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Large-scale genomics unveils the genetic architecture of psychiatric disorders

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Abstract

Family studies are consistent with genetic effects making substantial contributions to risk of psychiatric disorders such as schizophrenia, yet robust identification of specific genetic variants that explain variation in population risk had been disappointing until the advent of technologies that assay the entire genome in large samples. We highlight recent progress that has led to a better understanding of the number of risk variants in the population and the interaction of allele frequency and effect size. The emerging genetic architecture implies a large number of contributing loci (that is, a high genome-wide mutational target) and suggests that genetic risk to psychiatric disorders involves the combined effects of many common variants of small effect, as well as rare and *de novo* variants of large effect. The capture of a substantial proportion of genetic risk facilitates new study designs to investigate the combined effects of genes and the environment.

A genetic contribution to the risk of many psychiatric disorders has been well established by family studies^{1–5}, but the nature of their genetic architectures has not. Genetic architecture refers to the number of genomic loci contributing to risk, the distribution of their allelic frequencies and effect sizes, and the interactions of alleles in and between genes, all of which contribute to the relationship between genotype and phenotype. Understanding genetic architecture is the foundation on which progress in dissecting etiology is built because it dictates which study designs for identifying risk variants are likely to be most successful. Here we review how recent studies that employed whole-genome genotyping or exome sequencing have contributed to a better understanding of the joint spectrum of allele frequencies and penetrance of risk variants for psychiatric disorders. We focus particular attention on schizophrenia (SCZ), the genetic dissection of which is further advanced than other disorders considered in this review, including Alzheimer's disease (AD), anorexia

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nervosa (AN), attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), bipolar disorder (BPD), major depressive disorder (MDD), obsessive compulsive disorder (OCD) and Tourette's syndrome (TS).

Psychiatric disorders are best classified as 'complex traits'. The variability of such traits is a result of a large number of factors and can be dissected into sources of variation resulting from genetic factors, non-genetic factors and their interplay. With the exception of rare strictly monogenic disorders, almost any trait—for example, most common diseases, brain regional volume and the amount of DNA methylation of a particular gene in a particular tissue—can be considered a complex trait, so long as it can be measured and varies between individuals. In Box 1, we provide a primer on the genetic analysis of complex traits.

Box 1

Primer on genetic analysis of complex traits

Before the availability of direct measures of genetic variation at the level of DNA, epidemiological studies on psychiatric disorders endeavored to detect robust associations between measurable environmental factors and risk of disease, whereas genetic epidemiologists attempted to quantify the risk in the population into genetic and non-genetic sources of variation. Notably, one can quantify the proportion of variation in the population resulting from genetic factors (the heritability) without knowing anything about how many or which genetic variants underlie the trait using the observed risk to relatives and contrasting that with what would be expected given the proportion of the genome those relatives share by descent. Epidemiological studies have identified a number of environmental risk factors, such as maternal infection during pregnancy and risk of schizophrenia to their children⁹³. Reported recurrence risks to relatives are consistent with heritabilities of 40–80% for autism, schizophrenia and major depression. Genetic differences between individuals in their risk to psychiatric disorders are a result of one or more mostly unknown variants in the genomes of people. Such variants either segregate in the population or are de novo mutations not expressed in the parents. Segregating variants cause the observed similarity in risk between relatives, whereas new mutations do not, apart from rare exceptions such as mutations in monozygotic twins that arose before the embryo was split, and mutations shared by siblings as a result of germlin mosaicism.

The contribution of a specific genetic variant to trait variation in the population is determined by the combination of its allele frequency and its effect size. Variants are typically classified as common, low frequency or rare if their population frequencies are >0.01 , between 0.01 and 0.001, and <0.001 , respectively. At one extreme, rare variants of large effect are by definition carried by few individuals. They may have a very large effect on those people—for example if the variant is sufficient to cause disease—but tend to not contribute much of the variation in the population as a result of their rarity. At the other extreme, common variants of small effect are carried by lots of people, either in the heterozygous or homozygous state. The increased risk of disease to an individual from such variants may be trivial but the effect on population variance can be the same as for the rare variant of large effect (Fig. 3 in Box 1). For example, recurrent 22q11.21

deletions increase risk to schizophrenia from 1% to about 20–40%, yet are rare in the population (fewer than 1 in a 1,000 individuals carry the deletion), whereas a common variant in ZNF804A increases risk from 1 to 1.1% per allele, but is common (a proportion of 0.8 in the population has one or two alleles): both contribute about the same amount of variation in liability to schizophrenia (that is, $r^2 \sim 0.1\%$)⁷⁷. The majority of risk alleles for schizophrenia, common and rare, are likely to explain substantially less of the variation than these examples (Fig. 3 in Box 1).

A positive family history is often assumed to be indicative of inherited risk variants, whereas ‘sporadic’ cases of disease (that is, those with a negative family history) are sometimes assumed to harbor new (de novo) high penetrance mutations. Although there is some evidence for this classification in SCZ (for example, see refs. 44,60), and although focusing on sporadic cases makes sense when searching for de novo mutations, it is worth noting that a negative family history is expected for highly polygenic, low prevalence disorders (for example, SCZ)⁹⁴. Thus, under polygenicity, the delineation of affected individuals as familial and sporadic may be misleading. More data is needed to determine which genetic models are most appropriate for psychiatric disorders, but even for non-psychiatric diseases, such as amyotrophic lateral sclerosis, where there are clear-cut examples of Mendelian fully penetrant mutations, there is emerging consensus that the distinction between familial and sporadic amyotrophic lateral sclerosis is artificial⁹⁵.

Geneticists have used a number of ‘whole genome’ toolboxes to try to discover genes and genetic variants that are associated with risk to psychiatric disorders: genetic epidemiology studies to quantify the combined effect of the entire genome to risk of disease, genome-wide linkage studies, GWASs and WES studies¹². In the near future we can add whole-genome sequencing, which essentially will supersede genome-wide linkage studies, GWASs and WES studies.

Segregating variants in the population that predispose to psychiatric disorders are the results of our evolutionary past. The evolutionary forces that shaped our modern genomes include mutation, natural selection and genetic drift. Natural selection acts on ‘net’ fitness, which is much more than fitness with respect to any individual disease. Although there are multiple theories of what our genomes should look like with respect to variants that predispose to psychiatric disorders and other complex traits^{6–8}, testing their predictions awaits a better understanding of the genetic architecture of complex traits. Broadly speaking, for any given complex trait, the distribution of genetic variance explained as a function of minor allele frequency is expected to be uniform under a neutral evolutionary model, but should be shifted toward lower minor allele frequencies to the extent that alleles affecting the trait have been under selection⁹. Yet, irrespective of evolutionary arguments, we can study human genomes here and now to understand why some individuals are at higher risk of disease than others. The genomics revolution, particularly the ability to interrogate the entire genome through developments in high-throughput technologies such as genome-wide genotyping and sequencing, has provided the tools to dissect the genetic variation that was inferred from genetic epidemiological studies into contributions from individual variants.

Mutation, polymorphism, gene and pathway discovery

Important advances in psychiatric genetics have been made in recent years, with many replicated discoveries of common, rare and de novo risk factors that are converging on specific pathways and biological mechanisms. These successes have predominantly come about as a result of the experimental design of genome-wide association studies (GWASs)^{10,11} and, in particular, the international community combining resources and results across multiple GWASs and copy number variation (CNV) studies to maximize sample size and statistical power. Whole-exome sequencing (WES) has also begun to shed light on the role of rare and de novo coding sequence variation, particularly in autism. The flow of discoveries from these unbiased genome-wide methods stands in contrast to the weak and largely inconsistent findings from candidate gene studies¹².

GWAS

At the time of writing this review, GWASs have identified >100 independent loci for SCZ¹³, 20 loci for AD¹⁴, eight loci for BIP¹⁵, one locus for ASD¹⁶, and none for other common psychiatric disorders, including ADHD¹⁷, AN¹⁸, MDD¹⁹, OCD²⁰ and TS²⁰ (Fig. 1). In addition, cross-disorder GWAS meta-analyses had identified three loci for a combined SCZ-BPD phenotype²¹ and four loci for a broader psychiatric phenotype spanning ASD, ADHD, BPD, MDD and SCZ²². These genetic findings surpass accepted standards for genome-wide significance ($P < 5 \times 10^{-8}$) and replication in human genetics; the stringent type 1 error threshold of 5×10^{-8} corresponds to a Bonferroni correction of 0.05 divided by 1,000,000 tests, which is the estimated number of independent common variants across the human genome²³. The overt success for SCZ, the ‘flagship’ disorder of the Psychiatric Genomics Consortium (PGC)²⁴, is largely explained by greater sample size (that is, >35,000 cases compared with a maximum of ~17,000 cases for any other disorder), which was achieved by the PGC combining data across >50 studies¹³. Indeed, no single locus had been robustly associated with SCZ when sample sizes were similar to those currently available for many other disorders (for example, ADHD: ~900 cases¹⁷). MDD is an exception, given that no discoveries were made in the most recent PGC mega-analysis¹⁹ (9,240 cases, 9,519 controls), a study similar in scale to the PGC’s initial SCZ GWAS (9,394 cases, 12,462 controls), which identified seven loci²¹. However, sample sizes approximately five-fold greater than SCZ are predicted to be necessary for GWAS discovery in MDD, mostly as a result of its high population prevalence²⁵ (Fig. 2). Phenotypic heterogeneity may also be a factor contributing to differential success of GWAS in psychiatric disorders (discussed below). These considerations aside, the results for SCZ, the largest GWAS to date for any psychiatric disorder, show what might reasonably be expected for other disorders from larger studies that are currently in the pipeline.

The trajectory of GWAS discovery for SCZ, which increased from 1 locus^{26,27} to 7 (ref. 21) to 22 (ref. 28) to 62 (ref. 29) to >100 (ref. 13) as the number of cases increased from ~3,000 to >35,000, is not dissimilar to that of other (non-psychiatric) diseases (Fig. 1). Admittedly, late-onset diseases, including AD³⁰ and age-related macular degeneration³¹, and some autoimmune diseases (for example, Crohn’s disease)³² achieved success earlier, often with first generation technologies such as linkage mapping and GWASs of small samples, but

these discoveries involved risk alleles that explain an unusually large proportion of the total genetic risk (for example, APOE in AD). GWAS loci identified for SCZ, as with the majority of GWAS discoveries across the breadth of medicine, are very common (that is, the risk allele is often the major allele), have small effect size (for example, 1.1% absolute risk when the population prevalence is 1%) and individually explain only a small fraction of the total genetic risk (Fig. 3 in Box 1). The underlying genetic architecture is highly polygenic^{21,26,28}, as we discuss below, a fact that has driven, and continues to drive, international efforts coordinated by the PGC to assemble ever-larger samples for meta-analyses³³.

Why should neuroscientists' care about GWAS findings in psychiatric disorders given that identified loci have such small effects? First, although verified GWAS effects are usually small individually, their cumulative effect is not. Genetic profile scores derived from very large discovery samples can be applied to small target samples, such as those used in neuroscience studies, to facilitate more powerful experiments, for instance, by enabling stratification of samples according to upper and lower deciles of genetic risk. Second, there are now many examples of diseases for which GWAS has highlighted relevant biology (for example, see refs. 31,34), including known drug targets^{35,36}. For instance, numerous genes identified in a GWAS meta-analysis for rheumatoid arthritis are the targets of known drugs that are effective therapies for this disease³⁷, and the same is true for genes underlying natural variation in LDL levels that are the targets of statins³⁸. Results from the latest GWAS for SCZ suggest that similar insights may be forthcoming in psychiatric disorders, given that identified loci include known targets of existing antipsychotics¹³. These examples indicate that, although GWAS loci have small effect size, they nonetheless may help identify targets for novel therapeutics³⁸ or may identify existing drugs that can be repurposed for treatment of diseases that they were not initially developed to treat³⁶. More broadly, and consistent with other complex diseases (for example, inflammatory bowel disease³⁹) and traits (for example, height⁴⁰) for which large numbers of genetic associations have been identified, the 100+ GWAS loci identified for SCZ converge on biological pathways relevant to disease etiology, including neuronal calcium ion channel signaling, altered immune function and MIR137-mediated post-transcriptional regulation of gene expression¹³. Functional investigation of the biological basis of genetic associations in these pathways represents a formidable challenge and will be far more difficult than that for rare variants with larger effects. We are in the very early days of addressing this challenge, but there is nonetheless potential for such efforts to make profound contributions to our understanding of disease pathogenesis.

Structural variation studies

At the opposite end of the risk allele frequency spectrum, rare and de novo submicroscopic chromosomal deletions and duplications termed CNVs have been implicated in a range of psychiatric disorders. The unbiased genome-wide analysis of large CNVs (>100 kb) has been facilitated by data from high-density genomic arrays used in GWAS. Over the past decade, such studies have established that large rare (<1% frequency in the population) CNVs, particularly those arising de novo in the parental germline, occur at higher frequencies in ASD^{41,42}, SCZ^{43,44} and ADHD⁴⁵ than in healthy controls, implying that

some events contribute to risk. Rare CNVs have also been implicated in BPD, particularly early onset disease⁴⁶, but the evidence is inconsistent⁴⁷ and the contribution may be less than for ASD and SCZ. In addition to evidence for increased CNV burden, about a dozen recurrent CNVs have been identified, including deletions on chromosomes 2p16.3 (in the NRXN1 gene), 3q29 and 17q12, duplications on 7q11.23, 7q36.3 (in the VIPR2 gene), 15q11.2 and 16p13.11, and both deletions and duplications at 1q21.1, 15q13.3, 16p11.2 and 22q11.21 (refs. 45,48–51). At several loci there is evidence that ASD and SCZ are associated with reciprocal events; that is, deletions predispose to one disorder and duplications the other⁵². Most of the identified loci span multiple genes and confer risk for a range of psychiatric and neurodevelopmental disorders^{48,49}, consistent with other evidence for shared genetic etiology across diagnostic boundaries. Odds ratios are high compared with common loci, ranging from ~2 to >20 (refs. 48,49), but their frequency is very low in the general population (that is, the majority have a frequency < 0.001) and so large samples are nonetheless required for discovery and replication (similar to that for GWAS). For some loci, penetrance for ASD appears to be higher in males than females (for example, 16p11.2)⁵³, and de novo events in affected girls are more functionally disruptive than those in affected boys^{41,53}. This suggests that girls have greater resistance to ASD from genetic factors, consistent with the ~4:1 male bias in incidence, although the mechanisms responsible for this pattern remain to be deciphered^{41,53}.

WES

WES involves the targeted enrichment and high-throughput sequencing of all coding exons and non-coding RNAs in the genome. In recent years, the first WES studies investigating rare sequence variation in common psychiatric disorders have been published, with most attention to date on de novo mutations in ASD (for example, see refs. 54–57) and SCZ (for example, see refs. 58–60). WES studies of other psychiatric disorders are currently underway. Sequence-based discovery of genes involved in neurodevelopmental disorders is reviewed by Hoischen and Eichler⁶¹, so we focus here on implications of these studies for genetic architecture, with a brief overview of key findings.

Sample sizes for WES are still modest (for example, hundreds of families, up to ~5,000 cases and controls) compared with GWAS and CNV analyses, but results suggest an important, albeit limited (see below), role for de novo coding point mutations, particularly in early-onset neurodevelopmental disorders (for example, see refs. 54–57,62). Several key findings have emerged. First, about three quarters of de novo point mutations have a paternal origin and the mutation rate is correlated with paternal age at conception (for example, see refs. 63,64; Fig. 4). Advanced paternal age is a risk factor for a range of psychiatric disorders, including ASD and SCZ⁶⁵, but it remains unclear whether this risk is explained by the increased mutation rate or whether other mechanisms (for example, delayed fatherhood as a result of high polygenic risk⁶⁶; age-related epigenetic changes⁶⁷) have a role. Second, ASD probands harbor an excess of gene-disrupting mutations (for example, stop gain/loss, splice altering, frameshift; Table 1), particularly in brain-expressed genes^{54,57}. Notably, this enrichment is restricted to probands with low IQ⁶⁸. Given that similar enrichment has been reported in intellectual disability (for example, see ref. 62), these findings raise the question of whether gene-disrupting de novo mutations are related to

ASD per se or to intellectual impairment given ASD, or, conversely, to severe forms of ASD characterized by low IQ. Notably, in SCZ, the burden of gene-disrupting mutations is higher in SCZ probands with premorbid cognitive impairment compared with those without such impairment⁵⁸, which is an interesting parallel to the enrichment of such mutations in ASD probands with low IQ. The available evidence does not support an overall excess of gene-disrupting de novo mutations in SCZ⁵⁸, although one exception is a study (N = 146 case trios) involving SCZ probands that were carefully screened for a negative family history of psychosis⁶⁰, and it is possible that disruptive mutations are enriched in such cases. These points aside, there is some evidence for an excess of disruptive mutations in SCZ in several postsynaptic gene sets (although see refs. 41,60 for exceptions). These include members of the activity-regulated cytoskeleton-associated protein (ARC) and NMDA receptor (NMDAR) gene complexes and in genes associated with the fragile-X mental retardation protein (FMRP)⁵⁸. These gene sets were also enriched in a parallel SCZ case-control WES study⁵⁹ and in ASD (NMDAR, FMRP)⁵⁴ and intellectual disability (ARC, NMDAR, FMRP), pointing to substantial overlap of de novo signal between disorders^{58,59}. An excess of disruptive mutations in SCZ has also been identified in genes involved in voltage-gated calcium ion channel signaling⁵⁹, a notable overlap with GWAS findings¹³.

A third noteworthy finding is that specific genes have been identified in ASD and SCZ with recurrent gene-disrupting de novo mutations that exceed the number expected by chance. In SCZ, a single recurrence has been reported in the TAF13 gene⁵⁸, whereas, for ASD, a total of seven genes with recurrences have been identified in 1,043 families^{16,21,26}. These are important findings given that specific mutations in single genes are expected to be more amenable to functional follow-up than GWAS loci or multigenic CNVs. Attempts to identify specific genes using gene-based testing of segregating rare (as opposed to de novo) variants in WES case-control studies of SCZ⁵⁹ and ASD⁶⁹ have so far been unsuccessful (although see ref. 70), and much larger sample sizes, equivalent to those in current GWASs, are likely to be necessary⁵⁹. This also applies to whole-genome sequencing studies, which examine variants that exist between as well as within genes, which are expected to become increasingly prevalent in coming years.

Synthesis: genetic architecture and mutational target size

The results from recent GWAS, CNV and WES studies are enabling, for the first time, empirical assessment of fundamental questions about the genetic architecture of psychiatric disorders. For each disorder, how many loci are there? What are their frequencies and effect sizes? Taken together, how much of the heritability can be accounted for? How do the different disorders compare and how do they compare to non-psychiatric diseases? To what extent does the genetic contribution to one disorder overlap with others? And what is the evidence for gene-gene interaction? These are important questions because, without this knowledge, the field is operating in the dark when it comes to dissecting genetic etiology. Newly developed statistical methods that assess the joint contribution of common genetic variation across the genome are beginning to provide initial answers to these questions. The available evidence suggests that psychiatric disorders, including SCZ⁷¹, BPD⁷¹, ASD⁷¹, ADHD⁷¹, MDD⁷¹, OCD²⁰, TS²⁰ and AD⁷², are highly polygenic, with between one third and a half of the heritability being explained by common genetic variation distributed across

the genome. In the case of SCZ, an estimated 8,300 independent common loci collectively account for up to 50% of the genetic risk²⁸. A high degree of polygenicity (that is, high number of contributing genes or mutational target size) appears to be typical for most complex traits (for example, height⁷³) and common diseases (for example, Crohn's disease⁷⁴, type I diabetes⁷⁴) examined to date⁷⁵. However, although a substantial proportion of the genetic risk for some autoimmune diseases is a result of alleles that individually explain a substantial proportion of the heritability (for example, 1%), currently available data suggest that the polygenic risk for schizophrenia is dominated by alleles with very small effects (that is, 0.05% or less; Fig. 3 in Box 1). This is probably true for most psychiatric disorders (with AD being an exception). Whole-genome analysis methods also support substantial overlap of common genetic variation between disorders, in most instances consistent with clinical overlap and evidence for comorbidity from epidemiological studies.

A role for rare variants in psychiatric disorders has been well established by CNV and WES studies, but the overall contribution of rare variation is less well understood compared with common variation because coverage and sample sizes are not yet optimal. This is also true for low-frequency variation. A substantial contribution is possible if the heritability not explained by common variation (for example, half to two thirds for most disorders) is predominantly a result of rare and low-frequency variants, a question that will only be fully resolved by whole-genome sequencing studies that completely ascertain all genetic variation in large samples of cases and controls. In the interim, the PGC has developed the PsychChip, a single nucleotide polymorphism (SNP) array that features ~250,000 functional protein-coding variants, most of which are low frequency, in addition to high-density coverage of known and suggestive psychiatric disorder loci and a genome-wide backbone of common variation (enabling integration with existing data sets). In excess of 100,000 cases across multiple psychiatric disorders will be genotyped by the PGC with this array in the coming year, which should provide initial insights into the role of low-frequency variation in psychiatric disorders.

The overall contribution of de novo CNVs and coding mutations is also an open question, but the majority of new mutations do not contribute to heritability estimates⁷⁶, which are high for most psychiatric disorders (that is, ~0.6–0.8). Currently available WES data for ASD are consistent with ~5–10% of affected individuals harboring a damaging de novo point mutation with an odds ratio of ~5–20 (ref. 55). Importantly, in the context of using WES to assist clinical diagnosis, a genetic model for ASD involving fully penetrant mutations in many genes can be rejected⁵⁵ (although a proportion of cases may harbor new highly penetrant mutations). Existing CNV and WES studies are consistent with GWAS evidence for a large mutational target in psychiatric disorders. The data on de novo coding mutations in ASD suggests that between 370 (ref. 54) and 1,000 (ref. 57) genes contribute to disease, and similar figures have been reported in schizophrenia (for example, N = 850 genes)⁶⁰.

Although it is clear that genetic variation for psychiatric illness spans the entire spectrum of allele frequencies, there is evidence that the relative importance of rare and common variation may differ between disorders. For instance, SNPs with a minor allele frequency

<0.05 explain 21% of the heritability for TS, compared with 0% for OCD (in analyses that compared the two case samples to a common control), despite substantial overlap of common variation between these disorders²⁰. Studies that ascertain rare and low-frequency variation in large samples will help to clarify the distribution of genetic variation as a function of allele frequency in these and other disorders.

The heritability explained by individual common and rare variants identified to date is approximately the same⁷⁷ as a result of an inverse relationship between allele frequency and effect size (Fig. 3 in Box 1). This relationship is predicted by evolutionary theory due to the action of selection driving alleles with large effect size to lower frequency⁶, although it is important to note that many rare and low-frequency variants with small effect size are also likely to exist. The precise nature of the joint distribution of risk allele frequencies and effect sizes is yet to be elucidated.

Relationship between disorders: new insights from genomic data

In most other branches of medicine, diagnosis has moved on from classification based on self-reported symptoms and clinical observation to incorporate more objective tests of disease⁷⁸. Although the classification system in psychiatry has been standardized and regularly revised since the 1980s, the biological validity of the current diagnosis system is unknown. Probing underlying biology is problematic when 'case-ness' is often the only consistently recorded phenotypic data available for large-scale analyses⁷⁸. Both comorbidity between disorders and heterogeneity within disorders may be a reflection of the diagnostic label in the context of the current nosology. Dimensional scales have been proposed (for example, see ref. 79), but have not been widely adopted. A genetic contribution to the relationship between psychiatric disorders has been established from both clinical (for example, see ref. 80) and epidemiological (for example, see refs. 1,2) studies, showing increased risk of disorders in the relatives of those affected. However, accumulating large enough samples to achieve accurate results is a limiting factor.

The genomics era has provided powerful approaches to explore the genetic relationship between disorders in new ways. Specific variants associated with multiple disorders and cross-disorder phenotypes have been identified^{21,22}, as discussed above. These studies are too underpowered to identify the majority of shared genetic factors, but currently available GWAS samples collected independently for different disorders can be used to interrogate the genetic relationship between disorders at a genome-wide level. In this paradigm, although all individuals are unrelated in the classical sense, they nonetheless share genomic segments through common ancestors. Thus, genome-wide genotypes can be used to determine whether cases are genetically more similar to each other (that is, across disorders) than to controls⁷⁴ and to calculate the correlation between disorders on the basis of genome-wide SNPs (the SNP correlation)⁸¹. Given that the data sets have been collected independently, any relationship detected between disorders is directly attributable to shared DNA variants and contamination by shared environmental factors seems unlikely. The estimate of the genome-wide SNP correlation applied to SCZ and BPD data was 0.68 (s.e. of 0.04), implying important shared genetic etiology (Fig. 5)⁷¹. Theoretical modeling of potential misdiagnosis between disorders^{82,83} cannot explain the high correlation⁸⁴. In

contrast, a high genetic correlation between disorders is likely to generate individuals with mixed symptoms that may lead to changing diagnoses under the current nosology⁷¹. It is noteworthy that SNP correlations calculated between independently collected SCZ data sets were ~ 0.9 (Fig. 5), implying that the diagnostic classification system does indeed split out a genetically more homogeneous subset from the psychiatric spectrum⁷¹. Notably, the SNP correlations calculated between BPD sets were more variable (0.55–0.88), perhaps suggesting more genetic heterogeneity within BPD (Fig. 5). The same method has been applied to all pairs of disorders in the psychiatric genomics consortium (that is, SCZ, BPD, MDD, ADHD and ASD)⁷¹. These analyses demonstrated a moderate genetic relationship tagged by common polymorphisms between MDD and both BPD (0.47, s.e. 0.06) and SCZ (0.43, s.e. 0.06), implying an underlying genetic vulnerability to psychiatric disorders traditionally considered as adult onset disorders (Fig. 5).

Revisiting old questions with new data

The availability of genome-wide genetic data facilitates much more than gene and pathway discovery. It allows new experimental designs to address old scientific questions with new data. One example is the study of pleiotropy, whereby genes or genetic variants influence more than one trait. Pleiotropy is widespread, not just in humans, but across species⁸⁵. However, pleiotropy has been difficult to study in humans with family designs because multiple diseases and disorders are unlikely to co-segregate in families with sufficient prevalence, even if there are shared genetic factors. The cross-disorder study, described above, is one specific example of a population-based study that links individuals by genome-wide similarity. Notably, in these designs, different individuals can be measured for different traits. These methods are being used to explore epidemiological puzzles such as different rates of immune disorders and cancers in people with and without schizophrenia (for example, see ref. 86).

The importance of genotype \times environment interactions is another longstanding question that can be addressed with new genome-wide data. Such interactions have been suggested for psychiatric disorders, but we are not aware of any statistically significant and replicable interactions. The likely reason is that samples to date have been small and most studies have focused on only a small subset of candidate gene polymorphisms⁸⁷. Large genetically and environmentally informative samples will be needed to achieve the statistical power required given small expected effects. The findings from whole-genome studies can overcome some of these limitations by using the aggregate of multiple genetic risk factors identified in large genotyped samples to obtain a better estimate of genotype and applying this in smaller genotyped samples that are informative for relevant environmental risk factors. This design could be used to test whether genotype and environment act multiplicatively on risk or whether there is a real interaction⁸⁸.

Another hypothesis that was posed many years ago is the relationship between paternal age and risk of disease in offspring, but data on de novo mutation rates and the identification of specific new mutations has not been feasible until recently. The availability of direct estimates of the de novo mutation rate from sequencing studies in families offers new

opportunities for evaluating the relationship between paternal age, new mutations and the increased risk of ASD, SCZ and other disorders.

Conclusions

The genomics era has demonstrated the value of large data sets and international consortia and has narrowed down the genetic architecture dramatically. In Box 2, we summarize the current state of knowledge of genetics in psychiatric disorders. Efforts to accumulate and process very large samples for genotyping and sequencing are underway for multiple disorders and we can be confident that many additional genetic associations, common and rare, will be identified. The rate-limiting step for the field is now the availability (or lack thereof) of standardized phenotype data in large cohorts. The development of innovative ‘next-generation phenotyping’ methods for the quick and cost-effective collection of phenotype data in large samples should be a priority. Such efforts will require international collaboration, and should be geared toward testable hypotheses in evolution and epidemiology. Possibilities include the investigation of genotype \times environment interactions (provided the right environment risk factors can be identified), and the use of Mendelian randomization to infer causal effects of modifiable environmental risk factors. A third possibility relates to natural selection, for instance, comparing fecundity in those with large de novo CNVs versus those without. This type of approach is likely to be complemented by endophenotype studies, including brain imaging⁸⁹, and by efforts to characterize the functional basis of genetic associations. Together, these approaches, by refining our understanding of etiology, hold the promise of better treatments and prevention for a group of disorders that account for about one third of the global burden of disease⁹⁰.

Box 2

What we know and don't know about the genetics of psychiatric disorders

- Heritability estimates for most psychiatric disorders are high, ranging from 0.4–0.8 (refs. 1–4). These estimates are consistent across studies and cannot be explained by perceived ‘flaws’ in twin analyses.
- Psychiatric disorders are highly polygenic (for example, ref. 71), meaning that a large number of genomic loci contribute to risk (that is, the genome-wide mutational target is high). No single variant explains more than a small fraction (for example, ~0.1%) of the genetic variance (with the exception of AD, for which much of the variance is explained by a few common loci with large effects), which implies that large sample sizes are required for genetic discoveries⁷⁷.
- Genetic variation for psychiatric disorders spans the entire allelic spectrum from common to rare, and includes structural variation (CNVs) as well as SNPs. GWASs have identified >100 common loci for SCZ¹³ and smaller numbers for other disorders^{14–16}. These findings have survived rigorous attempts at falsification and cannot be explained by population stratification. About a dozen rare CNVs have been identified, many in association with multiple disorders⁴⁸.

- De novo mutations, including CNVs^{41–44,46,49} and single base mutations^{54–58,60}, are also important risk factors, and emerging evidence suggests that presence of these variants in the context of psychiatric disorders is associated with impaired cognition, consistent with evidence of de novo mutations in intellectual disability. The high heritability of most disorders limits the potential contribution of new mutations, the majority of which do not contribute to heritability estimates.
- Common risk loci (MAF > 0.05) are associated with small effect size (odds ratio ~1.05–1.2), whereas identified rare variants, including de novo mutations, have larger effects (odds ratio ~2 to >20). Common variants with odds ratios >1.5 can be ruled out for most disorders (excepting AD). Conversely, rare variants with smaller effects (odds ratio < 2) are likely to exist, but current studies lack the power to detect them. Low-frequency variants are poorly surveyed, but initial studies in SCZ suggest few if any “Goldilocks” variants (low-frequency variants with odds ratios ~1.5–2; that is, not too big, not too small) exist⁵⁹.
- Genetic variation tagged by common SNPs accounts for between one-third and half of the heritability for most disorders (for example, see refs. 19,26,28,71). These estimates are not inflated by population stratification and largely resolve the controversy of missing heritability (that is, that GWAS findings explain only a small proportion of the heritability estimated by family studies), as they imply that much of the heritability is merely hidden (that is, many common loci exist that do not surpass the threshold for genome-wide significance in GWAS).
- The contribution of rare variation is less well understood because coverage and sample size are not yet optimal, but it may be substantial if variation not explained by common variation (that is, half to one third) is a result of rare variants. Larger studies and improved ascertainment of rare variation (for example, by whole-exome and whole-genome sequencing) will be needed to clarify the overall distribution of genetic variance as a function of allele frequency.
- There is strong evidence for sharing of common genetic variation (pleiotropy) between disorders, particularly SCZ, BPD and MDD⁷¹. Rare and de novo CNVs also exhibit substantial overlap between disorders⁹⁶, and there is emerging evidence that the same may be true for rare and de novo point mutations^{58,59}. The latter is in the form of shared enrichment across disorders of mutations in particular gene sets (for example, targets of FMRP), although whether this overlap extends to the level of specific mutations is currently unclear.
- No fully penetrant mutations for SCZ have been identified, and the idea that SCZ is a set of monogenic disorders can be ruled out. Single mutations sufficient to cause illness are known for ASD, but, similar to SCZ, the idea that all cases can be explained by single mutations is inconsistent with the empirical data.

- Although it's clear that many common and rare variants exist for psychiatric disorders, we do not understand how these variants combine to influence disease pathogenesis and phenotypic heterogeneity. One possibility is that all risk variants, common and rare, contribute to an underlying liability for disease with individuals exceeding a threshold being affected. This could involve background common variation increasing or decreasing the effects of one or multiple rare high penetrance mutations, although other possible mechanisms exist and differentiating between them represents a major future challenge for the field.
- There are few (if any) causal variants known and the precise joint distribution of effect size and risk allele frequency, although coming into focus, is currently unknown. The interpretation of empirically derived joint distributions will depend on the biological validity of the diagnostic constructs.

Acknowledgments

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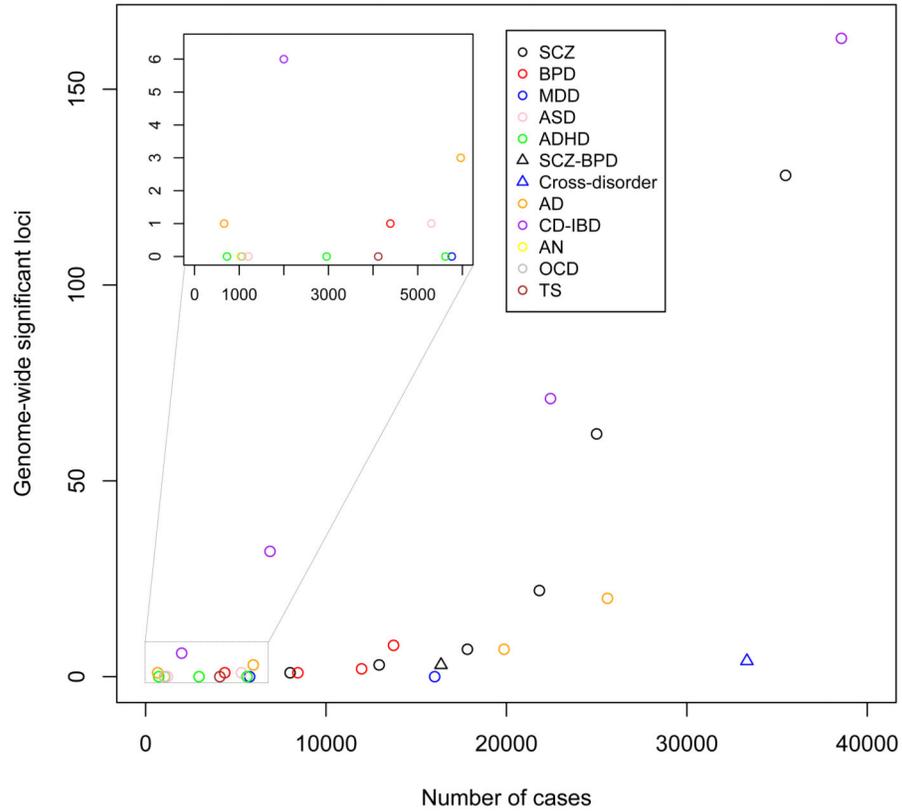
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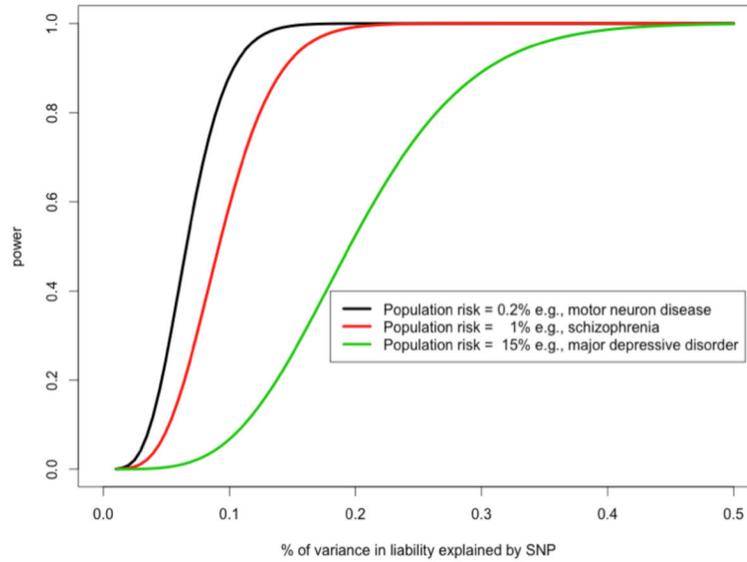


Figure 2.

Not all GWASs are created equal under a polygenic architecture. For the same sample size, less common diseases have more power. Statistical power for detection of gene variants associated with disease for different disorders given the same sample size (type-1 error of 10^{-8} , sample size of 10,000 cases and 10,000 controls). Different combinations of allele frequency and effect size can generate the same variance in liability. Examples of disorders with the prevalence shown are motor neuron disease (MND), SCZ and MDD.

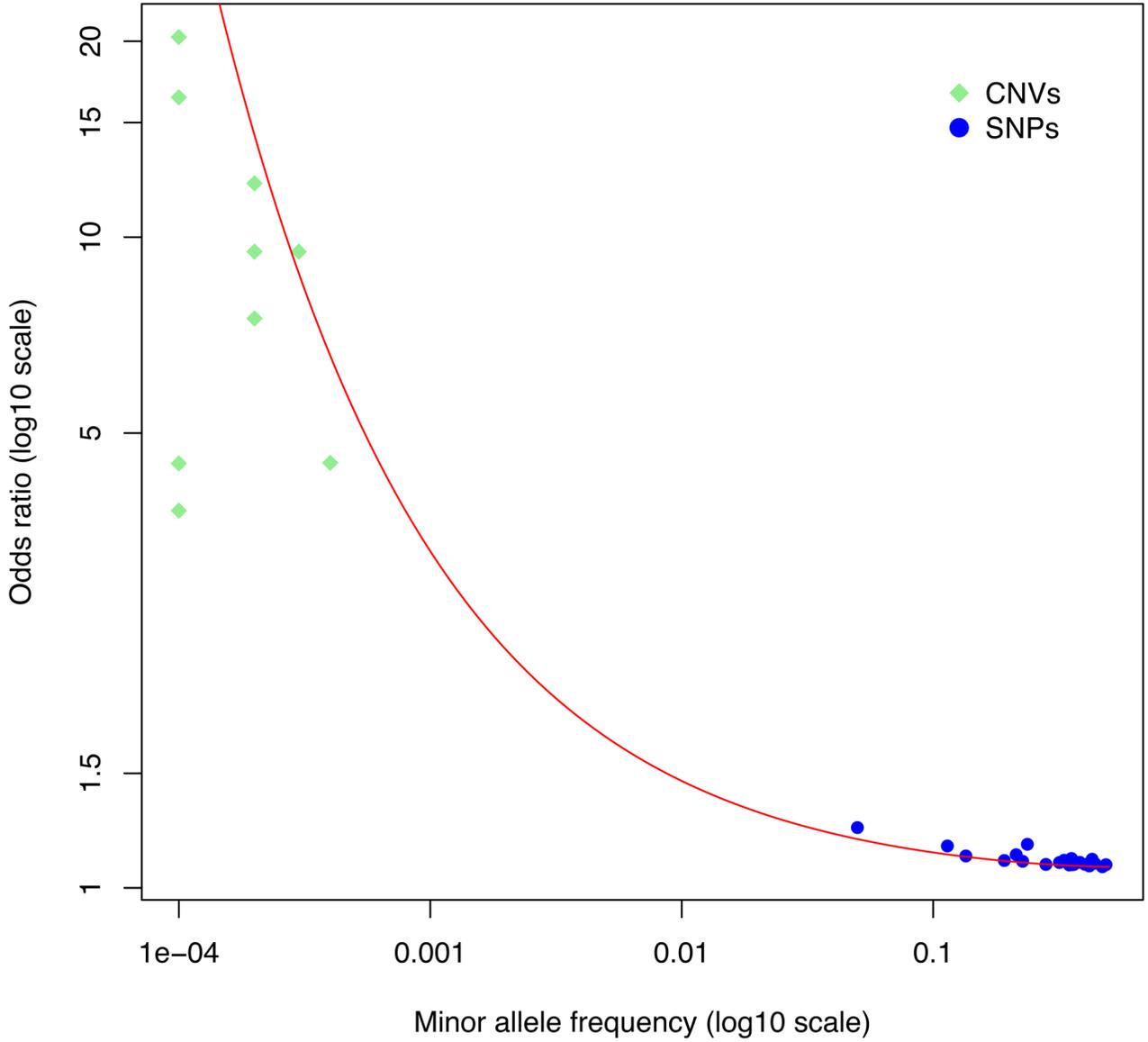


Figure 3. Genetic discoveries for SCZ, irrespective of risk allele frequency, variant type (SNP or CNV) or discovery method (GWAS or CNV analysis), explain approximately the same proportion of the genetic variance. The red line defines a constant r^2 of 0.04%, assuming a 1% prevalence of schizophrenia. Note that the population prevalence of some CNVs is set to 10^{-4} for convenience; some have not been observed in healthy controls and so the true allele frequency (and variance explained) will be lower.

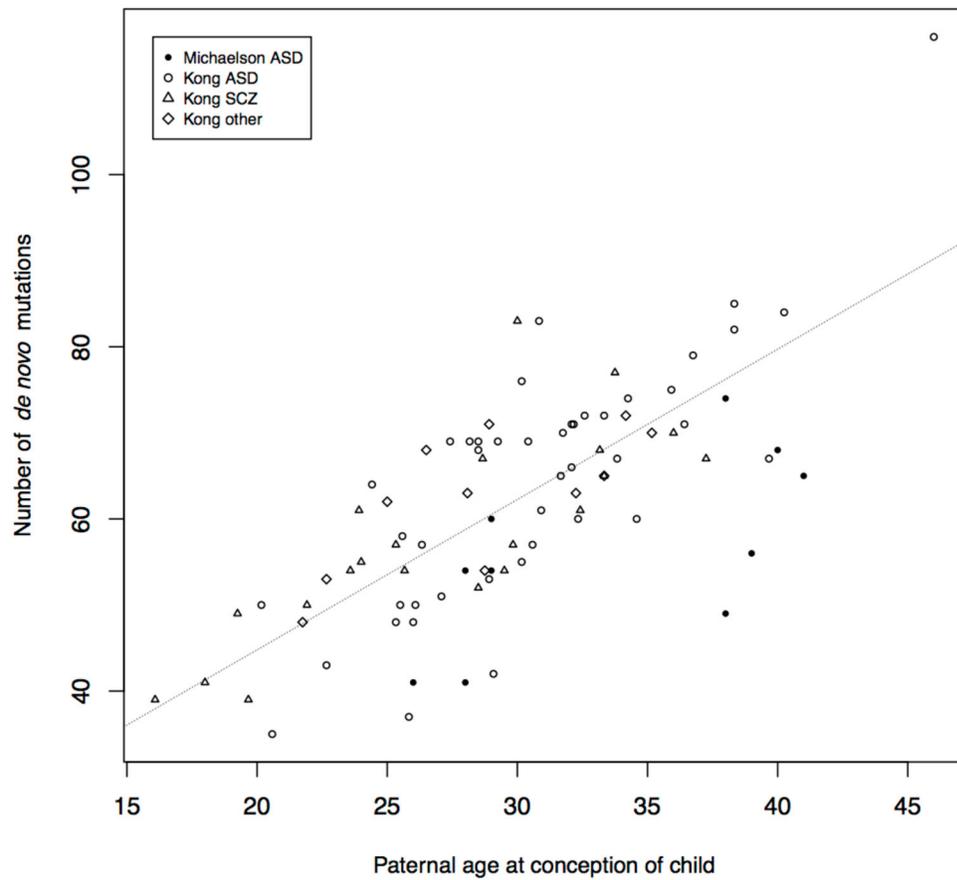


Figure 4. Paternal age at child's conception is associated with the burden of de novo mutations in the child's genome (Poisson regression, $P < 2 \times 10^{-16}$, linear slope = 1.75 mutations per year). Data are from refs. 63 ($N = 78$) and 64 ($N = 10$).

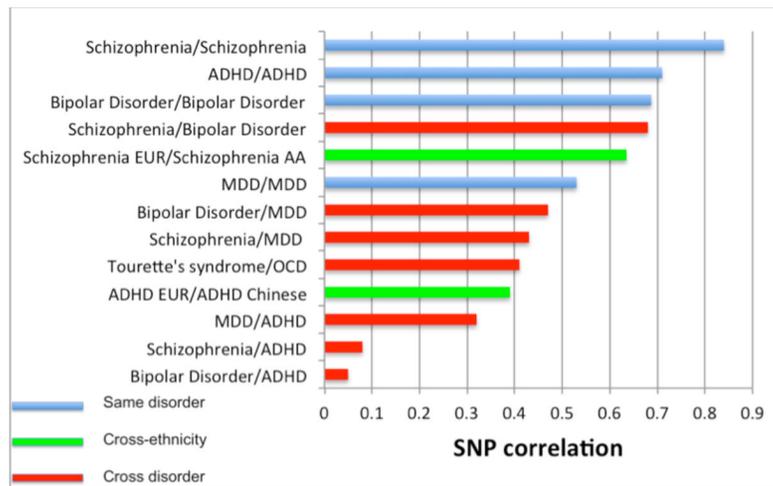


Figure 5. Quantifying the genetic relationship between independent data sets through the SNP correlation^{20,71,91,92}. AA, African American; CHN, Chinese; EUR, European including European American.

Table 1*De novo* gene-disrupting mutations are enriched in ASD

Mutation class	Mutations/person (mean/variance)		<i>P</i> *
	Probands	Siblings	
All	1.10 (1.23)	0.97 (1.00)	0.05
Silent	0.35 (0.37)	0.36 (0.41)	0.59
Missense	0.61 (0.64)	0.54 (0.53)	0.21
Gene disrupting**	0.15 (0.14)	0.06 (0.07)	2.63×10^{-5}

Data are from 590 ASD families with one affected child and one or more unaffected siblings (ref. 57, n = 200; ref. 54, n = 343; ref. 56, n = 47).

* Poisson regression with paternal age at conception fitted as covariate.

** Stop gain/loss, frameshift, essential splice site