the mode of voluntary movement: visually guided, self-initiated or memory-guided. *Experimental Brain Research*, 1992, **89**: 473–477.
2. **Woolf CJ, Decosterd I.** Implications of recent advances in the understanding of pain pathophysiology for the assessment of pain in patients. *Pain*, 1999 (Suppl. 6): 141–147.
3. **Berke J, Hyman SE.** Addiction and the molecular mechanisms of memory. *Neuron*, 2000, **25** (in press).
4. **Hyman SE.** The neurobiology of mental disorders. In: Nicholi AM, ed. *The Harvard guide to psychiatry,* 3rd edition. Cambridge, MA, The Belknap Press of Harvard University Press, 1999.
5. **Reber PJ, Squire LR.** Parallel brain systems for learning with and without awareness. *Learning and Memory*, 1994, **1**: 217–229.
6. **Damasio AR.** Emotion in the perspective of an integrated nervous system. *Brain Research Brain Research Reviews*, 1998, **26**: 83–86.
7. **LeDoux J.** Fear and the brain: where have we been, and where are we going? *Biological Psychiatry*, 1998, **44**: 1229–1238.
8. **Braver TS, Cohen JD.** Dopamine, cognitive control, and schizophrenia: the gating model. *Progress in Brain Research*, 1999, **121**: 327–349.
9. **Craddock N, Jones I.** Genetics of bipolar disorder. *Journal of Medical Genetics*, 1999, **36**: 585–594.
10. **Kendler KS et al.** Independent diagnoses of adoptees and relatives as defined by DSM-III in the provincial and national samples of the Danish Adoption Study of Schizophrenia. *Archives of General Psychiatry*, 1994, **51**: 456–468.
11. **McGuffin P et al.** A hospital-based twin register of the heritability of DSM-IV unipolar depression. *Archives of General Psychiatry*, 1996, **53**: 129–136.
12. **Risch NJ et al.** A genomic screen of autism: evidence for a multilocus etiology. *American Journal of Human Genetics*, 1999, **65**: 493–507.
13. *Genetics and mental disorders: report of the National Institute of Mental Health's Genetics Work-Group*. Rockville, Maryland; National Institute of Mental Health; 1998 (http://www.nimh.nih.gov/research.htm).
14. **Hyman SE.** Introduction to the complex genetics of mental disorders. *Biological Psychiatry*, 1999, **45**: 518–521.
15. **Barondes SH.** An agenda for psychiatric genetics. *Archives of General Psychiatry*, 1999, **56**: 549–552.
16. **Frankel WN, Schork NL.** Who's afraid of epistasis? *Nature Genetics*, 1996, **14**: 371–373.

17. **Suddath RL et al.** Anatomical abnormalities in the brains of monozygotic twins discordant for schizophrenia. *New England Journal of Medicine*, 1990, **322**: 790.
18. **Amir RE et al.** Rett syndrome is caused by mutations in X-linked MECP2 encoding methyl-CpG-binding protein 2. *Nature Genetics*, 1999, **23**: 185–188.
19. **George-Hyslop PH.** Molecular genetics of Alzheimer's disease. *Biological Psychiatry*, 2000, **47**: 183–199.
20. **Lander ES, Schork NJ.** Genetic dissection of complex traits. *Science*, 1994, **273**: 2037–2048.
21. *The ICD-10 classification of mental and behavioural disorders: diagnostic criteria for research.* Geneva, World Health Organization, 2000.
22. *Diagnostic and statistical manual of mental disorders,* 4th edition. Washington DC, American Psychiatric Association, 1994.
23. **Tsuang MT, Faraone SV.** *The Genetics of Mood Disorders.* Baltimore, MD, John Hopkins University Press, 1990.
24. **Kendler KS et al.** A population-based twin study of major depression in women: the impact of varying definitions of illness. *Archives of General Psychiatry*, 1992, **49**: 257–266.
25. **Kruglyak L.** Prospects for whole-genome linkage disequilibrium mapping of common disease genes. *Nature Genetics*, 1999, **22**: 139–144.
26. **Cargill M et al.** Characterization of single-nucleotide polymorphisms in coding regions of human genes. *Nature Genetics*, 1999, **22**: 231–238.
27. **Risch NJ, Merikangas K.** The future of genetic studies of complex human diseases. *Science*, 1996, **273**: 1516–1517.
28. **Levy DL et al.** Eye tracking and schizophrenia: a selective review. *Schizophrenia Bulletin*, 1994, **20**: 47–62.
29. **Cade JFJ.** Lithium salts in the treatment of psychotic excitement. *Medical Journal of Australia*, 1949, **36**: 349–352.