1

Exploring and Exploiting Genetic Risk for Psychiatric Disorders

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Even before a basic understanding of genetic principles became widely available, careful clinical observation identified the hereditary underpinnings of mental illness (Kendler 2021). Building on these early observations, large-scale twin, adoption, and family studies ultimately solidified the notion that genetic factors contribute strongly to psychiatric illness. With the advent of robust molecular tools and large-scale collaborative consortia, the structure of genetic risk as well as many of the individual genetic factors conferring this risk have been elucidated. Indeed, the pace of progress in psychiatric genetics has been dizzying. No sooner is an article published that identifies yet another tranche of loci or genes linked to a disorder than it is out of date, and new advances have been posted to preprint servers.

Despite this remarkable progress, critics continue to maintain that the genetic revolution has led neither to increased understanding of the nature of mental illness nor to the development of novel therapies for these disabling conditions. Indeed, it is important to recognize the limits of progress in psychiatric genetics and to consider carefully how success in understanding and identifying genetic risk can be translated into understanding and treatment of mental illness. Such was the purpose of the Ernst Strüngmann Forum on Exploring and Exploiting Genetic Risk for Psychiatric Disorders, and such is the purpose of this book which arises from those proceedings. The Forum brought together experts in psychiatric and statistical genetics, neurobiology, and clinical psychiatry to discuss the state of psychiatric genetics and chart a path forward for further discovery and translation in the field. Discussions at the Forum centered around three issues:

- Whether and how to pursue discovery of additional genetic risk factors for mental illnesses.
- How best to use existing knowledge of genetic risk factors to enhance our understanding of the biology underlying mental illnesses.

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- How best to use existing knowledge of genetic risk to improve the care of patients with mental illnesses.

Here, we provide an overview of these issues and crystallize the aims and structure of the Forum and this book. In doing so, we hope to inform the reader of the current issues in the field and to foreshadow the principle overarching outcome of the Forum: that a coordinated, strategic approach to further discovery and translation in psychiatric genetics is imperative to accelerate scientific and clinical progress.

Discovering Genetic Loci and Describing Genetic Architecture

Thanks to the combination of technical advances and a shift toward large collaborative efforts, this past decade has seen unprecedented progress in unraveling the genetics of psychiatric disorders. We now have many hundred robust risk loci for psychiatric disorders, including both common as well as rare variants, and a deeper understanding of the genetic architecture of these disorders (for a review, see chapters by Robinson et al., Wray, and Hu and Won, this volume). For array-based genotyping, costs have dropped below 50 USD/sample, covering most common genetic variants with arrays available that can account for the linkage disequilibrium structure of different ethnic backgrounds, which increase diversity. Whole-genome sequencing approaches can now generate data for one individual for less than 500 USD, and new methods allow turnover times of about five hours, so that these results can even be used in critical care medicine (Gorzynski et al. 2022). Meanwhile, the Psychiatric Genomics Consortium (Sullivan et al. 2018) has spearheaded collaborative science in psychiatric genetics, facilitating the gathering of the very large sample sizes required for statistical power to detect variants. The work of the Consortium focuses on attention deficit hyperactivity disorder (ADHD), Alzheimer disease, autism spectrum disorder (ASD), bipolar disorder, eating disorders, major depressive disorder (MDD), obsessive-compulsive disorder/Tourette syndrome (OCD/TS), posttraumatic stress disorder (PTSD), schizophrenia, substance use disorders, and all other anxiety disorders. It includes well over 800 investigators from over 150 institutions and over 40 different countries and data from several 100,000 patients and controls. In addition, there are initiatives and resources for large-scale genetic analyses that focus on discovery of both rare and common variants. These include additional large consortia such as the Autism Sequencing Consortium and the Schizophrenia Exome Meta-Analysis Consortium (SCHEMA), consumer-directed genotyping (e.g., 23andme, GeneDx, Regeneron), large national biobank initiatives (e.g., UK Biobank or iPSYCH), all of which have contributed to the discovery of risk genes.

Thus far, the payoff has been tremendous, especially for disorders such as schizophrenia and intellectual/neurodevelopmental disorders (ID/NDD),

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which are farthest along in terms of our understanding. These two disorders illustrate different types of observed genetic architecture, with *de novo* variants being the largest contributor of risk for ID/NDD and a mix of common and rare variants contributing to the risk of schizophrenia. The number of risk variants that have been identified for both disorders is high. Common variation at 270 distinct loci have been definitively demonstrated to contribute to the polygenic risk for schizophrenia, each conferring a small amount of risk (with odds ratios well below 1.5×). Meanwhile, with more modest sample sizes, whole-exome and whole-genome sequencing has identified ultra-rare variants in at least ten genes, which have been definitively identified as conferring substantial risk for the disorder, each with an odds ratio of 10× or greater. For ID/NDD, rare (frequently *de novo*) variation in over 80 genes confers substantial genetic risk. Overall, these studies confirm an inverse relationship of disease risk and variant frequency (Robinson et al., this volume; Singh et al. 2022). Both risk scenarios necessitate large sample sizes for discovery, and the range of middle frequency variants located between these common and rare ranges is thus far mostly unchartered territory (Robinson et al., this volume).

Given the hundreds of loci that have already been discovered, the question emerges as to when we will have discovered the majority of genetic risk variants in this field. Currently, we still are far from this point. Across psychiatric and neuropsychiatric disorders, we continue to identify new loci and do not see evidence of plateauing (Robinson et al., this volume), even though current sample sizes for genome-wide association studies now often reach one million subjects, and more exome sequencing studies are being performed in well over 100,000 individuals. Indeed, for most disorders beyond schizophrenia and autism, the field is still very much in discovery mode, with the numbers of identified genetic risk factors merely in the dozens. Moreover, an important limitation of the current body of genetic evidence is the lack of diversity in the samples; by far, most individuals who participate in these genetic studies are of European descent. This lack of diversity has implications for both discovery and translation of genetic risk (see Ronald et al., this volume). Thus, an important aspect of efforts focused on finding additional genetic risk factors needs to be focused on expanding the diversity of our genetic samples.

Understanding Biology

Even if there is still room for discovery, the fact that many genetic associations have been cataloged raises the question whether this has improved our understanding of the biology of psychiatric disorders. At the level of understanding the structure of genetic risk, the field can justifiably claim significant progress for at least some mental illnesses. Schizophrenia, as noted above, demonstrates high levels of polygenicity, well beyond those observed for other common disorders (Zeng et al. 2021). This polygenicity could relate to its intrinsic

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brain-based biology (with the highest numbers of genes expressed in the brain) or to the potential heterogeneity of the biological disease underpinning the common current diagnostic label (see Hu and Won, this volume). Schizophrenia, however, is also a disorder with very high "genetic correlation with itself"; that is, high genetic correlation between one schizophrenia case-control data set to another (over 0.9), indicating that influences of common variants on schizophrenia are extremely similar, regardless of the circumstances of ascertainment of the individuals with the diagnosis. Other psychiatric disorders, such as ASD or MDD, have lower cross-cohort correlations (Robinson et al., this volume), suggesting larger diagnostic heterogeneity. Both polygenicity and genetic heterogeneity will likely impact progress for these disorders. This indicates the necessity for even larger samples with additional (deep) phenotypes, including information on environmental risk (Nivard, this volume) available for further discovery.

Heterogeneity within a diagnosis is only one part of the complex story that genetic risk is telling us about mental illnesses. Another important finding that has emerged from both rare and common variant associations is pleiotropism of genetic disease risk (Lee et al. 2021). There is a large proportion of shared genetic risk across psychiatric disorders, as well as neurological and some medical disorders and traits (Brainstorm Consortium et al. 2018). In large-scale healthcare data sets, the polygenic risk score for schizophrenia, for example, has been found to associate not only with schizophrenia and psychotic disorders, but also with other psychiatric and medical disorders, often with confidence intervals of odds ratios mostly overlapping with those of odds ratios for schizophrenia and psychosis (Zheutlin et al. 2019). Such pleiotropy is also seen with rare variants of large risk for neuropsychiatric disorders. To date, no genes have been identified that exclusively confer risk for ASD and not also for ID or other neurodevelopmental disorders. This pleiotropy has impacted our progress in understanding genotype to phenotype correlation, and thus biological understanding of diagnoses, as well as our progress in utilizing genotype data to guide clinical diagnostic and treatment algorithms. The pleiotropy across multiple brain disorders raises the question whether more specific genotype to phenotype relationships should be evaluated specifically for individual diagnoses, or whether these diagnoses should be thought of as manifestations of underlying developmental brain dysfunction and thus investigated together. Indeed, cross-disorder approaches have already been taken for common psychiatric disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium 2019).

Despite the issues of heterogeneity and pleiotropy, risk variants are indeed beginning to tell us more than just the structure of genetic risk; the identity of these risk variants is beginning to inform us about relevant neurobiology. Deleterious genetic variants in genes related to neurogenesis and nervous system development have been associated with increased risk for ASD, neurodevelopmental disorders but also schizophrenia (Iakoucheva et al. 2019; Singh

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et al. 2022). Pathway analyses of genome-wide association studies often point to similar biological systems implicated in different psychiatric disorders, such as synapse function (schizophrenia, ASD, bipolar, ADHD), chromatin remodeling (schizophrenia, ASD, depression), or immune function (depression, schizophrenia, ASD)—again not providing strong evidence for disorder-specific disruptions (Lee et al. 2021; Network Pathway Analysis Subgroup of Psychiatric Genomics Consortium 2015). Such pleiotropy also impacts how to move from genetic risk variant to function and ultimately pathomechanisms. For rare, but mainly common variants, the generation of large-scale data sets—annotating genetic variants to gene expression (including non-coding RNAs and splicing) and epigenetic modifications and 3D chromatin structure, specifically in brain tissue—has hugely accelerated our understanding of the potential function of these variants through system biology approaches (Gandal, this volume), especially since most associated common variants lie within regulatory and not coding regions of the genome.

While these resources have hugely accelerated discovery, there are important gaps, especially in cell-type specific annotations, missing developmental timepoints, and molecular resolution, especially in the protein space. The next step in functional understanding is to test how these variants influence function, from altered protein levels to cellular function and system-level changes. For psychiatric disorders this involves often specific brain circuits and influences risk of disease. This can only be achieved by using model systems. Human-induced pluripotent stem cell (iPSC)-derived model systems coupled with the possibility to generate humanized rodent and primate models now allow unprecedented possibilities to investigate gene-function relationships, including polygenic risk, on multiple levels up to complex behavior over the course of development. How such models can be best used, their promises as well as current limitations, is discussed by Brennand and Kushner (this volume).

While we have in-depth understanding of gene-function relationships in some specific rare (but also a few common) risk variants (e.g., Pak et al. 2021; Yilmaz et al. 2021), this information is lacking for a vast majority of associated variants. For all variants, it is so far unclear how they ultimately alter human disease risk. Especially for polygenic disorders, it remains to be understood which are the points of convergence (molecular, cellular, or circuit level) that lead to similar symptom presentation despite heterogeneous individual genetic risk composition, including different subsets of polygenic risk, rare variants, as well as a combination of rare and common variants.

Clinical Applications

The second major issue that we addressed is whether current advances in psychiatric genetics have impacted clinical practice. As with biology, the field can claim at least one significant advance. Currently, use of exome or genome

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sequencing is recommended as first-line testing for neurodevelopmental disorders such as autism; something on the order of one-fifth of children will have an identifiable, large effect size rare variant that likely played a causative role in their diagnosis. While such knowledge in and of itself can be important for individuals with a neurodevelopmental disorder and their families, the specific rare risk variant an individual carries does not typically affect clinical decision making, nor does it inform disease course. Thus, the practical utility of genetic diagnostics, even in this case, has not yet been fully realized (Chawner et al. 2021; Douard et al. 2021; Raznahan et al. 2022). Moreover, while sequencing is now offered to children with these disorders, adults with brain disorders are still underserved (Finucane et al. 2020). In the common variant space, aggregated polygenic risk scores hold potential to influence diagnoses, but the many caveats attached, including nonspecificity and low predictive value, are even more limiting. Indeed, even for well-characterized disorders like schizophrenia, polygenic risk scores are not ready for clinical use (see Smoller, this volume).

The promise of identifying genetic risk factors lies in their ability to reveal direct treatment targets. Small molecules from drug repurposing that interfere with pathways affected by the disrupted genes have been tested for tuberous sclerosis complex disorders and Fragile X disease. In neurology, genetic investigation has already led to the first successful antisense oligonucleotides trials and an FDA-approved treatment for spinal muscular atrophy. There are promising results and ongoing trials for gene replacement therapy using viral vector delivery, mainly for metabolic disease (for an overview, see Sahin, this volume). However, several obstacles need to be overcome, including gene delivery to the specific organ/cell type and delivery of the right amount of gene product to the end target, at the right time. Timing and dosing are particularly important in neurodevelopmental disorders like Rett syndrome, where decreased (Rett syndrome) but also increased (MECP2 duplication syndrome) function of the affected gene MECP2 is pathogenic (Sandweiss et al. 2020).

The coincidence of tremendous progress and increased knowledge as well as the relative lack of actionable clinical consequences prompts new questions regarding genetic counseling, especially for polygenic disease risk (see Austin, this volume), as well as ethical questions related to polygenic prediction. Before rolling out these diagnostic tools to clinical application (e.g., for predictions of disease vulnerability, treatment response, and disease course), careful evaluation of the risks and benefits of such technologies is required, as adverse effects (including stigmatization, demoralization, therapeutic nihilism, and self-fulfilling prophecies) have not been sufficiently evaluated (see Appelbaum, this volume).

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The Ernst Strüngmann Forum: Exploring and Exploiting Genetic Risk for Psychiatric Disorder

In the context of these advances and the need to make further progress, this Ernst Strüngmann Forum was convened to discuss how best to realize the tremendous opportunities afforded by genetic discoveries. The task was to identify areas in the translation of genomics to neurobiology where a systematic, consensus-based, and collaborative approach to experimental science could help reveal the key neurobiological mechanisms associated with genetic risk for mental illness and foster translation of this knowledge into clinically useful approaches.

As noted above, experts from a variety of related disciplines were invited to participate. To ensure all participants were equally informed regarding the current state-of-the-art, papers were commissioned in advance to cover aspects of optimal sample collection (Robinson et al., this volume) and the impact of environmental risk and gene–environment interactions to further gene discovery (Nivard, this volume). Other papers address how common variants create risk for psychiatric disorders (see chapters by Hu and Won as well as Wray, this volume), how systems biology approaches have helped to understand underlying biology (Gandal, this volume), and optimal model systems for follow-up functional analyses of common and rare variants (Brennand and Kushner, this volume). A further set considers how new knowledge can be best communicated and translated to patients, delineating future steps in psychiatric genetic counseling (Austin, this volume), debating promise and challenges of precision medicine in rare neurodevelopmental disorders (Sahin, this volume), reviewing how polygenic risk score can be used in clinical psychiatry (Smoller, this volume), and, importantly, the ethical challenges associated with advances in genetic prediction of neuropsychiatric disorders (Appelbaum, this volume). Collectively, these authors demonstrate the tremendous progress made to date, while also highlighting the gaps in knowledge and challenges ahead.

One collective takeaway, implied in the theme of the Forum, is that psychiatric genetics seems to be at a turning point, with expectations running high on a return for biological understanding and clinical application. Accordingly, the Forum participants sought a critical evaluation of the status of this field and current knowledge to project the path forward. To accomplish these tasks, participants were divided into four working groups, each of which was tasked with addressing major challenges faced by the field.

Ronald et al. (this volume) focused on how best to identify additional genetic risk factors since much of the risk for psychiatric disorders remains unexplained. They looked at the importance of discovering additional risk factors as well as approaches on how best this could be achieved and explored the following issues:

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- The advantages and disadvantages of studying quantitative versus categorical phenotypes and developmental phenotypes versus diagnostic outcomes.
- How to exploit heterogeneity and co-occurrence to do better gene discovery and hypothesis testing.
- What the costs and benefits of capturing the entirety of the allelic frequency spectrum will be both translationally and biologically, and how this differs by condition.
- How best to increase diversity in samples, and how this contributes to discovery, translation, and justice and equity.
- How to explore the space of environmental risk and gene–environment relationships.

Bearden et al. (this volume) focused on variants of large effect and discussed how best to move from lists of genes to insight into cell type, circuit-level action, developmental time and, ultimately, novel therapeutics. They structured their discussion around key issues in the field, including prioritization, convergent neurobiology, models, and clinical trials, and asked:

- With the goal of improving therapeutics, what are the key dimensions to prioritize genes and loci for neurobiological investigation?
- Which strategies will permit us to test for convergence/divergence in mechanisms between genetic loci, and how can we determine meaningful convergence?
- Which models should be used to interrogate genetic loci, how should they be leveraged, and how can their predictions be validated in humans?
- What are key advances required in natural history, biomarkers, and clinical endpoints to optimize the probability of success in clinical trials?
- How do we establish infrastructure and incentives to generate rigorous reproducible findings?

Won et al. (this volume) investigated common variants and how to understand the collective impact of common alleles with small effect size. Most genetic risk for psychiatric disorders seems to come from common alleles with small effect sizes, likely numbering in the hundreds to thousands. These common alleles of small effect are challenging as a starting point for understanding neurobiology. Won et al. present recommendations on how to best move from associated locus to causal variant, then from causal variant to gene, and ultimately from gene to function and phenotype. An important consideration in all these steps is context dependence (cell type, developmental period, exposure to cellular stressors) as well as gene–environment interplay. They present a new experimental paradigm that can capture polygenicity and allow us to

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move forward in understanding the aggregated functional impact of polygenic disease risk.

Davis et al. (this volume) explored clinical applications that leverage genetic associations to psychiatric disorders, specifically on how to move forward for diagnosis, treatment, and patient stratification: What can we do now? What can we envision doing in the near foreseeable future? And how do we get there? Their discussion considered the impact of genetic counseling and testing on the clinical management of mental illness, as well the impact of genetic education on the public discourse focused on mental illness. Further, they delineate near-term opportunities and challenges for copy number variants and rare variants in ethical clinical mental health practice as well as the opportunities and challenges for polygenic scores in ethical clinical mental health practice. Finally, they posit possible next steps and recommendations to maximize near-term clinical opportunities.

In conclusion, the chapters in this volume aim to convey the extensive discussions and recommendations that emerged from this Forum. We hope they will inspire the field to move forward in a coordinated, expeditious way, building on the tremendous advances of the past decade. In addition, we hope they will prompt further conversation and consensus-building. All these steps are necessary if we are to realize the true promise of psychiatric genetics; namely, to clarify the pathophysiological mechanisms of mental illness and transform the clinical practice of psychiatry.

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