Genome **Medicine**

RESEARCH HIGHLIGHT

Genomics and the classification of mental illness: focus on broader categories

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Abstract

Coinciding with the release of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders, two recently published molecular genetics analyses suggest large overlaps in genetic liability to schizophrenia, bipolar disorder and major depressive disorder. This indicates that a broader category of severe mental illness may be an important target for future large-scale etiological and therapeutic investigations. Studies of patient groups not restricted to current diagnostic categories may lead to a genetically informed nosology.

Introduction

The year 2013 may be a turning point in the history of psychiatry. In May 2013, the American Psychiatric Association published the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [1]. In April and September 2013, the Psychiatric Genomics Consortium (PGC) published key reports on the genetic relationships between five major psychiatric disorders [2,3]. A comparison of these publications highlights issues that psychiatry will have to grapple with in the next decade.
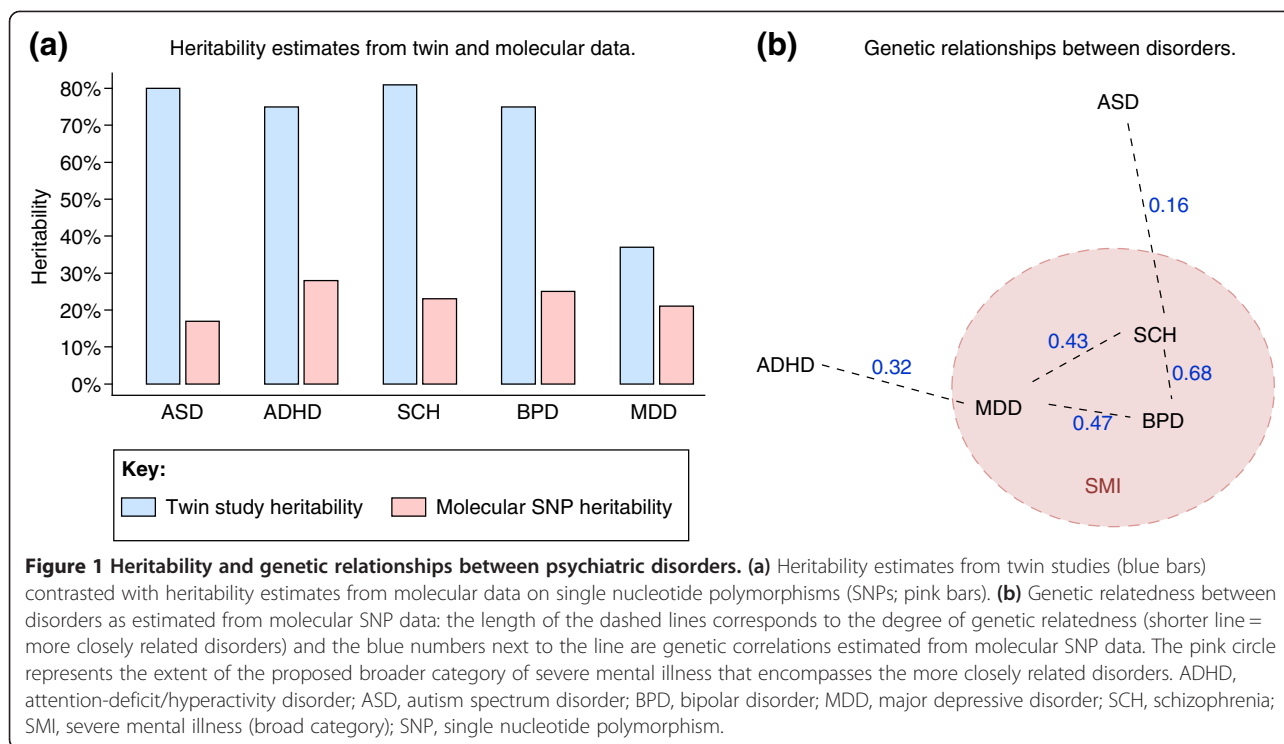
Genetics is one of the major sources of information on the classification of mental illness. Unlike cognitive or neuroimaging measurements, genetic information is stable across an individual's life and can be interpreted as a cause rather than a consequence of psychopathology. For decades, information on the genetic contribution to liability and genetic relationships between disorders was derived indirectly from family, twin and adoption studies. With the application of genomic approaches, it is now possible to estimate the magnitude of the genetic contribution and the degree of relatedness between disorders directly from molecular data. The results of these analyses are not without surprises. Here, I discuss the new findings and their implications for the classification of psychiatric disorders.

Mental illness: not as heritable as we thought?

The first finding of the recent PGC studies [2,3] concerns the overall magnitude of the genetic contribution to mental illness. This is typically indexed as heritability, a measure ranging from 0 to 1 that reflects the proportion of differences between people that are attributable to genetic factors. It has been known for decades that mental illness runs in families, and twin studies have produced heritability estimates ranging from 0.37 to 0.90 [4]. Researchers from the PGC have used a new method to estimate heritability from molecular genetic data. By comparing the overall number of genetic similarities between patients with an illness to the number of genetic similarities between patients and controls, they estimated that common genetic variants contributed between 17% and 29% of the variation in liability to mental illness, approximately one-third of the heritability estimates derived from twin studies (Figure 1a) [2]. It is also less than heritability estimates for non-disorder phenotypes, such as the response to antidepressants or reported stressful life events obtained with the same molecular method [5,6]. The discrepancy between molecular and twin estimates may be partly because some of the risk is carried by rare genetic variants that are only partly tagged by the measured common variants. The large differential between twin and molecular estimates of heritability for autism spectrum disorders, for which a large contribution of rare genetic variants is likely, suggests that this might be the case [4]. However, it is also likely that twin studies overestimated heritability by assuming that monozygotic twins share a common environment in a similar way to dizygotic twins, and by including gene-environment interactions (those involving shared aspects of environment) in estimates of heritability [4]. In any case, the magnitude of the difference

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Figure 1 Heritability and genetic relationships between psychiatric disorders. (a) Heritability estimates from twin studies (blue bars) contrasted with heritability estimates from molecular data on single nucleotide polymorphisms (SNPs; pink bars). **(b)** Genetic relatedness between disorders as estimated from molecular SNP data: the length of the dashed lines corresponds to the degree of genetic relatedness (shorter line = more closely related disorders) and the blue numbers next to the line are genetic correlations estimated from molecular SNP data. The pink circle represents the extent of the proposed broader category of severe mental illness that encompasses the more closely related disorders. ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; BPD, bipolar disorder; MDD, major depressive disorder; SCH, schizophrenia; SMI, severe mental illness (broad category); SNP, single nucleotide polymorphism.

between twin and molecular findings suggests caution when using twin studies to inform nosology.

Relationships between psychiatric disorders: time to re-focus on broader categories

One of the changes in DSM-5 was the separation of 'mood disorders' into two chapters, one on bipolar and the other on depressive disorders. The PGC has shown that there are more genetic similarities than differences between mood and psychotic disorders. Schizophrenia shared 68% of genetic liability with bipolar disorder and 43% of genetic liability with depression. Bipolar disorder and depression shared 47% of the genetic disposition (Figure 1b) [2]. Four specific genetic variants were independently associated with two or more of these disorders, but not a single one was differentially associated with one disorder as opposed to others [3]. A recent meta-analysis of family studies corroborates these results by showing that familial risk goes beyond the disorder diagnosed in a relative and extends to all types of mood and psychotic disorders [7]. The fact that bipolar disorder has more genetic overlap with schizophrenia than with depression justifies the placement in the DSM-5 of bipolar as a separate chapter between psychotic and mood disorders. However, the large commonality among all three disorders (which is apparent in both molecular and family study data) is not reflected in the DSM-5. This suggests that both etiological investigations and intervention studies may benefit by broadening the

scope beyond single DSM categories to focus on common factors across disorders. It may be more informative to target broader categories, such as severe mental illness, which encompasses all major mood and psychotic disorders that typically start in late adolescence or young adulthood and are severe enough to require specialist psychiatric care.

Other broad categories are less well supported by molecular genetic data: DSM-5 has introduced a grouping of 'neurodevelopmental disorders' that includes autism spectrum disorders (ASD) and attention-deficit/hyperactivity disorder (ADHD). The assumption behind this grouping was that the etiologies of these disorders are related, but the PGC found no detectable overlap between the genetic liability to ASD and ADHD [2,3]. The fact that the molecular measurements were limited to common genetic variants leaves the option open that specific rare variants may contribute to both ASD and ADHD. However, since the common variants carry at least some information about rare genetic variants (through linkage disequilibrium), the lack of any detectable overlap presents a challenge to including ASD and ADHD in a single grouping and suggests that their etiologies may need to be studied separately.

The new molecular analyses also inform the continuity between child and adult disorders. One major issue that DSM-5 had to deal with was the surge in diagnoses of childhood bipolar disorder based on relaxed DSM-IV criteria, including non-episodic irritability and ADHD

symptoms as indicative of bipolar illness. In DSM-5, the criteria for bipolar disorder do not include such presentations; instead, a new diagnostic category, disruptive mood dysregulation disorder, has been created, which covers chronic irritability in children and is included among depressive disorders. These DSM-5 decisions are supported by the PGC finding of no genetic overlap between ADHD and bipolar disorder [2,3]. This contrasts with family studies, which found overlapping familial risks for bipolar disorder and ADHD [7,8]. The discrepancy between molecular and family studies implicates reasons other than common genetic variants for the co-occurrence of ADHD and bipolar disorder in families. Somewhat surprisingly, a significant overlap was found between ADHD and major depressive disorder. This is in agreement with a meta-analysis of family studies that found that the risk of ADHD was elevated to a greater extent among offspring of parents with major depressive disorder than among offspring of parents with bipolar disorder [7].

Distinctiveness of disorders and number of categories: the need to study unselected patient groups

DSM-5 continues a trend of producing an increasing number of disorders by splitting and creating new categories. The PGC took five of the most distinctive disorders and showed that there were more genetic similarities than differences between them [3]. This is yet more evidence of the limited validity of DSM categories [9]. Most available evidence suggests that having relatively few broader categories may be more useful than the current DSM classification in both research and clinical settings [10]. The alternative approach is a dimensional classification. This was rejected late in the DSM-5 development because there was no consensus on how many and which dimensions are needed and how they could be practically applied in clinical settings [1,10]. While the PGC cross-disorder analyses are informative in many ways, they may not help with the biggest question: how many categories or dimensions are needed to classify psychopathology. The PGC reports were based on a collection of case–control studies, each of which started with a DSM category. In a typical case–control study, participants who fulfill the criteria for a specific disorder are classified as cases, those who are relatively free of psychopathology as controls, and those who fulfill criteria for other disorders or fall in between are excluded. Without including the latter individuals - those who fall in between the criteria for disorders - in investigations, we cannot expect a major advance in psychiatric classification [10]. Some of the most remarkable discoveries in psychiatry, including the use of lithium for bipolar disorder and stimulants for ADHD, started with investigations of unselected patient groups. These discoveries may have been missed had the initial study focused on a single DSM-type category. Modern molecular genetics provides the tools to inform psychiatric classification in novel ways, free of assumptions and historical baggage. To do this, it needs large samples of individuals with mental illness that were not pre-selected based on a previous classification that is known to be of limited validity [4,10]. Investigation of such unselected groups coupled with emerging genomic methods, such as new generation sequencing, has the potential to create a classification derived from genomic data. The contrast between DSM-5 and molecular genetic cross-disorder analyses could make 2013 the starting point for new psychiatric science.

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