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

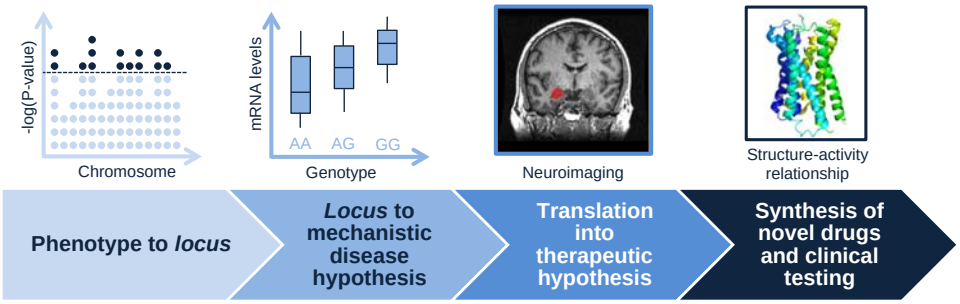

Figure 1. A path to apply human genetics to drug discovery. [Brain image and crystal structure of H_1 receptor with doxepin (60) reproduced from Wikimedia Commons (61,62)]. mRNA, messenger RNA.

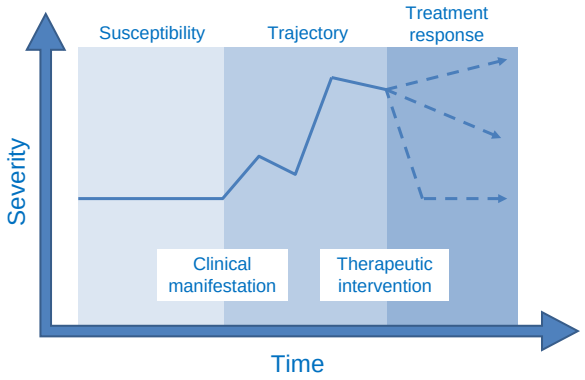

Figure 2. Schematic representation of disease stages. Each stage (susceptibility, trajectory, and treatment response) can be conceptualized as a separate, medically relevant phenotype for human genetics studies. To date, most genetic studies have focused on disease susceptibility.

therapeutics should be targeted, ideally in conjunction with intermediate phenotypes such as determined by neuroimaging. Specifically, now that we are becoming successful at identifying loci through lumping, we need to take these loci back to more deeply phenotyped cohorts to define the effect of genetic variants on disease severity and trajectory.

Response to Standard of Care

An additional approach to deconstructing disease phenotypes is to classify patients on the basis of their response to approved and widely used medications. Many different scales for treatment resistance and side-effect profiles are used across neuropsychiatric disorders in clinical trials (30,31). A key practical consideration for medicines development is the extent to which a new drug can offer clinical benefit beyond the current standard of care. Even if approved, payers in all markets increasingly demand evidence for substantial benefit above standard of care to justify coverage and reimbursement (32). Given that the market is replete with inexpensive generic drugs for important neuropsychiatric disorders such as schizophrenia, bipolar disorder, anxiety disorders, and major depressive disorder, many efficacy trials for new drug candidates are designed in an adjunctive setting to test for benefit beyond standard of care. Parenthetically, this adjunctive setting is rarely investigated in preclinical studies in rodent or primate models creating a significant translational gap.

This indirect approach to stratified medicine based on nonresponse or partial response to standard of care can be used to define phenotypes for genetic analyses. Specifically, the classification of response to an intervention with selective pharmacologic agents itself can be considered a biologically robust phenotype. For example, response to antidepressants has been shown to be a substantially heritable trait (33). The available cohorts needed to identify loci for antidepressant response are not yet in the required range of several thousand individuals (34). Given that sizable cohorts with hundreds and sometimes thousands of patients are being recruited for late-stage clinical trials, defining the genetics of drug response remains an area with considerable potential for drug discovery. Such an effort requires collaboration across companies and consortia. However, the collection and analysis of DNA samples, which would enable the construction of large-scale cohorts to study response variability, is not routine in every clinical trial. Looking forward, new medicines development will benefit from a much stronger emphasis on defining the neurogenomics of drug response or nonresponse for any given diagnostic category.

Domain-Based Phenotypes

In many areas of neuropsychiatric disease, objective clinical criteria are not available to establish diagnosis and assess disease trajectory. Classification of mental disorders has historically been based on the diagnostic reliability of symptom-based, descriptive psychopathology. In many instances, such nosology may lack biological validity. One effort to connect neuropsychiatric disease classification to underlying biological processes is the Research Domain Criteria framework proposed by the U.S. National Institute of Mental Health (35). The concept is to create a biologically more valid classification of mental disorders, and central to the Research Domain Criteria framework is interrogation of neural circuit function, connectivity, and network activity associated with core domains of psychopathology. Examples include the linkage of working memory to sustained activity in the prefrontal cortex (36) and the correlation of amygdala response with fearful stimuli and anxiety disorders (37). Identification of neural circuit endophenotypes is attractive given the more objective, quantitative, and increasingly standardized paradigms in neuroimaging (38,39). Ideally, these quantitative measures will be associated with disease-relevant neurofunctional domains that can then serve as traits for genetic analyses. However, caution is warranted because the degree to which any given circuit endophenotype or neurofunctional domain measurement is robustly heritable (or genetically associated), reversible, and related to functional improvement remains unknown. Any medicines documented to have an impact on neurofunctional domains must ultimately provide benefit recognized by patients, providers, regulators, and payers. We need a much more systematic dissection of neurofunctional domains, association with genetic variation, standardization of measurement modalities, and assessment of the impact of existing and novel drugs in the coming years to accelerate the relevance of domain-based phenotyping for drug discovery.

For therapeutics development, the promise of the domain-based approach is identification of novel pharmacology coupled to neurofunctional domains rooted in human genetic variation. To date, practical examples of the utility of such an approach at scales required for large phase 3 studies are limited. As one example of this domain-based approach, Papassotiropoulos *et al.* (40) conducted a GWAS in >2500 healthy volunteers of aversive memory and used bioinformatic pathway analyses to implicate the histamine H_1 receptor gene. The authors demonstrated an acute effect of diphenhydramine (which, among other mechanisms, is an antagonist at H_1 receptors) on aversive, but not on positive or neutral, memory in a single-dose, double-blind, placebo-controlled crossover study in healthy volunteers. Although it remains to be seen if this observation can be extrapolated to conditions with

impairment of aversive memory reconsolidation such as post-traumatic stress disorder, the approach provided a proof of principle for a population genetics–based nomination of drug targets for neuropsychological domains.

CHALLENGE NO. 2: FROM LOCUS TO DISEASE MECHANISM

Using Big Data

Once robust loci have been identified, the next step consists of interpreting these genetic variations for their molecular impact on gene and organ system function (Figure 1). One approach to derive novel hypotheses in silico for disease mechanisms consists of systematic computational analyses, such as transcriptomics from relevant human tissues, literature mining, and pathway analyses. Many of these analyses take advantage of large-scale data available in the public domain. The activities we prioritize are 1) mapping the "causal" gene for each locus, 2) determining the functionality of identified polymorphisms and genes, and 3) assessing druggability of implicated gene products and their proximate pathways. We describe the first two stages in detail and how we approach target and pathway identification.

From Locus to Gene

Identifying the implicated gene for each locus can range from straightforward to extremely complex if the lead variant with the lowest *p* value points to a large genomic region with many annotated genes. Genetic distance (i.e., the gene in highest linkage disequilibrium with the locus) as well as detectable messenger RNA levels in relevant tissue are among the most useful criteria. In addition, we consider biological plausibility based on our best understanding of a trait or phenotype. When candidate genes have been mapped, at the present time we deprioritize loci implicating genes that do not encode proteins because they are much more challenging to investigate further for functionality and are typically not amenable to traditional small-molecule chemical modulation. However, as molecular approaches to modify RNA species advance and we are increasingly able to define pathways influenced by microRNAs and other RNAs, we envision expanding our net to capture non–protein coding loci.

Functionality of Polymorphism and Gene

One of the most direct means by which a polymorphism can affect gene functionality is by changing the amino acid sequence of the expressed protein. However, very few loci are nonsynonymous variants. Arguably the next best possibility is a genetic variation that alters gene expression. Thus, a next useful step is using transcriptomics data in conjunction with genome-wide genotyping. This area is one of the most actively developing fields as more and more multi-omics data sets are being generated on a population basis. As is becoming standard in most large GWAS publications, at the present time we test all associated variants of interest for allele-specific effects on mRNA expression levels (expression quantitative trait locus). The advent of RNA sequencing–based data makes this a high-throughput, data-rich analysis that provides excellent dynamic range and sensitivity as well as information on splicing, editing, and strandedness that can have a strong bearing on defining the molecular impact of a given genetic variant (41). One important data set across many different tissues is being generated at the present time by the Genotype-Tissue Expression Project (42). In the future, it will be essential to expand this analysis to tissue and homogeneous cell populations from donors with specific diagnoses and neurofunctional domain phenotypes. Such efforts are underway in autism (43) and schizophrenia (44,45) and should be duplicated across all major neuropsychiatric diseases.

From Risk Genes to Novel or Refined Biological Pathways

As mentioned earlier, an important limitation in GWAS findings is the small effect size of risk variants. However, if cohort sizes are large enough to identify many risk genes simultaneously, a key advantage of GWAS emerges—the identification of biological risk pathways. Although pathways are only as informative as the underlying depth of biological evidence that define them, they are particularly powerful when derived from human genetics data pointing toward disease causation. Pathway analyses have been applied successfully to several disorders and corroborated or refined based on known mechanisms. For example, pathway analysis has pointed to novel candidate mechanisms such as the innate immune system in Alzheimer's disease and inflammatory bowel disease (46,47). Likewise, the recently published GWAS of schizophrenia has validated two long-standing neuropsychopharmacologic hypotheses—the dopamine D_2 receptor and *N*-methyl-D-aspartate receptor pathways (15)—while also pointing to novel mechanisms such as calcium channel signaling that were not previously prioritized for this disease (48).

Druggability

With a gene (or ideally pathway) and some understanding of the molecular lesion, the next step is to examine the implicated genes for druggability of the gene product itself or a proximate pathway. This assessment consists of two main parts: an assessment of physicochemical properties of drug candidates for absorption and distribution (49) and structure-based approaches to predict potential binding sites. These topics are reviewed in more detail elsewhere (50).

CHALLENGE NO. 3: DETERMINING HOW MUCH BIOLOGICAL EVIDENCE IS NEEDED FOR A GOOD DRUG TARGET ORIGINATING FROM GENETICS

Once robust loci have been analyzed, have been contextualized with other "omics" data, and point to a mechanistic hypothesis, the real challenge begins. This challenge consists of defining the minimal amount of experimental validation necessary to invest fully in a new mechanism with medicinal chemistry and clinical trials. This early validation process is not well defined in industry at the present time. Traditionally, new drug targets have many years of existing literature available to understand key biological mechanisms in greater depth than new genetically derived targets. If we expect the same amount of data for targets from human genetics, progress will falter

because it will take many years of experimental biology to follow up on the rich substrate of emerging genetic loci. As it stands, the biopharmaceutical industry (and field as a whole) is struggling to cope with the large number of disease-associated genetic loci. We tackle the translation of genetic hypotheses into therapeutic hypotheses from two different and ruthless angles: kill fast and kill many. It will be many years before some (it is hoped many) of these novel hypotheses survive and are tested in clinical trials, and acceleration requires generation and prioritization of biological evidence to support translation of loci into drug targets.

Clinical Stratification Informed by Human Genetics: A Step Toward Precision Medicine

In addition to using human genetics to derive novel neurobiological hypotheses of disease, one can analyze longitudinal cohorts for deeper genotype-phenotype studies. Such genotyped cohorts can be particularly powerful when they interrogate important endophenotypes such as connectivity deficits in schizophrenia (51) or span the typical age range of initial disease manifestation (e.g., adolescence in schizophrenia). Such cohort analysis can refine or even test emerging neurobiological hypotheses of disease, provide clues for a genetically defined responder subgroup, or point to the time for therapeutic intervention. The last point can be critical to guide clinical drug development because most human genetics studies point to risk factors of disease causation and might best be therapeutically addressed as early in the disease course as possible. Such genotype-phenotype analyses need not be based on exactly the same risk variants (which are typically of small effect and intronic or intergenic) that first implicated the specific gene. As the identification and cataloging of exonic variants proceeds rapidly as a result of advances in massively parallel sequencing (52), we will increasingly have rare variants available that are often more readily interpretable and informative given their stronger impact on gene function. Patients or healthy subjects who carry these variants can provide extremely valuable insights into disease susceptibility or resilience mechanisms (e.g., the role of the amyloid precursor protein gene in Alzheimer's disease) (53,54), but they require very large recallable cohorts with dense genotype and phenotype data.

Translation Requires Ruling Hypotheses Out Rather Than Accumulating "Converging" Evidence

We have argued in this review for more and better data sets to support the molecular dissection of neuropsychiatric disease loci. Yet, eventually there needs to be a tipping point where we no longer look to build or generate a hypothesis and find additional "converging" evidence, but rather focus on disproving or otherwise deprioritizing a genetically driven hypothesis. Such falsification need not be related to the role of a genetically identified mechanism in the disease process but can be specific to drug R&D. For example, one of the most consistent loci in several neuropsychiatric disorders is *CACNA1C* (20), which encodes the α1C subunit of the L-type voltage-gated Ca^{2+} channel ($Ca_V1.2$). This channel is a therapeutic target for many long-approved Ca^{2+} channel blockers in the heart and vascular smooth muscle, and rare mutations are associated with severe cardiovascular and central nervous system phenotypes (55,56). One can anticipate that broad modulation of $Ca_V1.2$ will produce substantial cardiac and vascular effects that are undesirable. From a neuroscience drug discovery perspective, it will be essential to determine if this channel or its pathway can be modulated selectively in the brain to enable a sufficiently broad therapeutic index that avoids cardiovascular effects. Although there is no evidence at the present time that L-type Ca^{2+} channel modulation is of therapeutic benefit in neuropsychiatric disorders, this step needs to occur for the Ca^{2+} channel hypothesis to become an attractive drug target. If such selectivity cannot be achieved, no matter how strong the genetic signal, this is not an attractive mechanism to carry forward and should be deprioritized as a drug target. Although there can be a strong incentive in the form of publication potential to produce new evidence that weakly supports a therapeutic hypothesis, there remains insufficient stimulus to produce definitive data that nullify a therapeutic hypothesis. We need a much greater, incentivized commitment to value "negative" data that is squarely aimed at ruling out therapeutic hypotheses and reduce incentives for proliferating subtle hints or tangential support across myriad hypotheses.

Building a New Collaboration Paradigm Between Academia and Industry

Human genetics evidence is exploding at a rate that surpasses traditional incremental increases in biological knowledge. This expansion in human genetics information demands novel ways to conduct early translational experiments and requires that such experiments be carried out on a much greater scale and with faster tempo. Many academic laboratories have specialized expertise in the physiology of specific gene products and pathways, and the pharmaceutical industry is in a good position to provide tools such as experimental compounds and samples from subjects in drug studies. However, substantial time and energy are spent (and arguably wasted) in circumlocution around whether a newly identified locus, genetic variation, or pathway has therapeutic potential. Instead, expanded efforts are needed for public/private collaboration that enable rapid execution of go/no-go experiments. For execution of a new translational paradigm, it will be essential that involved academic laboratories, at least for this undertaking, move away from aiming for elegant biological stories that mature over many years and accept the desired high attrition at this stage. Such an approach is challenged by the current model where downstream publications and funding require promising positive data. Industry must invest by substantially supporting the human genetics studies and associated validation of new targets and pathways.

Such support needs to consider the incentives and goals of several groups, which include large pharmaceutical companies, small biotechnology companies, academic laboratories, and consortia. Large pharma is primarily incentivized to bring new revenue-generating products to the market, and this aim is aligned, through regulators and payers, with providing meaningful medicines that address health needs. To the extent that drugs based on human genetics lead to streamlined clinical studies, larger clinical effects, and a more favorable reception by patients and payers, large pharmaceutical companies stand to meet their goal. For small biotechnology

companies, one area of high emphasis has been developing therapeutics targeting defined genetic diseases such as cystic fibrosis, fragile X syndrome, and Duchenne muscular dystrophy, and the generation of meaningful neurogenomics data sets will provide an opportunity for smaller companies to discover and develop new medicines that target a more restricted patient population. For individual academic laboratories, findings that reveal novel biology for publication and advance of a mechanistic program of research are the proximal incentive. Consortia have a typical goal to build infrastructure or data sets that are not achievable by individual laboratories or companies, and they can act as "honest brokers." The incentives of consortia often consist of demonstrating synergistic advances across sectors, institutions, or laboratories and thus can be very powerful when industry and academia come together in public/private partnerships (57,58).

CONCLUSIONS: IS OPTIMISM WARRANTED OR IS THIS ANOTHER ROUND OF WISHFUL THINKING?

The current and expected future availability of many new robust loci as starting points for new neuroscience drug targets presents a remarkable opportunity. However, the promise alone is insufficient given the stark reality of the steady decrease in the number of new drugs approved per billion dollars spent on R&D (59). Can neurogenomics change the equation? We are bullish, but key questions remain. When is the "omics" evidence sufficient to reach a translational tipping point where one can advance from hypothesis generation mode to hypothesis killing? How much biological evidence is necessary to warrant admission to the classic industry R&D pipeline and investment in medicinal chemistry programs and clinical trials? Can we scale up early biological validation experiments to follow up on a sufficient number of genetic hypotheses? Can we work toward incentivizing and scaling biological validation and invalidation within academia? There is ultimately one metric on which we will be judged as a proxy for improved therapeutic options for patients: more approved medicines based on novel mechanisms and meaningful added medical benefit.

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REFERENCES

1. Hyman SE (2012): Revolution stalled. Sci Transl Med 4:155cm111.
2. McCarroll SA, Hyman SE (2013): Progress in the genetics of polygenic brain disorders: Significant new challenges for neurobiology. Neuron 80:578–587.
3. Buckner RL, Krienen FM, Yeo BT (2013): Opportunities and limitations of intrinsic functional connectivity MRI. Nat Neurosci 16:832–837.
4. Risch N, Merikangas K (1996): The future of genetic studies of complex human diseases. Science 273:1516–1517.
5. Dudbridge F, Gusnanto A (2008): Estimation of significance thresholds for genomewide association scans. Genet Epidemiol 32:227–234.
6. Panagiotou OA, Ioannidis JP, Genome-Wide Significance Project (2012): What should the genome-wide significance threshold be? Empirical replication of borderline genetic associations. Int J Epidemiol 41:273–286.
7. Prinz F, Schlange T, Asadullah K (2011): Believe it or not: How much can we rely on published data on potential drug targets? Nat Rev Drug Discov 10:712.
8. Perrin S (2014): Preclinical research: Make mouse studies work. Nature 507:423–425.
9. Krystal JH, State MW (2014): Psychiatric disorders: Diagnosis to therapy. Cell 157:201–214.
10. Kendler KS (2013): What psychiatric genetics has taught us about the nature of psychiatric illness and what is left to learn. Mol Psychiatry 18:1058–1066.
11. Sullivan PF, Daly MJ, O'Donovan M (2012): Genetic architectures of psychiatric disorders: The emerging picture and its implications. Nat Rev Genet 13:537–551.
12. Craddock N, Sklar P (2013): Genetics of bipolar disorder. Lancet 381:1654–1662.
13. Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium, Ripke S, Wray NR, Lewis CM, Hamilton SP, Weissman MM, *et al*. (2013): A mega-analysis of genome-wide association studies for major depressive disorder. Mol Psychiatry 18:497–511.
14. Lambert JC, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R, Bellenguez C, DeStafano AL, *et al*. (2013): Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nat Genet 45:1452–1458.
15. Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014): Biological insights from 108 schizophrenia-associated genetic loci. Nature 511:421–427.
16. Psychosis Endophenotypes International Consortium, Wellcome Trust Case-Control Consortium, Bramon E, Pirinen M, Strange A, Lin K, *et al*. (2014): A genome-wide association analysis of a broad psychosis phenotype identifies three loci for further investigation. Biol Psychiatry 75:386–397.
17. Iacono WG, Vaidyanathan U, Vrieze SI, Malone SM (2014): Knowns and unknowns for psychophysiological endophenotypes: Integration and response to commentaries. Psychophysiology 51:1339–1347.
18. Goldman D (2014): The missing heritability of behavior: The search continues. Psychophysiology 51:1327–1328.
19. Cross-Disorder Group of the Psychiatric Genomics Consortium, Lee SH, Ripke S, Neale BM, Faraone SV, Purcell SM, *et al*. (2013): Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. Nat Genet 45:984–994.
20. Cross-Disorder Group of the Psychiatric Genomics Consortium, Genetic Risk Outcome of Psychosis Consortium (2013): Identification of risk loci with shared effects on five major psychiatric disorders: A genome-wide analysis. Lancet 381:1371–1379.
21. American Psychiatric Association (2013): Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Washington, DC: American Psychiatric Association.
22. American Psychiatric Association (1994): Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, DC: American Psychiatric Association.
23. World Health Organization (1992): The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines. Geneva: World Health Organization.
24. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, *et al*. (1993): Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 261:921–923.
25. Samtani MN, Farnum M, Lobanov V, Yang E, Raghavan N, Dibernardo A, *et al*. (2012): An improved model for disease progression in patients from the Alzheimer's disease neuroimaging initiative. J Clin Pharmacol 52:629–644.

26. Samtani MN, Raghavan N, Shi Y, Novak G, Farnum M, Lobanov V, *et al*. (2013): Disease progression model in subjects with mild cognitive impairment from the Alzheimer's disease neuroimaging initiative: CSF biomarkers predict population subtypes. Br J Clin Pharmacol 75:146–161.
27. Crenshaw DG, Gottschalk WK, Lutz MW, Grossman I, Saunders AM, Burke JR, *et al*. (2013): Using genetics to enable studies on the prevention of Alzheimer's disease. Clin Pharmacol Ther 93:177–185.
28. Santarelli L (2013): An audience with … Luca Santarelli. Interview by Alexandra Flemming. Nat Rev Drug Discov 12:14–15.
29. Anderson-Schmidt H, Adler L, Aly C, Anghelescu IG, Bauer M, Baumgartner J, *et al*. (2013): The "DGPPN-Cohort": A national collaboration initiative by the German Association for Psychiatry and Psychotherapy (DGPPN) for establishing a large-scale cohort of psychiatric patients. Eur Arch Psychiatry Clin Neurosci 263:695–701.
30. Demyttenaere K, De Fruyt J (2003): Getting what you ask for: On the selectivity of depression rating scales. Psychother Psychosom 72: 61–70.
31. Mortimer AM (2007): Symptom rating scales and outcome in schizophrenia. Br J Psychiatry Suppl 50:s7–14.
32. Eichler HG, Bloechl-Daum B, Abadie E, Barnett D, Konig F, Pearson S (2010): Relative efficacy of drugs: An emerging issue between regulatory agencies and third-party payers. Nat Rev Drug Discov 9: 277–291.
33. Tansey KE, Guipponi M, Hu X, Domenici E, Lewis G, Malafosse A, *et al*. (2013): Contribution of common genetic variants to antidepressant response. Biol Psychiatry 73:679–682.
34. Murphy E, McMahon FJ (2013): Pharmacogenetics of antidepressants, mood stabilizers, and antipsychotics in diverse human populations. Discov Med 16:113–122.
35. Cuthbert BN, Insel TR (2013): Toward the future of psychiatric diagnosis: The seven pillars of RDoC. BMC Med 11:126.
36. Wager TD, Smith EE (2003): Neuroimaging studies of working memory: A meta-analysis. Cogn Affect Behav Neurosci 3: 255–274.
37. Rauch SL, Shin LM, Wright CI (2003): Neuroimaging studies of amygdala function in anxiety disorders. Ann N Y Acad Sci 985: 389–410.
38. Buckholtz JW, Meyer-Lindenberg A (2012): Psychopathology and the human connectome: Toward a transdiagnostic model of risk for mental illness. Neuron 74:990–1004.
39. Millan MJ, Agid Y, Brune M, Bullmore ET, Carter CS, Clayton NS, *et al*. (2012): Cognitive dysfunction in psychiatric disorders: Characteristics, causes and the quest for improved therapy. Nat Rev Drug Discov 11: 141–168.
40. Papassotiropoulos A, Gerhards C, Heck A, Ackermann S, Aerni A, Schicktanz N, *et al*. (2013): Human genome-guided identification of memory-modulating drugs. Proc Natl Acad Sci U S A 110: E4369–E4374.
41. Wang Z, Gerstein M, Snyder M (2009): RNA-Seq: A revolutionary tool for transcriptomics. Nat Rev Genet 10:57–63.
42. GTEx Consortium The Genotype-Tissue Expression (GTEx) project. Nat Genet 45:580–585.
43. Voineagu I, Wang X, Johnston P, Lowe JK, Tian Y, Horvath S, *et al*. (2011): Transcriptomic analysis of autistic brain reveals convergent molecular pathology. Nature 474:380–384.
44. Common Mind Consortium. Available at: http://commonmind.org/. Accessed April 24, 2014.
45. Jaffe AE, Shin J, Collado-Torres L, Leek JT, Tao R, Li C, *et al*. (2015): Developmental regulation of human cortex transcription and its clinical relevance at single base resolution. Nat Neurosci 18:154–161.
46. Jostins L, Ripke S, Weersma RK, Duerr RH, McGovern DP, Hui KY, *et al*. (2012): Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature 491:119–124.
47. Jones L, Holmans PA, Hamshere ML, Harold D, Moskvina V, Ivanov D, *et al*. (2010): Genetic evidence implicates the immune system and cholesterol metabolism in the aetiology of Alzheimer's disease. PloS One 5:e13950.
48. Schubert CR, Xi HS, Wendland JR, O'Donnell P (2014): Translating human genetics into novel treatment targets for schizophrenia. Neuron 84:537–541.
49. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ (2001): Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev 46:3–26.
50. Fauman EB, Rai BK, Huang ES (2011): Structure-based druggability assessment—identifying suitable targets for small molecule therapeutics. Curr Opin Chem Biol 15:463–468.
51. Kochunov P, Hong LE (2014): Neurodevelopmental and neurodegenerative models of schizophrenia: White matter at the center stage. Schizophr Bull 40:721–728.
52. Lim ET, Wurtz P, Havulinna AS, Palta P, Tukiainen T, Rehnstrom K, *et al*. (2014): Distribution and medical impact of loss-of-function variants in the Finnish founder population. PLoS Geneti 10:e1004494.
53. St George-Hyslop PH (2000): Molecular genetics of Alzheimer's disease. Biol Psychiatry 47:183–199.
54. Jonsson T, Atwal JK, Steinberg S, Snaedal J, Jonsson PV, Bjornsson S, *et al*. (2012): A mutation in APP protects against Alzheimer's disease and age-related cognitive decline. Nature 488: 96–99.
55. Splawski I, Timothy KW, Sharpe LM, Decher N, Kumar P, Bloise R, *et al*. (2004): Ca(V)1.2 calcium channel dysfunction causes a multisystem disorder including arrhythmia and autism. Cell 119:19–31.
56. Antzelevitch C, Pollevick GD, Cordeiro JM, Casis O, Sanguinetti MC, Aizawa Y, *et al*. (2007): Loss-of-function mutations in the cardiac calcium channel underlie a new clinical entity characterized by ST-segment elevation, short QT intervals, and sudden cardiac death. Circulation 115:442–449.
57. Katsnelson A (2014): Drug development: The modelling challenge. Nature 508:S8–S9.
58. Sullivan PF (2010): The psychiatric GWAS consortium: Big science comes to psychiatry. Neuron 68:182–186.
59. Scannell JW, Blanckley A, Boldon H, Warrington B (2012): Diagnosing the decline in pharmaceutical R&D efficiency. Nat Rev Drug Discov 11: 191–200.
60. Shimamura T, Shiroishi M, Weyand S, Tsujimoto H, Winter G, Katritch V, *et al*. (2011): Structure of the human histamine H1 receptor complex with doxepin. Nature 475:65–70.
61. Wikimedia Commons. Available at: http://commons.wikimedia.org/wiki/File:MRI_Location_Amygdala_up.png. Accessed April 24, 2014.
62. Wikimedia Commons. Available at: http://commons.wikimedia.org/wiki/File:H1_Receptor_with_Doxepin.png. Accessed April 24, 2014.