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The current and potential impact of genetics and genomics on neuropsychopharmacology

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Abstract
One justification for the major scientific and financial investments in genetic and genomic studies in medicine is their therapeutic potential, both for revealing novel targets for drugs which treat the disease process, as well as allowing for more effective and safe use of existing medications. This review considers the extent to which this promise has yet been realised within psychopharmacology, how things are likely to develop in the foreseeable future, and the key issues involved. It draws primarily on examples from schizophrenia and its treatments. One observation is that there is evidence for a range of genetic influences on different aspects of psychopharmacology in terms of discovery science, but far less evidence that meets the standards required before such discoveries impact upon clinical practice. One reason is that results reveal complex genetic influences that are hard to replicate and usually of very small effect. Similarly, the slow progress being made in revealing the genes that underlie the major psychiatric syndromes hampers attempts to apply the findings to identify novel drug targets. Nevertheless, there are some intriguing positive findings of various kinds, and clear potential for genetics and genomics to play an increasing and major role in psychiatric drug discovery.

1. Introduction

Neuropsychopharmacology continues to search for new and improved treatments for psychiatric disorders, as well as to make more effective and safe use of current medications. It is widely hoped, and often assumed, that genetic information can contribute in both respects, taking advantage of the remarkable technological progress of the past decade. Indeed, one justification and rationale for the massive investments in psychiatric genetics has been the hope that the findings will lead to therapeutic benefits. This review considers the extent to which genetic discoveries have already made a difference to neuropsychopharmacology, and the extent to which they are likely to do so in the next few years. It focuses primarily on current and future drugs for the treatment of schizophrenia, but the principles, problems, and potential which it illustrates apply broadly across neuropsychopharmacology (Malhotra et al., 2012b).

Before proceeding, two prefatory comments are worth making. The first concerns the methods used to find the genetic contributions to drug effects. These have paralleled the approaches taken to finding genes contributing to diseases and other phenotypes. Until recently, most studies were 'candidate gene' or 'pharmacogenetic' in nature, whereby one (or a few) genes, selected on the basis of a plausible relationship to the target or metabolism of the drug were

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investigated to identify allelic variants (mostly single nucleotide polymorphisms [SNPs]) which showed genetic association (i.e. a statistical over-representation) in one group compared to another (e.g. responders vs. non-responders). Whilst the candidate gene approach has produced a wealth of data, and continues to be employed, it has largely been supplanted by pharmacogenomic (i.e. genome-wide) association studies (GWAS), in which hundreds of thousands of SNPs across the genome are assayed simultaneously (Kingsmore et al., 2008; Daly, 2010). The main advantage of a genomics rather than a genetics approach is that the search is unbiased, and not limited to candidate genes. However, because of the large number of statistical tests performed in a GWAS, and the need to control for multiple testing, very large samples (many thousands) are required in order to have sufficient power. To date, only a few pharmacogenomic GWAS have been reported, and all have been much smaller than this. The second comment is that, in addition to SNPs, an important source of genetic variation arises from copy number variants (CNVs, also known as structural variants), in which a length of DNA (from hundreds to millions of nucleotides) is either deleted or duplicated. Major psychiatric disorders, especially schizophrenia and autism, are associated with an increased frequency of CNVs at several genomic loci (Malhotra and Sebat, 2012). Any given CNV is very rare but, if present, can represent a major risk factor. There may also be similar rare but penetrant pharmacogenetic effects of CNVs (e.g., a CNV which involves the dopamine D2 receptor might affect response to antipsychotics), but these have not yet been investigated; as such, this review only considers SNPs.

2. Genetic predictors of efficacy or side-effects of current psychotropic drugs

Genetic factors can affect pharmacodynamics or pharmacokinetics; the former concerns allelic variation in the target of the drug (e.g. receptor, transporter), whereas the latter primarily refers to the cytochrome P450 (CYP) enzymes which metabolise most drugs. It is worth noting however that this does not translate simply into genotype-associated efficacy differences being due to pharmacodynamics factors, and side-effects to pharmacokinetic ones. For example, a drug causing many side-effects (due to slow metabolism and thence high plasma levels) may lead to poor compliance, and thence apparent low efficacy.

2.1. Pharmacogenetics and pharmacogenomics of antipsychotic response

Taking antipsychotics as an example, there have been many hundreds of pharmacogenetic studies relating genotype to their effects and side-effects. Initial enthusiasm was stimulated by Arranz et al., who showed that SNPs in *HTR2A* (the 5-HT2A receptor) and in several other neurotransmitter receptor genes helped predict response to clozapine (Arranz et al., 1995, 2000). However, the many subsequent studies lead to a more sanguine interpretation: a large number of isolated positive findings, a moderate number of studies with at least one independent replication, and a very small number which have been consistently replicated and/or are significant by meta-analysis. This applies both to therapeutic response (see Arranz et al., 2011 for a comprehensive recent review and discussion) and to the common side-effects (Table 1).

The antipsychotic literature also illustrates the fact that, to date, pharmacogenomic studies are limited in number and size. The most notable GWAS are in a subgroup of subjects from the CATIE trial, with positive (or equivocally positive) results regarding SNP correlates of treatment response (McClay et al., 2011), and of metabolic (Adkins et al., 2011) and movement-related (Aberg et al., 2010) adverse effects; the positive GWAS results do not include

Table 1 Genetic associations of selected antipsychotic side-effects: replicated findings from case-control studies, and positive findings from GWAS.

Phenotype, gene, and SNP	>2 positive reports?	Meta-analysis?	GWAS-positive?	Overall evidence
Weight gain				
ADRA2A-1291C/G	Yes	N/A	No	+
GNB3 rs5443	Yes	Trend	No	++
HTR2A 267C/T	Yes	N/A	No	+
HTR2C 759C/T	Yes	Positive	No	+++
Leptin 2548A/G	Yes	N/A	No	++
MC4R rs489693	No	N/A	Yes	+++
MEIS2 rs1568679	No	N/A	Yes	++
Agranulocytosis				
HLA-DRB1	Yes	N/A	No	+
HLA-DRB5	Yes	N/A	No	+
HLA-DQB1	Yes	N/A	No	++
Tardive dyskinesia				
COMT rs4680 158V/M	Yes	Positive	No	++
CYP2D6	Yes	Mixed	No	+
D2R/ANKK1 rs1800497	Yes	N/A	No	+
MnSOD rs4880 9A/V	Yes	Mixed	No	+

The table is based on results presented or summarised in Adkins et al. (2011), Arranz et al. (2011), Arranz and Munro (2011), Lett et al. (2012), Malhotra et al. (2012a) and Risselda et al. (2011), N/A, not available. 'Overall evidence' is a subjective interpretation of the available data, on a + to ++++ scale.

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