Abstracts

FOR GENETICS AND PSYCHIATRY

Given space limitations and varying reprint permission policies, not all of the influential publications the editors considered reprinting in this issue could be included. This section contains abstracts from additional articles the editors deemed well worth reviewing.

Variation in the Gene Encoding the Serotonin 2A Receptor Is Associated with Outcome of Antidepressant Treatment

McMahon FJ, Buervenich S, Charney D, Lipsky R, Rush AJ, Wilson AF, Sorant AJM, Papanicolaou GJ, Laje G, Fava M, Trivedi MH, Wisniewski SR, Manji H

Am. J. Hum. Genet. 2006; 78:804–814

Depressive disorders account for a large and increasing global burden of disease. Although the condition of many patients improves with medication, only a minority experience full remission, and patients whose condition responds to one medication may not have a response to others. Individual variation in antidepressant treatment outcome is, at present, unpredictable but may have a partial genetic basis. We searched for genetic predictors of treatment outcome in 1,953 patients with major depressive disorder who were treated with the antidepressant citalopram in the Sequenced Treatment Alternatives for Depression (STAR*D) study and were prospectively assessed. In a split-sample design, a selection of 68 candidate genes was genotyped, with 768 single-nucleotide—polymorphism markers chosen to detect common genetic variation. We detected significant and reproducible association between treatment outcome and a marker in *HTR2A* (P range 1×10^{-6} to 3.7×10^{-5} in the total sample). Other markers in *HTR2A* also showed evidence of association with treatment outcome in the total sample. *HTR2A* encodes the serotonin 2A receptor, which is downregulated by citalopram. Participants who were homozygous for the A allele had an 18% reduction in absolute risk of having no response to treatment, compared with those homozygous for the other allele. The A allele was over six times more frequent in white than in black participants, and treatment was less effective among black participants. The A allele may contribute to racial differences in outcomes of antidepressant treatment. Taken together with prior neurobiological findings, these new genetic data make a compelling case for a key role of *HTR2A* in the mechanism of antidepressant action.

Continuities and Discontinuities in Psychopathology Between Childhood and Adult Life

Rutter M, Kim-Cohen J, Maughan B

Journal of Child Psychology and Psychiatry 2006; 47(3–4):276

The possible mechanisms involved in continuities and discontinuities in psychopathology between childhood and adult life are considered in relation to the findings from systematic, prospective, long-term longitudinal studies. Findings on schizophrenia, neurodevelopmental disorders, emotional disturbances, antisocial behaviour and substance abuse are used as conditions illustrating the key issues. The overarching themes are then discussed in relation to heterotypic continuity and psychopathologic progression, early age at onset and a range of possible mediating mechanisms—including genetic mediation, 'kindling' effects, environmental influences, coping mechanisms and cognitive processing of experiences. Some of the key research challenges that remain concern the testing of competing hypotheses on mediating processes, the changes involved in adolescence, the transition from prodromal phase to overt schizophrenia and the emergence of adolescent-limited antisocial behaviour. Greater use needs to be made of genetic research strategies and of the testing of possible cognitive processing mediation effects.

Clinical Guidelines for Psychiatrists for the Use of Pharmacogenetic Testing for CYP450 2D6 and CYP450 2C19
de Leon J, Armstrong SC, Cozza KL
Psychosomatics 2006; 47:75–85

Pharmacogenetics has arrived in clinical psychiatric practice with the FDA approval of the AmpliChip CYP450 Test that genotypes for two cytochrome P450 2D6 (CYP2D6) and 2C19 (CYP2C19) genes. Other pharmacogenetic tests, including those focused on pharmacodynamic genes, are far from ready for clinical application. CYP2D6 is important for the metabolism of many antidepressants and antipsychotics, and CY2C19 is important for some antidepressant metabolism. Poor metabolizers (PMs), lacking the enzyme, account for up to 7% of Caucasians for CYP2D6 and up to 25% of East Asians for CYP2C19. Patients having three or more active CYP2D6 alleles (up to 29% in North Africa and the Middle East), are called CYP2D6 ultra-rapid metabolizers (UMs). CYP2D6 phenotypes (particularly PMs) are probably important in patients taking tricyclic antidepressants (TCAs), venlafaxine, typical antipsychotics, and risperidone. The CYP2C19 PM phenotype is probably important in patients taking TCAs and perhaps citalopram, escitalopram, and sertraline. On the basis of the literature and the authors' clinical experience, the authors provide provisional recommendations for identifying and treating CYP2D6 PMs, CYP2C19 PMs, and CYP2D6 UMs. The next few years will determine whether CYP2D6 genotyping is beneficial for patients taking the new drugs aripiprazole, duloxetine, and atomoxetine. Practical recommendations for dealing with laboratories offering CYP2D6 and CYP2C29 genotyping are provided.

Genes for Schizophrenia and Bipolar Disorder? Implications for Psychiatric Nosology
Craddock N, O'Donovan MC, Owen MJ
Schizophrenia Bulletin 2006; 32(1):9–16

It has been conventional for psychiatric research, including the search for predisposing genes, to proceed under the assumption that schizophrenia and bipolar disorder are separate disease entities with different underlying etiologies. These represent Emil Kraepelin's traditional dichotomous classification of the so-called "functional" psychoses and form the basis of modern diagnostic practice. However, findings emerging from many fields of psychiatric research do not fit well with this model. In particular, the pattern of findings emerging from genetic studies shows increasing evidence for an overlap in genetic susceptibility *across* the traditional classification categories—including association findings at *DAOA(G72)*, *DTNBP1 (dysbindin)*, *COMT*, *BDNF*, *DISC1*, and *NRG1*. The emerging evidence suggests the possibility of relatively specific relationships between genotype and psychopathology. For example, *DISC1* and *NRG1* may confer susceptibility to a form of illness with mixed features of schizophrenia and mania. The elucidation of genotype-phenotype relationships is at an early stage, but current findings highlight the need to consider alternative approaches to classification and conceptualization for psychiatric research rather than continuing to rely heavily on the traditional Kraepelinian dichotomy. As psychosis susceptibility genes are identified and characterized over the next few years, this will have a major impact on our understanding of disease pathophysiology and will lead to changes in classification and the clinical practice of psychiatry.

Genomics and the Human Genome Project: Implications for Psychiatry
Kelsoe JR
International Review of Psychiatry 2004; 16(4):294–300

In the past decade the Human Genome Project has made extraordinary strides in understanding of fundamental human genetics. The complete human genetic sequence has been determined, and the chromosomal location of almost all human genes identified. Presently, a large international consortium, the HapMap Project, is working to identify a large portion of genetic variation in different human populations and the structure and relationship of these variants to each other. The Human Genome Project has approached human genetics on a scale not previously seen in biology. This has been made possible by dramatic advances in high throughput technology and bio-informatics. Tools such as gene chips and micro-arrays have spawned an entirely new strategy to examine the function and expression of genes in a

massively parallel fashion. Together these tools have dramatically advanced our knowledge about the human genome. They promise powerful new approaches to complex genetic traits such as psychiatric illness. The goals and progress of the Human Genome Project and the technology involved are reviewed. The implications of this science for psychiatric genetics are discussed.

Ethical Issues in the Use of Genetic Information
Dinwiddie SH, Hoop J, Gershon ES
International Review of Psychiatry 2004; 16(4):320–328(9)

Brittanus . Caesar: this is not proper. Theodotus . How! Caesar . Pardon him, Theodotus: he is a barbarian, and thinks that the customs of his tribe and island are the laws of nature. George Bernard Shaw , Caesar and Cleopatra , Act II Advances in molecular genetics promise to deepen our understanding of the biological basis of human behavior and shed light on the pathophysiology of mental illness. Genetic research is likely to improve our ability to develop somatic treatments for psychiatric syndromes as well as to identify targets for environmental intervention. However, population-screening tests for disorders with multifactorial inheritance may offer little clinical benefit to outweigh their potential for misuse. Relevant legal issues surrounding the use of genetic information in psychiatry include the perceived need for laws to prevent insurance and employment discrimination, and concerns about genetic status as a possible excuse for criminal behavior. Relevant ethical issues include threats to patient privacy and confidentiality and the importance of fairly distributing the benefits and burdens of genetic advances.

Genetic Approaches to the Study of Anxiety
Gordon JA, Hen R
Annual Review of Neuroscience 2004; 27:193–222

Anxiety and its disorders have long been known to be familial. Recently, genetic approaches have been used to clarify the role of heredity in the development of anxiety and to probe its neurobiological underpinnings. Twin studies have shown that a significant proportion of the liability to develop any given anxiety disorder is due to genetic factors. Ongoing efforts to map anxiety-related loci in both animals and humans are underway with limited success to date. Animal models have played a large role in furthering our understanding of the genetic basis of anxiety, demonstrating that the genetic factors underlying anxiety are complex and varied. Recent advances in molecular genetic techniques have allowed increasing specificity in the manipulation of gene expression within the central nervous system of the mouse. With this increasing specificity has come the ability to ask and answer precise questions about the mechanisms of anxiety and its treatment.

Schizophrenia, Epigenetics and Ligand-activated Nuclear Receptors: A Framework for Chromatin therapeutics
Sharma RP
Schizophrenia Research 2004; 72:2–3

Covalent modifications of DNA and its surrounding chromatin constitute an essential and powerful regulatory mechanism for gene transcription. Epigenetics is the study of this regulatory system. There is now strong albeit indirect evidence that epigenetic mechanisms contribute to the pathophysiology of schizophrenia. Furthermore, the discovery that valproic acid, a widely used psychotropic, has powerful epigenetic effects in clinically relevant concentrations suggests new therapeutic possibilities, i.e., drugs that act on chromatin structure. Fortunately, many proteins engaged in these processes, particularly chromatin remodeling, are accessible to pharmacological agents that have a high likelihood of crossing the blood brain barrier. This review will first summarize the essentials of the epigenetic regulatory system, then address the molecular evidence for altered epigenetic mechanisms in schizophrenia, and finally focus on the retinoic acid family of ligand-activated nuclear transcription factors as a likely system for new drug development in the management of schizophrenia-related symptoms.

Genomic Priorities and Public Health
Merikangas KR, Risch N
Science 2003; 302:559–601

Given the continuing difficulty of identifying genes for complex disorders in a robust, replicable manner, and the extensive resources devoted to this effort, it is becoming increasingly important to analyze the relative benefits of genomics research for public health applications and for the understanding of disease pathogenesis. To establish priorities for genetics research, we review and evaluate several characteristics of selected exemplary complex diseases, including phenotypic accuracy, knowledge of specific and nonspecific genetic and environmental risk factors, and population prevalence and impact. We propose that complex diseases with the strongest evidence for genetic etiology, limited ability to modify exposure or risk factors, and high public health impact should have the highest priority for genetics research.

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