Thoughtful Phenotype Definitions Empower Participants and Power Studies

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Introduction

Substantial advances in understanding the genetic architecture of complex traits have been achieved through large global collaborations that maximize sample size [1] and strive for highly homogeneous phenotype definitions. Consequently, we have identified >500 genome-wide significant loci associated with 15 psychiatric disorders [1]. However, these associations have not yet yielded translational insights into disease; we have not identified new drugs or therapeutics based on these findings. Further, progress has been uneven, with the majority of associations in very large and homogeneous samples of primarily European origin [2, 3]. In order to move towards our ultimate goal of precision psychiatry and, consequently, better outcomes for our patients, new strategies will be needed. Continuing to amass additional samples following the same approach is unlikely to yield insights into psychiatric disorders with heterogeneous presentations (such as, for example, PTSD), to achieve functional insights, or to increase equity among our studies.

In this editorial, I would like to reflect on phenotype definitions within our studies, and how careful attention to these might both empower our study participants and

yield higher powered studies. At their core, GWAS represent a series of regression analyses, testing an association between a genetic variant and a phenotype. As a field, we have spent a lot of time refining the "SNP" portion of this equation: efforts to more delicately or precisely interpret how a specific variant could induce some disease outcome or to pinpoint the precise "causal" variant in an associated locus. Similar efforts must be made to refine the left side of our regression to carefully interpret the phenotype definitions we rely on. The same precision and dissection of phenotype definition is warranted in order to maximize the translational output and impact of our GWAS studies.

Since our genetic associations are only as good as the inputs to our studies, relying on overly simplistic, restrictive, biased, or uneven diagnoses will result in overly general or unhelpful associations. Diagnoses applied too liberally, unevenly, or incorrectly will reduce study power; application of case/control criteria rather than quantitative traits will restrict our ability to ask nuanced questions about disease severity or progression; stereotyped or biased diagnostic definitions may alienate patients and bias study results; and study designs that do not reflect clinical decision making are unlikely to be useful in achieving our

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goal of precision psychiatry. Here, I outline key issues in phenotype definitions for psychiatric GWAS, describe the impact of these issues on our patients and our studies, and offer potential solutions.

Phenotypes Rarely Present in Isolation

GWAS designs typically present inclusion and exclusion criteria: inclusion defined on specific clinical diagnostic factors or self-diagnosis; exclusion based on the presence of potentially confounding factors or diagnostic histories. For example, researchers may exclude histories of schizophrenia when researching bipolar disorder, or histories of bulimia nervosa when studying anorexia nervosa. On the one hand, this simplifies study design: we can confidently interpret genetic associations. On the other hand, removing individuals with comorbidities risks overestimating genetic liability by truncating the liability scale [4]; excludes individuals with complex diagnostic histories from our studies, potentially removing those patients with the most persistent or severe forms of a disorder; and/or excludes specifically those patients who might face barriers in obtaining accurate diagnoses due to societal bias [5]. Consequently, our studies become underpowered, and our patients are excluded.

Diagnoses Are Unevenly Applied or Distributed

Diagnoses are not arrived at in a vacuum; rather, symptoms, behaviours, and the consequences thereof are affected by our environment. Most perniciously, implicit and explicit biases occur due to societal and structural racism, sexism, homophobia, and transphobia. These issues extend beyond psychiatry, although the lack of specific diagnostic tests leaves our field especially vulnerable to bias and misconduct [5, 6]. These issues have been reviewed and discussed in depth previously, and readers should prioritize the insights of researchers and patients of colour, and those from historically marginalized communities in science and medicine, on these topics [7–13].

The consequence of this bias is that phenotypes are unevenly arrived at between patient groups, and case definitions become less accurate due to biased over- or under-diagnosis. For example, lower diagnostic thresholds are applied when diagnosing black men with schizophrenia compared to all other groups, leading to over-diagnosis [14]. Biased diagnostic definitions, written based on stereotyped assumptions about disease presentation, will also result in uneven diagnostic accuracy. In these instances, even perfectly followed or applied diagnostic guidelines will result in imperfect diagnoses, since symptoms listed rely on stereotypes rather than disease pathology. For example, the inclusion of amenorrhoea in anorexia nervosa diagnostic guidelines biases diagnosis towards people who menstruate – away from children, cis men, and post-menopausal women, all of whom are nevertheless at risk of developing eating disorders [15–17]. Similarly, ADHD symptoms may be rated more highly among boys, leading to under-diagnosis in girls [18]. These biases may be internal as well as external, preventing affected individuals from seeking diagnoses because they do not see themselves reflected in a stereotyped description of a disorder [15].

Psychiatric Phenotypes Are Rarely "Case/Control"

In the absence of a diagnostic test or laboratory result, psychiatric diagnoses rely on assessing the presence or absence of a set of symptoms and behaviours which in various combinations represent a clinical case of a given disorder. Although in some few psychiatric disorders, we might reasonably expect any member of the general public to be free of all symptoms of a disorder (for example, it is unlikely that any given individual will be experiencing diagnostic symptoms for schizophrenia), for many diagnoses, this will not be the case. For example, many features of eating disorder diagnostic criteria are broadly endorsed throughout the population: picky eating is a common childhood behaviour [19]; dieting and body dissatisfaction are pervasive (~56% of women have tried to lose weight in the past 12 months [20]); disordered eating practices such as skipping meals are common dietary behaviours [20]. Similarly, depressive episodes are highly common [21]; anxiety and somatization symptoms are widely observed in response to global stressors such as COVID-19 [22]; occasional substance use is pervasive [23]; and the majority of cannabis users do not have cannabis use disorder [24]. This is not to say that individuals experiencing some aspects of psychiatric disease should be considered "cases"; rather, that delineating disorders into cases and controls rather than along quantitative measures or spectra will likely result in substantial presence of disease symptomatology among control groups.

The reduction in power resulting from use of binary traits rather than quantitative traits has been shown statistically [25] and is not novel. However, reduction of psychiatric diagnoses to simple case/control also obscures

our ability to interrogate specific facets or symptoms of the disorder or to distinguish between the genetic underpinnings of disease onset versus severity.

Case/Control Is Not Clinically Useful

Increasing accuracy or ease of diagnosis is an oft-cited goal of precision medicine. We hope that by incorporating genetic data into clinical practice, we will be better able to help patients presenting in our clinics: to predict a diagnosis, outcome, improvement, or treatment. However, our favourite study design is not ideally suited to this goal; and consequently, the majority of our genetic association results are not optimally suited to answer our favourite question. Consider the diagnostic journey of the typical patient seeking an accurate diagnosis. Prior to seeking clinical care, they have experienced a range of symptoms, connected to one or possibly several psychiatric disorders. These symptoms may have resulted in earlier inaccurate or incomplete diagnoses or may have led to specific treatments, either prescribed by a doctor or following patient-driven research. The question facing our clinicians is not whether the presenting patient is a "case" or a "control"; the patient themselves, or referring clinicians, have already established that there exist some behaviours that warrant diagnosis or at least investigation. Rather, the challenge is to identify which of several potential diagnoses best fit the patient; to identify one of several potential trajectories or outcomes are the most likely; to rank many available medications to identify the most helpful. In order for genetic information to usefully inform these decisions, we should be able to associate specific variants or risk scores with the likelihood of developing one disorder rather than another or with the severity or specific symptom profile of disease.

Case/Control Does Not Reflect Patient Experience

Supporting individuals suffering with mental ill health requires that we act on their terms: respecting their experience, understanding and reporting of their own symptoms. Towards this goal, the use of case/control definitions are likely unhelpful at best and damaging at worst. Dismissing symptoms because they do not fit a specific diagnosis is likely to alienate patients; this will be especially dangerous if symptoms are dismissed because they do not yet meet sufficient criteria for severity (for example, dismissing individuals with insufficiently low BMI in eating disorder clinics [15]). Further, the use of overly clinical or old-fashioned language may alienate patients or may prevent young people from identifying with or engaging in appropriate and helpful interventions or research studies. Researchers should seek out the views and input of individuals with lived experiences of the disorders we study and allow them to discuss and reflect on their experiences and diagnoses using their own terms, descriptions.

Solutions

Studies of Quantitative Traits

As discussed in the first half of this editorial, case/control analyses are limited in their clinical applicability and statistical power [25]. Quantitative trait analyses allow us to interrogate the genetic variants associated with the full spectrum of disease or, by truncating the search space to only include cases (or any other group of interest), to ask questions about disease severity or trajectory. Those disorder groups who have adopted a quantitative trait approach do indeed observe differential genetic architectures underpinning different portions of the severity spectrum; for example, distinct genetic risk factors are associated with continuous versus problematic alcohol use [26]; with continuous BMI increase compared to extreme low or extreme high BMI [27]; or with ADHD symptoms within the neurotypical population compared to among neurodivergent individuals [28].

Notably, case/control GWAS associations can still be used to identify genetic underpinnings for specific symptoms; for example, my own team recently demonstrated that anorexia nervosa genetic risk scores are associated with weight loss among adults without documented histories of eating disorders. Where it is not possible or feasible to quantify specific symptoms within a population (for example, when subjects cannot be re-contacted), researchers should instead turn to these types of approaches to interpret genetic associations with specific symptoms.

Case/Case GWAS

GWAS or other statistical genetics analyses that explicitly compare case genetics may yield vital insights towards the problem of clinical differentiation between diagnoses. By comparing only individuals with diagnoses, we may discover variants predisposing to one disorder rather than another, either through association with diagnosis-defining symptoms (such as, for example, re-

strictive behaviours in anorexia or psychotic experiences in schizophrenia [30, 31]) or through identifying factors that may protect against specific disorders compared to another.

Studies of Specific Symptoms

Studies of specific symptoms or facets of disorders, rather than diagnoses, may yield more significant insights into disease aetiopathology and may more easily identify targets for specific medications. Such analyses may be achieved by partitioning existing GWAS samples into individuals with and without a certain symptom (or ideally according to symptom severity); however, in the absence of this detailed information, researchers may also aggregate across disorders having this single symptom in common, essentially employing cross-disorder fine-mapping to identify causal variants for a given symptom or outcome. Previous analyses have, for example, meta-analysed across schizophrenia and bipolar disorder to identify genes associated with shared symptomatology [30] or across individual experiencing suicidal ideation [32], regardless of initial psychiatric diagnosis. These study designs allow us to tease apart cause and effect, identifying whether a specific symptom is part of disorder pathology or consequence.

Electronic Health Record Analyses

Electronic health record (EHR) analyses offer immediate expansion of studies, without the need to recruit new patients, allow analysis of comorbidities or longitudinal effects [29], and provide some degree of comparability across cases and controls, who by necessity are usually sampled from within the same healthcare system. Nevertheless, some uneven access to treatment and specialized care may occur within these systems due to uneven health insurance coverage, or other societal and structural inequities. However, since EHR captures the entire medical record, rather than restricting to a specific diagnosis, we may be able to spot "missing" diagnoses. By identifying patients who present with similar complaints, or who have similar diagnostic histories or patterns, but who differ in their final diagnoses, we may be able to identify systematic differences in diagnosis and/or may be able to pinpoint individuals who likely suffer from undiagnosed or misdiagnosed disorders. These approaches may be enacted through machine learning phenotyping algorithms [33–35], automatic phenotyping [36], or through manual chart review.

Dedicated Studies of Bias

While some systematic under- and over-diagnoses have been documented and explored in depth, it is highly likely that other imbalances pervade our clinics due to implicit or explicit bias [5], systemic discrimination, intersection of our healthcare systems with unfair financial systems, the prison/military-industrial complex, and immigration systems [7–13, 37]. For example, uneven access to health insurance is likely to result in systematically different prescription patterns among our patients; fears about incarceration or restrictions on military service, immigration opportunities, and access to certain veteran benefits may preclude treatment seeking for specific diagnoses or substance use.

Consequently, the true extent to which these biases pervade our diagnostic practices, trajectories, and outcomes may not be obvious from secondary analyses of existing EHR or GWAS data. It is unlikely that even the best intentioned researchers seeking to study a specific psychiatric trait will have sufficient resources or skills to fully investigate these factors within their own data. Therefore, dedicated studies should be designed and funded to investigate biases within psychiatric diagnosis, EHRs, and healthcare systems. These results should actively and continuously inform our study design and phenotype definitions.

Conclusion

The challenges and solutions presented herein are not exhaustive and represent only one step towards our eventual goal of equitable precision psychiatry. Efforts to improve phenotyping and diagnostic definitions must take place in tandem with approaches to understand the biological mechanisms implicated by the results of our studies. For example, work to interpret the functional consequences of GWAS associations, disentangle polygenic risk scores, integrate common and rare variants studies, understand the role of environmental exposures in disease and in conjunction with genetic associations, and assess the impact of these various sources of risk using iPS cells will all be required in order to yield the highest possible insights from our existing genotype data.

However, many of the recommendations outlined here are vital; without the involvement of our patients, our studies will fail. Ultimately, our work as a field is in service of better outcomes for patients; if we do not centre their experiences, opinions, and symptoms, we cannot succeed. While this editorial has primarily focused on the role of research-

ers, the involvement and support of funding bodies will also be key. Funding should be made available to explicitly examine diagnostic biases, phenotyping approaches, symptom-specific analyses, as well as genetic counselling and other approaches to communicate genetic association studies, their goals and outcomes, to our patients.

Conflict of Interest Statement

Dr. Huckins declares no conflicts of interest.

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Author Contributions

Dr. Huckins is the sole contributor to this work.

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