Review

Biological Psychiatry

Translating Neurogenomics Into New Medicines

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ABSTRACT

Brain disorders remain one of the defining challenges of modern medicine and among the most poorly served with new therapeutics. Advances in human neurogenetics have begun to shed light on the genomic architecture of complex diseases of mood, cognition, brain development, and neurodegeneration. From genome-wide association studies to rare variants, these findings hold promise for defining the pathogenesis of brain disorders that have resisted simple molecular description. However, the path from genetics to new medicines is far from clear and can take decades, even for the most well-understood genetic disorders. In this review, we define three challenges for the field of neurogenetics that we believe must be addressed to translate human genetics efficiently into new therapeutics for brain disorders.

Keywords: Brain disorders, Circuits, Genes, Genomics, GWAS, Human genetics, Psychiatry, Translational medicine

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Despite pockets of success (e.g., multiple sclerosis) and periodic spurts of optimism, most drugs for neuropsychiatric disorders used in clinical practice today are based on mechanisms identified serendipitously many years ago (1). Human genetics holds the potential for a more mechanistic and causally linked approach to identify therapeutic hypotheses and to prioritize drug discovery programs (2). Together with progress in basic neuroscience and technologies to measure human brain function (3), we are now in a position to address historical shortcomings in neuroscience drug discovery—evidence for disease causality of targeted mechanisms in humans and a means to identify disease-relevant brain circuitry in humans.

There are four specific advantages to using human genetics and genomics in central nervous system drug research and development (R&D): 1) less bias toward established hypotheses, 2) an emphasis on human biology, 3) a statistical framework to establish causality, and 4) the potential for patient selection to maximize response and clinical benefit. Traditionally, the bias in industry is to work on hypotheses based on animal models assumed to be relevant to specific clinical symptoms (e.g., forced swim test for depression and elevated plus maze for anxiety) or on serendipitous human neuropsychopharmacology (e.g., the dopamine hypothesis in schizophrenia, the serotonin hypothesis in depression, or the glutamate hypothesis in just about everything). Human genetics has the potential to overcome this tyranny of old ideas through less biased, genome-wide approaches to identify novel mechanisms and by being ab initio based on human phenotypes. Starting drug discovery with human genotypes and phenotypes averts the risk of pursuing pathways of ultimately nondemonstrable causal relevance to human disease before expensive clinical trials. Moreover, technological advances have made generation of human genome-wide data far simpler, and analytic principles and approaches are creating a theoretical framework to understand the variability of common human genetic variation that minimizes spurious or irreproducible findings.

After the theoretical concept of genome-wide association studies (GWAS) was first presented (4), analyses of large-scale cohorts estimated the threshold for genome-wide significance in European ancestry at $p < 7.2 \times 10^{-8}$ (5). In subsequent studies of larger cohorts and across different phenotypes, this threshold has generally held up well, in that the association signals with p values below genome-wide significance can be considered robust and unlikely to become nonsignificant as cohort size increases further (6). Although the effect size for most robustly identified common variants is small, and even in aggregate across loci identified variants can explain only a small amount of phenotypic variance, GWAS have been clearly shown to identify risk genes above noise. This statistical robustness is a remarkable and sometimes overlooked advantage of GWAS over other high-throughput "omics" approaches in an era that is plagued by a high degree of concern over the reproducibility of published findings (7,8). Once statistically robust mechanisms have been identified through human genetics, it becomes possible to identify biomarkers that are rooted in causal pathways and can be incorporated into the drug discovery process from the beginning of a program.

Although these advantages are significant, there are also important hurdles in the systematic exploitation of new disease loci for the discovery and development of novel therapeutics. In this review, we present an industry perspective on key challenges and outline a path from locus to therapeutic hypothesis that is amenable to established, targeted medicinal chemistry approaches and testable in clinical trials. The methods, advantages, disadvantages, and current status of various human genetics approaches to neuropsychiatric disease have been reviewed extensively elsewhere (9–12); We focus here on a

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framework to derive and test novel treatments derived from this emerging knowledge. The three key challenges we see are 1) getting from (the right) phenotype to locus, 2) converting identification of a genetic locus into mechanistic disease insight, and, arguably the most demanding, 3) translating knowledge of disease mechanism into a therapeutic hypothesis (Figure 1).

CHALLENGE NO. 1: FROM PHENOTYPE TO LOCUS

Cohort Size Matters, but Are We Selecting the Right Phenotypes?

Large cohorts of thousands of individuals are necessary for adequately powered GWAS. Although no guarantee for success (13), the availability of large sample sizes for meta-analyses has resulted in the identification of many novel robust loci for neuropsychiatric disorders such as schizophrenia and Alzheimer's disease (14,15). To analyze multiple cohorts for the same disorder, it is often necessary to relax eligibility criteria with regard to phenotypic ascertainment and disorder definitions. Although this "lumper" approach comes at the expense of phenotypic homogeneity, the increase in statistical power has enabled a breakthrough for numerous neuropsychiatric phenotypes. One concern of lumping phenotypes together is the potential to introduce pathogenic heterogeneity. However, efforts to date have failed to demonstrate that patient cohorts with more homogeneous phenotypes based on psychopathology alone or circuitry-based measurements (also known as subphenotypes or endophenotypes) reflect more homogeneous disease etiology or underlying genetic architecture that would make the identification of disease loci more likely (16–18). The lack of demonstrable genetic subarchitecture could change as the size of well-phenotyped patient cohorts increases to levels comparable to case-control cohorts aimed at identifying susceptibility loci for traditional disease categories. At the same time, molecular cross-disorder analyses of schizophrenia, bipolar disorder, major depressive disorder, autism spectrum disorders, and attention-deficit/hyperactivity disorder with genome-wide data have revealed substantial genetic correlation among these phenotypes (19) and identified several shared risk loci (20). Thus, it is the genetic risk variants that provide commonality across multiple diagnostic categories.

Despite the identification of shared risk loci across neuropsychiatric diagnoses, it is unclear to what degree current disease definitions used to recruit individuals into GWAS are relevant to the phenotypes that are probed in interventional clinical trials. We refer to this as the phenotype leap in translational psychiatric genetics. Here we outline different scenarios that caution against an oversimplified extrapolation from susceptibility loci to clinical endpoints suitable for drug registration. We further discuss complementary approaches to define relevant phenotypes for drug discovery and development.

Susceptibility, Severity, and Trajectory

Most phenotypes analyzed in clinical GWAS are aimed at identifying loci that predispose to disease. Typically, neuropsychiatric cohorts consist of patients meeting psychopathologic criteria based on DSM-IV or DSM-5 (21,22) or ICD-10 (23). Cohorts meeting criteria are compared with matched control populations, and the resulting case-control comparison attempts to find disease variants associated with disease. This emphasis on disease susceptibility in genetic studies contrasts with most efficacy end points in central nervous system clinical trials, which assess disease severity or disease progression (Figure 2). Measures of disease severity and progression are typically required for new drug registration with regulators because they serve as proxies for medically relevant impact on patients' lives and function. Variation at susceptibility loci may or may not influence disease severity or progression. Even perfectly targeted investigational drugs derived from susceptibility loci may not produce detectable effects on the severity or course of disease. One such example is the apolipoprotein E locus—the strongest and best established genetic susceptibility factor for late-onset Alzheimer's disease (24). The apolipoprotein E ε4 variant associated with susceptibility to late-onset Alzheimer's disease has little, if any, effect on disease progression when individuals fulfill the clinical criteria of dementia or mild cognitive impairment (25,26). In such instances, trials to prevent progression as early as possible, or even delay initial clinical manifestation, will likely be required to demonstrate efficacy of compounds acting on disease-causing mechanisms (27,28). In the case of psychosis, longitudinally phenotyped cohorts are only now being recruited to understand better the genetic architecture of disease susceptibility, severity, recurrence, and progression over many years (29).

For drug discovery, genetic loci and mechanisms associated with disease severity and progression are at least as important as those associated with disease susceptibility. It will be essential to determine the role of susceptibility variants in more deeply and longitudinally phenotyped cohorts to help define precisely for whom, when, and for how long novel

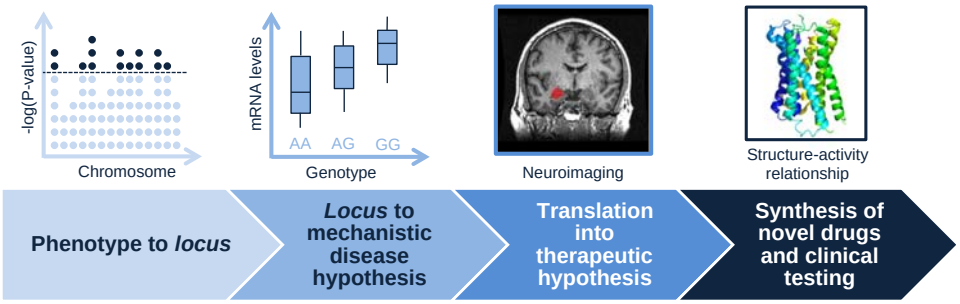

Figure 1. A path to apply human genetics to drug discovery. [Brain image and crystal structure of H_1 receptor with doxepin (60) reproduced from Wikimedia Commons (61,62)]. mRNA, messenger RNA.