The Limitations of Genetic Testing in Psychiatry

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Despite the burgeoning number of psychiatric treatments, we still do not know how to predict which one will work best for which patient. The hope that genetic (single gene effects) and genomic (multiple gene effects) testing might be useful for diagnosis and treatment has been encouraged by decreased costs of genome sequencing and studies demonstrating an association between mutations in more than 3,000 genes and specific disease phenotypes [1–3]. Are the data as promising in psychiatry as they are in other fields?

Cancer Genomics

Genetic testing has been most promising in oncology. For example, about 10% of cases of breast cancer have an autosomal dominant pattern of transmission, most commonly mutations in the tumor suppressor genes BRCA1 and BRCA2 [4]. When BRCA1/2 mutations are found, healthy women are offered a very close follow-up, as well as prophylactic antiestrogen therapy or surgery, yet in one study only 9.5% of high-risk women even underwent genetic counseling, let alone testing [5]. Breast cancer risk alleles have also been found for p53, PTEN (phosphate and tensin homolog deleted from chromosome 10), STK11, CDH1 and PALB2; however, these genetic factors are rare, and there is not much research on screening pro-

ocols for them [4]. In moderately differentiated breast cancers, which comprise 50% of breast tumors, gene expression signatures for mitotic index, angiogenic potential, p53 mutational status, and estrogen and progesterone dependence provide better stratification of prognosis than histology [6]. However, despite such advances, there is still not much clear integration between genomics and clinical practice in oncology [7].

Psychiatric Diagnosis

Numerous markers have been associated with psychiatric disorders, including genes for BDNF (brain-derived neurotrophic factor), FOS (FBJ murine osteosarcoma viral oncogene homolog), COMT, DRD1, DRD2, DISC1, GABABR1 (γ -aminobutyric acid B receptor 1), NR4A2 (nuclear receptor subfamily 4, group A, member 2), ADORA2A (adenosine A2a receptor), CACNA1C (calcium channel gene), sirtuin 1, LHPP, 5HTR1A, RNA-binding proteins, and genes for myelination, glutamatergic and GABAergic neurotransmission, oxidative stress, signal transduction, response to the environment, cell survival and proliferation, and cell shrinkage and apoptosis, among others [8–13]. Yet no genetic marker has yet been shown to be useful in prospectively identifying any specific psychiatric disorder [14]. Because genetic predis-

position in psychiatry is thinly distributed over thousands of loci, each contributing a small effect, with considerable overlap of brain systems and shared genetic factors [14], sample size in most association studies has generally been too small to produce meaningful, replicable results [1, 15, 16]. In addition, epigenetic and other factors that alter DNA conformation can determine whether susceptibility genes are expressed or suppressed [10], complicating analyses of the relationship between genotype and phenotype. Even relevant genetic markers can be difficult to interpret because inherited gene factors appear to interact with each other and the environment to contribute to both illness susceptibility and clinical presentation [17, 18].

Descriptive diagnoses in psychiatry have multiple domains such as age of onset, constellations of specific symptoms, functioning, comorbidity, and evolution over time that assort differently in different patients in the same category to produce functionally different conditions [19]. Genetic profiles associated with any one of these features are not likely to predict more global diagnoses. If the direct path from genotype to phenotype ends at discrete endophenotypes such as arousal, anhedonia, information processing, stress responses, inflammation and mood, rather than global diagnosis, attempts to link the latter to specific genes are likely to prove frustrating [20–23], just as descriptive diagnoses in psychiatry do not adequately consider important subtypes that exhibit different assortments of features such as age of onset, severity, progression or functioning.

Genetic Pharmacokinetic Studies

Since cytochrome P450 (CYP450) 1A2, 2D6, 2C9, 2C19, and 3A4 account for 60% of psychiatric drug metabolism [24], considerable interest has centered on using the CYP450 genotype to predict response to psychotropic medications [3]. However, genotype does not inevitably predict phenotype because multiple copies of a more or less active gene can result in more or less metabolic activity than would be expected from the allele that is identified. In addition, the metabolizer phenotype associated with a particular genotype can be inhibited or enhanced by a number of medications, substances, and foods [25–30]. In an open study of 900 patients treated with venlafaxine who were both genotyped and phenotyped for CYP2D6, 4% were genotypically poor metabolizers, while 27% were phenotypically poor metabolizers, suggesting that 23% of patients with other genotypes had converted

to a poor metabolizer phenotype as a result of concomitant medications [31].

Even if genotype inevitably predicted phenotype, the correlation is stronger between CYP450 phenotype and drug level than clinical response [32], which is modified by metabolism of most medications by more than one enzyme, lack of linear kinetics and saturable elimination for many drugs, unclear correlations between blood level and response for many medications, and therapeutic windows requiring therapeutic monitoring anyway for some of them [24, 26, 33, 34]. Expression of CYP450 enzymes in the brain, which influences drug effect, may be different from their expression in the blood, or even in the intestine and liver [24].

Drug Transporter Studies

Drug transporters, including P-glycoprotein (P-gp), organic ion transporters, and multidrug and toxin extrusion proteins, modify the effect of CYP450 phenotype on drug levels and drug action because they influence gastrointestinal absorption, tissue uptake, and renal elimination as well as transport in and out of the brain [35, 36]. In the iSPOT-D (International Study to Predict Optimized Treatment in Depression), two different MDR1 single nucleotide polymorphisms (SNPs) of the gene for P-gp (MDR1 or ABCB1) were associated with better responses either to escitalopram and sertraline or to venlafaxine, but there was no *a priori* hypothesis, other relevant factors such as drug metabolism, ethnicity, age, specific symptoms, or concomitant illness were not addressed [36], and DNA was collected after results were known rather than prospectively [37].

Pharmacodynamic Studies

Both a deletion (short polymorphism or s-allele) and an insertion (long polymorphism or l-allele) have been found in the gene (SCL6A4) for the promoter region (5-HTTLPR) of the gene for the serotonin transporter (SERT) [32]. The short polymorphism (s) decreases and the long polymorphism (l) increases SCL6A4 transcription rates, resulting in less or more SERT expression, respectively [32]. Research on the association of the s/s genotype with a lower response rate to serotonin reuptake inhibitors in some ethnic groups has been contradictory [38–40], and even without correction for multiple statistical tests, the SCL6A4 genotype explains at most 5% of the variance in antidepressant response [30]. Attempts have

been made to correlate SNPs of the brain-specific voltage-gated rectifier potassium channel (Kv11.1–3.1) and the cardiac specific version (Kv11.1–1A) with risperidone treatment response and changes in cardiac conduction, respectively, in schizophrenia [41], but the results have not been robust.

Gene Network Studies

Because treatment outcome seems to be influenced by multiple genetic polymorphisms, each with a small effect [3, 21], research has moved toward analysis of networks of genes in the hope of developing more clinically useful information [42–44]. However, such studies have not produced clinically meaningful results [43, 44]. The Genome-Based Therapeutic Drugs for Depression (GEN-DEP; $n = 811$) study, a substudy of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D; $n = 1,491$) study, and the Munich Antidepressant Response Study ($n = 339$), did not find any combination of genetic markers that influenced treatment response in depression [1, 44]. Genome-wide association studies did not reveal any SNPs associated with response or remission of nonbipolar, nonpsychotic, major depressive disorder treated openly with serotonin reuptake inhibitors [45], and the STAR*D study did not reveal any positive genome-wide association or top 25 SNP associations with treatment response [45]. A genome-wide association study from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE, $n = 738$) did not find any combinations of genetic markers that influenced treatment response in schizophrenia [1, 44].

Prospective Treatment Studies

Only a small number of reports have involved the prospective use of genotyping to make treatment decisions. An open study of 58 depressed inpatients reported that genotyping for ABCB1 was associated with a shorter hospital stay because patients with the TT/GG genotype were more likely to have an increase in the dose of an antidepressant that was a P-gp substrate, although changing to a non-P-gp substrate did not affect outcome [46]. The study was not randomized, and numerous intervening variables, including pharmacokinetics, comorbidity, and history, were not considered.

Four studies have been supported by the manufacturer of a proprietary survey (GeneSight) of CYP2D6, 2C19,

2C9, and 1A2, SLC6A4, and 5HTR2A genotypes that generates a ‘composite report’ classifying antidepressants and antipsychotic drugs used in the treatment of depression into three categories: ‘use as directed’, ‘use with caution’, and ‘use with caution and with more frequent monitoring’. An 8-week open study of 44 patients assigned in a nonrandom manner to treatment guided by the composite report (guided treatment) or nonguided treatment by the same clinicians, who were involved with the product, reported that patients in the guided group were less likely to receive medications in the ‘use with caution and with more frequent monitoring’ category, presumably because of reluctance by the guided clinicians to prescribe medications that required more monitoring [47]. Although improvement of depression was similar for the first 4 weeks in both groups, a single measure at 8 weeks indicated increased depression scores for the nonguided but not the guided group. No explanation was offered for the final increase in depression scores in the nonguided group, when multiple earlier ratings demonstrated a steady decrease in scores. Improvement in the guided group was not impressive, and it is impossible to know whether comorbid factors, concomitant medications, treatment adherence, patient enthusiasm, substance use, adjunctive psychotherapy, clinician knowledge of treatment condition, and open ratings affected the conduct of treatment or the outcome assessment.

A second open, nonrandomized study conducted by the same group in 227 mildly-moderately depressed patients, 165 of whom completed 8 weeks of treatment, reported that patients in the guided group were twice as likely to respond [48]. Since clinicians reported substantial levels of confidence in the genetic reports, it is possible that they worked more vigorously with patients in the guided group, that patients in the guided group were more adherent with a treatment approach they thought would be more effective, or that they reported better results to please the investigators.

In a double-blind, randomized, controlled trial of GeneSight, 25 depressed patients were assigned to treatment as usual and 26 to guided treatment [49]. Improvement was numerically greater in patients in the guided than in the treatment-as-usual group, but none of the group differences were statistically significant. In a fourth report from the same company [50], 97 patients with a depressive or anxiety disorder treated openly by a single psychiatrist with one of the medications in the genetic survey were followed openly for 1 year. The 9 patients taking at least one medication in the ‘use with caution’ category had significantly more total health care visits and nonpsy-

chiatric medical visits than the other subjects and had a higher average cost of care. However, these patients also took more medications than the other subjects, and there was a significant correlation between the number of medications taken and the two outcome variables. When different statistical analyses were performed on the same data (e.g. analysis of variance and t tests), some were significant and some were not, and no correction was made for multiple statistical tests. Although the authors contended that their genetic analysis could save health care costs, this hypothesis was not actually tested. Since no data were available on medical comorbidity and severity of psychiatric illness, the possibility was not considered that the small number of patients in the 'use with caution' category had more health care visits and took more medications because they were sicker psychiatrically or medically.

Gene Expression

Current genotyping approaches in psychiatry consider the presence or absence of a particular allele or group of alleles, but expression of those genes may be suppressed, modified, or enhanced by a number of factors, including circadian transcription patterns, epistasis (gene interactions), regulatory regions, epigenetic factors, and noncoding RNA [14]. Histone modification and DNA methylation in response to experience, inflammation, the illness, and the medications used to treat it can induce or suppress multiple genes, and genotype itself can affect methylation of regulatory sites that leads to epigenetic changes in brain development [51]. Micro-RNAs and short interfering RNAs are short, noncoding posttranslational regulators of gene expression that target hundreds of mRNA transcripts to influence gene networks [27, 52, 53]. The expression of genes for CYP450 enzymes is altered by promoter methylation, micro-RNAs associated with inflammation and other illnesses [27], and some medications [54], resulting in an altered CYP450 phenotype.

Limitations of Pharmacogenetic Testing in Psychiatry

No matter how much we may want to translate directly to clinical diagnosis reports of an association between a diagnosis and a genetic marker, the nature of the current level of knowledge does not permit this application. Sample sizes in most existing studies have been too small to

produce meaningful, replicable results because of the clinical and genetic heterogeneity of psychiatric disorders [55], and the combined influence of multiple genes, each with a small effect size [1, 15, 16]. Most studies have utilized retrospective or post hoc analyses rather than prospective a priori hypotheses [56], and statistical significance is often inflated by lack of correction for multiple statistical tests [16]. The majority of studies lack replication in independent samples, especially by different investigators [16]. Even robust findings would not be clinically applicable until a prospective study demonstrated their ability to preferentially predict one diagnosis or even clinically relevant feature over another.

Using genotype to predict response to medications is even more problematic. Pharmacogenetic studies have been conducted in normal subjects or patients who are not taking other medications and who do not have other illnesses, limiting extrapolation to most clinical settings [33, 34]. Most studies do not control for the effect on the expression of CYP450 and other genes of age [27], ethnicity [30], smoking [30, 34], and use of substances such as alcohol, hormones, St. John's wort, caffeine, cabbage, and grapefruit juice [30]. Genetic studies of treatment outcome have not measured nonadherence [57], but as the rate of nonadherence increases in any population, statistical power to detect a genotype effect decreases substantially [1]. For medications that are chiral mixtures of enantiomers with different actions, the metabolism of each enantiomer may be by different enzymes [58]. Active metabolites with their own metabolic pathways may enhance or interfere with therapeutic or toxic effects predicted by the presumed metabolism of the parent drug [59, 60]. In most instances, more than one genetic factor affects drug levels and disposition [3], and interactions between these factors can be difficult to predict.

A clear demonstration of a genotype/blood level relationship in a single dose or 8-week study may not correlate with chronic treatment, in which compensatory changes in secondary metabolic pathways and drug transporters, gene up- or downregulation, saturation pharmacokinetics and other factors may modify the impact of oxidative enzyme polymorphisms on final drug level [24, 59]. With chronic treatment, some psychotropic drug metabolites form complexes with P450 enzymes that alter or even reverse the acute effect on metabolism [25]. Long-term changes in P450 enzymes also occur in the brain, with further unpredictable effects, not only on the substrate drug, but on neurotransmitters and neurosteroids metabolized by the same enzymes on which the medication may act [25]. Another complicating factor is that the

illness, as well as medications used to treat it, can alter the relationship between pharmacologic genotype and phenotype. For example, many proinflammatory cytokines and acute-phase proteins that are associated with mood and anxiety disorders [61] act on transcription or post-translational protein modification to downregulate some CYP450 genes and upregulate others [62]. At the same time, suppression of cytokines by antidepressants can alter gene expression in directions that antagonize improvement of depression [25]. The impact of evolution of the illness and its response to different treatments in modifying therapeutic strategies during the course of treatment of cancer is relatively straightforward to study by virtue of methodologies for examining genotype and phenotype of cellular clones, but it is still difficult to develop the correct approach to well-characterized tumors [63]. The absence of such measures in psychiatric diagnoses makes this prospect considerably more difficult.

Where Do We Go from Here?

Psychiatrists, whose work frequently involves ambiguous clinical problems, and who must often consider contradictory elements of patient presentations and avoid premature closure, can have a remarkably low tolerance for ambiguity, conflict, and delayed gratification when it comes to the latest laboratory study. The hope that pharmacogenetic testing will result in unambiguous 'personalized psychiatry' should not lead to quick adoption of

technologies that have not yet been demonstrated to reliably predict a specific course or a need for a specific medication, the choice of which remains largely empirical. After all, genetic associations are statistical, but medical practice is personal [14]. Yet there is tremendous pressure to translate each new report of such associations to our patients, not only from our own need to appear 'scientific' and from industry marketing of proprietary tests, but from the marketing of ideas by thought leaders with an intellectual attachment to the latest conceptualization of genetic causality [64].

It is a continuing challenge to examine new genetic findings critically without applying them immediately in the clinic. When adequately powered studies that address gene number and expression and that control for real-life factors that affect outcome such as comorbidity, polypharmacy, environmental exposure, age, gender, ethnicity, substance use, and treatment adherence emerge [44], clinicians who have not put new information into action before integrating it with emerging knowledge about diagnosis, neurobiology, and the evolution of complex disorders will be ready to apply them effectively.

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