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The genetics driven revival in neuropsychiatric drug development

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Drug development for central nervous system (CNS) disorders has dramatically slowed over the past decade, despite the growing burden attributable to neuropsychiatric disease worldwide (1). The fundamental challenges in developing treatments to target brain-based illnesses include limited understanding of underlying disease pathogenesis and pathophysiology, lack of quantitative disease biomarkers, inherent challenges in developing predictive preclinical models, and the inaccessibility of the brain to direct investigation. Most currently approved classes of psychiatric medications were discovered by serendipity and continue to target the same molecular mechanisms as their prototypes, developed 50+ years ago (1). Candidate drugs entering clinical trials for CNS disorders have some of the lowest rates of ultimate regulatory approval, often due to lack of clinical efficacy. These candidates have historically been advanced based on performance in rodent models, which may be inherently limited in their ability to represent the complex human cognitive and behavioral processes that are affected by neuropsychiatric disease. Given this challenging atmosphere, a critical question is how can the field move forward to tackle such an enormous public health need. In this issue of *Biological Psychiatry*, Wendland and Ehlers provide a sagacious framework championing the promise, while emphasizing the challenges, of using genetics to revitalize drug discovery programs in neuroscience (2). Melding this industry perspective with academic culture is likely necessary to create a common ground for accelerating discovery.

The substantial heritability of nearly all neuropsychiatric disorders has been a tantalizing clue that genetics could ultimately resolve disease biology. However, due to a highly

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complex and generally non-mendelian genetic architecture, only recently have investigators begun to identify high confidence genetic variants associated with disease risk (3–6). Genetic risk factors take the form of common variants tagged by single-nucleotide polymorphisms (SNPs) identified in genome wide association studies (GWAS), rare coding variants identified with whole exome or genome sequencing (WES; WGS), and rare chromosomal structural variation such as copy-number variants (CNVs). Several recent, high-profile successes identifying genetic risk factors for CNS disorders have instilled much optimism that neurogenetic approaches will ultimately identify novel targets for therapeutic intervention (3–6).

Genetics-based approaches help circumvent a number of the limitations that may have contributed to previous drug development failures. First, heritability estimates indicate that additive genetic factors contribute substantially to neuropsychiatric disease risk, generally more than shared or non-shared environmental factors. Second, genetics establishes biological causality and is grounded in human biology. This is especially important as many of the most striking biological features of CNS disorders appear to converge on processes that have evolved relatively recently and may not be well conserved in other mammals. Finally, surveying a genetic search space (with appropriate statistical rigor) can avoid the potential confirmation bias of hypothesis-driven approaches.

While Wendland and Ehlers are optimistic that neurogenetics can elucidate new disease pathways, they also identify several critical challenges. First, they emphasize that genetic loci associated with disease risk ("susceptibility loci") may not be relevant to disease trajectory or severity, which is the focus of most therapeutics. Sample size has been the critical limiting factor in the effort to find genes. To maximize power, recent GWAS studies have taken a "lumper" approach, combining results across multiple sites and relaxing criteria for diagnostic assessment, which has been highly successful in schizophrenia (4). However, it remains to be seen whether benefit could be gained by investigating association with illness severity, trajectory, or more specific and quantitative symptom domains. In depression, focusing on the most severe, recurrent cases may be the reason why a recent study identified the first genome-wide significant loci (6). Taking this approach could increase power to identify the neurobiological mechanisms contributing to severity or treatment-resistance (or response), which may be distinct from those underlying disease susceptibility. A recent study of lithium response in bipolar disorder identified a significant genome-wide significant locus, which prospectively predicted lower relapse rates in subjects treated with the medication (7). This locus was only nomimally associated (P_{min} =0.0065, uncorrected) with disease susceptibility in a larger powered study (5). Polygenic risk scores, representing the composite effect of SNPs passing a nominal threshold of association with a disorder (3), can now be used to directly assess how alleles conferring disease susceptibility overlap with or are distinct from those that affect treatment response or disease trajectory.

Once genetic risk variants are identified, the next challenge is to elucidate their underlying neurobiological effects. *De novo*, non-synonymous variants identified from WES/WGS are easiest to interpret as they directly alter a protein's amino acid sequence. However, the pathological significance of these mutations is frequently unclear, as unaffected individuals carry ~1 such mutation on average and these variants are frequently balanced by a normal

allele. Identifying the biological effects of GWAS-associated variants is often more challenging, as SNPs exhibit complex linkage disequilibrium (LD). The most highly associated schizophrenia locus spans several megabases of the major histocompatibility complex region, which harbors hundreds of genes (4; 8). But, recent work provides a critical proof-of-principle for this approach, finding that a significant portion of the schizophrenia GWAS signal at this locus is imparted by variation in C4a which upregulates the expression of its mRNA in brain (8). The majority of SNPs implicated by neuropsychiatric GWAS lie in noncoding regions of the genome and cannot be directly linked to a single gene. These variants are thought to play a regulatory role, which is often difficult to elucidate as many affect genes that are not in close physical proximity. The long range physical interactions between a gene and its distal regulators can be measured using chromosomal conformation capture methods (e.g., Hi-C), which have yet to be done in human brain at genome-wide scale. Such functional relationships can also be statistically predicted, as is done in expression quantitative trait loci (eQTL) studies. Not all of the regulatory relationships identified with eQTL have so far been replicated, however, perhaps due to dynamic changes across tissue, cell-type, and developmental stage.

Wendland and Ehlers also raise the question of how to use other "-omics" data to inform biological mechanisms, and when insights from such are data sufficient to motivate drug discovery efforts. We view data such as transcriptomics, epigenetics, and proteomics as an important step in understanding genetic mechanisms, as alterations at these levels can mediate or modify genetic effects and provide points of convergence with environmental influences. Moreover, these data, if genome-wide, provide an unbiased manner in which to generate mechanistic hypotheses that can be directly tested, especially when placed into an appropriate systems biological context (9). Transcriptomic analyses of disease brain tissue can provide critical insight, by identifying whether up- or down-regulated disease pathways are enriched for risk genes. Further *in silico* dissection can be made by identifying whether genes converge within specific brain cell-types, laminar or regional identity, or developmental time-points using publicly available datasets (9; 10).

Finally, as plausible biological mechanisms are identified, the remaining challenge as outlined by Wendland and Ehlers is to determine how to prioritize these targets. This will in part be dictated by their inherent "drugability". Other critical questions include when to intervene, whether to biologically stratify patients, how to demonstrate appropriate target engagement, and what outcome measures to employ. To have a disease-modifying effect, targeted therapies may have to be given during the early or even prodromal phase of an illness, as being investigated by anti-amyloid therapies in asymptomatic Alzheimer's disease (A4 trial; NCT02008357). Prospective, deep phenotyping of large cohorts of at-risk individuals will be necessary to characterize underlying genotype-phenotype associations and determine whether genetically stratified subgroups are more homogenous. The remarkable pleiotropy of even highly deleterious mutations such as 22q11.2 deletions, however, suggests this may not be the case. This also prompts the question of whether to target rare, but moderately penetrant genetic variants versus common variants with small effect sizes. Historically, more focus has been given to rare variants, as they have been easier to identify, interpret, and model pre-clinically. However, these different forms of genetic variation may converge on distinct biological processes, at least in autism spectrum

disorders (10). It is also reasonable to consider that the genes affected by common variants may actually be more amenable to therapeutic intervention, given that their effects are additive and likely influenced by the environment.

In conclusion, there is much optimism that recent successes in neuropsychiatric genetics will reinvigorate a stalled CNS drug development pipeline and improve treatment options for diseases imparting significant morbidity worldwide. As Wendland and Ehlers articulate, there remain significant hurdles in identifying genetic risk loci, deciphering the underlying biological mechanisms, and developing targeted therapeutic interventions. The ultimate success of this approach will rely on large-scale, collaborative, and integrative initiatives combining the expertise of multiple investigators, institutions, and sectors to tackle fundamental neurobiological questions most efficiently. The remarkable scientific successes of consortia founded on this model, including the Psychiatric Genomics Consortium, Genotype-Tissue Expression (GTEx) Program, BrainSpan, Common Mind, and Enigma Consortia (among others) are highly encouraging. Spurred by the remarkable advances in neuropsychiatric genetics and mixed with some well-deserved luck, the next decade promises new hope for CNS drug discovery.

Acknowledgments

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