Psychiatry and the 'new genetics': hunting for genes for behaviour and drug response*

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The understanding that genes are important in determining both normal and abnormal behaviour has emerged largely through increasingly sophisticated investigations into their inheritance and particularly through twin studies. As a result, we can apply a rough rule of thumb that about half of the variation we see for the major behavioural disorders in the population results from differences in the genes we share. The overall picture emerging is one in which complex behaviour is determined by a wide range of factors, some of them environmental and some genetic. Each of the latter is presumed to contribute individually only a small amount, but by acting in concert with environmental triggers they can have an enormous impact on the final phenotype. Because each factor adds to the overall combination of predisposing factors, they are referred to as quantitative trait loci (QTLs). Such QTLs provide a challenging quarry for psychiatry in the post-genomic era. The benefits of the human and other genome projects can be harnessed to enable extensive scans of the chromosomes to detect tell-tale patterns of altered genes in affected individuals and to follow these through further at the level of gene expression and protein product.

THE SEARCH FOR GENES INFLUENCING BEHAVIOUR

In this editorial we will describe three methods of behavioural gene hunting.

(a) *Coordinated pathway genotype analysis* is an efficient methodology enabling a simultaneous survey of several genes, such as within the serotonin and dopamine transmitter systems. This has been successful in detecting potential gene variants associated with anxiety and depression through the GENESiS programme (Genetics and Environmental Nature of Emotional States in Siblings) (e.g. Eley *et al* 2004). Furthermore, when coupled with careful evaluation of life events of affected individuals, it has demonstrated the need to include environmental measures in association studies. Both antisocial behaviour (in males) and depression (in males and females) have been linked in our studies, which were carried out within the Dunedin longitudinal cohort programme, to low-transcription variants of neurotransmitter genes (monoamine oxidase and serotonin transporter, respectively), but only for those individuals subjected to stressful early life environments (Caspi *et al*, 2002, 2003).

(b) *Genome-wide linkage scans.* When searches extend beyond the obvious candidates implicated in neurotransmitter pathways, genome scans employing linkage or association strategies are necessary. Linkage is systematic but not powerful. With just 300–400 markers it is possible to search the genome for genes influencing a behavioural disorder because each marker can scan up to ten million base pairs for a gene of large effect. Linkage is inefficient at detecting genes of small effect but can identify chromosomal regions harbouring potential candidate genes. A recently completed genome-wide linkage scan employing concordant and discordant sibling pairs (GENESiS) has identified several interesting chromosomal regions that embrace genes implicated in anxiety and depression. Encouragingly, these appear to replicate observations from other studies and now represent targets for detailed investigation (Nash *et al*, 2004).

(c) *Genome-wide association studies.* Allelic association looks for associations between marker alleles and the trait in the population, rather than within families, and is more powerful for detecting QTLs of small effect. Allelic association scans the affected individuals for DNA segments retaining the pattern of genetic markers embracing an ancestral disease-predisposing mutation or QTL, a pattern not shared by non-affected individuals. In the population, recombination breaks up alleles for a marker and a QTL unless the marker and the QTL are very close. This means that to detect such diagnostic allele pattern differences, a very large number of markers are required. The most recent estimates indicate that between 100 000 and 1 000 000 markers may be required for an exhaustive sweep of the genome for all QTLs contributing to a disorder. We have adopted a pragmatic approach in devising strategies for incrementally increasing the number of markers employed, such as pooling strategies in which DNA from hundreds of individuals is combined and the allele frequencies of the group are estimated. We have extended the pooling approach to examine a series of presumptively functional non-synonymous single nucleotide polymorphisms (SNPs) in candidate genes, employing a multi-stage strategy with some success (Butcher *et al*, 2004*a*). Most recently, we have investigated the potential of combining microarray technology with pooling to scan 10 000 SNP markers on hundreds of individuals in a single experiment (Butcher *et al*, 2004*b*). With the new generation of microarrays, this will provide the basis to scan 100 000 SNPs on pools of DNA, thereby breaking the theoretical barrier to the detection of QTLs of small effect size that contribute to major behavioural disorders.

Our molecular studies also have been employed to investigate the contribution of sex chromosomes to determining gender differences in behaviour, by examining discordance in phenotypes between male and female, monozygous or dizygous twin pairs and through the use of microarrays to examine the expression differences of X chromosomal genes in males and females (Craig *et al*, 2004; Loat *et al*, 2004). These studies have drawn attention to the significance of X-linked QTLs in the development of language and

cognition skills as a topic for future in-depth investigations.

PHARMACOGENETICS

When molecular approaches of this type are extended to understand individual variation in response to drug treatments, we enter the field of pharmacogenetics or pharmacogenomics.

Not everyone responds in the same way to the same dose of the same medication. This is dependent on a range of different factors, including age, organ function (in particular, renal and hepatic), psychological factors (most apparent in the placebo response), drug interaction and genetic factors. Pharmacogenetics is concerned with the role of genetic factors in predicting both drug response and potential adverse effects (Basu *et al*, 2004). The pre-genomic era saw the study of how variants at the DNA level related to drug response. This required some prior knowledge of either the drug's pharmacokinetic (i.e. what the body does to the drug in terms of the drug's metabolism) or pharmacodynamic (i.e. what the drug does to the body) profile so that 'candidate genes' could be studied. For example, if a drug's pharmacokinetic profile is at least partially understood, then the genes coding for the relevant drug-metabolising enzymes, such as cytochrome P450 1A2 (CYP1A2) and clozapine, would be suitable candidates to study (Aitchison *et al*, 2000). Similarly, for a drug's pharmacodynamic profile, polymorphisms within genes coding for the relevant receptors or transporters may be associated with different therapeutic outcomes. Patients who display marked intolerance to certain medications may be fruitful subjects for investigation. For example, a mutation screening study in a monozygotic twin pair, both of whom were affected with schizophrenia and had multiple intolerances to various antipsychotics, revealed that the twins had two novel alleles for the gene encoding CYP2D6, which metabolises many drugs used in psychiatry (details available from the authors upon request). A pilot genetic association study of genes *CYP2D6* and *DRD2* (the gene encoding the dopamine D_2 receptor) and hyperprolactinaemia showed a significant association between a *DRD2* variant and degree of hyperprolactinaemia, which was strengthened by controlling for *CYP2D6* genotype. A larger study of hyperprolactinaemia is in progress.

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PHARMACOGENOMICS

Now that the human genome has been sequenced, however, much pharmacogenetic research is evolving into 'pharmacogenomics', or indeed psychopharmacogenomics (as applied to psychiatry). Pharmacogenomics has been defined as a non-hypothesis-based approach that studies the relationship between whole genome factors (including the expressed transcriptome and proteome) and drug response at cellular, tissue, individual or treatment group level (Aitchison & Gill, 2003). This exciting new field is the latest in drug design, discovery and clinical development.

Antidepressant response is a particular focus of pharmacogenomics research at present. One in five people, at some time in his or her life, suffers from an episode of depression severe enough to warrant antidepressant treatment. However, choosing one antidepressant over another, while considering optimal response with minimum side-effects, is largely a matter of educated guess-work. This means that patients may not get better on the first drug they try, or they may suffer considerable side-effects. Only 40–60% of patients respond to the first antidepressant that they are prescribed, and cessation of medication because of adverse effects is common. A multi-centre integrated project (GENDEP), funded by the European Commission under the Framework 6 Programme, aims to find a way to use information about patients' genes to help doctors decide which antidepressant treatment will work best for which patient and with the minimum side-effects. GENDEP consists of three closely interconnected major themes, with programmes of working being conducted across an 18-member consortium: a large-scale multi-centre human pharmacogenomics study focused on the prediction of therapeutic response to antidepressants and adverse effects; a set of basic science studies using rodent models and *in vitro* experiments; and a programme of work to address the relevant ethical, social and legal issues. It is hoped that this new generation of pharmacogenomic studies will lead to the prediction of response to psychiatric drug treatment, reduction of adverse effects, rational prescribing practices and the identification of new targets for drug discovery.

DECLARATION OF INTEREST

None.

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