Title

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Journal

Psychiatric Genetics, 29(5)

ISSN

0955-8829

Authors

Smeland, Olav B

Frei, Oleksandr

Fan, Chun-Chieh

et al.

Publication Date

2019-10-01

DOI

10.1097/ypg.0000000000000234

Peer reviewed

HHS Public Access

Author manuscript

Psychiatr Genet. Author manuscript; available in PMC 2023 December 27.

Published in final edited form as:

Psychiatr Genet. 2019 October ; 29(5): 152–159. doi:10.1097/YPG.0000000000000234.

The emerging pattern of shared polygenic architecture of psychiatric disorders, conceptual and methodological challenges

Olav B. Smeland[a], **Oleksandr Frei**[a], **Chun-Chieh Fan**[b], **Alexey Shadrin**[a], **Anders M. Dale**[c,d,e], **Ole A. Andreassen**[a]

[a]NORMENT Centre, Institute of Clinical Medicine, Division of Mental Health and Addiction, University of Oslo and Oslo University Hospital, Oslo, Norway

[b]Center for Human Development, University of California, San Diego, USA

[c]Department of Radiology, University of California, USA

[d]Department of Neuroscience, University of California, San Diego, USA

[e]Center for Multimodal Imaging and Genetics, University of California, San Diego, La Jolla, California, USA

Abstract

Genome-wide association studies have transformed psychiatric genetics and provided novel insights into the genetic etiology of psychiatric disorders. Two major discoveries have emerged; the disorders are polygenic, with a large number of common variants each with a small effect and many genetic variants influence more than one phenotype, suggesting shared genetic etiology. These concepts have the potential to revolutionize the current classification system with diagnostic categories and facilitate development of better treatments. However, to reach clinical impact, we need larger samples and better analytical tools, as most polygenic factors remain undetected. We here present statistical approaches designed to improve the yield of existing genome-wide association studies for polygenic phenotypes. We review how these tools have informed the current knowledge on the genetic architecture of psychiatric disorders, focusing on schizophrenia, bipolar disorder and major depression, and overlap with psychological and cognitive traits. We discuss application of statistical tools for stratification and prediction.

Keywords

bipolar disorder; depression; pleiotropy; polygenic architecture; schizophrenia; GWAS

Correspondence to Ole A. Andreassen, MD, PhD, Professor of Biological Psychiatry, Division of Mental Health and Addiction, University of Oslo and Oslo University Hospital, Kirkeveien 166, 0424 Oslo, Norway Tel: +47 23027350; fax: +47 23 02 73 33; o.a.andreassen@medisin.uio.no.

Conflicts of interest

O.A.A. has received speaker's honorarium from Lundbeck and is a consultant for Healthlytix. A.M.D is a co-founder of NeuroQuant and HealthLytix. For the remaining authors, there are no conflicts of interests.

Introduction

Psychiatric disorders are recognized as leading causes of morbidity and are among the most costly disorders to affect humans (GBD 2015 DALYs and HALE Collaborators, 2016). At the individual level, suffering is large, and the disorders are associated with impaired quality of life and low socioeconomic status. Identifying the underlying pathophysiology for these disorders, as well as resilience factors, is imperative and can lead to major health benefits through better treatment regimens. Further, development of risk prediction in mental disorders could inform prevention strategies and enrich clinical trials. Although there has been a remarkable improvement in life expectancy for the general population the last decades, there is a marked social inequality in the field of mental disorders (Laursen *et al.*, 2011). Patients and their families display significantly higher mortality than the general population (Eaton *et al.*, 2008; Ringen *et al.*, 2014), both from natural causes (somatic conditions where cardiovascular disease is most important) and unnatural causes (suicide, homicide or accidents). Register-based studies demonstrate that patients with mental illness have 15–20 years shorter life expectancy than the general population (Wahlbeck *et al.*, 2011). To reduce this gap, knowledge of underlying disease causes and effective prevention strategies are urgently required (Insel, 2010).

Psychiatric disorders are regarded as complex disorders with heritability estimates between 40% and 80% (Lichtenstein *et al.*, 2009). Although there is clear evidence for rare sequence variants and copy-number variants with large effects associated with schizophrenia (Marshall *et al.*, 2017) and attention deficit hyperactivity disorder (Williams *et al.*, 2010), large-scale genome-wide association studies (GWAS) conducted during the last decade have shown that a moderate fraction of the heritability of most psychiatric disorders is accounted for by numerous common genetic variants with small ‘polygenic’effects (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Demontis *et al.*, 2019; Grove *et al.*, 2019; Howard *et al.*, 2019; Stahl *et al.*, 2019). Due to the revolution in genetics technology and the assembly of large genotyped samples, many genetic variants have successfully been associated with severe psychiatric disorders in recent years. Today, updates from the Psychiatric Genomics Consortium (PGC) include discoveries of 30 genomic loci for bipolar disorder (Stahl *et al.*, 2019), 102 for major depression (Howard *et al.*, 2019), five for autism spectrum disorder (Grove *et al.*, 2019), 12 for ADHD (Demontis *et al.*, 2019) and approximately 250 for schizophrenia (Pardiñas *et al.*, 2018). One characteristic finding is the large degree of genetic overlap between mental disorders (Lee *et al.*, 2013; Anttila *et al.*, 2018), and between mental disorders and related psychosocial traits (Lo *et al.*, 2017; Day *et al.*, 2018; Savage *et al.*, 2018; Jansen *et al.*, 2019), which may indicate shared molecular genetic mechanisms and possibly overlapping etiology. Yet, despite the assembly of very large GWAS samples, often involving more than 100 000 participants, most of the polygenic architectures underlying psychiatric disorders still remain undetected (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Demontis *et al.*, 2019; Grove *et al.*, 2019; Howard *et al.*, 2019; Stahl *et al.*, 2019). This can be attributed to the polygenic nature of psychiatric disorders that poses considerable challenges on analytical methods and GWAS sample size (Sullivan *et al.*, 2018). In short, a GWAS allows for genome-wide analysis of millions of common genetic variants [tag

single-nucleotide polymorphisms (SNPs)], estimating their effects on a given phenotype. Given the large numbers of SNPs tested, a GWAS must correct for multiple testing using a stringent threshold of genome-wide significance (typically, $P < 5 \times 10^{-8}$) to avoid false-positives. Thus, only a subset of all involved genetic variants is revealed, with a large fraction of the polygenic architecture remaining to be uncovered (i.e. 'the missing heritability') (Manolio *et al.*, 2009). This has motivated efforts to develop 'Big Data' analytical approaches that improve the yield of existing GWAS. In particular, mathematical models building on empirical Bayesian statistical approaches have emerged, which are specifically designed to handle polygenic scenarios, resulting in substantially improved power for genetic discovery (Andreassen *et al.*, 2013b; Schork *et al.*, 2016). Here we review some of the recent discoveries of polygenic architecture in major psychiatric disorders (schizophrenia, bipolar disorder, major depression) enabled by novel statistical tools, which has revealed genetic overlap across psychiatric disorders, psychosocial traits and several somatic traits and diseases. Moreover, we discuss how these tools may improve genetic prediction and estimate discovery trajectories of future GWAS for psychiatric disorders. For example, whereas the PGC now aims for 1 million genotyped participants for each mental disorder (Sullivan *et al.*, 2018), recent causal mixture modeling analysis (Frei *et al.*, 2019) estimated that this will explain approximately 60% of the SNP-heritability in schizophrenia and bipolar disorder, but only approximately 10% in major depression (Fig. 1).

Genetic overlap between psychiatric disorders and traits

The increasing wealth of GWAS data now available on human traits and disorders have shown that a large number of genetic variants influence more than one phenotype (Visscher *et al.*, 2017), that is, they exhibit allelic pleiotropy. This has profound implications for understanding the underlying biology of complex phenotypes. The standard approach to evaluate the polygenic relationship between two phenotypes today is to measure genetic correlation using tools such as polygenic risk scores (Purcell *et al.*, 2009) and linkage disequilibrium (LD) score regression (Bulik-Sullivan *et al.*, 2015). These tools have provided important insights into the shared genetic etiology between human phenotypes, including mental disorders (Visscher *et al.*, 2017; Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2018; Anttila *et al.*, 2018). However, the methods do not provide a complete picture of the complex genetic relationship between polygenic phenotypes. Similar to twin studies, genetic correlations are unable to reveal the individual genetic variants shared between the phenotypes, which is needed to identify the molecular genetic mechanisms involved. Further, the tools estimating genetic correlation can only detect genetic overlap when the effect directions are consistent (Purcell *et al.*, 2009; Bulik-Sullivan *et al.*, 2015). This is a clear limitation, as increasing evidence shows that overlapping genetic variants between several human phenotypes involve a mixed pattern of allelic effect directions (Baurecht *et al.*, 2015b; Lee *et al.*, 2016; Schmitt *et al.*, 2016; Bansal *et al.*, 2018; Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2018; Smeland *et al.*, 2018; Frei *et al.*, 2019; Smeland *et al.*, 2019).

Cross-trait analytical approaches such as the conditional False Discovery Rate (condFDR) approach complements the standard measures of genetic correlation by allowing

identification of individual overlapping variants that did not reach genome-wide significance, and by allowing identification of variants regardless of their allelic effect directions. The condFDR is a model-free strategy designed for polygenic phenotypes inspired by Empirical Bayes approaches (Efron, 2010). It leverages overlapping SNP associations (cross-trait enrichment) between two separate GWAS to improve statistical power for genetic discovery (Andreassen *et al.*, 2013a; Schork *et al.*, 2016). The conjunctional FDR (conjFDR) is a natural extension of the condFDR, which allows discovery of overlapping loci by providing a conservative estimate of the FDR for a SNP association with both phenotypes simultaneously (Andreassen *et al.*, 2013a; Schork *et al.*, 2016). Application of the condFDR and conjFDR approaches has increased genetic discovery and uncovered genetic overlap in a wide specter of complex human traits, including the psychiatric disorders schizophrenia (Andreassen *et al.*, 2013b; Andreassen *et al.*, 2015; Le Hellard *et al.*, 2017; McLaughlin *et al.*, 2017; Smeland *et al.*, 2017a; Smeland *et al.*, 2017b; Shadrin *et al.*, 2018; Smeland *et al.*, 2018; van der Meer *et al.*, 2018; Zuber *et al.*, 2018; Smeland *et al.*, 2019), bipolar disorder (Andreassen *et al.*, 2013b; Andreassen *et al.*, 2015; Drange *et al.*, 2019; Smeland *et al.*, 2019) and ADHD (Shadrin *et al.*, 2018).

Notably, the conjFDR approach has demonstrated genetic overlap between several phenotypes that are not genetically correlated, such as schizophrenia and brain structure volumes (Smeland *et al.*, 2018), schizophrenia and personality traits (Smeland *et al.*, 2017a), and bipolar disorder and intelligence (Smeland *et al.*, 2019). Moreover, it has helped elucidate the complexity of the genetic relationship between many complex phenotypes, for example, that between schizophrenia and cognitive function. It is well established that schizophrenia is associated with cognitive impairment (Kahn and Keefe, 2013), and many genetic studies have demonstrated a negative genetic correlation between schizophrenia and various cognitive measures using tools such as polygenic risk scores (Lencz *et al.*, 2014; Hubbard *et al.*, 2016) and LD score regression, with genetic correlations ranging between −0.2 and −0.4 (Hagenaars *et al.*, 2016; Hill *et al.*, 2016; Liebers *et al.*, 2016; Sniekers *et al.*, 2017; Trampush *et al.*, 2017; Anttila *et al.*, 2018; Davies *et al.*, 2018; Savage *et al.*, 2018). Complementing these studies, a recent condFDR investigation analyzed large GWAS on schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) and intelligence (Savage *et al.*, 2018), and identified 75 shared loci at conjFDR <0.01 (Smeland *et al.*, 2019). A gene-set enrichment analysis of the shared loci implicated biological processes related to neurodevelopment, synaptic integrity and neurotransmission, among others. Among the shared loci, schizophrenia risk was linked to lower intelligence at 61 (81%) of the loci (Smeland *et al.*, 2019). These findings corroborate a prior condFDR study on smaller GWAS samples on cognitive traits which found that schizophrenia risk was associated with poorer cognitive performance at 18 of 21 shared loci, where the implicated genes were globally expressed across the developing and adult human brain (Smeland *et al.*, 2017b). Thus, in addition to identifying more loci shared between schizophrenia and cognitive traits compared to the standard GWAS analysis, these conjFDR studies indicate that the shared genetic etiology between schizophrenia and cognitive function involves a mixture of agonistic and antagonistic effect directions, and is more complex than what is suggested by their moderate negative genetic correlation (Hagenaars *et al.*, 2016; Hill *et al.*, 2016; Liebers *et al.*, 2016; Sniekers *et al.*, 2017; Trampush *et al.*, 2017; Anttila *et al.*, 2018;

Davies *et al.*, 2018; Savage *et al.*, 2018). This is clinically important and in compliance with some reports that not all patients with schizophrenia perform poorly on cognitive tests (Palmer *et al.*, 1997).

Several methods for cross-trait GWAS analysis have been developed during the last decade, which have been extensively reviewed elsewhere (Gratten and Visscher, 2016; Schork *et al.*, 2016; Hackinger and Zeggini, 2017; Pasaniuc and Price, 2017). Building on the meta-analysis approach (Willer *et al.*, 2010), many techniques aim to identify shared or unique genomic loci across separate GWAS, including the COMBINE approach (Ellinghaus *et al.*, 2012), restricted and weighted subset search (association analysis based on subsets) (Bhattacharjee *et al.*, 2012), and compare and contrast meta-analysis (Baurecht *et al.*, 2015a). In contrast to such meta-analytical approaches, condFDR analysis intrinsically incorporates multiple testing via the FDR framework by directly working with the entire original set of *P* values from two investigated GWAS (Efron, 2010). Newer methods such as MTAG (Turley *et al.*, 2018) or Genomic SEM (Grotzinger *et al.*, 2019) leverage genetic correlation between phenotypes to improve discovery of shared loci. This is a powerful feature for highly correlated phenotypes, but not optimal for phenotypes with a low or non-significant genetic correlation. Conversely, the condFDR method improves genetic discovery by leveraging overlapping SNP associations regardless of the direction of their allelic effects and may boost discovery of loci jointly influencing phenotypes even in the absence of genome-wide correlation, such as done for bipolar disorder and intelligence (Smeland *et al.*, 2019). Loci prioritized by standard GWAS analysis or other cross-trait analytical methods can be further interrogated with tools that aim to disentangle LD structure and uncover causal genetic mechanisms. For example, several available Bayesian approaches can explore whether two association signals in the same genomic region obtained from two different GWAS share a single causal variant or multiple causal variants (Giambartolomei *et al.*, 2014; Pickrell *et al.*, 2016).

Variations in polygenicity and heritability define ‘discoverability’

To provide further insights into the genetic relationship between complex human phenotypes, we have developed a statistical model that estimates the number of causal genetic variants influencing a given phenotype (which is termed ‘polygenicity’) (Holland *et al.*, 2019) and the number of variants unique and shared between phenotypes (Frei *et al.*, 2019). The mathematical models build on a mixture modeling framework (Thompson *et al.*, 2015; Holland *et al.*, 2016), in which only a fraction of causal variants in the genome are assumed to influence a given phenotype, while a null-component is assumed to have no effect on the phenotype. The mixture modeling framework is increasingly applied by novel statistical tools for analysis of complex polygenic phenotypes (Zeng *et al.*, 2018; Zhang *et al.*, 2018). Our model works with GWAS summary statistics, and incorporate detailed LD structures, disentangling their effects on the GWAS signals. Building on this approach, we have introduced the term *discoverability* (Fan *et al.*, 2018). This is defined as the power to detect genetic variants for a given phenotype depending on its unique genomic architecture and GWAS sample size. Given a fixed GWAS sample size, the power to detect novel loci is determined by the effect size distribution of the causal loci. Correspondingly, a larger number of true causal loci (i.e. higher polygenicity) at a fixed heritability, will

make SNP effects harder to detect, since they will be increasingly difficult to separate from the background signal (Fan *et al.*, 2018). In addition to estimating polygenicity, the models also estimate the narrow-sense heritability, and the proportion of heritability captured by genome-wide significant SNPs (Frei *et al.*, 2019; Holland *et al.*, 2019). The latter is a function of GWAS sample size and enables power analysis of existing and future GWAS (Holland *et al.*, 2019). The univariate model thus explains why certain traits have lower yield of genome-wide significant hits despite having larger GWAS sample size and higher heritability (Holland *et al.*, 2019) (Fig. 1). For example, even though current GWAS sample sizes are substantially larger for major depression (246 363 cases and 561 190 controls) (Howard *et al.*, 2019) than for schizophrenia (34 241 cases, 45 604 controls and 1235 parent-affected offspring trios) (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) and bipolar disorder (20 352 cases and 31 358 controls) (Stahl *et al.*, 2019), recent univariate analysis shows that while the proportion of identified variance is around 3% in schizophrenia, and close to 1% in bipolar disorder, it is even lower in major depression (Fig. 1). This both reflects the larger number of variants estimated to influence major depression (14.9k variants) compared to schizophrenia (8.3k variants) and bipolar disorder (6.4 variants), as well the lower SNP-heritability of major depression (0.08) compared to the other two disorders (0.45 for schizophrenia and 0.34 for bipolar disorder) (Holland *et al.*, 2019). Altogether, these parameters yield a lower *discoverability* for major depression variants, and the model estimates that with 1 million GWAS participants, the expected genome-wide significant loci will explain approximately 60% of SNP-heritability in schizophrenia and bipolar disorder, but less than 10% for major depression (Fig. 1). Hence, although the PGC now aims for 1 million genotyped participants for each mental disorder (Sullivan *et al.*, 2018), this will seemingly not be sufficient to completely uncover the common variant architecture for these psychiatric disorders using standard statistical tools, in particular not for major depression. This warrants phenotypic refinement to reduce disease heterogeneity or applying more cost-effective statistical approaches to increase the yield of existing and future GWAS, for example, by leveraging overlapping genetic signal across traits and disorders to improve discovery.

The bivariate extension of the causal mixture model can estimate the extent of polygenic overlap between complex phenotypes, allowing shared GWAS participants (Frei *et al.*, 2019). For example, it estimated that there is substantial polygenic overlap between schizophrenia and educational attainment, which involves almost all causal variants for schizophrenia. However, there is a mixture of agonistic and antagonistic effect directions among the shared variants, yielding a low effect size correlation of 0.06 within the shared genomic fraction (Frei *et al.*, 2019). This is in line with the genome-wide correlation of 0.08 estimated between these phenotypes using LD score regression (Okbay *et al.*, 2016; Lee *et al.*, 2018), and prior genetic studies reporting mixed allelic effects among their overlapping genomic loci (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Okbay *et al.*, 2016; Le Hellard *et al.*, 2017). Moreover, the bivariate model estimated a substantial polygenic overlap between schizophrenia and bipolar disorder, which seems to involve almost all causal variants conferring risk to bipolar disorder (Frei *et al.*, 2019) (Fig. 2). Interestingly, the model also estimated that there are smaller fractions of causal variants that are specific to either schizophrenia and bipolar disorder, which may

offer important insights into the genetic differences between these disorders. We also find extensive overlap between bipolar disorder and major depression, but less overlap between schizophrenia and major depression (Fig. 2). Overall, these data suggest that in order to more completely understand the distinct genetic architecture underlying these disorders, it is important to characterize both their disorder-specific effect size distributions within the shared genomic fractions, as well as the disorder-specific non-overlapping fractions. To this end, three-way causal mixture model analysis may help mapping out unique and overlapping genetic mechanisms between groups of traits and disorders. This is a subject of our future research.

Improved prediction and clinical utility of polygenic statistical tools

Despite the significant advances in psychiatric genetics during the last decade, there is still no utility for individual genetic prediction in clinical psychiatry to aid prevention, diagnostic accuracy and predict therapeutic response and disease course. In comparison, polygenic risk scores have reached promising predictive power for various somatic conditions, but the evidence for clinical use is still sparse (Torkamani *et al.*, 2018; Abraham *et al.*, 2019; Khera *et al.*, 2019). Nevertheless, the discovery of genetic influences underlying mental traits and disorders may already inform psychiatric nosology, epidemiological associations, and provide insights into pathobiological underpinnings (Smoller *et al.*, 2018). For example, the converging evidence that psychiatric disorders share a considerable proportion of genetic risk variants with each other (Lee *et al.*, 2013; Anttila *et al.*, 2018; Frei *et al.*, 2019), poses a challenge to the current diagnostic classification systems, in which psychiatric disorders are considered categorically distinct (Smoller *et al.*, 2018). Additional data indicate that psychiatric disorders overlap genetically with a range of normal psychosocial traits such as cognition (Savage *et al.*, 2018), personality (Lo *et al.*, 2017), sleep patterns (Jansen *et al.*, 2019) and social traits (Day *et al.*, 2018). This indicates that most psychiatric disorders and psychosocial traits may exist on continua in genomic space, and are influenced by many overlapping genetic variants. Importantly, these results may support ongoing efforts to develop novel classification systems in which psychiatric disorders are considered continuous with normal variation in neurobiological and behavior dimensions (Cuthbert and Insel, 2010). Such a refinement of the psychiatric diagnostic system may help in establishing diagnostic categories that are more closely linked to distinct pathobiological processes.

The frequently used liability threshold models in genetic testing algorithms are designed to be insensitive of age (Falconer, 1965; Martin *et al.*, 2018). Yet, most psychiatric disorders have strong age-dependent clinical manifestations. To capture time-dependent pathological changes and predict onset of brain diseases, we have developed the Polygenic Hazard Score (PHS) (Desikan *et al.*, 2017), which provides a framework for exploitation of polygenic information towards clinical utility. In short, PHS models the time-dependent disease process by estimating the risk of onset as a hazard function, incorporating genetic variants that influence the age-of-disease-onset (Desikan *et al.*, 2017). By profiling disease risk in the temporal domain, PHS can quantify age-specific genetic risk for Alzheimer's disease and other complex diseases (Desikan *et al.*, 2017; Seibert *et al.*, 2018), providing grounds for clinical prediction and disease risk stratifications. We are currently working to revise and extend the PHS method by integrating other approaches to improve prediction of psychiatric

disorders, where an important feature will be to include non-genetic data (Seibert *et al.*, 2018). Although the genetic impact on temporal pathophysiological processes may not be monotonically increased over time for psychiatric disorders, it is of high importance to investigate whether there are polygenic effects that may accelerate or delay disease mechanisms. The PHS algorithms may also aid clinical trials as improved genetic risk stratification can help in selecting groups of high-risk individuals for study inclusion that are more likely to develop disease further on or respond to novel therapeutic agents.

Conclusion

Increasing evidence has shown that psychiatric disorders are highly polygenic and that genetic pleiotropy is pervasive among psychiatric disorders and related traits, providing important biological insights into underlying mechanisms. Although larger GWAS samples will increase the number of disease-associated variants, recent analyses suggest that not even GWAS sample sizes reaching 1 million participants will uncover most of the SNP-heritability for schizophrenia, bipolar disorder and major depression. Hence, more efficient statistical tools, that better take into account the distinct polygenic architecture underlying each disorder, may help move the field forward. As more disease-associated variants for psychiatric disorders will be uncovered, this may have a profound impact on understanding their underlying etiology and provide novel biomarkers to increase diagnostic accuracy and prediction algorithms.

Acknowledgements

This study was supported by NIH (NS057198; EB00790); NIH NIDA/NCI: U24DA041123; the Research Council of Norway (229129; 213837; 248778; 223273; 249711); the South-East Norway Regional Health Authority (2017–112); KG Jebsen Stiftelsen (SKGJ-2011-36).

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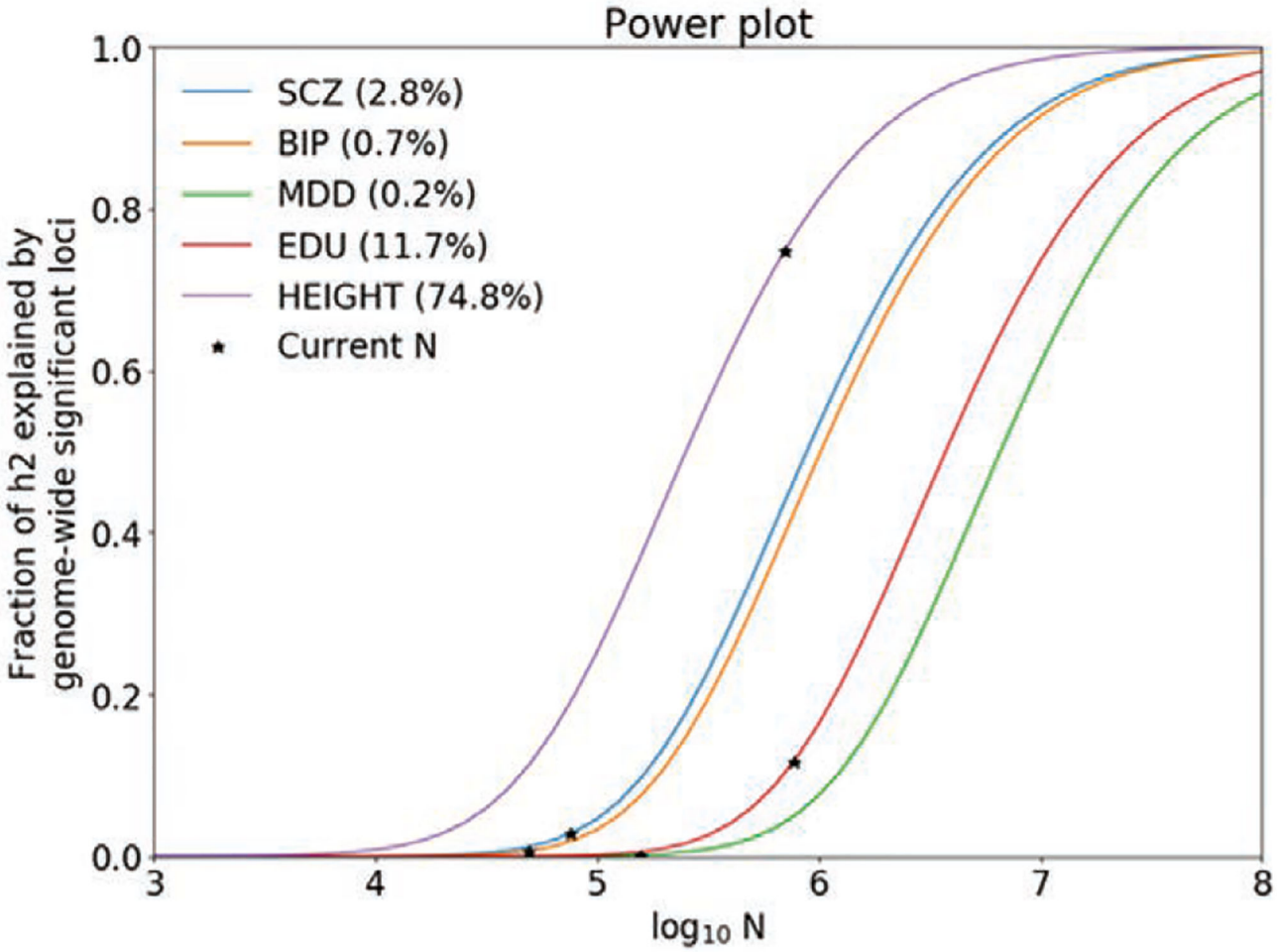

Fig. 1.

Power plots for schizophrenia (SCZ, blue), bipolar disorder (BIP, orange), major depression (MD, green), educational attainment (EDU, red) and height (purple) estimated using the causal mixture model (Holland *et al.*, 2019). The plots were originally presented in the article by Holland *et al.* (2019). Proportion of SNP-heritability, captured by genome-wide significant SNPs, projected to current and future GWAS sample sizes, N. Values for current GWAS sample sizes are shown in parentheses. GWAS, genome-wide association studies; SNP, single-nucleotide polymorphism.

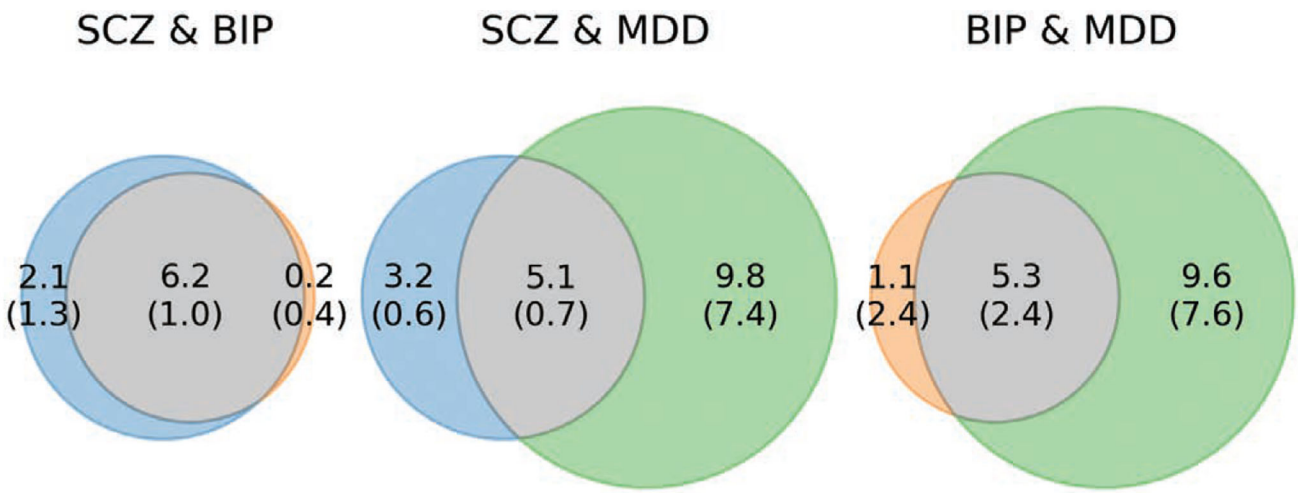

Fig. 2.

Venn diagram of unique and shared polygenic components at the causal level, showing polygenic overlap (gray) between schizophrenia (SCZ, blue), bipolar disorder (BIP, orange) and major depression (MD); the numbers indicate the estimated quantity of causal variants (in thousands) per component, explaining 90% of SNP heritability in each phenotype, followed by the standard error. The size of the circle reflects the degree of polygenicity. The diagrams were generated using the bivariate causal mixture model (Frei *et al.*, 2019), and were originally presented in the article by Frei *et al.* (2019). SNP, single-nucleotide polymorphism.