Psychiatric genetics – the new era: genetic research and some clinical implications

Sridhar Prathikanti and Daniel R. Weinberger#

Clinical Brain Disorders Branch, Genes, Cognition, and Psychosis Program, National Institute of Mental Health, National Institutes of Health, Bethesda, MD, USA

Impressive advances in the last decade have been made in the genetics and neuroscience of neuropsychiatric illness. Synergies between complex genetics, elaboration of intermediate phenotypes (Egan et al. (2004) Schizophrenia. London: Blackwell) and novel applications in neuroimaging (Bookheimer et al. (2000) N Engl J Med, 343, 450–456) are revealing the effects of positively associated disease alleles on aspects of neurological function. Genes such as NRG-1, DISC1, RGS4, COMT, PRODH, DTNB1, G72, DAAC, GRM3 (Harrison and Weinberger (2005) Mol Psychiatry, 10, 40–68) and others have been implicated in schizophrenia along with 5-HTPR (Ogilvie et al. (1996) Lancet, 347, 731–733; Caspi et al. (2003) Science, 301, 386–389) and BDNF (Geller et al. (2004) Am J Psychiatry, 161, 1698–1700) in affective disorders. As the genetics and complex neurocircuits of these and disorders are being untangled, parallel applications in pharmacogenomics and gene-based drug metabolism are shaping a drive for personalized medicine. Genetic research and pharmacogenomics suggest that the subcategorization of individuals based on various sets of susceptibility alleles will make the treatment of neuropsychiatric and other illnesses more predictable and effective.

Overview

The medical approach to mental illness is changing dramatically in the twenty-first century. Physicians in other areas of medicine are beginning to have in their clinical armamentarium tests to consider unique genetic information in selecting medications and doses of medications for a wide variety of common conditions such as cardiac disease and cancer.1 Similar possibilities for psychiatric practice are closer than ever.

Prior to the discovery of mental illness-susceptibility genes, the biological investigation of psychiatric disorders was confined to pharmacologic manipulations. The treatment of mental disorders focused on dopamine/norepinephrine-serotonin medication combinations, which appear to modulate complex neurocircuitry in the brain. The pharmacological
approach to mental illness is evolving from this manipulation of relatively few targets, mostly neuroreceptors and transporters, to identifying genetic biological markers and mechanistic pathways that underlie the development and function of relevant neurocircuitry.

In the rapidly maturing study of schizophrenia, macroscopic findings have increasingly pointed to compromised functioning of the prefrontal cortex, hippocampus, superior temporal cortex and thalamus. Evidence for this has emerged from numerous studies using neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) and neuropsychological testing. Histological findings in postmortem tissue support the conclusion of subtle changes in the synaptic microcircuitry of these regions, ranging from alterations in the morphology of the dendritic tree to molecular changes at interneuronal synapses and also including associated glial elements. But results vary considerably, as they are likely confounded by clinical heterogeneity, effects of chronic illness and medications. The genetic approach to mental illness may elucidate some of the uncertainties that have plagued the phenomenological study of these disorders.

This article briefly discusses the rationale for studying genes and their importance in medical research. Schizophrenia research examples are cited throughout this article and are intended for illustrative purposes. The concepts of linkage and association are introduced as the entryway to genetic research. Using these basic but powerful tools, several genes have been positively associated with psychiatric illnesses. The inherent weaknesses of these studies have involved primarily the limited sample size and the complex genetics involved. We discuss some approaches to increasing the power of studies and how to approach complex genetic heterogeneity. The final sections discuss the research implications and possible clinical implementations.

Genetics and heredity of illness

Why study genes?

Individual variation is limited to an extremely small percentage of the overall genome. Approximately 99.9% of our DNA sequence is conserved relative to other great apes, leaving only the remaining 0.1% of the human genome to account for the entire diversity of the human species. DNA variation includes insertions and duplications, deletions and single-nucleotide polymorphisms (SNPs) that are the driving force in psychiatric genetics. Genes represent primary mechanisms of disease, and as such they offer unique information about causes of mental disorders that heretofore could only be speculated upon based on their phenomenology.
We can think of genes as the basic instruction blocks of human development and maintenance. Genes code for the expression primarily of protein products at the molecular level that will direct an organism’s development and help sculpt phenotypic characteristics. Should a mutated gene be defective and its product translated into an unintelligible command, the result at the molecular level may manifest in an adverse measurable manner. This result could overwhelm biological compensation and be strongly penetrant, as occurs in mutations that disrupt protein function and tend to present as rare Mendelian disorders, e.g. cystic fibrosis. On the other hand, the effects of genetic variation may not substantially alter protein structure and function, and thus may be much more weakly penetrant at the clinical level. This is especially likely when variation impacts on regulation of gene expression or subtle changes in the translational machinery, as is likely the case in psychiatric disorders.

This scenario for how subtle gene effects are likely to relate to mental illness is illustrated in a landmark longitudinal cohort study of risk for depression. Caspi et al. demonstrated that a functional polymorphism in the promoter region of the serotonin transporter (5-HTT) gene, which effects transcriptional activity and expression of the transporter protein, modulates the influence of stressful life events on predisposition to depression. They evaluated over 900 subjects in the South Island of New Zealand who had been followed-up for over 25 years from birth and found that carriers of the risk allele who experienced several major life stress events in a 5 year period had a 3-fold increase in the probability of having a clinical depressive episode. Their study illustrated three fundamental aspects of genetic risk for depression based on this genetic variation: (1) the gene itself does not cause depression, but biases the effect of negative environmental experience, a so-called gene–environment interaction; (2) the effects of stress during early development may be especially effected by this genotype; and (3) the nonrisk allele appears to confer some resilience to negative environmental experience.

Because genes initiate molecular pathways that mediate biological risk, they are also potential new targets for therapeutic intervention. Genes may lead to new treatment strategies in three major ways: (1) Direct genetic manipulation. Maladaptive genes may be identified as treatment targets. Targeting of genetic modulators such as promoter regions and terminators is plausible, at least in theory. However, these direct genetic approaches are not likely relevant to psychiatry in the foreseeable future, though certain genes, for example NRG1, G72 or their receptors and molecular partners may themselves be targets for the development of new drugs. Animal models are an important approach to using genes to elucidate mechanisms of disease and to find and test for new treatments. (2) Neutralizing pathological gene translation.
Attempts to silence mRNA with antisense RNAs or with siRNA (small interfering RNA) and attempts to neutralize the protein product and secondary messengers are still in the very distant future for psychiatry. However, even if the susceptibility gene itself may not be targetable, some of its protein partners in molecular pathways may be more attractive.

(3) Genetic-based pharmacology. An individual’s unique profile of genetic variation can be used to optimize clinical response. For example, gene-expression profiling has been used to compare the molecular phenotype of individuals who respond to a given treatment in comparison with those who do not. The results of such studies may eventually allow genetically calibrated treatment dosing and minimization of adverse side effects.

Where are we today in Psychiatry?

Genetic research has gained traction in some areas of psychiatric illnesses such as schizophrenia. Currently the genes showing a somewhat positive association with schizophrenia are COMT, Dysbindin, NRG1, RGS4, G72/DAAO, PRODH, DISC1, GRM3, AKT1 and CHRNA7 (see Harrison and Weinberger for a more complete discussion of these genes). New associations are found yearly; yet no single gene appears to carry by itself a major risk effect. Neuropsychiatric illnesses are complex genetic disorders, analogous to heart disease, diabetes and obesity. Family studies indicate that simple Mendelian genetics with one gene–one phenotype are not applicable to psychiatric illnesses; rather, complex genetic models suggest that gene effects may be environmentally triggered, detrimental only in critical contexts (e.g. a development stage), protective, additive or epistatic in their effect on the expression of a phenotype. These models assume that each gene would confer only fractional risk. Hence, no definitive group of genes will comprise an illness, but several heterogeneous susceptibility sets may converge on the pathophysiologic processes that underlie the disease. This is similar to the assumptions about other common medical conditions, such as obesity, adult-onset diabetes, hypertension and many cancers.

Before specific genes were identified, microsatellite-based genome scans were performed in high-density families looking for regions of the genome that showed linkage with the clinical diagnosis. This led to a confusing literature, with some promising linkage regions (e.g. 6p22–24, 8p21–22, 1q21–22 and 10q25.3-q26), but much controversy and dispute. In fact, these regions have now all led to the identification of candidate-susceptibility genes, indicating that linkage has been of value in gene discovery in psychiatry. Despite the initial controversy, the apparent success of linkage studies in schizophrenia is somewhat unexpected, because...
linkage is ill suited to find genes of small effect. The success in schizophrenia appears to reflect that linkage regions contain multiple small-effect genes, accounting for a strong linkage signal across families, even in the context of genetic heterogeneity.2

**Linkage**

As polymorphic DNA markers became available in the 1980s and 1990s, there was enormous interest in collecting large family pedigrees and scanning their chromosomes for evidence of linkage with a disease of interest. The technique was appealing because it required no biologic knowledge about genetic causation and had been successful in finding susceptibility loci in Mendelian disorders. Psychiatry also leaned heavily towards this methodology. It was impractical to procure neoteric brain/neurological tissue. Hence, patient DNA was extracted from WBCs in blood and examined in linkage studies.

Clinicians often use the terms linkage and association interchangeably, but they are not equivalent; in fact they are considerably different. Linkage studies rest on the principle that parents and offspring are separated by only one meiosis per parent, as large blocks of DNA are inherited unchanged by meiotic crossover in the offspring. Thus, a single DNA marker can be used to trace transmission of one of these blocks from parents to offspring. Linkage works because the blocks represent a ‘long-distance’ phenomenon; thus, just a few markers can effectively span large amounts of the genome (23 chromosomal pairs). Linkage studies take several-hundred polymorphic DNA markers and evenly distribute them across the entire genome and observe whether specific parental alleles are inherited within a family by ill offspring, i.e. the marker alleles co-segregate with illness within the family. If certain markers show this pattern across families more than would be predicted by chance, the marker is said to show linkage to the clinical phenotype and presumably to the gene responsible for it. These markers are usually microsatellites (regions within DNA where short sequences of nucleotides – A,T,G and C are tandemly repeating), but they also may be SNPs. Linkage studies are usually conducted using the DNA from extended families (though sib pairs also can be used in linkage studies) and measures allele sharing within families.

The majority of positive findings of specific genes, such as Dysbindin (6p22), NRG1 (8p12–21), RGS4 (1q21–22), G72/DAAO (13q34/12q24) and PRODH (22q11), were initially investigated based on the original genome scans. Hence, many of the significant genetic findings in psychiatric illness have resulted from a refinement of these initial scans, which were initially greeted with scepticism.
Association

Association studies are predominantly case–control studies in large, unrelated populations, though they also can be performed in families. Whereas linkage is the study of the relationship of a genetic locus with a phenotype, association is the study of the relationship of a specific allele within a specific gene with a phenotype. Association studies centre on ancestral chromosomes and an initial ancestral mutation in the DNA. The founders of an early population would include an individual who introduced the disease to that population – who had a ‘founder mutation’ that would be responsible for a specific illness. This DNA mutation would be passed down across hundreds of generations in the population. Most of these mutations are in the form of SNPs, which are transformations of one nucleotide into another, e.g. C→T. An SNP presumably emerged in an ancestral block of DNA, and largely due to recombination over generations, the size of the contiguous ancestral block shrinks with successive meioses (i.e. generations). This shrinking original sequence is passed down as a ‘small, segmental block’, and other polymorphisms within this same block can serve as potential markers for the nearby etiological disease SNP. These markers are said to be in linkage disequilibrium because they are not independently inherited but travel intact together as a contiguous sequence across generations.

Association is thus a much finer mapping strategy than is linkage. To the extent that the family of human beings is a very large family indeed, association is linkage at very small distance. Association studies identify whether or not an allele of a marker (or a few markers) in a small segment of DNA is itself the disease-causing mutation or is close to it (i.e. in linkage disequilibrium with it). Association studies accomplish this by measuring whether a hypothesized disease allele is more frequent in ill individuals relative to the control population.

The advantage of the association study is that it can detect with smaller sample size weak allelic correlations that are not easily detected with linkage. Association studies are also a strategy for directly testing mutations in a gene and their relationship to the genetic illness. However, the weakness of an association study is that only a very small segment of DNA can be tested at a time.

Increasing sample power and the future of association testing

Since individual gene effects on behaviour and mental disorders are presumably small, current linkage and association studies are generally underpowered in sample size, and techniques are being employed to increase power. The most straightforward approach to increasing sample size is to undertake large, multicentre studies that recruit more families.
This effort is being undertaken in several countries. Because association tests are powerful but narrow, new technology is being created that will greatly increase its application to large areas of the genome. Because association tests are reserved for fine mapping in a very specific DNA segment, it would literally take hundreds of thousands of markers to do an association test across an entire genome. Private companies have developed relatively inexpensive 100K (100,000) ‘SNP chips’ and are looking to create even larger SNP chips approaching 500K–1m SNPs\(^8\) that would allow association testing across the entire genome. Another futuristic endeavour to add power to association studies is the attempt to sequence an individuals’ entire genome (current cost of $50 million) down to $1000 by the National Institutes of Health (NIH) within a decade.\(^9\) This again will result in affordable but powerful cross-genome association tests.

A currently available method to increase power for association studies is by employing haplotypes. A haplotype is a combination of alleles at two or more loci in a region of a single chromosome or the linear, ordered arrangement of alleles on a haploid set of chromosomes that is generally conserved over thousands of generations. A haplotype is an expression of linkage disequilibrium of an intact ancestral block of DNA. Recent studies across world populations have shown that the human genome, despite the many generations that separate unrelated individuals, exists in definable and surprisingly frequent haplotype blocks. However, more recent variants as occurs in ethnic diversification may arise on chromosomes and form new haplotypes that would not have been conserved over as long a time span. This in part also explains haplotype block variation in newer ethnicities emerging from \textit{Homo sapien} founders out of Africa.

The reason haplotypes add power to gene-mapping strategies such as association is because haplotypes subdivide a population into more genetically distinct subgroups. An SNP is by definition biallelic. So, as a method of comparing two populations, e.g. one healthy and one ill, a single SNP can divide the population into only two genetic groups (i.e. one with one allele and one with the other). Because a haplotype will reflect ancestral differences that are more complex allelic combinations, genetic differences in populations can be further elaborated. The other reason haplotypes add power is that fewer SNPs need to be typed. This is because the entire block usually can be defined with only a relatively few of the SNPs that are contained within it, the so-called tag SNPs. Thus, there is the potential to identify heritable traits that consist of multiple SNP variants, by detecting only one or a few SNP in a given haplotype block.\(^8\) The power of haplotypes allows a smaller number of cases to be employed to identify ancestral blocks that are more likely to be strongly related to the original disease-causing mutation in the founder population.
Another technique to simplify the genetics and increase power is by looking for association not at the level of clinical diagnosis but by using intermediate phenotypes or so called endophenotypes. An intermediate phenotype is a measurable risk trait that is presumably causally closer to the pathogenic genotype than the clinical phenotype itself. For example, colonic polyps represent an intermediate phenotype in colon cancer, and the degree of insulin receptor resistance is an intermediate phenotype in the search for diabetes genes.

Intermediate phenotypes in psychiatry are based on similar concepts; however, complex genetic traits such as those studied in mental illness present unique problems which require careful assessment. Every biologic measure is not an intermediate phenotype. The characterization of intermediate phenotypes must in general follow certain principles. Again, schizophrenia is cited here, but it is likely that analogous intermediate phenotypes will be identified as related to mood disorders and to anxiety disorders, as well as other psychiatric conditions. The first of these is that the putative deficits that comprise the intermediate phenotype must be stable over time and trait-like in patients. Second, the deficits should be found in mildly ill but nonpsychotic relatives and also must be found even in some psychiatrically well relatives to establish that these phenotypes are related to risk for illness and not illness itself.

Since siblings share on average 50% of their genes, they will share 50% of the risk alleles, and to the extent that these alleles affect brain biology related to risk for schizophrenia (i.e. intermediate phenotypes), siblings on average should manifest these intermediate phenotypes more frequently than the general population, even if they do not share clinical illness. The two key concepts here are namely the fulfilment of the heritability criteria of the trait, which in turn increases the relative risk for the siblings. The third criteria is that a valid risk indicator may be milder or less common in other disorders or in the relatives of individuals with other disorders, depending on whether the intermediate phenotype is specific for schizophrenia. However, there is no strong basis for assuming that this must be the case.

Intermediate phenotypes measure the neurobiology underlying the genetics of the illness. They measure the more direct effects of susceptibility alleles, with individual loci sharing a larger percent of the phenotypic variance measured. This is a more accurate way to ‘concentrate the alleles’ or genes for subclassification rather than relying on the complex spectrum of observed clinical phenotypes. Geneticists can further test these segregated samples for a more definitive disease-causing locus. This technique in principle should increase the power of linkage and association while decreasing the sample size required.
In schizophrenia research, several clinical measures have been found to be consistent with the concept of intermediate phenotypes. These include executive cognitive deficits, various electroencephalogram (EEG)-evoked potential abnormalities and other physiological deficits related to cortical information processing (e.g. inefficient cortical activity measured with fMRI). In an illustrative example of when intermediate phenotypes have been utilized to help in gene discovery related to schizophrenia, Egan et al. studied a large sample of patients, their healthy siblings and controls and showed that the valine allele at codon 108 of the COMT gene, an allele weakly and inconsistently associated with schizophrenia, strongly predicted abnormal prefrontal brain function across all the samples. The pattern of abnormal prefrontal function was analogous to that which had been identified earlier in patients with schizophrenia and in their healthy siblings, suggesting that it was a biological reflection of genetic risk for schizophrenia (i.e. an intermediate phenotype). Egan et al. then showed that the COMT valine allele was also weakly associated with schizophrenia. This was one of the first validated experiments of using intermediate phenotypes and ascertaining genetic correlation in psychiatry to clarify how a gene related to the complex clinical diagnosis.

In another example, Egan et al. demonstrated that a mutation in the GRM3 gene, another allele that had been weakly but inconsistently associated with schizophrenia, had a measurable but weak effect on cognitive functioning and was a risk factor for schizophrenia. Focusing on their most positively associated SNP, they studied its effects on several specific endophenotypes, including abnormalities of specific cognitive processes and the fMRI characteristic of inefficient prefrontal function. A cognitive phenotype is the categorization of subjects based on their ability to perform on various standard cognitive tests. Several measures of cognition are impaired in schizophrenia and appear to be related to genetic risk. GRM3 genotypes were phenotypically scored on (1) three tests of episodic memory, (2) three measures of working memory, (3) one measure of attention, (4) verbal fluency for letters and (5) trails B scores. Significant effects of genotypes on verbal list learning in episodic memory and verbal fluency for letters were noted. Moreover, the intermediate phenotype of inefficient prefrontal function showed association to the risk allele at this SNP even in normal subjects.

The endophenotype approach does have its inherent weaknesses with neuropsychiatric illnesses like schizophrenia. It may be impacted by factors such as medications, chronic medical illness, substance abuse, psychotropic and environmental interactions, making precise characterization of the phenotype in ill subjects difficult. These confounding factors, however, would not affect the expression of the phenotype in well relatives and certainly not in well-screened normal controls. Also, current studies include mostly sib-pair or proband–parent measurements, which do not
allow one to clearly separate environmental impact. Though this carries inherent risk and assumptions, studies\textsuperscript{16} endorse that most familial aggregation of schizophrenia and psychiatric illness is largely genetic and not environmental.

**Bringing genes and neurobiology together**

Perhaps one of the most promising advances in psychiatry has been the coming together of cognitive phenotypes, neuroimaging and genetics. To date, scientists who have tried to study neurobiology, neuroimaging, cognition or genetics in isolation have had difficulty identifying consistent associations in psychiatric disease. However, when correlations are made between these three fields of study, the findings have been provocative. Indeed, when neuroimaging findings are taken in combination with intermediate phenotypes and genetic associations, the findings have been particularly provocative. For example, Bookheimer \textit{et al.}\textsuperscript{17} in a pioneering application of genetics to imaging evaluated the effects of APOE genotypes on the fMRI response in the hippocampus during memory processing and found that APOE4 alleles, the risk allele for Alzheimer’s disease, affected hippocampal physiology even in healthy subjects. Similar synergistic success occurred when Egan \textit{et al.}\textsuperscript{18} showed that a functional polymorphism in the gene for BDNF, which impacts on hippocampal learning and memory in animals, predicted episodic memory performance and hippocampal activity in normal humans. In a final example, Hariri \textit{et al.}\textsuperscript{19} measured fMRI neuroimaging of the amygdala during the perceptual processing of fearful faces and showed that a functional genetic variation of the serotonin transporter, which was later studied by Caspi \textit{et al.} and related to depression, predicted the engagement of the amygdale during the task. These groundbreaking papers illustrate the convergent use of these three methodologies to characterize genetic mechanisms in brain: neuroimaging, genetics and endophenotyping; they may indeed point out an important direction that future research will take.

**Pharmacogenetics/pharmacogenomics**

\textit{Epistasis: unseen interactions}

The emerging list of positively associated genes to one neuropsychiatric illness as seen in schizophrenia suggests that at some level, there is likely a functional convergence of these genes, but the mechanisms remain unclear. Are their critical biological pathways at which the various genes
intersect? How many genes or pathways are sufficient? Clearly, no one gene is necessary in most subjects, but are there combinations that are? Since no one has only one gene, each of the susceptibility genes presumably interact to increase, amplify or mollify the effects of other genes. When genes interact in nonadditive ways, it is called epistasis. With no definitive group of genes to comprise an illness, several heterogeneous susceptibility sets may lead to manifestation of the disease via unseen epistasis. One approach to parsing these susceptibility sets lies in pharmacogenetics. It is by no means a definitive technique but another tool in the armamentarium to observe epistasis.

Clinicians are all too familiar with the experience of slowly titrating the doses of medications such as neuroleptics or antidepressants with a refractory patient and switching the medications several times, often with mixed results. One goal of pharmacogenetics is to ascertain how individuals parsed by genotype respond phenotypically to medication. The hope is to subcategorize patients into groups that might share a similar genetic composition at critical alleles and explore epistasis i.e. how these unseen interactions occur among the alleles on different genes. This differs from classic genotype comparisons in genes positively associated with disease susceptibility. Pharmacogenetics based on clinical drug response has the potential to accelerate research into neurobiologically relevant pathway interactions previously dismissed due to lack of credible scientific evidence at the level of disease causation.

In a nascent area of psychiatric research, Bertolino et al. and Weickert et al. explored the effects of COMT genotype on the cognitive response to antipsychotic medication. They found that patients who were homozygous for the met allele of COMT had improved working memory tasks after standard antipsychotic treatment. In these studies, COMT genotype did not impact on the effect of the drug on psychotic symptoms. Inada et al., however, reported that patients with met/met genotypes of COMT gene, required higher doses of typical neuroleptics to achieve a significant reduction in psychotic symptoms. These studies raise the possibility that COMT activity, based on genotype, may differentially impact on cognitive and antipsychotic effects of these drugs. In an effort to address genetic interactions, Anttila et al. reported an interaction between SNPs in NOTCH4, another potential schizophrenia-susceptibility gene, and COMT in accounting for poor response to neuroleptics. These preliminary results require replication in large, unselected samples, but they illustrate the potential of reducing heterogeneity in treatment outcome by looking at interacting genetic factors in the complex response to treatment.

In the example of the 5-HTTLPR polymorphism which was found by Caspi et al. to predict the effect of environmental stress on risk for depression, further studies revealed a role in SSRI-antidepressant response. Pharmacogenetic trials based on this mutation have shown at
times paradoxical SSRI responses in individual ethnic groups with differing genotypes. Clearly, if these results turn out to be valid, the pharmacological response may be variable depending on the ethnic genotype combination observed, further driving the hypothesis of individualized medicine which will be discussed further below.

These examples are preliminary observations with many methodological uncertainties, but the principle of searching for a genetic basis for treatment response is an emerging field. A careful pharmacological targeting of select genes and measuring their physiological and epistatic interactions may be a new dimension in defining future treatment options.

Ethnicity: obstacle or opportunity?

An SNP that occurs in 42% of the Caucasian population may appear in only 5% of African Americans and lead one to conclude that disease-causing polymorphisms account in part for population differences in the prevalence of certain illnesses. This may help in disease gene or treatment response identification because various ethnic populations may be more homogeneous with respect to the original disease mutations.

Race-based therapeutics has become controversial with stigmatization and negative connotations. This is unfortunate and unscientific. Ethnic genotypic variation presents an opportunity for narrowing the aetiological focus. For example, ethnic variation informed the design of clinical trials for specific medications involving heart disease. In psychiatric research, Dettling et al. demonstrated that clozapine-induced agranulocytosis was significantly associated with HLA regions B-38, DRB1 *0402, DRB4 *0101, DQB1 *0201 and DQB1 *0302 haplotypes in Jewish patients. Also noted is a 21-fold higher rate of clozapine-induced agranulocytosis among Finnish people compared to other ethnic backgrounds. They suggest subcategorizing ethnic groups prone to agranulocytosis to search for specific diseases related to these histocompatibility complexes. The feasibility may be initially limited by power of sample size, but the overall concept is rational. Ethnicity may transform psychiatric trials as well as accelerate the era of personalized medicine. Another technique of subcategorization using drug metabolism has immediate and practical implications, which will be explored further below.

Drug metabolism

Genetic implications and personalized medicine

The US Food and Drug Administration and the pharmaceutical industry are formulating procedures and preparing for individualized medicine.
Psychotropic medication efficacy varies widely from patient to patient, and part of the basis for this is likely to be genetic. Genes can impact on medication effects in a variety of ways, including changes in drug metabolism, biodistribution, in varying disease neurobiology and in susceptibility to side effects.

Currently, 88% of *H.sapiens* metabolize most drugs at the same rate and are labelled extensive metabolizers. Most of these people receive their medication based on their weight in kilogram to achieve a therapeutic range. However, 10% of *H.sapiens* are known as poor metabolizers (PMs). A very small minority may have adverse reactions to the medications for other reasons, but most of these 10% metabolize drugs so slowly that significant side effects occur and they are taken off their medications or they stop them on their own. Unbeknownst to the clinician, PMs may actually reach toxic levels of medications, often at relatively low clinical doses. The remaining 2% have a different genetic architecture; they complain of absolutely no improvement after taking medications because they rapidly metabolize the medication as ultra-rapid metabolizers (UMs). Clinicians may mistakenly try a new medication with the UMs in the belief that they were treatment refractory to that particular medicine. There are also intermediate metabolizers who are heterozygous in their relevant genotypes and whose activity varies greatly. Current drug metabolism categorization is based on hepatic CYP2C19 and CYP2D6 drug-metabolizing enzyme genotypes. The four categories probably affect psychotropic dosing regimens, though this has not been systematically been explored.

Ten per cent of all adverse drug events involved psychotherapeutic medications in 2001.\(^30\) Olanzapine and sertraline are respectively the third and tenth best-selling drugs of 2004\(^31\) and also happen to have high rates of adverse drug events. Drug-induced illness costs in the US have been estimated at about $76.6 billion USD annually.\(^32\) Studies suggest that eradicating *Helicobacter pylori* by ascertaining metabolic rates by genotyping CYP2C19 in the United States would be cost effective relative to traditional treatment.\(^33\) Analogously, Fishbain *et al.*\(^34\) advocates that it would be economically justified to test for metabolic genotypes in the context of psychotropic medications. In 1999, the treatment cost of drug reaction to antidepressants among CYP2D6 poor metabolizers alone was $420 million in the United States.\(^35\) We anticipate that these recommendations will be tested in the near future.

**Pharmacogenetics in action: the cytochrome p450 story**

The majority of antipsychotics (and most medications) are lipophilic and taken up in the liver for excretion. Cytochrome p450 enzymes act within
the hepatocytes to extensively metabolize most antipsychotics and many antidepressants. Cytochrome p450 genes are generally highly polymorphic; for example, CYP2D6 has over 40 functional genetic polymorphisms that have been associated with a diverse spectrum of treatment effects, from variation in metabolism to clinical side effects. Common CYP2D6 alleles are predictably different between Caucasians, Africans and East Asians, likely impacting on population differences in effects of drugs.

Kirchheiner et al. found CYP2D6 polymorphisms to cause a wide range of variability in trimipramine metabolism. The mean systemic clearances in UM of CYP2D6 trimipramine substrates were 2.5-fold higher than in poor metabolizers, and bioavailability differed 6-fold between poor and ultra-fast metabolizers. This resulted in approximately a 15-fold difference in total oral clearance with extremes as low as 3.5 l/h in the poor metabolizer group and as high as 712.6 l/h in the UM group. Such a broad range of effects may greatly influence the dosing regimen based on individual metabolic genetics of the psychiatric patient. Other preliminary evidence suggests that P450 alleles may impact on metabolism of haloperidol, codeine, propranolol, dextromethorphan, desipramine and risperdal. Even an effect of differential activity of cytochrome p450 on smoking and clozapine has been demonstrated. It is yet to be determined how much of clinical outcome can be predicted by this genetic approach, but the tools exist to explore this question and determine its importance.

Conclusion

The new era of psychiatric genetics began with the first linkage studies, which paved the way for subsequent major advances in gene discovery. Association studies for fine mapping and gene identification have yielded a growing list of susceptibility genes related to psychiatric conditions. Other methods of increasing power are the synergistic use of genotyping, neuroimaging and intermediate phenotypes to elucidate the mechanisms in human brain of these genetic associations with neuropsychiatric illness. New and ongoing studies reveal the possibility that diagnostic boundaries may be modified based on genetic information, and some genes such as NRG1, DTNBP1 and BDNF may relate risk for both schizophrenia and mood disorders. Compelling advances in pharmacogenetics and drug metabolism are paving the way for personalized medicine. Our expanding research of complex genetic pathways will help lead to specific targeting for more predictable and effective treatment of psychiatric illness in the relatively near future. Psychiatric genetics in the next 20 years will achieve breakthroughs previously unattainable.
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