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Reading About

Psychiatric Genetics

"Human Genetics has sparked a revolution in medical science on the basis of the seemingly improbable notion that one can systematically discover the genes causing inherited diseases without any prior biological clue as to how they function" (Lander & Schork, 1994).

Every psychiatrist should read and give careful consideration to the above sentence. Within the next few years susceptibility genes for psychiatric disorders will be discovered. This will have a major impact on the practice of clinical psychiatry and it is important for all clinicians, both in their initial training and in their continuing professional development, to keep abreast of developments, even though it is well known that excessive exposure to terms such as 'lod score', 'DNA polymorphism', or 'cloning vector' can induce dysphoria in susceptible individuals. The aim of this article is to provide a user-friendly guide to reading about the rapidly expanding field of psychiatric genetics with particular emphasis on developments in molecular genetics. I hope the reader will pick up a flavour of the exciting advances within this area of research but the article is not intended to be an exhaustive review nor a critical academic appraisal of other work. References cited will often fulfil these additional functions and provide branches to other topics.

The article is intended to be of use to a variety of readerships. Trainees and general readers are likely to find it most useful to concentrate on reviews supplemented by interesting recent papers but additional references are included that should satisfy those with a more specialised agenda. Much of the discussion focuses on the functional psychoses because the genetic contributions to these disorders are relatively large and because much recent work has concentrated upon them. Successes in psychiatric genetics are, therefore, likely to come first for these disorders. However, the principles and methods of modern genetics are equally applicable to the other psychiatric disorders for which genes convey susceptibility and it should be recognised that research is also ongoing in these areas.

General overview of psychiatric genetics

Seminars in Psychiatric Genetics (McGuffin *et al*, 1994) in the College Seminars series provides an excellent introduction to all aspects of psychiatric genetics. I would commend this concise text to all psychiatrists as a useful source of basic information about classical and molecular methodology in psychiatric genetics as well as providing an overview of the main findings from family, twin and adoption studies of the major psychiatric disorders. If the reader wants a single, inexpensive reference text, this is it. The inevitable weakness of any textbook is that it cannot give a guide to the 'cutting edge' of research. However, issue 2 of volume 52 of the *British Medical Bulletin* (published July 1996) is devoted to biological psychiatry and includes two articles on psychiatric genetics which are, for the moment, as up-to-date as is possible. Craddock & Owen (1996) review 'Modern Molecular Genetic Approaches to Psychiatric Disease' and Sham (1996) reviews 'Psychiatric Genetic Epidemiology'. Together, this book and these two articles will provide a readable, comprehensive and up-to-date overview of the main areas of psychiatric genetics. In the sections that follow, the reader will be directed both to references that provide more thorough introductions to or overviews of specific topics and to recent papers reporting interesting findings.

Behaviour genetics

Psychiatric genetics is the study of the inheritance of human psychopathology and, thus, represents one aspect of the broad field of behaviour genetics. An excellent introductory textbook, *Behavioral Genetics. A Primer*, by Plomin *et al* (1990) reviews the methodology and main findings in the field of animal and human behaviour and includes a brief section devoted to psychiatric genetics. Three review articles in the journal *Science* help to place psychiatric genetics within this broader context of

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behaviour genetics. First, Plomin (1990) summarises the main findings of animal behavioural genetic research: (a) most behaviours are influenced by genes; (b) for most behaviours several genes are involved, and (c) for most behaviours environmental factors are also important. Second, Bouchard *et al* (1990) summarise the findings of the Minnesota study of twins reared apart which shows that genetic factors are important in determining many human behaviours including IQ, temperament, occupation and leisure time interests and social attitudes. Third, Plomin *et al* (1994) review research on the genetic basis of complex human behaviours, including psychiatric disorders, and discuss approaches to the identification of genes (so-called quantitative trait loci or QTLs) that control dimensional or quantitative traits.

Classical genetics: family, twin and adoption studies

Family, twin and adoption studies are the work horse of classical genetics. Many such studies have been conducted for psychiatric disorders throughout this century and they provide evidence of genetic predisposition to many psychiatric disorders including schizophrenia, bipolar disorder, unipolar depression, panic disorder, obsessive–compulsive disorder, personality disorder, alcoholism and Alzheimer's disease. References for many of the relevant studies can be found in McGuffin *et al* (1994). More detailed reviews of the classical genetics of schizophrenia can be found in the monograph by Gottesman (1991) and for affective disorders in the monograph by Tsuang & Faraone (1990). Recently published high quality family studies that are not reviewed in these monographs include the Mainz family study of functional psychosis (e.g. Maier *et al*, 1993), the Roscommon family studies of schizophrenia (e.g. Kendler *et al*, 1993) and the Camberwell Collaborative Psychosis Study (e.g. Sham *et al*, 1994). Recent important twin studies include the study of unipolar disorder in the Maudsley twin series by McGuffin *et al* (1996) and Kendler and colleagues' studies of the Virginia twin series which demonstrate the complex structure of genetic predisposition to a range of psychiatric disorders including major depression and anxiety (e.g. Kendler *et al*, 1992; Kendler *et al*, 1995).

Mode of inheritance

Disorders for which genes are known or suspected to play a role in determining susceptibility but for which there is no simple pattern of inheritance are known as 'complex genetic disorders'. This category includes many common familial diseases including type 1 diabetes mellitus, asthma, rheumatoid arthritis, ischaemic heart disease and several psychiatric disorders. The hallmark of complex diseases is that, in spite of evidence for the involvement of genes, inheritance does not follow simple Mendelian patterns. The various genetic mechanisms that may lead to complex patterns of inheritance are discussed in Craddock & Owen (1996). At least for bipolar disorder and schizophrenia, it seems most unlikely that single gene mechanisms account for the majority of cases of disease and recent analyses of rates of illness in relatives of probands show that mechanisms involving several (or many) genes that interact to determine disease susceptibility are more plausible (McGue & Gottesman, 1989; Risch, 1990; Craddock *et al*, 1995).

Chromosome studies

Identification of a chromosome abnormality associated with disease can provide an important clue as to the location of the disease susceptibility gene. The literature has been reviewed recently by Bassett (1992) for schizophrenia and Craddock & Owen (1994) for bipolar disorder. No consistent findings have yet emerged from chromosome studies but there have been important recent methodological advances in cytogenetics, such as the introduction of fluorescent *in situ* hybridisation (FISH), which make possible the detection of small deletions or other abnormalities in chromosomes. A recent finding of interest to psychiatric geneticists is discussed by Murphy & Owen (1996). Velo-Cardio-Facial Syndrome (VCFS), a syndrome comprising developmental abnormalities, mental handicap and predisposition to functional psychosis, is caused by micro-deletions on chromosome 22 which raises the possibility that a susceptibility gene for functional psychosis resides in the deleted region, thus providing a candidate region on which to target molecular genetic studies.

Molecular genetics

The advances in molecular genetics over the last 15 years have made it possible to investigate the pathophysiology of diseases with a genetic basis using purely genetic approaches that do not require prior knowledge about disease pathophysiology. This has obvious attractions for the study of

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psychiatric disorders. The advances have been rapid and dramatic with several revolutions in technology, including the introduction of the polymerase chain reaction (PCR) and more recently the development of semi-automated fluorescent sequencing and genotyping methods. An excellent, readable introduction to modern molecular genetics aimed at the intelligent layman is given in Bodmer & McKie's *The Book of Man* (1995). A concise account of methods available to modern molecular geneticists is given by Nicholl (1994), and an authoritative but readable introduction is given by Watson *et al* (1992). Strachan (1992) provides an excellent short primer on *The Human Genome* and a detailed, up-to-date overview of *Human Molecular Genetics* (Strachan & Read, 1996). As mentioned earlier, a single chapter introduction to modern molecular genetic methods aimed at psychiatrists is given by Craddock & Owen (1996). A useful glossary of important terms used in molecular genetics appeared in a recent issue of the *Drugs and Therapeutic Bulletin* (Anonymous, 1996).

The developments in molecular genetics are taking place within the context of the Human Genome Project, a large collaborative international initiative aimed at identifying and sequencing all human genes. The nature and scope of this project is described by Watson (1990). At each stage targets have been reached earlier than originally anticipated and it is predicted that the project will be completed successfully within the opening few years of the next century (Jordan & Collins, 1996). Some idea of the immense progress to date can be gained by leafing through the *Genome Directory* which was recently published as a supplement to the journal *Nature* (supplement to Volume 377, 28 September 1995).

Genetic epidemiology

'Genetic epidemiology' refers to the study of aetiology, distribution and control of disease in groups of relatives, and of the inherited causes of disease in populations. It is the term usually used to describe the statistical approaches to the genetics of complex diseases and represents an interface between quantitative genetics and epidemiology. Khoury *et al* (1993) provide the standard introductory text to genetic epidemiology and Sham (1996) presents a single chapter review of methods and results applicable to adult psychiatric disorders. A broad based overview of quantitative genetics is provided by Falconer (1989) in his classic *Introduction to Quantitative Genetics*. A comprehensive and up-to-date review of the methodology and sophisticated statistical modelling applied to family and twin studies is provided by Neale & Cardon (1992).

Linkage and association studies

Linkage and association studies using DNA markers are the work horse of modern psychiatric genetics. Linkage studies use families in which more than one member is affected by disease whereas association studies use unrelated affected individuals and appropriate control individuals. A simple introduction to the principles of linkage analysis is provided by Yates & Connor (1986) in a review article in the *British Journal of Hospital Medicine*. (This is unlikely to induce dysphoria except in the most susceptible individuals.) The standard introductory text to linkage analysis is Jurg Ott's book *Analysis of Human Genetic Linkage* (Ott, 1991) (not recommended for the casual reader). A comprehensive review article discussing the methodology of association studies is given by Cooper & Clayton (1988). A review of methodology and statistical analysis of linkage and association studies of complex disorders can be found in the authoritative review articles by Lander & Schork (1994) and by Lander & Kruglyak (1995). An important recent refinement in association studies is use of family based association methods in which the parents of a proband can be used to provide a well matched control sample. Several experimental strategies and statistical tests of association have been proposed using these approaches and have recently been reviewed by Schaid & Sommer (1994). An experimental paradigm, proposed by Sobell *et al* (1992), which is likely to become increasingly important in psychiatric genetics involves the detection of Variations Affecting Protein Structure or Expression (VAPSE) in candidate genes for psychiatric illness which are then used in association studies to determine if these genetic variations affect disease susceptibility. An introductory discussion of the application of linkage and association methods to psychiatric disorders is given in Craddock & Owen (1996), Sham (1996) and McGuffin *et al* (1994).

Studies of functional psychoses

Early linkage studies of functional psychosis used very large families and were based on the implausible assumption that all disease was caused by a single major gene. In the late 1980s there were several high profile claims of linkage published in the journal *Nature*; Baron *et al* (1987) and Egeland

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et al (1987) for bipolar disorder and Sherrington *et al* (1988) for schizophrenia. Other workers were unable to replicate these findings in other families and eventually in each case the original group published updated and extended analysis of their own data in which the significant evidence of linkage vanished (Kelsoe *et al*, 1989; Baron *et al*, 1993; Mankoo *et al*, 1991). The reason for these dramatic reversals in findings included: (a) family members originally diagnosed as unaffected became ill for the first time during follow-up; (b) new family members were examined who did not show evidence for linkage, and (c) additional DNA markers were examined which reduced the evidence for linkage. After initial pessimism following these disappointments there has been a move towards use of smaller families (particularly affected sibling pairs) and of analytic methods that are less sensitive to diagnostic changes or errors.

Many groups around the world have been conducting molecular genetic studies of the functional psychoses and promising linkage findings are beginning to emerge. For bipolar disorder these include: chromosome 4 (Blackwood *et al*, 1996); chromosome 12 (Dawson *et al*, 1995); chromosome 18 (Berrettini *et al*, 1994; Stine *et al*, 1995; Freimer *et al*, 1996); chromosome 21 (Straub *et al*, 1994), and the X chromosome (Pekkarinen *et al*, 1995). For schizophrenia these include chromosome 6 (Moises *et al*, 1995; Schwab *et al*, 1995; Straub *et al*, 1995); chromosome 8 (Pulver *et al*, 1995); chromosome 13 (Lin *et al*, 1995), and chromosome 22 (Schizophrenia Collaborative Linkage Group (chromosome 22), 1996). The encouraging pattern is of multiple research groups finding modest evidence for linkage in similar genomic regions in their individual data sets. Undoubtedly at least some of the regions of current interest will eventually be proven to harbour disease susceptibility genes. The current 'best bets' are chromosome 18 for bipolar disorder and chromosome 6 for schizophrenia.

The field is moving rapidly and interested readers will need to keep an eye on new publications. It is worth noting that most psychiatric genetic research appears in non-psychiatric journals although significant advances are likely to be described in editorials or commentaries in mainstream psychiatric journals. Association studies are an important complement to linkage studies, as discussed in the editorial by Owen & McGuffin (1992) and are likely to play an increasingly important role in future molecular genetic research in psychiatry. To date no well substantiated positive findings have emerged from association studies although very promising early reports suggesting that the serotonin 5-HT_{2A} receptor may be involved in predisposition to schizophrenia are given by Inayama *et al* (1996) and Williams *et al* (1996).

Alzheimer's disease: a taste of the future for genetics of 'functional' psychiatric disorders

Fifteen years ago many people would have claimed that genes had little to do with Alzheimer's disease. So far three genes have been identified, mutations in which can cause early onset Alzheimer's disease (Goate *et al*, 1991; Sherrington *et al*, 1995; Rogaev *et al*, 1995), and an additional locus (ApoE) has been identified that influences susceptibility to late onset Alzheimer's disease (e.g. Corder *et al*, 1993). The state of this exciting field is reviewed by Sandbrink *et al* (1996) but developments are rapid, with an additional susceptibility locus for late onset disease recently reported (Wragg *et al*, 1996), although this awaits confirmation. Linkage studies have played the major part in locating the genes involved in early onset disease whereas association studies have been crucial in identifying loci involved in later onset disease.

It is worth noting that genetic investigation of Alzheimer's disease has some advantages over study of 'functional' psychiatric disorders: the disease can be confirmed pathologically and a small number of early onset families exist that have clear-cut simple patterns of inheritance. This explains why Alzheimer's genetics is ahead of genetic research in functional disorders. However, like bipolar disorder and schizophrenia, late onset Alzheimer's disease is a complex genetic disease and the current rapid progress of Alzheimer research provides a foretaste of the likely future for 'functional' psychiatric disorders.

Dynamic mutations

A current 'hot topic' within psychiatric genetics is the possibility that so-called dynamic mutations may play a role in susceptibility to schizophrenia and bipolar disorder. For several neurological/neuropsychiatric diseases, such as Huntington's disease, myotonic dystrophy and fragile X syndrome, it has been demonstrated that DNA sequences of trinucleotide repeats expand as they are transmitted through generations and produce disease once a certain threshold has been exceeded. The phenomenon of genetic 'anticipation' (progressively more severe disease and/or earlier age at onset as the disease is transmitted through successive

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generations) occurs in these diseases and it has been found that trinucleotide repeat expansion is the mechanism responsible. Anticipation was originally described with reference to psychiatric rather than neurological disorders (Mott, 1910) and has been reported in some recent studies of bipolar disorder (e.g. McInnis *et al*, 1993) and schizophrenia (e.g. Bassett *et al*, 1994) leading to the hypothesis that trinucleotide repeat expansion may play a role in these disorders (reviewed by O'Donovan & Owen, 1996). In agreement with this hypothesis, association studies have been consistent in demonstrating that trinucleotide repeat sequences are significantly larger in bipolar patients compared with controls (Lindblad *et al*, 1995; O'Donovan *et al*, 1995; O'Donovan *et al*, 1996) and in schizophrenics compared with controls (O'Donovan *et al*, 1995; Morris *et al*, 1995; O'Donovan *et al*, 1996). These findings are very promising but the aetiological significance of trinucleotide repeat expansion in bipolar disorder and schizophrenia can only be verified when genes containing enlarged repeats are themselves identified.

Impact of molecular genetics on clinical psychiatry

Over the coming years susceptibility genes for several psychiatric disorders will be identified. This will lead to dramatic improvements in the understanding of the pathophysiology of these disorders and will enable the development of more rational and specific therapies as well as the possibility of preventing illness developing in some susceptible individuals. Clinical psychiatry in the 21st century is likely to be revolutionised by these developments. Psychiatrists will need to familiarise themselves with the various practical and ethical issues which will arise from these research advances. A thoughtful discussion of these issues is provided by Farmer & Owen in the *British Journal of Psychiatry* (1996).

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