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

Olav B. Smeland¹, Oleksandr Frei¹, Chun-Chieh Fan², Alexey Shadrin¹, Anders M. Dale³,⁴,⁵ and Ole A. Andreassen¹

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. Psychiatry Genetics 2019, 29:152–159 Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.

Keywords: bipolar disorder, depression, pleiotropy, polygenic architecture, schizophrenia, GWAS

¹NORMENT Centre, Institute of Clinical Medicine, Division of Mental Health and Addiction, University of Oslo and Oslo University Hospital, Oslo, Norway, ²Center for Human Development, University of California, San Diego, ³Department of Radiology, University of California, ⁴Center of Neuroscience, University of California, San Diego and ⁵Center for Multimodal Imaging and Genetics, University of California, San Diego, La Jolla, California, USA

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; e-mail: o.a.andreassen@medisin.uio.no

Received 15 May 2019 Accepted 18 July 2019

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).

![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.](image-url)
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 conjunctual 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 spectrum 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; Oranje 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; Snickers 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; Snickers 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 (Giambartolomé 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; 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).

Conflicts of interest

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

References

Abraham G, Malik R, Yonova-Doing E, Salim A, Wang T, Danesh J, et al. (2019). Genetic risk score offers predictive performance comparable to clinical risk factors for ischaemic stroke. bioRxiv 689935. doi: 10.1101/689935.

Andreasen OA, Djurovic S, Thompson WK, Schork AJ, Kendler KS, O’Donovan MC, et al.; International Consortium for Blood Pressure GWAS; Diabetes Genetics Replication and Meta-analysis Consortium; Psychiatric Genomics Consortium Schizophrenia Working Group (2013a). Improved detection of common variants associated with schizophrenia by leveraging pleiotropy with cardiovascular-disease risk factors. Am J Hum Genet 92:187–209.

Andreasen OA, Harbo HF, Wang Y, Thompson WK, Schork AJ, Mattingsdal M, et al.; Psychiatric Genomics Consortium (PGC) Bipolar Disorder and Schizophrenia Work Groups; International Multiple Sclerosis Genetics Consortium (IMSGC). (2015). Genetic pleiotropy between multiple sclerosis and schizophrenia but not bipolar disorder: differential involvement of immune-related gene loci. Mol Psychiatry 20:207–214.

Andreasen OA, Thompson WK, Schork AJ, Ripke S, Mattingsdal M, Kelsoe JR, et al.; Psychiatric Genomics Consortium (PGC); Bipolar Disorder and Schizophrenia Working Groups, (2013b). Improved detection of common variants associated with schizophrenia and bipolar disorder using pleiotropy-informed conditional False Discovery Rate. PLoS Genet 9:e1003455.

Anttila V, Bulik-Sullivan B, Finucane HK, Walters RK, Bras J, Duncan L, et al.; Brainstorm Consortium (2018). Analysis of shared heritability in common disorders of the brain. Science 360:eaap8757.

Bansal V, Mitjans M, Burik CAP, Linner RK, Okbay A, Rietveld CA, et al. (2018). Genome-wide association study results for educational attainment aid in identifying genetic heterogeneity of schizophrenia. Nat Commun 9:3078.

Baurecht H, Hotze M, Brand S, Buning C, Cormican P, Corvin A et al. (2015a). Genome-wide comparative analysis of autism dermatics and psoriasis gives insight into opposing genetic mechanisms. Am J Hum Genet 96:104–120.

Baurecht H, Hotze M, Brand S, Buning C, Cormican P, Corvin A et al. (2015b). Genome-wide comparative analysis of atopic dermatitis and psoriasis gives insight into opposing genetic mechanisms. Am J Hum Genet 96:104–120.

Bhattacharjee S, Rajaraman P, Jacobs KB, Wheeler WA, Melin BS, Hartge P, et al.; GliomaScan Consortium. (2012). A subset-based approach improves power and interpretation for the combined analysis of genetic association studies of heterogeneous traits. Am J Hum Genet 90:821–835.

Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium (2018). Genetic dysfunction of bipolar disorder and schizophrenia, including 28 subphenotypes. Cell 173:1705–1715 e1716.

Bulik-Sullivan B, Finucane HK, Anttila V, Gusev A, Day FR, Loh PR, et al.; ReproGen Consortium; Psychiatric Genomics Consortium; Genetic Consortium for Alzheimer’s Nervosa of the Wellcome Trust Case Control Consortium 3. (2015). An atlas of genetic correlations across human diseases and traits. Nat Genet 47:1236–1241.

Cutbent BN, Insel TR. (2010). Toward new approaches to psychotic disorders: the NIMH research domain criteria project. Schizophr Bull 36:1061–1062.

Davies G, Lam M, Harris SE, Trampush JW, Luciano M, Hill WD, et al. (2018). Study of 300,466 individuals identifies 148 independent genetic loci influencing general cognitive function. Nat Commun 9:2098.

Day FR, Ong KK, Perry JRB (2018). Elucidating the genetic basis of social interaction and isolation. Nat Commun 9:2457.

Demonitis D, Walters RK, Martin J, Mattheisen M, Als TD, Agerbo E, et al.; ADHD Working Group of the Psychiatric Genomics Consortium (PGC); Early LifeCourse & Genetic Epidemiology (EAGLE) Consortium; 23andMe Research Team. (2019). Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. Nat Genet 51:63–75.

Desikan RS, Fan CC, Wang Y, Schork AJ, Cabral HJ, Cupples LA, et al. (2017). Genetic assessment of age-associated Alzheimer disease risk: development and validation of a Polygenic Hazard Score. PLoS Med 14:e1002258.

Drange OK, Smeland OB, Shadrin AA, Finseth PI, Witkoara E, Frei O, et al.; Psychiatric Genomics Consortium Bipolar Disorder Working Group. (2019). Genetic overlap between Alzheimer’s disease and bipolar disorder implicates the MARK2 and VAC14 genes. Front Neurosci 13:220.

Eaton WW, Martins SS, Nestadt G, Bienvenu OJ, Clarke D, Alexandre P. (2008). The burden of mental disorders. Epidemiol Rev 30:1–14.

Efron B (2010). Large-Scale Inference: Empirical Bayes Methods for Estimation, Testing, and Prediction. Cambridge, New York; Cambridge University Press.

Ellinghaus D, Ellingham A, Nair RP, Stuart PE, Esko T, Metspalu A, et al. (2012). Combined analysis of genome-wide association studies for Crohn disease and psoriasis identifies seven shared susceptibility loci. Am J Hum Genet 90:636–647.

Falcomer DS (1965). The inheritance of liability to certain diseases, estimated from the incidence among relatives. Ann Hum Genet 29:51–76.

Fan CC, Smeland OB, Schork AJ, Chen CH, Holland D, Lo MT, et al. (2018). Beyond heritability: improving discoverability in imaging genetics. Hum Mol Genet 27:R22–R28.

Frei O, Holland D, Smeland OB, Shadrin AA, Fan CC, Maeland S, et al. (2019). Bipolar causal mixture models: identifying common genomic risk variants between complex traits beyond genetic correlation. Nat Commun 10:2417.

GBD 2015 DALYs and HALE Collaborators (2016). Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 388:1603–1658.

Giambartolomei C, Vukcevic D, Schadt EE, Franke L, Hingorani AD, Wallace C, Plagnol V (2014). Bayesian test for colocalisation between pairs of genetic association studies using summary statistics. PLoS Genet 10:e1004383.

Gratzen J, Visscher PM (2016). Genetic pleiotropy in complex traits and diseases: implications for genomic medicine. Genome Med 8:78.

Grotzinger AD, Rhenntullia M, de Vlaming R, Ritchie SJ, Malland TT, Hill WD, et al. (2019). Genomic structural equation modelling provides insights into the multi-variant genetic architecture of complex traits. Nat Hum Behav 3:153–525.

Grove J, Ripke S, Als TD, Mattheisen M, Walters RK, Won H, et al.; Autism Spectrum Disorder Working Group of the Psychiatric Genomics Consortium; BUPGEN; Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium; 23andMe Research Team. (2019). Identification of common genetic risk variants for autism spectrum disorder. Nat Genet 51:431–444.

Hackerin S, Zeggini E (2017). Statistical methods to detect pleiotropy in human complex traits. Open Biol 7:170125.

Hagenaars SP, Harris SE, Davies G, Hill WD, Liewald DC, Ritchie SJ, et al.; METASTROKE Consortium, International Consortium for Blood Pressure GWAS; SpiroMeta Consortium; CHARGE Consortium Pulmonary Group, CHARGE Consortium Aging and Longevity Group. (2016). Shared genetic aetiology between cognitive functions and physical and mental health in UK biobank (N=121151) and 24 GWAS consortia. Mol Psychiatry 21:1624–1632.

Hill WD, Davies G, Liewald DC, McIntosh AM, Deary IJ; CHARGE Cognitive Working Group. (2016). Genome-wide pleiotropy between general cognitive function and major psychiatric disorders. Biol Psychiatry 80:266–273.

Holland D, Frei O, Desikan R, Fan CC, Shadrin AA, Smeland OB et al. (2019). Beyond SNP heritability: polygenicity and discoverability of phenotypes estimated with a Univariate Gaussian mixture model. BioRxiv 133132. doi: 10.1101/133132.
Enhancing Neuro Imaging Genetics through Meta Analysis Consortium. (2018). Estimating effect sizes and expected replication probabilities from genetic studies. Front Genet 9:225.

Howard DM, Adams MJ, Clarke TK, Halferty JD, Gibson J, Shirali M, et al.; 23andMe Research Team; Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium. (2019). Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. Nat Neurosci 22:343–352.

Hubbard L, Tansey KE, Rai D, Jones P, Ripke S, Chamberl NT, et al. (2016). Evidence of common genetic overlap between schizophrenia and cognition. Schizophren Bull 42:832–842.

Insel TR. (2010). Rethinking schizophrenia. Nature 468:187–193.

Jansen PR, Watanabe K, Stringer S, Skene N, Broyis J, Hammerschlag AR et al. (2019). Genome-wide analysis of insomnia in 1,331,010 individuals identifies new loci and functional pathways. Nat Genet 51:934–940.

Kahn RS, Keefe RS (2013). Schizophrenia is a cognitive illness: time for a change in focus. JAMA Psychiatry 70:1107–1112.

Khera AV, Chaffin M, Wade KH, Zahid S, Brancala J, Xia R, et al. (2019). Polygenic prediction of weight and obesity trajectories from birth to adulthood. Cell 177:587–596.e9.

Laursen TM, Munk-Olsen T, Gasse C (2011). Chronic somatic comorbidity and excess mortality due to natural causes in persons with schizophrenia or bipolar affective disorder. PLoS One 6:e24597.

Le Hellard S, Wang Y, Witteoler A, Zuber V, Betetella F, Hugdahl K et al. (2017). Identification of gene loci that overlap between schizophrenia and educational attainment. Schizophren Bull 43:654–664.

Lee PH, Baker JT, Jahanshad N, Ge T, Jung JY, et al. (2016). Partitioning heritability analysis reveals a shared genetic basis of brain anatomy and schizophrenia. Mol Psychiatry 21:1680–1689.

Lee SH, Ripke S, Neale BM, Faraone SV, Purcell SM, Perlis RH, et al.; Cross DISORDER Group of the Psychiatric Genomics Consortium. (2013). Genetic relationship between five psychiatric disorders estimated from genome-wide association studies. Nature genetics 45:894–899.

Lee JJ, Wedow R, Okbay A, Kong E, Maghzhian O, Zacher M, et al.; 23andMe Research Team; COGENT (Cognitive Genomics Consortium); Social Science Genetic Association Consortium. (2018). Gene discovery and polygenic prediction from a genome-wide association study of educational attainment. Nat Genet 50:112–114.

Lencz T, Knowles E, Davies G, Guha S, Liewald DC, Starr JM, et al. (2014). Molecular genetic evidence for overlap between general cognitive ability and risk for schizophrenia: a report from the Cognitive Genomics Consortium (COGENT). Mol Psychiatry 19:168–174.

Lichtensten P, Yip BH, Björk C, Pawitan Y, Cannon TD, Sullivan PF, Hultman CM. (2014). Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. Lancet 373:234–239.

Liebers DT, Pirooznia M, Seifuddin F, Musliner KL, Zandi P, Goes FS. (2016). Polygenic risk of schizophrenia and cognition in a population-based survey of older adults. Schizophren Bull 42:984–991.

Lo MT, Hinds DA, Tung JF, Franz C, Fan CC, Wang Y, et al. (2017). Genome-wide analysis for personal traits identify six genetic loci and show correlations with psychiatric disorders. Nat Genet 49:152–156.

Manolio TA, Collins FS, Cox NJ, Goldstein DK, Hindorff LA, Hunter DJ, et al. (2009). Finding the missing heritability of complex diseases. Nature 461:747–753.

Marshall CR, Howrigan DP, Menico D, Thiruvahindrapuram B, Wu W, Greer DS, et al.; Psychosis Endophenotypes International Consortium; CNV and Schizophrenia Working Groups of the Psychiatric Genomics Consortium. (2017). Contribution of copy number variants to schizophrenia from a genome-wide study of 41,321 subjects. Nat Genet 49:27–35.

Martin AR, Daly MJ, Robinson EB, Hyman SE, Neale BM (2019). Predicting polygenic risk of psychiatric disorders. Biol Psychiatry 86:97–109.

McLaughlin RL, Schijven D, van Rienen W, van Eijck KR, O’Brien M, Kahn RS, et al.; Project MinE GWAS Consortium; Schizophrenia Working Group of the Psychiatric Genomics Consortium. (2017). Genetic correlation between amyotrophic lateral sclerosis and schizophrenia. Nat Commun 8:14774.

Okinaka Y, Beauchamp JP, Fontana MA, Lee JJ, Pers TH, Rietveld CA, et al.; LifeLines Cohort Study. (2016). Genome-wide association study identifies 74 loci associated with educational attainment. Nature 533:539–542.

Palmer BW, Heaton RK, Paulsen JS, Kuck J, Brall D, Harris MJ, et al. (1997). Is it possible to be schizophrenic yet neuropsychologically normal? Neuropsychology 11:437–446.

Pardinas AF, Howrigan DP, Rockling AJ, Escott-Price V, Ripke S, Herrera N, et al (2018) Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. Nat Genet 50:381–389.

Pasanisuc B, Price ML (2017). Dissecting the genetics of complex traits using summary association statistics. Nat Rev Genet 18:117–127.

Pickard JK, Berisa T, Liu JZ, Segurel L, Tung JY, Hinds DA (2016). Detection and interpretation of shared genetic influences on 42 human traits. Nat Genet 48:709–717.

Purcell SM, Wray NR, Stone JL, Visscher PM, O’Donovan MC, Sullivan PF, et al. (2009). Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nat Genet 41:56–61.

Ripke S, Saleh J, Grimes CL, Breen G, et al.; Project MinE GWAS Consortium; NeuroCHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) Cognitive Working Group. (2017a). Identification of genetic loci jointly influencing schizophrenia risk and the cognitive traits of verbal-numeral reasoning, reaction time, and general cognitive function. JAMA Psychiatry 74:1065–1075.

Shadmir AA, Smeland OB, Zayats T, Schork AJ, Frei O, Bettelot E, et al. (2018). Novel loci associated with attention-deficit/hyperactivity disorder are revealed by leveraging polygenic overlap with educational attainment. J Am Acad Child Adolesc Psychiatry 57:86–95.

Smeland OB, Bahrami S, Frei O, Shadrin A, O’Connell K, Savage J, et al. (2019). Genome-wide analysis reveals extensive genetic overlap between schizophrenia, bipolar disorder, and intelligence. Mol psychiatry. doi: 10.1038/s41386-018-0132-z [Epub ahead of print].

Smeland OB, Frei O, Kauppi K, Hill WD, Li W, Wang Y, et al.; NeuroCHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) Cognitive Working Group. (2017a). Identification of genetic loci jointly influencing schizophrenia risk and the cognitive traits of verbal-numeral reasoning, reaction time, and general cognitive function. JAMA Psychiatry 74:1065–1075.

Smeland OB, Wang Y, Lo MT, Li W, Frei O, Witteoler A, et al. (2017b). Identification of genetic loci shared between schizophrenia and the big five personality traits. Sci Rep 7:22222.

Smigielski JW, Andreassen OA, Edenberg HJ, Faraone SV, Glatt SJ, Kendler KS (2018). Psychiatric genetics and the structure of psychopathology. Mol Psychiatry 24:409–420.

Snickers S, Stringer S, Watanabe K, Jansen PR, Coleman JR, Kraphol E, et al. (2017). Genome-wide association meta-analysis of 78,308 individuals identifies new loci and genes influencing human intelligence. Nat Genet 49:1107–1112.

Stahl EA, Breen G, Forstner AJ, McQuillin A, Ripke S, Trubetskoy V, et al.; eQTlGen Consortium; BIOS Consortium; Bipolar Disorder Working Group of the Psychiatric Genomics Consortium. (2019). Genome-wide association study identifies 30 loci associated with bipolar disorder. Nat Genet 51:793–803.

Sullivan PF, Agraval A, Bulik CM, Andreassen OA, Berglund AD, Breen G, et al.; Psychiatric Genomics Consortium. (2018). Psychiatric genetics: an update and an agenda. Am J Psychiatry 175:15–27.

Thompson WK, Wang Y, Schork AJ, Witteoler A, Zuber V, Xu S, et al.; Schizophrenia Working Group of the Psychiatric Genomics Consortium. (2015). An empirical basis for subtyping major psychiatric disorders in genome-wide association studies. PLoS One 11:e0150717.

Torkamani A, Wineinger NE, Topol EJ. (2018). The personal and clinical utility of Genomics. Front Genet 9:281.

Urquhart JW, Yang ML, Yu J, Knowles E, Davies G, Liewald DC, et al. (2017). GWAS meta-analysis reveals novel loci and genetic correlates for general cognitive function: a report from the COGENT consortium. Mol Psychiatry 22:1651–1662.

Turley P, Walters RK, Maghzhian O, Okbay A, Lee JJ, Fontana MA, et al.; 23andMe Research Team; Social Science Genetic Association Consortium. (2018),
Multi-trait analysis of genome-wide association summary statistics using MTAG. *Nat Genet* **50**:229–237.

van der Meer D, Rokicki J, Kaufmann T, Cordova-Palomera A, Moberget T, Alnaes D, et al. (2018). Brain scans from 21,297 individuals reveal the genetic architecture of hippocampal subfield volumes. *Mol Psychiatry*. doi: 10.1038/s41380-018-0262-7. [Epub ahead of print].

Visscher PM, Wray NR, Zhang Q, Sklar P, McCarthy MI, Brown MA, Yang J (2017). 10 years of GWAS discovery: biology, function, and translation. *Am J Hum Genet* **101**:5–22.

Wahlbeck K, Westman J, Nordentoft M, Gissler M, Laursen TM (2011). Outcomes of Nordic mental health systems: life expectancy of patients with mental disorders. *Br J Psychiatry* **199**:453–458.

Willer CJ, Li Y, Abecasis GR (2010). METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics* **26**:2190–2191.

Williams NM, Zaharieva I, Martin A, Langley K, Mantripragada K, Fossdal R, et al. (2010). Rare chromosomal deletions and duplications in attention-deficit hyperactivity disorder: a genome-wide analysis. *Lancet* **376**:1401–1408.

Zeng J, de Vlaming R, Wu Y, Robinson MR, Lloyd-Jones LR, Yengo L, et al. (2018). Signatures of negative selection in the genetic architecture of human complex traits. *Nat Genet* **50**:746–753.

Zhang Y, Qi G, Park JH, Chatterjee N (2018). Estimation of complex effect-size distributions using summary-level statistics from genomewide association studies across 32 complex traits. *Nat Genet* **50**:1318–1326.

Zuber V, Jönsson EG, Frei O, Witoelar A, Thompson WK, Schork AJ, et al. (2018). Identification of shared genetic variants between schizophrenia and lung cancer. *Sci Rep* **8**:674.