The heritability and molecular genetics of mental disorders

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Key points

- Genetic influences play a substantial role in mental disorders.
- Twin and family studies show that the heritability of mental disorders is moderate-to -high. In general, the contribution of genetic and environmental variance to psychiatric trait variation is "fifty-fifty."
- Genome-wide approaches have identified numerous genetic variants associated with mental disorders.
- Understanding the genetic underpinnings of mental health will eventually bring us closer to a better understanding of the etiology, counseling and treatment of mental disorders.

Glossary

Deoxyribonucleic acid (DNA) Hereditary material in a cell that contains instructions for making proteins

Dizygotic twin pairs These twins are the product of two sperm and two egg cells. The conception of these twins is at the same time, and so they share the pregnancy in the womb. Like normal siblings, they are, on average, 50% genetically identical

Gene-environment interaction These interactions occur when genes influence the sensitivity to certain elements in the environment. People with different genotypes could respond differently to the same environment

Genetic correlation Estimate of the genetic overlap between traits or disorders

Genetic variant Single nucleotides of the DNA that may vary between people (similar to SNPs; see definition below)

Genome-wide association studies (GWAS) Observational study design that uses regression analysis to test for an association between a large set of genetic variants and a heritable trait. The genetic variants studied in GWAS are called single-nucleotide polymorphisms (SNPs; see definition below)

Heritability (h2) That part of the observable variation in a trait or disorder in a population that is explained by genetic variation in that population

Monozygotic twin pairs These twins are the product of one sperm and one egg cell. However, the fertilized egg divides at a very early stage in the pregnancy and results in two embryos. MZ twin pairs are 100% genetically identical

Polygenic score (PGS) A genetic score that reflects someone's genetic liability for a trait or disorder. Polygenic scores are calculated by summing weighted genetic variants that an individual carries. Genetic variants are weighted by the effect sizes that are estimated in GWASs

R^2 PGS Differences between people in a trait or disorder that are explained by variation in PGS

Single-nucleotide polymorphism (SNP) Substitutions of a single nucleotide at a specific genomic location. In other words, SNPs are locations on the genome that vary between people. SNPs are common in the population (similar to genetic variants; see definition above)

SNP heritability That part of the observable variation in a trait or disorder in a population that is explained by the SNPs measured using GWASs. The SNP heritability is typically much lower than the total heritability, because not all genetic influences are captured in GWAS

Abstract

People differ in their feelings, emotions, and behavior, and for centuries, scholars have been interested in the sources of this variation. Modern research in the last four decades, using family and twin designs, has shown that variation in mental health and disorders is explained by both genetic and environmental variation. The influence of genetic variation (i.e., heritability) on mental disorders differs. Neurodevelopmental disorders are among the most heritable disorders while internalizing disorders, like major depressive disorder, show lower heritability estimates. Genome-wide association studies (GWAS) are used to search the whole genome for associations between genetic variants and mental disorders. These analyses have resulted in multiple associations between particular genetic variants and mental disorders; however, genetic variants explain only a relatively small proportion of variation in mental disorders, and more research is needed to unravel their biological function. GWAS results confirmed that different mental disorders have many genetic variants in common, which may explain the co-occurrence of mental disorders and the overlap in disorder symptoms that is often observed. Finally, GWAS results can be used to obtain polygenic scores that provide an indication of the degree of genetic risk for mental disorders that may become of clinical utility in the near future.

Introduction

Importantly, mental health, or mental disorders, are not dichotomous traits (present or not) in a population but instead show variation. People vary in traits that reflect how they feel, behave and think; indeed, when plotted on a curve, mental health is normally distributed in the population. Let us take depression as an example: most people feel a little bit depressed from time-to-time and function very well in daily life. A small part of the population never has "the blues," while, at the other end of the distribution,

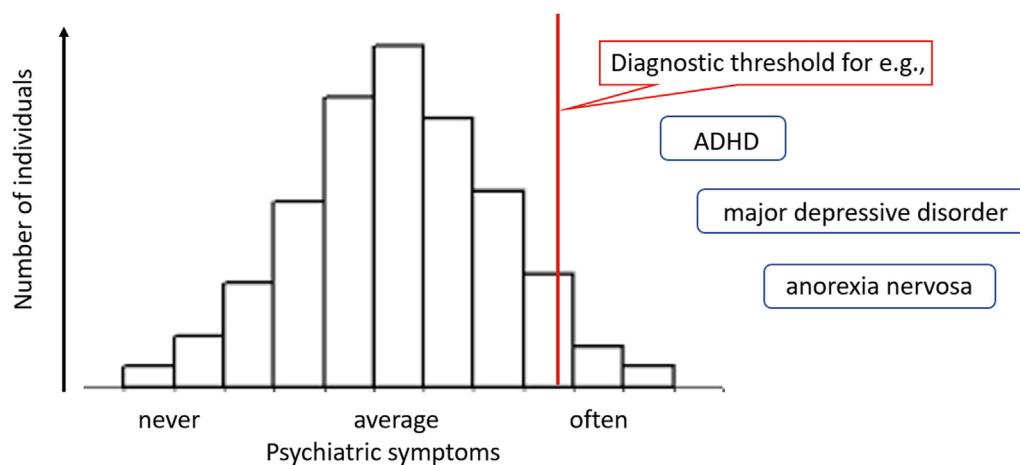**Fig. 1** A representation of the variation of psychiatric disorders in the population. Most people show "average behavior" while fewer people show almost never (left) or very often or much (right) psychiatric behavior. The vertical red line on the right represents the threshold for how we, based on diagnostic criteria, distinguish "normal behavior" from "disordered behavior." ADHD = attention deficit/hyperactivity disorder.

a small proportion of the population is so depressed they cannot function well in daily life and need clinical care. Hence, mental disorders are positioned at the end of the distribution (Fig. 1).

This variation is not only present for mental disorders, but is basically applicable to every trait, from intelligence, to height, to personality, to mental health. Identifying the causes of this variation has been of interest to scientists and physicians for centuries. Hippocrates (∼400 BC) was the first to suggest that individual differences in feelings of anxiety, melancholia or depression had a biological basis. He thought the most important contributors were blood, phlegm, and yellow and black bile. He hypothesized that too much black bile would increase melancholic feelings, while too much phlegm would make you feel calm. A specific diet would help improve mental conditions when needed (Pinault, 1992).

We now know that blood, phlegm, and bile have no direct effect on mental health, but the suggestion of a biological basis has proven to be correct. Research into individual differences in mental disorders goes back to the first "nature versus nurture" studies in the late 19th century, but in particular, research in the last four decades has robustly established that genetic factors contribute to variation in mental health and disorders (Polderman et al., 2015; Pettersson et al., 2019). Although our knowledge about the function (or biological basis, if you wish) of these genetic factors is still very limited (Uffelmann and Posthuma, 2021), there is no doubt that genetic research is a promising direction to enhance our understanding of the human mental state.

This entry provides an overview of genetic studies of mental disorders. Specifically, we aimed to (A) describe the family-based study designs that are suitable to estimate the degree of genetic influence on a trait or disorder, (B) list the estimates of genetic influences of the most common mental disorders, (C) explain how genetic data are used to identify genes associated with mental disorders, (D) discuss follow-up genetic analyses that can reveal how mental disorders are genetically correlated, and (E) look ahead to the potential implications of genetic studies of mental disorders. To enhance readability, the mental disorders in this article are clustered into neurodevelopmental, internalizing and externalizing mental disorders.

Heritability of mental disorders

How do we study heritability?

Heritability is an often-used term that describes the part of individual differences (or variation) in a trait or disorder in a population that is explained by genetic variation. It is often listed as a percentage that reflects the percent of variation in a trait or disorder in a population that is due to genetic factors. For example, the heritability for depression is estimated at 35%. This means that in a given population, 35% of the variation in depressive feelings (from no depressive feelings, to sometimes having "the blues," to severe depression) is explained by genetic differences between people of that population. To be clear, heritability is never an estimate of genetic influences for one individual but a group statistic; it is always referring to the complete variation in a population.

A large meta-analysis (Polderman et al., 2015) showed that mental disorders are most studied in the history of heritability studies (see also the related Website http://match.ctglab.nl/). Indeed, heritability studies of mental disorders go back to the last century. One of the earliest heritability studies of mental disorders was a family study of schizophrenia in Ireland. It took researchers many years to collect data of multiple generations within families (Kendler et al., 1996). The findings showed that schizophrenia was not distributed randomly in the population but more often occurred in certain families. In other words, the closer the family relationship to a person with schizophrenia, the more likely an individual would develop schizophrenia too. This observation led the researchers to conclude that genetic influences could be important in schizophrenia. Yet, they also acknowledged the clear downside of the family design, namely that genetic and environmental influences cannot be disentangled, as these influences are often shared to a similar extent between family members. Hence, with family designs it is difficult to robustly determine if it is shared genes or a shared environment that increases the likelihood of developing schizophrenia.

A more optimal design that avoids this problem is a twin study. With the twin design, the co-occurrence of traits or disorders in identical, or monozygotic (MZ) twin pairs, is compared to fraternal, or dizygotic (DZ) twin pairs. When raised in the same family, both types of twin pairs share their common environment since they are born at exactly the same time, and even shared their prenatal environment. The only thing in which MZ and DZ twin pairs differ is the within-twin pair genetic similarity: for MZ pairs this is 100%, and for DZ pairs this is, on average, 50% (like in regular siblings). Therefore, when a measured trait or disorder shows more similarity within MZ twin pairs, this indicates that genetic influences likely play a role in that trait. An important assumption when interpreting MZ and DZ within pair similarity is the so-called Equal Environment Assumption (EEA) where it is assumed that the environmental sharing is equal for MZ and DZ twin pairs. Critics of the twin design have argued that this assumption is false (e.g., MZ twin pairs are often dressed the same) and that it inflates the estimates of genetic influences. However, several studies have established that a violation of the EEA might indeed be present in studies of particular traits but that the effect of this violation on estimates of genetic and environmental influences is very limited (Bulik et al., 1998; Hwang et al., 2021; Kendler et al., 1993; Xian et al., 2000). Additionally, a huge heritability study on mental disorders comparing estimates based on full- and half-siblings instead of twins revealed very similar estimates (see Fig. 2—(Pettersson et al., 2019)).

In twin studies, the total variance of a trait or disorder can be divided into genetic variance, environmental variance shared by family members (i.e., shared environmental factors that make co-twins similar to each other), and environmental variance unique to an individual (i.e., nonshared environmental factors that make co-twins different from each other) (Van Dongen et al., 2012). The twin design is a powerful design to disentangle these sources of variance. For this reason, since the late 1980s, many twin registers have been established. Here, families with twins participate in research providing a wealth of data to conduct heritability studies and related research (Hur et al., 2019).
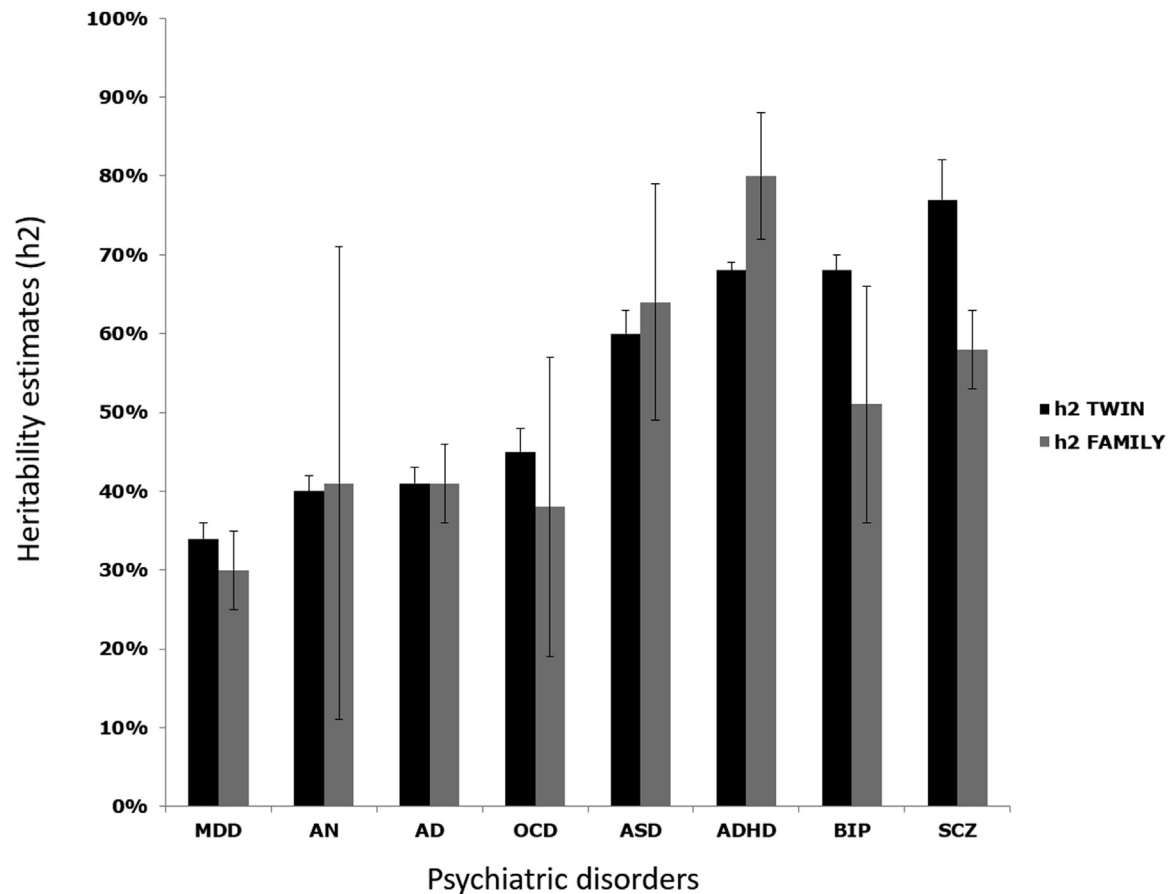
Fig. 2 Heritability estimates (h2) based on data from twin studies and family studies of full and half siblings. The figure data are ordered from low-to-high based on the heritability from twin studies. The figure is based upon Pettersson et al. (2019), and presented as Poster presentation at World Congress of Psychiatric Genetics, Glasgow (2018). AD = alcohol dependence, ADHD = Attention Deficit/Hyperactivity Disorder, AN = anorexia nervosa, ASD = autism spectrum disorder, BIP = bipolar disorder, MDD = major depressive disorder, OCD = obsessive-compulsive disorder, SCZ = schizophrenia.

Two other powerful, but more rarely applied designs are the "MZ twins reared apart" and "adoption" design. In the first design, MZ twin pairs were separated early in life, and reunited later in life. Thomas Bouchard and Nancy Segal are considered the founders of this type of study (Bouchard et al., 1990). The main findings of their work showed that for a whole range of traits MZ twins raised apart showed the same resemblance for these traits as MZ twins raised together, providing a strong indication that genes play a role in all of those traits (Kendler et al., 2000). In the adoption design, the resemblance for traits between adopted children and their biological and adopted parents is investigated. If adopted children are more like their adopted parents for a given trait, this would indicate that the environment plays an important role. In contrast, if children are more like their biological parents, this would mean genetic factors are important for that particular trait. Important restrictions of both designs are that children have already been exposed to environmental influences, prenatally and in the first years of life, which are considered crucial in mental development (Easey et al., 2019; Van den Bergh et al., 2020).

Heritability estimates range from moderate-to-high

In the meta-analysis by Polderman et al. (2015), traits were categorized by applying the international standards of ICF (International Classification of Functioning, Disability and Health) and ICD (International Statistical Classification of Diseases and Related Health Problems). Based on ICF and ICD, traits were classified at three levels, from very broad to a more specific classification (i.e., 28 broad domains, 54 chapters, and 31 sub-chapters). For the domain "Psychiatric" and the more specific article "Mental and Behavioral Disorders," the contribution of genetic variation is about 50%. However, when looking more specifically at the sub-chapter level that contains specific psychiatric disorders, the heritability estimates differ substantially. In general, variation in the neurodevelopmental disorders is mostly due to genetic variation, while for internalizing and externalizing disorders, and addictions and compulsions, the influence of genetic and environmental variation is more in balance. The sections below provide an overview of heritability estimates of the most common psychiatric disorders.

Neurodevelopmental disorders

Attention deficit/hyperactivity disorder (ADHD) and autism spectrum disorder are the most common neurodevelopmental disorders. The role of genetic and environmental influences on these disorders have been investigated comprehensively, both in clinical samples that focus on the heritability of the disorders, as well as in population-based samples that focus on symptoms of the disorders. The heritability estimates in children are relatively high, varying from 70% to 80% for ADHD (Brikell et al., 2021) and 60% to 90% for autism spectrum disorder (Havdahl et al., 2021). Some data have suggested that heritability estimates might be lower in adolescence and adulthood, but longitudinal studies still confirm strong heritability throughout development (Chang et al., 2013).

Schizophrenia, despite its later onset, is often considered a neurodevelopmental disorder (Eyles, 2021; Owen and O'Donovan, 2017). The early family studies, as mentioned above, showed that schizophrenia runs in families (Kendler et al., 1996). A meta-analysis of twin studies confirmed this with a consistently high heritability estimate of around 80% (Sullivan et al., 2003).

Internalizing disorders

Internalizing disorders include many disorders, including mood, anxiety, eating, and trauma-related disorders, as well as obsessive-compulsive and tic disorders. We discuss the heritability of the most common disorders below.

In contrast to the heritability of neurodevelopmental disorders, for some internalizing disorders, like major depressive disorder and anxiety disorders, nonshared environmental variation is more important in explaining variation than genetic influences. For example, a meta-analysis of six twin studies in 2000 showed an overall heritability of 37% for major depressive disorder (Sullivan et al., 2000). The large meta-analysis of Polderman et al. (2015) and a more recent study in clinical cases (Kendler et al., 2018) showed a higher heritability of major depressive disorder for females (40%) than males (34%), although the heritability of recurrent depressive disorder was similar for both sexes (38% and 37% respectively). Importantly, higher heritability estimates have been reported for bipolar disorder. Family, adoption, and twin studies of bipolar disorder have consistently shown a heritability of around 75% (Smoller and Finn, 2003).

There are multiple types of anxiety disorders, with general anxiety disorder, phobias, social anxiety disorder, and panic disorder being most common. A meta-analysis of twin studies showed a heritability estimate of 32% for generalized anxiety disorder and 48% for panic disorder (Hettema et al., 2001). Phobias can be specific for certain things (e.g., animals, insects), experiences (e.g., blood injury), or social interactions (as is present in social anxiety disorder). Heritability estimates differ between these different phobic situations ranging from 24% (for social phobias) to 43% (for agoraphobia) (Kendler et al., 2001).

Variation in eating disorders, such as anorexia nervosa, bulimia nervosa, and binge-eating disorder, and their symptoms is also heritable. Although some data suggest higher heritability estimates in females (45%) than males (37%) (Polderman et al., 2015), most twin studies have only included females, as eating disorders are much more common in females than males. In general, most twin studies suggest that eating disorders are at least 50% heritable, although some studies show higher estimates (e.g., 82%—(Bulik et al., 1998), 74%—(Klump et al., 2001)), especially for the clinical disorders rather than just the symptoms.

Post-traumatic stress disorder (PTSD) is one of the most common trauma-related disorders that has been studied extensively using the US-based, Vietnam Era Twin Register (Forsberg et al., 2020). An early study found heritability estimates of 23% (Wolf et al., 2014), while a more recent study of twins at an older age reported a heritability of about 50% (Wolf et al., 2018). It may be that heritable factors become more important across the lifespan and/or are more strongly associated with enduring (rather than acute) PTSD symptoms.

A comprehensive review of obsessive compulsive disorder (OCD) heritability studies revealed that genetic influences on disorder and symptom variation range from 25% to 55%, with no sex differences in heritability estimates (Mahjani et al., 2021). Heritability of tic disorders and Tourette syndrome has been estimated to be substantially higher at 77% (Mataix-Cols et al., 2015).

Externalizing disorders

Externalizing disorders are comprised of a variety of behaviors related to self-regulation, including aggression, hostility, violence, addictive behavior, and disruptive and risk-taking behaviors. The most common disorders include conduct disorder (in youth) and antisocial personality disorder (in adults), alcohol use disorder, and drug use disorder. Unlike most disorders and complex traits, some externalizing disorders often show a substantial shared environmental component (~20%), suggesting that the environment that is shared by co-twins (e.g., parenting, neighborhood characteristics) contributes robustly to disorder/behavior variation. For example, Bartels et al. (2004) found heritability estimates of around 35% in a large sample of Dutch twins, while the shared and unique environment also contributed about one-third of the variance each to externalizing behavior. Burt and Klump (2012) also showed substantial genetic (50% heritability) and shared environmental influences (20%) on rule-breaking behavior. However, heritability estimates may vary depending on the type of externalizing behavior that is examined, with the more severe forms being more heritable. For instance, heritability was much higher (with minimal shared environmental influences) for aggressive behavior (e.g., fighting, bullying) in Burt and Klump (2012), and another study found higher heritability (60%) and no shared environmental influences on anger (measured as the frequency of anger over time and in response to a variety of situations) (Distel et al. (2012).

The number of twin studies on illicit drugs like cocaine and opioids is limited, while studies on more common addictions such as alcohol, smoking, and cannabis have been conducted on a larger scale. These studies generally show substantial heritability with minimal shared environmental influences, although the shared environment does appear to be substantial (25%) for cannabis use and misuse (Verweij et al., 2010). Heritability estimates generally range from 45% to 77% for the use and abuse/dependence on these substances (Kendler et al., 2012; Mbarek et al., 2015; Polderman et al., 2015; Waaktaar et al., 2018).

The quest for genes

Family and twin studies described above consistently show that mental disorders and their symptoms are at least partly heritable. These findings spark the question "Which genes are responsible for this heritability?" Genetic research has focused more and more on identifying these genes.

The structure of genes

A gene is a segment of deoxyribonucleic acid (DNA). DNA consists of millions of the molecules cytosine (C), guanine (G), adenine (A) and thymine (T). While people carry the same molecules on 99.9% of the genome, there are around 15 million places on the genome where these molecules may differ between people (Collins et al., 2003). These places are called single-nucleotide polymorphisms (SNPs) or genetic variants. SNPs are common in the population, and one gene may contain multiple SNPs. In 2003, researchers of the Human Genome Project finished and published the first complete map of the human genome, its genes, and SNPs (Collins et al., 2003). Before the Human Genome Project, advances in molecular genetics were relatively slow, but after its publication, new developments emerged quickly.

The candidate gene era: a design with flaws

Early attempts to identify associations between specific genetic variants and disorders/traits focused on candidate genes. That is, one or a couple of genes that were hypothesized to be related to the studied disorders or traits. Candidate genes were selected based on known functions. Often, one or a couple of specific SNPs within that gene would be studied. For example, the 5-hydroxytryptamine (5-HT) receptor variant, a variant within a gene that was known to be associated with the serotonin system, was studied extensively in relation to depression. Early studies often found that the serotonin transporter gene was predictive of developing depression (Border et al., 2019).

Candidate gene studies received a lot of attention in their first decade and continue to be published every now and then. Nonetheless, many concerns have been raised about this approach, especially since initially described associations failed to replicate. As an example, many researchers failed to replicate the association between the 5-HT T variant and major depressive disorder (Border et al., 2019).

These conflicting results led critics to conclude that previously found associations were false negative results. Caspi et al. (2003), however, argued that the inability to replicate candidate gene associations could be due to the presence of gene-environment interactions, where associations would only be present in combination with certain environmental influences. He and his co-authors published one of the most influential papers in psychiatric genetics (Caspi et al., 2003). The paper described how individuals with a short version of the 5-HT T variant were more likely to develop depression after a stressful life event, while those with the long version were less likely to develop depression after a stressful life event. This study was followed by many research teams aiming to replicate this finding, which again led to many non-replications and conflicting findings (Risch et al., 2009).

Caspi et al. (2003)'s study is a typical example of candidate gene research; ground-breaking findings that often fail to replicate. Similar findings have been reported for a multitude of candidate genes and gene-environment interactions for schizophrenia (Johnson et al., 2017) and depression (Border et al., 2019). It has been argued that these inconsistent findings are, for the most part, caused by a lack of power due to small sample sizes, along with publication bias for positive results (Duncan and Keller, 2011). We now know that sample sizes of at least 30,000 participants (preferably more) are needed to detect a significant SNP effect. Yet the median sample size in past candidate gene studies was 345 participants (Border et al., 2019). Indeed, modern large-scale analyses (i.e., genome-wide association studies (GWAS)) most often fail to replicate candidate gene associations (Duncan et al., 2019). Hence, candidate gene studies should be considered outdated in current genetic research.

Genome-wide association studies (GWAS)

In the past decade, molecular genetic research has shifted from candidate-gene, hypothesis-driven approaches toward large-scale, hypothesis-free genomic approaches (Duncan et al., 2019). The most commonly used method is the GWAS. In a GWAS, thousands of independent regression analyses are performed to test for an association between a disorder/trait and a common SNP. Common SNPs are variants that occur relatively often in the population. Common SNPs that are found to be significantly associated with the studied disorder/trait are called "hits." Rare variants (e.g., de novo mutations) may have a strong impact on mental health as well. For example, Rett's syndrome is a monogenic disorder that results from the MECP2 genetic mutation and causes several severe symptoms (e.g., impairments in language and motor coordination, autistic traits). Unfortunately, influences of rare variants are not captured in GWAS since only common genetic variants are included.

A GWAS typically includes around 1 million common SNPs. GWAS revealed that most disorders/traits, including mental disorders, are highly polygenic and complex. This means that many genes with very small effects are involved, and complex interactions exist. Since the influence of a single common SNP on a phenotype is very small, it requires extremely large sample sizes to detect these influences. Sample sizes of individual datasets are most often not large enough, which has led to a variety of worldwide collaborations. The Psychiatric Genomics Consortium (https://www.med.unc.edu/pgc/) was founded in 2007 and unifies over 800

researchers in psychiatric genetics in over 40 countries to advance genetic discoveries in 11 psychiatric disorders/traits. As a result of these increasing sample sizes, GWAS hits are increasing.

The emergence of GWAS has led to many advances beyond identifying specific disorder/trait-associated genetic variants. Myriad methods have emerged where GWAS can, among other things, be used to estimate heritability (Yang et al., 2010), study genetic correlations between traits (Bulik-Sullivan et al., 2015), and determine causality (Burgess et al., 2013; Smith and Ebrahim, 2003). Before GWAS, heritability, genetic correlations and causality were typically studied using twin or family designs. GWAS offers a new perspective here but does not necessarily make twin and family studies futile. In fact, all of these designs have their own strengths and weaknesses, that are largely unrelated to each other and therefore complement each other (see for an overview Table 1). Combining different research approaches to investigate the same research question provides a powerful strategy, that was recently coined "triangulation," and importantly, enhances the reliability of particular findings (Lawlor et al., 2016).

The heritability estimate derived from a GWAS is called SNP-based heritability (h^2_{SNP}) (Yang et al., 2010). The h^2_{SNP} only captures the variance that is explained by measured common genetic variants that are captured in the GWAS. Thus, for instance, rare genetic variants are not included in the h^2_{SNP}. Heritability estimated from twin and family studies on the other hand captures all variance explained by genes. Therefore, h^2_{SNP} is usually substantially lower than heritability estimated from family and twin designs. The difference between heritability estimates from twin studies and GWAS is called "missing heritability" and is thought to diminish when the power of GWAS analyses increases (Manolio et al., 2009). However, since GWAS never include all genetic variants across the human genome, GWAS heritability estimates will always remain lower than twin heritability estimates.

Table 1   Comparison of twin and genome-wide association studies (GWAS).

Attribute	Twin studies	GWAS
Goals and uses	• Decompose variation of a disorder into genetic and environmental influences • Causal models Applies to both approaches • Estimate heritability (h^2) • Calculate genetic correlations	• Identify genetic variants associated with a disorder • Causal models • Study underlying biological pathways • Polygenic (risk) scores
Strengths (+) & weaknesses (−) of design	+ Small samples suffice (e.g., 400+ twin pairs) − MZ and DZ twin pairs needed + Potential for more complex phenotyping, including longitudinal data + h^2 includes the effects of all genetic variants (common and rare) − No information regarding the types or location of genetic variants that give rise to h^2 − Assume equal environments for MZ and DZ twin pairs − Estimating genetic correlations requires both traits are measured in the same sample	− Require large samples (10s–100s of thousands of individuals) + Unrelated individuals needed − Often has minimal phenotyping − h^2 includes only effects of a limited set of genetic variants + Provides information regarding the types or location of genetic variants that give rise to h^2 + In unrelated individuals, genetic similarities are unlikely to be confounded with environmental similarity after controlling for ancestry + Can estimate genetic correlations across different samples
	Applies to both approaches − Historic lack of diverse samples (with particular concern about exacerbating health disparities for GWAS discoveries)	

Note. MZ = monozygotic, DZ = dizygotic.
Table adapted with permission from Friedman et al. (2021).

GWAS findings are increasing

Sample sizes in GWAS are exponentially increasing, and so are GWAS results. Here we describe GWAS results in mental disorders of studies including >10,000 participants. All GWAS results are also presented in detail in Table 2.

Neurodevelopmental disorders

Although autism spectrum disorder and ADHD are among the most common neurodevelopmental disorders and have relatively high twin study-based heritability estimates (∼70%), GWAS results are still behind compared to other disorders. This is in part due to the relatively small sample sizes for these disorders. The largest GWAS to date for autism spectrum disorder included 46,350 participants (18,381 cases and 27,969 controls) and identified 5 genome-wide SNPs (Grove et al., 2019). The h^2_{SNP} was 11.8%. The latest ADHD GWAS included 225,534 participants (38,691 cases and 186,843 controls) and identified 27 genome-wide SNPs (Demontis et al., 2022). The h^2_{SNP} was 14%. The limited sample sizes for the ADHD and autism spectrum disorder GWAS likely constrain the number of hits (i.e., significantly associated SNPs).

Schizophrenia, on the other hand, is one of the most extensively studied mental disorders. With 69,369 cases and 236,642 controls, 270 significantly associated SNPs were identified (Schizophrenia Working Group of the Psychiatric Genomics Consortium et al., 2020). The h^2_{SNP} was estimated at 24%.

Internalizing disorders

Genetic influences generally play a smaller role in internalizing disorders than they do in most neurodevelopmental disorders. Still, one of the largest GWAS to date has been conducted for major depressive disorder. With 807,553 participants (246,363 cases and 561,190 controls), 102 genome-wide significant SNPs were identified (Howard et al., 2019). The h^2_{SNP} was estimated at 8.9%, which is in accordance with the lower overall heritability compared to neurodevelopmental disorders. The latest bipolar disorder GWAS included around half of this sample with a total of 413,466 participants (41,917 cases, 371,549 controls), and identified 64 genome-wide significant SNPs (Mullins et al., 2021). For bipolar disorder, h^2_{SNP} was estimated at 15.6%–18.6%. When combining major depressive disorder and bipolar disorder into a single GWAS, Coleman et al. (2020) identified 73 SNPs associated with a broader spectrum of mood disorders. They argued that statistical power could increase if major depressive disorder and bipolar disorder are combined in GWAS, since they share genetic associations. Such a combined GWAS enables detecting associated variants that would not be detected when analyzing just one of the disorders.

As noted above, anxiety disorders consist of a broad spectrum of disorders including generalized anxiety disorder, phobias, and panic disorder. Similar to major depressive disorder and bipolar disorder, however, it is expected that anxiety disorders share part of their etiology (Eley et al., 2003). The largest anxiety GWAS to date therefore combined several anxiety and stress-related disorders, including agoraphobia, generalized anxiety disorder, panic disorder, social phobia, specific phobia, PTSD, acute stress reaction, and adjustment disorder (Meier et al., 2019). Still, sample sizes were relatively small (12,655 cases, 19,225 controls) and just one associated SNP has been identified so far. The h^2_{SNP} was relatively high however, at 28%. The few GWAS where anxiety disorders were analyzed separately had sample sizes smaller than 10,000 and have not yet resulted in many hits.

A recent study on post-traumatic stress disorder (32,428 cases, 174,227 controls) found 3 genome-wide significant SNPs and was able to show that genetic liability differs between ancestries and between sexes (Nievergelt et al., 2019). So far, one SNP is significantly associated with obsessive-compulsive disorder (Strom et al., 2021). Although eating disorders entail a variety of eating problems, GWAS have only been conducted on anorexia nervosa. The largest GWAS included 16,992 cases and 55,525 controls and identified 8 genome-wide significant SNPs. The h^2_{SNP} was estimated at 11%–17% (Watson et al., 2019). GWAS of Tourette syndrome and tic disorders included 4819 cases and 9488 controls and found 1 genome-wide significant SNP (Yu et al., 2019). The h^2_{SNP} was estimated at 21%.

Externalizing disorders

In general, not many genetic variants have been identified for individual externalizing disorders. The few GWAS on substance use disorders have not rendered many results. In a study of 4503 opioid-dependent cases, 4173 opioid-exposed (not opioid-dependent, but had used opioids before) controls, and 32,500 opioid-unexposed controls, no SNPs were significantly associated with opioid dependence, but one was associated with opioid exposure (Polimanti et al., 2020). Similarly, for both alcohol dependence (14,904 cases, 37,944 controls) (Walters et al., 2018) and cannabis use disorder (20,916 cases 363,116 controls), two SNPs were identified (Johnson et al., 2020). For problematic alcohol use, which includes both alcohol dependence and problematic drinking, a larger GWAS was performed, and 29 SNPs were significantly associated (Zhou et al., 2020).

GWAS for other individual disorders related to impulse control are scarce. Interestingly, Karlsson Linnér et al. (2021) combined traits into a broader phenotype that included multiple disorders and behaviors related to self-regulation. By pooling results of multiple GWAS, they arrived at a sample of around 1.5 million participants and identified more than 500 genetic variants associated with externalizing behaviors (f.e., ADHD and alcohol or cannabis use). In a similar way, Tielbeek et al. (2021) combined multiple samples and identified one genome-wide significant SNP associated with a broad measure of antisocial behavior.

Remarks

The number of SNPs that can be identified in a GWAS depends on several elements. The typical trend in GWAS is that larger samples and higher heritability render more significantly associated SNPs. Yet, it is important to note that the number of associated SNPs

Table 2   Results of most recent genome-wide association studies (GWAS).

Disorder/trait	Number of participants	Number of significant SNPs	h^2SNP	R^2 PGS
Neurodevelopmental disorders				
ADHD	38,691 cases	12	14%	–
(Demontis et al., 2022)	186,843 controls			
Autism spectrum disorder	18,381 cases	5	11.8%	2.45%
(Grove et al., 2019)	27,969 controls			
Schizophrenia	22,778 EEA cases	21	23%	2.9%
(Lam et al., 2019)	35,362 EEA controls			
Schizophrenia	69,369 cases	270	24%	7.7%
(Schizophrenia Working Group of the Psychiatric Genomics Consortium et al., 2020)	236,642 controls			
Internalizing disorders				
Major depressive disorder	246,363 cases	102	8.9%	1.5%–3.2%
(Howard et al., 2019)	561,190 controls			
Bipolar disorder	41,917 cases	64	15.6%–18.6%	4.57%
(Mullins et al., 2021)	371,549 controls			
Mood disorders	185,285 cases	73	8.8%	–
(Coleman et al., 2020)	439,741 controls			
Anxiety	12,655 cases	1	28%	–
(Meier et al., 2019)	19,225 controls			
Anorexia nervosa	16,992 cases	8	11%–17%	1.7%
(Watson et al., 2019)	55,525 controls			
Post-traumatic stress disorder	32,428 cases	3 total (2 EA and 1 AA)	5%	0.15%–1.2%
(Nievergelt et al., 2019)	174,227 controls			
Obsessive-compulsive disorder	14,140 cases	1	16.4%	3.3%–3.9%
(Strom et al., 2021)	562,117 controls			
Tourette's syndrome and tic disorders	4819 cases	1	21%	0.42%–0.78%
(Yu et al., 2019)	9488 controls			
Externalizing disorders				
Opioid dependence	4503 OD	0 OD	8%–28%	–
(Polimanti et al., 2020)	4173 OE	1 OE		
	32,500 OU			
Alcohol dependence	14,904 cases	2 total (1 EA and 1 AA)	9%	0.3%–1.7%
(Walters et al., 2018)	37,944 controls			
Problematic alcohol use	435,563 total participants	29	6.8%	0.77%–2.12%
(Zhou et al., 2020)				
Cannabis use disorder	20,916 cases	2	6.7%–12.1%	0.04%
(Johnson et al., 2020)	363,116 controls			
Externalizing disorder	~1,5 million total participants	579	–	8.9%–10.5%
(Karlsson Linnér et al., 2021)				
Antisocial behavior	85,359 total participants	1	8.4%	0%–3.7%
(Tielbeek et al., 2021)				

Note. ADHD = attention deficit/hyperactivity disorder; SNPs = Substitutions of a single nucleotide at a specific genomic location; h^2SNP = SNP heritability; R^2 PGS = variance explained by polygenic score; EEA = East Asian Ancestry; EA = European Ancestry; AA = African Ancestry; OD = opioid dependent cases; OE = opioid exposed controls; OU = opioid unexposed controls. Where possible, we included studies performed on diagnosed disorders. However, some of the included studies explored broader traits. Consequently, the number of participants is either the number of cases and controls (for diagnosed disorders) or the total number of participants for whom the continuous symptom/trait was assessed. h^2SNP is described as a range for some traits and disorders, because it is dependent on the prevalence of the trait or disorder in the population, which sometimes is a range. R^2 PGS is sometimes calculated on slightly different phenotypes than the initial GWAS and is sometimes applied to multiple samples. Therefore, we have included ranges for R^2 PGS as described in the papers.

does not necessarily directly relate to the heritability of a disorder. Some disorders may involve a smaller number of SNPs with a bigger impact, whereas other disorders involve a large number of SNPs with smaller impact. Furthermore, results are highly dependent on the definition of the trait. Karlsson Linnér et al. (2021)'s GWAS demonstrate that the broader the definition of the disorder/phenotype, the more genes are involved.

In order to understand the underlying biological pathways of mental disorders, SNPs identified in GWAS are often studied for their functionality. Although this may be challenging (Tam et al., 2019), it is clear that SNPs and genes that are associated with mental disorders are often involved in synaptic function and neurogenesis (i.e., the growth of neural tissue). Studying gene functions could help increase understanding of the biological underpinnings of mental health and develop effective behavioral or pharmacological treatments where needed.

Are mental disorders genetically unique?

The p-factor

Mental disorders were traditionally viewed as entirely distinct conditions, but high rates of comorbidity between disorders point toward the existence of higher-order factors. In an attempt to identify these factors, initially two categories of mental disorders were described: internalizing (e.g., mood disorders, anxiety disorders, eating disorders, trauma-related disorders) and externalizing (e.g., antisocial behavior, substance use, conduct disorder). However, research has shown mental disorders may even be explained by one factor, the so-called psychopathology factor or p-factor (Caspi et al., 2013). The p-factor reflects an overall propensity toward mental disorders.

Not only does the p-factor for mental disorders appear to account for overlap/comorbidity between disorders, it appears to reflect genetic overlap as well. Using a variety of methodological approaches, it has been consistently shown that genetic influences on mental disorders partially overlap. Twin studies show a myriad of genetic correlations between mental disorders. An early example of genetic correlation was described by Kendler (1996), who found in a twin study that major depressive disorder and generalized anxiety disorder are caused by the same genetic factors (i.e., a genetic correlation of one). Although later studies have nuanced these findings (Kendler et al., 2007), it is clear that substantial genetic overlap exists. Twin studies offer numerous examples of that genetic overlap, for example between anxiety and depression (Middeldorp et al., 2005), schizophrenia and bipolar disorder (Lichtenstein et al., 2009), obsessive-compulsive disorder and anorexia nervosa (Cederlöf et al., 2015), ADHD and autism spectrum disorder (Polderman et al., 2014; Ronald et al., 2014), and many more. In line with these findings, using a multivariate twin model, Allegrini et al. (2020) describe that multiple psychopathologies can be explained, in part, by one underlying factor (the p-factor). They find that this factor is substantially stable over time and highly heritable. However, significant disorder-specific genetic factors are found as well. For example, both Ronald et al. (2014) and Polderman et al. (2014) show that some subdomains of autism spectrum disorder and ADHD overlap strongly, whereas others do not, a finding that underlines both genetic similarities and differences between psychiatric disorders.

Data from GWAS shows genetic overlap between mental disorders as well. The first GWAS across mental disorders examined five psychiatric traits (autism spectrum disorder, ADHD, bipolar disorder, major depressive disorder and schizophrenia) and found substantial genetic overlap, especially between bipolar disorder, schizophrenia and major depressive disorder (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). With increasing availability of GWAS data, many more cross-disorder correlations have been identified (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). Anttila et al. (2018) examined genetic overlap between 17 brain disorders including both psychiatric and neurological disorders. The high degree of genetic correlation between the psychiatric disorders in their sample underlines that mental disorders are not genetically unique. More recently, it was described that three broad factors (i.e., compulsive/perfectionistic behavior, mood and psychotic behavior, and early-onset neurodevelopmental disorders) underlie eight mental disorders: autism spectrum disorder, ADHD, bipolar disorder, major depressive disorder, obsessive-compulsive disorder, anorexia nervosa, Tourette syndrome and schizophrenia. These factors explained over 50% of the genetic variance in the eight disorders. In addition, they showed that specific genetic loci are overlapping between mental disorders; 109 genetic loci were associated with at least two psychiatric disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019). Similarly, Peyre et al. (2021) found that 37.5% of the SNPs associated with autism spectrum disorder are also associated with ADHD, and 19.6% of the SNPs associated with ADHD are also associated with autism spectrum disorder. Thus, genetic loci are not uniquely associated with just one psychopathology.

Polygenic scores

A promising application of GWAS is the polygenic score (PGS). PGS reflects an individual's genetic liability for a disorder or trait. PGS is computed by summing an individual's genetic variants weighted by their estimated effect size. These effect sizes are derived from GWAS results. Most GWAS also describe the degree to which a PGS that is based on their study results is associated with the same trait or disorder in a different sample. In other words, these studies describe how much variation in the studied disorder/trait is explained by the PGS (R^2 PGS) in an independent sample. This explained variation is often relatively small (see Table 2). Still, PGS show much stronger associations than individual genetic variants. Currently, explained trait variation ranges from below 1% (e.g., Tourette syndrome) to about 10%. The highest trait variance explained by PGS for a mental health trait to date was described by

Karlsson Linnér et al. (2021), whose PGS explained 8.9%–10.5% of the variation in externalizing behavior. The power of PGS is likely to increase with increasing GWAS sample sizes.

PGS offers several applications in genetic research. Some advantages of PGS are that they can be used in smaller samples and can be easily recalculated if new results or methods are available. This makes it a particularly useful tool.

As described above, PGS can be used to find associations with the same specific disorder or trait in an independent sample. For example, a schizophrenia PGS in a sample of first-episode psychosis patients reliably predicted case-control status and distinguished patients that would later be diagnosed with schizophrenia from patients that would be diagnosed with other psychoses (Vassos et al., 2017). Likewise, the PGS for ADHD has been associated with ADHD diagnosis (disorder) and ADHD behavior (trait) in independent samples (Ronald et al., 2021), and the major depressive disorder and bipolar PGSs have been associated with depression diagnoses/behavior and bipolar disorders/behavior, respectively (Mistry et al., 2018a).

It appears that many disorder-specific PGS are also associated with other psychiatric disorders and with non-psychiatric traits like cognition, creativity, physical health, addiction and suicide risk, among other things (Mistry et al., 2018b; Ronald et al., 2021). Karlsson Linnér et al. (2021) showed that a polygenic score based on their GWAS of externalizing behavior was not only associated with externalizing behaviors, but with many other life outcomes as well. For example, significant associations with socioeconomic attainment, substance use disorders, and involvement in the criminal justice system were observed. This underscores the fact that mental disorders are not genetically unique but show substantial overlap. It also highlights how PGSs can help identify individuals at risk for a range of specific disorders and additional problems.

In addition, PGS may serve as a control variable in research to ensure the equality of groups and prevent confounding due to genetic factors. For example, when testing the effect of a medication for a disorder, one might want to ensure that on average, the group that receives and the group that does not receive the medication have similar PGSs.

Lastly, PGS may be exploited to study interactions between genetic liability and environmental risk factors (Assary et al., 2018). For example, one study described interactions between genetic liability for depression, childhood trauma, and stressful life events on the development of major depressive disorder (Peyrot et al., 2014) (although larger, more recent studies do not replicate this gene-environment interaction, see Mullins et al., 2016; Peyrot et al., 2018).

Clinical utility

Although knowledge of the genetics of mental disorders is increasing exponentially, its clinical utility is still relatively low. Given the current state of affairs, PGS may be the most promising tool for future clinical use. Wray et al. (2021) described that PGS may be applied within the general population: (1) to identify individuals at high risk for disorders; (2) as an additional diagnostic tool early in the illness process; and (3) as a potential tool for choosing adequate treatment. That is, to personalize healthcare. However, it is important to note that although PGS may help in personalizing healthcare in the future, there are many ethical issues that need to be addressed first (Sankar and Parker, 2016). Moreover, several limitations apply to the clinical use of PGS.

For instance, the variation in a disorder/trait that is explained by genetic variants is still relatively small. Although variation explained by genetic variants will likely increase with increasing statistical power, PGS will never be able to capture all genetic influences since it only includes a selection of all genetic variants on the human genome. Some mental health traits may be strongly related to the rare variants that are not included in GWAS. In addition, complex interactions may exist between genes, and research addressing this in human genetics is still in its infancy (Ritchie and Van Steen, 2018). Therefore, it is highly unlikely that PGS could ever explain the complete heritability of complex traits. Lastly, mental disorders are not only influenced by genes, but are also significantly influenced by the environment. The association between a PGS and a trait or disorder therefore also depends on the role of the environment in trait variation, and interactions between genes and environment. Such interactions will not be captured in a PGS. This makes PGS unsuitable as a stand-alone diagnostic tool (Wray et al., 2021). Indeed, many PGS for mental disorders are currently only applicable in research (Ronald et al., 2021).

A different route in which GWAS knowledge could be used in clinical care is by advancing drug treatment (Tam et al., 2019). First, GWAS results could help identify new drug targets (De Jong et al., 2016). Drug targets that are supported by genetic research are much more likely to be approved and eventually applied. This could potentially reduce costs and time invested in clinical drug research (Nelson et al., 2015). Second, GWAS may help in personalized drug selection and dosage and may prevent adverse drug events. However, the path from GWAS discoveries to functional description in psychiatry has proven more difficult than for other medical pathologies. This may be due, in part, to the highly polygenic nature of mental disorders. For example, many protein-coding genes are involved in schizophrenia, which makes it difficult to pick the most effective drug target (Tam et al., 2019).

Lastly, quick developments in genetic science have resulted in the emergence of gene editing techniques. Although gene editing has proven to be effective in the treatment and prevention of single-gene disorders, it is important to note that gene editing for mental disorders is currently not possible and will most likely not be possible in the (near) future. Mental disorders are highly polygenic, with single genetic variants only having very small effects. Moreover, exact functions of many of these variants are unknown. Genetic overlap between disorders/traits also makes gene modification problematic, as the dynamics of gene function may differ for different (genetically related) traits. As described above, the influence of genetic loci is often not limited to one psychiatric disorder or even to just mental health traits. Insufficient knowledge of the potential deleterious effects of gene editing has led to proposals supporting a worldwide block on the practice (Lander et al., 2019). All in all, gene editing for polygenic disorders, such as mental disorders, is and will most likely never be possible.

An important shortcoming of genetic studies thus far is that results mainly apply to individuals of European ancestry (Hindorff et al., 2017; Mills and Rahal, 2019). Past behavior genetics research examining the biological basis of racial/ethnic differences has often contributed to harm for individuals from marginalized racial and ethnic groups. As a result, mistrust is reported as one of the main barriers for individuals who identify as racial and ethnic minorities to participate in research (George et al., 2014). Yet causes of disease can differ strongly between ancestries (Wojcik et al., 2019)—a difference that for instance substantially decreases the strength of the association when applying genetic data from European ancestry participants to individuals of different ancestries (Martin et al., 2017). To be able to prevent and overcome health inequalities in access to and delivery of health care, it is critically important for genetic research to be conducted in racially and ethnically diverse samples (Wojcik et al., 2019). Although multi-ethnic research is being promoted and increasingly conducted, sample sizes have not yet reached those of research in European samples. For example, a recent comparative GWAS of East Asian and European populations included 22,778 cases and 35,362 (Lam et al., 2019) of East Asian ancestry, a sample much smaller than the most recent GWAS in European participants (69,369 cases and 236,642 controls; Schizophrenia Working Group of the Psychiatric Genomics Consortium et al., 2020). As an illustration, we have included some recent GWAS results in non-European samples in Table 2. Thus, while genetic research in different racial and ethnic populations is increasing, there is still a long road ahead (Martin et al., 2019).

Conclusions

The fact that all genetic designs, despite their unique approaches and biases, share the observations that genetic influences play a substantial role in mental disorders supports Hippocrates' initial ideas of "a biological basis" of mental disorders. These data have motivated scientists worldwide to identify the specific genes involved in psychiatric disorders. This quest has only recently begun, and the avenue to find those genes and their function in mental disorders is still long and not straightforward. However, it is a promising endeavor as it will eventually bring us closer to understanding the etiology and treatment of mental disorders.

Acknowledgment

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