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Genetic Architectures of Psychiatric Disorders: The Emerging Picture and Its Implications

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Abstract

Psychiatric disorders are among the most intractable enigmas in medicine. In the past five years, there has been unprecedented progress on the genetics of many of these conditions. In this review, we discuss the genetics of nine cardinal psychiatric disorders (Alzheimer's disease, attention-deficit hyperactivity disorder, alcohol dependence, anorexia nervosa, autism spectrum disorder, bipolar disorder, major depressive disorder, nicotine dependence, and schizophrenia). Empirical approaches have yielded new hypotheses about etiology, and now provide data on the often debated genetic architectures of these conditions, which have implications for future research strategies. Further study using a balanced portfolio of methods to assess multiple forms of genetic variation is likely to yield many additional new findings.

Keywords

psychiatric disorders; genetics; structural variation; copy number variation; genome-wide association; meta-analysis; sequencing

Introduction

A core set of psychiatric conditions – madness, mania, melancholia – have been perplexing for millennia. Although mortality is increased for many psychiatric disorders, [1] their major impact is on morbidity: psychiatric disorders account for around a third of disability worldwide, [2] and cause enormous personal and societal burden. [3]

In the past century, considerable efforts to understand the nature of psychiatric disorders have been undertaken. There have been successes, and a few diseases with prominent

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psychiatric manifestations that were once prevalent are now rare in many parts of the world (e.g., pellagra [4] and neurosyphilis [5]). These few triumphs stand in contrast to decades of frustration and occasional notoriety when highly publicized and plausible findings failed to replicate. Indeed, most psychiatric disorders have been intractable to approaches that were fruitful in other areas of medicine. Thus, psychiatric syndromes are generally referred to as "disorders" (illnesses that disrupt normal function) and only a few as "diseases" (disorders with known pathophysiology or structural pathology). An obvious goal of psychiatric research is to convert idiopathic disorders into pathophysiologically-defined diseases.

Since 2007, numerous robust and replicable genetic findings have been reported for psychiatric disorders. These advances have mostly been via genome-wide association (GWAS) and structural variation (SV) studies, although studies of uncommon or rare exonic variation are likely to play a prominent role in the next few years. These results meet community standards in human genetics for significance and replication. [6] Although these findings often appeared in high-profile journals, sentiments like "genetics has failed in psychiatry" or "there are no genes for psychiatric disorders" are still heard. A review of psychiatric genetics is thus particularly opportune.

Over 300 psychiatric disorders have been described, and nine are covered in this review. The conditions selected are: all psychiatric disorders; have been subjected to intensive genetic study; and have published genome-wide results (usually GWAS and SV but also genome-wide linkage and resequencing). The disorders and their abbreviations are defined in Tables 1 and S1, and the heritabilites and lifetime prevalences are depicted in Figure 1a. Mental retardation could have been included, but its voluminous literature has been reviewed at length. [7–9] Studies of other psychiatric disorders are in progress, but the published data are few (e.g., obsessive-compulsive disorder, Tourette's syndrome, and panic disorder).

The genetic dissection of complex traits has been frequently reviewed. [6,10–12] Box 1 provides an overview of the approaches and study design considerations. Advances in genetics are often yoked to technological advancements. Major approaches that have been informative in psychiatric genetics include assessment of: structural variation (SV) via karyotyping, array-based methods, and high-throughput sequencing (Tables 2 and S2); [13–16] genome-wide association studies (GWAS) using highly multiplexed SNP arrays and, potentially, high-throughput sequencing (Table 3); [12,17–19] and high-throughput sequencing to uncover rare variants of relatively strong effect (perhaps arising *de novo*). [20,21] Genome-wide linkage and hypothesis-driven candidate gene association studies have also been conducted, and, as in many areas of biomedicine, with uncertain yield. [22–26]

Box 1

Study design considerations: simplex and multiplex

Study design is a crucial component of human genetics research. The major designs are case-control and pedigree-based studies. The most common design is the case-control study in which the frequency of a genetic variant in those with a disorder is contrasted with the appropriate control group. Case-control designs are used in most GWAS [155] and

next-generation sequencing studies as they are efficient and conceptually straightforward. [156] Case-control studies are simpler, and most biases can be surmounted by careful study procedures, but cannot delineate rare inherited from *de novo* variation. Family-based designs are more complex but can be used for association testing as well as for linkage evaluation of co-segregation of genotypes and phenotypes within pedigrees. They provide protection against a key form of bias (population stratification artifacts), but are less efficient given that the unit of analysis is a set of relatives; however, it is possible to identify mutations that arise *de novo*.

An additional decision is whether to focus on the presence or absence of other affected family members ("multiplex" and "simplex" pedigrees, respectively). Human genetic studies have classically focused on multiplex pedigrees under the assumption that these pedigrees are enriched for causal genetic variation with higher penetrance. A focus on multiplex pedigrees has led to the identification of specific mutations underlying hundreds of Mendelian disorders (including ASD and AD). Simplex pedigrees have become popular for ASD and SCZ. Simplex-based ascertainment is tailored to evaluate *de novo* mutations, and predicated on a model in which disorder with dramatically reduced fecundity and a proven role of *de novo* SV might be explicable as a series of Mendelian disorders attributable to recent high-penetrance mutations in any of a large number of genes.

However, this important choice is not simple, and continues to be moderately controversial. Some investigators believe a focus on simplex pedigrees to be optimal, and other investigators have concerns about the implications of this decision. Some of the issues are listed below. (a) Correct classification as simplex or multiplex requires confident knowledge of family history – many people either do not know their family psychiatric histories, true episodes of illness may have been kept private from other relatives, and some affected individuals can over-call illness in their relatives (e.g., an individual with ALC labeling all relatives who drink as the same). (b) Fecundity is a major confound. If there are greater numbers of relatives, there is a greater chance of multiplex classification. In addition, the presence of a psychiatric disorder can reduce fecundity (e.g., fecundity is reduced in SCZ and having a child with ASD can be a powerful inducement not to reproduce further). If fecundity had not been inhibited due to a psychiatric disorder, some apparently simplex families might have been revealed to be multiplex. (c) Simplex designs often require both parents. This complicates recruitment, increases genetic assay costs, and becomes increasing less practical for disorders with later ages of onset. (d) Both designs have a hidden weakness in the possibility of enriching for environmental causes of illness. Many psychiatric disorders have multiple different but rare environmental risk factors sufficient to cause a disorder. These potent exposures are sometimes very difficult to detect or not routinely evaluated. Examples include mercury poisoning and ASD or viral meningitis and SCZ. Contrary to its intent, simplex cases may be enriched for difficult to detect, individual-specific environmental causes. Multiplex ascertainment could enrich for shared environmental causes.

Some recent data pertain to this choice. Unexpectedly, simplex and multiplex ASD pedigrees show relatively similar *de novo* mutation rates for SV [80,81] and exonic variation. [83–85] It is possible that larger studies will find simplex/multiplex differences in

de novo mutation rates but the magnitude is likely to be smaller than anticipated. For SCZ, the available data are insufficient to resolve this issue. [45,50] It has also been pointed out that *de novo* events must confer risk in multiplex families, as such mutations increase the chance that an individual is affected and increase risk in that person's offspring. Intriguingly, there are three instances of ASD cases with *de novo* deletions of 16p11.2 who also had an affected sibling without this deletion [157–159] along with similar observations for SV in 1q21.1 and 17p12. [158]

In this Review, we summarize the literature for the nine disorders in Table 1 with particular emphasis on the findings that appear to meet community standards for replication in human genetics (i.e., robustly significant with consistent effects across samples). [6] We highlight new hypotheses that have emerged across the allelic spectrum including *de novo* and rare exonic mutations, rare SV, and common variation from GWAS. Critically, these results provide empirical insights into the genetic architectures of these disorders, data that are essential to guiding future work in this area.

Alzheimer's Disease (AD)

Rare variation

Prior to 2007, rare autosomal dominant mutations in *APP*, *PSEN1*, and *PSEN2* were known to cause early-onset familial AD. [27] These loci have atypically large effect sizes, which facilitated identification using "past generation" technologies like candidate gene association and genome-wide linkage studies (Table S2). Treatments for AD based on these findings have been developed and are undergoing testing. Rare SV duplications containing *APP* have been associated with AD. [28,29] Small exome sequencing studies of AD have been published, [30,31] and larger studies are in progress and should provide a more nuanced understanding of the role of rare exonic mutations in the pathogenesis of AD.

Common variation

In the early 1990's, *APOE* was identified by candidate gene association as a susceptibility gene for late-onset AD in no small part due to its unusually large effect size (Table 3). [27,32] In 2009, GWAS from two large consortia [33,34] implicated three novel loci and six additional loci were identified in 2011. [35,36] Full meta-analyses are keenly awaited, but the 10 loci identified to date account for ~20% of the total variation in risk or ~33% of the risk attributable to genetic effects, with the major contribution being from *APOE*. Note that the association of one gene identified by GWAS, *CR1*, might result from SV. [37]

Intriguingly, pathway analyses (Box 2) of AD implicate cholesterol metabolism and the innate immune response. [38] Genes attaining genome-wide significance point toward immune and inflammatory processes (*CLU* and *CR1*), lipid processing (*APOE*, *CLU*, and *ABCA7*), and endocytosis (*PICALM*, *BIN1*, *CD2AP*, and *CD33*). Altered immune function and lipid metabolism had previously been proposed as AD risk factors, but whether these represented causation or reverse causation was unclear. [39] The genetic findings now strongly point to the former.

Box 2

Pathway analysis

Pathway analysis is based on the assumption that risk variants for a disease will converge on sets of genes whose functions are more closely related to each other than to random sets of genes. For example, dominant forms of AD are caused by mutations in *APP*, *PSEN1*, and *PSEN2*; the latter two genes encode protein components of γ-secretase, a protease that cleaves *APP*. The availability of GWAS and SV results for many psychiatric disorders, along with increasing amounts of sequence data, have generated interest in using analytic methods for exploiting non-random functional relationships between genes containing risk variants. Many approaches have been developed (e.g., ALIGATOR, [161] INRICH, [162] [162] DAPPLE, [163] and GRAIL [164]) and reviewed in detail elsewhere. [146,165,166] Although the algorithms differ, the principle behind these methods is to evaluate whether a given set of genomic regions (i.e., a broadly inclusive definition of "pathway") is enriched for genetic variants showing some relationship with disease compared to a null expectation.

There are important subsidiary considerations. The first is the definition of a "pathway." Standard pathways consist of sets of genes found in the Gene Ontology, [167] the Kyoto Encyclopedia of Genes and Genomes, [168] or PANTHER databases. [169] Other pathway gene sets are manually curated by experts in a particular area (e.g., genes known to make proteins that function at the synapse). [170,171] In addition, a "pathway" can consist of genomic regions selected for a particular property such as high degree of conservation [172] or eQTL associations. [173] Finally, other pathways consist of genes known to be connected via experimental data (e.g., via protein-protein interaction screens, micro-RNA target sites, or gene expression modules).

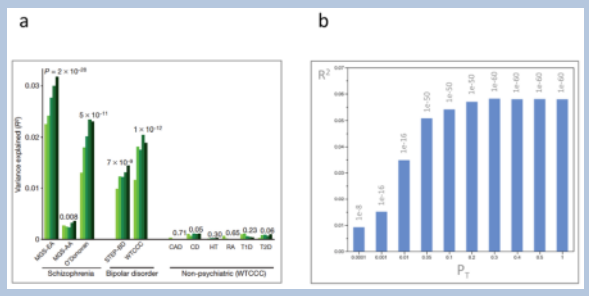
It is advantageous that these pathway datasets are defined independently of genetic studies of psychiatric disorders, but they do have limitations and can contain errors of omission and commission. Standard gene sets can have highly overlapping pathways that complicate some analyses, and the pathway content can have variable quality. Expert-curated pathways can be more specific, but can be vulnerable to *post-hoc* bias (i.e., including genes in a pathway based on results from genetic studies). Pathways based on empirical approaches depend on the quality and completeness of the primary data (e.g., existing protein-protein interaction databases cover the interaction space partially).

A second question concerns what is required before a member of a pathway is accepted as having some relationship with disease. For common variation, the analysis might be restricted to genes within recombination regions containing SNPs that are genome-wide significant, an approach which was used successfully to implicate broad biological pathways relevant to height. [75] However, much of the interest in pathway analysis involves exploiting much weaker associations under the assumption that these associations more reflect true associations in the context of limited power (signal) rather than chance (noise). If so, those weakly associated SNPs may also be non-random with respect to gene-sets (see also Box 3). The threshold at which SNPs or genes are chosen is arbitrary, and the signal-to-noise ratio for a given arbitrary threshold can vary

substantially with sample size and genetic architecture. For rare variants in complex diseases, based on recent empirical results for ASD, it is probably reasonable to assume that pathway analysis will by necessity be based on sets of genes whose involvement in disease is unclear (e.g., genes with a single observed *de novo* exonic deleterious mutation). [83,84]

A third consideration concerns the null expectation to which the observed pathways are compared. Early SV pathway analysis did not account fully for important biases such as that large genes are more likely to be intersected by CNVs by chance and that some functional pathways – often related to brain development – are enriched for large genes. [164] Early GWAS pathway analysis sometimes did not fully allow for the variable numbers of SNPs per gene and their degree of linkage disequilibrium both of which impact the probability of a high-ranking association. [161] Thus, one must be cautious about the utility of pathway based approaches. In psychiatric disorders, some results give cause for optimism. [3845,81]

Finally, in pathway analyses the unit of inference is the pathway. Tempting though it may be, it is generally inappropriate to make strong inferences about specific variants or genes based upon their membership of pathways that attain some level of significance. It may be possible to do so if the variants or genes are subsequently evaluated in datasets independent of those from which the significance of the pathways are derived, using a statistical framework that adequately deals with multiple testing.



Box 3

Common variant risk profile

For SCZ and BIP, sign tests comparing the consistency of association tests from discovery GWAS and replication samples for sets of top signals are usually highly significant even if most loci do not meet genome-wide significance. [58,59,174] This implies that sample sizes are insufficient and that additional loci can be discovered in larger samples. Tests of the existence of large numbers of true but weakly associated variants have been conducted for SCZ, BIP, and many other biomedical disorders.

Based on theoretical work by Visscher and colleagues, one study used GWAS results as a discovery set (after removing correlated SNPs), and subjects in 11 independent test GWAS datasets were assigned risk profile scores (i.e., the number of SCZ risk alleles weighted by their effect sizes in the discovery set). The mean risk profile scores for cases

were compared to the mean scores for controls in these independent datasets. [69] Panel **a** of the figure (reproduced from Figure 2 in reference [69]) shows risk profile scores for extremely relaxed p-value thresholds (P_T < 0.1, 0.2, 0.3, 0.4, and 0.5, light to dark green bars). Risk profile scores were derived (after LD-based SNP pruning) from a discovery SCZ sample, and then applied to three independent SCZ samples, [174,175] two BIP samples, [176,177] and six non-psychiatric diseases (CAD=coronary artery disease, CD=Crohn's disease, HT=hypertension, RA=rheumatoid arthritis, T1D=type 1 diabetes, and T2D=type 2 diabetes). [177] In three independent GWAS, SCZ cases had significantly higher risk profile scores than controls. Remarkably, the same set of markers also discriminated BIP cases from controls indicating substantial genetic contributions between SCZ and BIP. As an important test of specificity, the SCZ risk profile was not predictive of case status for any of six non-psychiatric diseases. [177] A recent paper evaluated risk profile scores in a trio sample, and could exclude population stratification as an explanation. [178]

The proportion of variance explained by the risk profile score increased with relaxation of the significance thresholds. This suggests the discovery sample was insufficiently large to identify many true risk loci at even nominal levels of significance: adding more SNPs contributed more genetic signal than noise. This is partly a feature of sample size. Panel **b** of the figure (data from Figure S6 in reference [58]) shows a similar analyses based upon a larger discovery sample, and the proportion of variance explained is approximately double [58] and, instead of increasing with P_T, the proportion of variance reaches a plateau. If sample size were truly adequate, the first P_T bin would explain the greatest amount of variance, and relaxing P_T would decrease R^2.

Finally, estimates from two different methods indicated that the risk profile component for SCZ contributes between a quarter and a third of the overall variance in liability to SCZ, [69,130] a substantial fraction of the 65–81% heritability of SCZ. [179,180] These estimates suggest that "missing heritability" is merely hidden and imperfectly assayed by current genotyping technologies.

It is unclear how the above findings relate to accumulation of beta-amyloid (Aβ) in AD pathogenesis, but some relationship seems likely. For example, PICALM (phosphatidylinositol-binding clathrin assembly protein) and other endocytic molecules can modify Aβ toxicity in yeast and other model systems. [40] Although these genetic findings provide support for novel causal relationships that could be targeted by treatments, the association data point to genomic regions, not genes. Moreover, the proximal steps from genotype to phenotype are unclear, and many of the implicated genes are plausibly involved in multiple relevant functions (e.g., *CLU* is involved in altered immune function and lipid processing).

Psychotic Disorders (BIP and SCZ)

Rare variation

Unfortunately, unlike AD, no Mendelian forms of BIP and SCZ have been identified. [41] However, rare (frequency < 0.5%) but potent (genotypic relative risk, GRR, 5–20) SVs play

a role in a small proportion of cases with SCZ (Table 2, Figure S1). None is fully penetrant, and nearly all appear to be non-specific as risk is often increased for SCZ, ASD, developmental delay, mental retardation, epilepsy, somatic dysmorphism, and extremes of body mass and head size. Most of these SV regions are fairly large (hundreds of kb to mb) and generally center on SV hotspots. [42] Two rare SVs affect single genes (*NRXN1* and *VIPR2*) [43,44] offering opportunities for down-stream functional studies. Pathway analyses of genes intersected by rare SV suggest enrichment for neuronal processes of plausible etiological relevance (e.g., post-synaptic signaling). [45–47] The SV regions in Table 2 probably represent "low-hanging fruit" and more discoveries are likely with application of improved technologies for SV detection to larger samples. [15]

A complementary approach is to evaluate SV "burden" in cases compared to controls (e.g., number of SV per person). [48,49] This tests an explicitly multigenic model whereby many rare but different genomic disruptions impact disease risk. Increased SV burden in SCZ cases has been reported by multiple groups. [47,48,50] One report found more rare SV in SCZ cases (odds ratio, OR=1.15), particularly for large deletions (OR=3.6). [48] *De novo* SV are also more common in SCZ cases. [45] For BIP, there are reports of increased [51–53] and similar SV burden in cases versus controls [54,55] *De novo* SV may be relevant in BIP (OR=4.8), particularly in cases with earlier ages of onset (OR=6.3). [53]

Multiple studies are now evaluating the role of *de novo*, rare, and uncommon exonic variation in BIP and SCZ using resequencing or genotyping approaches. Two small exome sequencing studies [56,57] reported rates of putatively functional mutations that exceeded null expectations in SCZ cases (although the rate of *de novo* point mutations was not elevated in cases and specific genes were not identified). Larger studies are ongoing and will illuminate this area in 2012–2013.

Common variation

The Psychiatric Genomics Consortium (PGC) recently published mega-analyses for SCZ and BIP. [58,59] In SCZ, 9,394 cases and 12,462 controls were combined in a single analysis and the top 81 statistically independent loci from that analysis were then tested in over 8,000 cases. The mega-analysis identified seven significant loci (Table 3). A sign test for consistency between the mega-analysis and follow-up stage was highly significant, implying that many of the 81 top loci include true risk loci but that power was insufficient. For BIP, the discovery phase consisted of 7,481 cases and 9,250 controls with follow-up of 34 statistically independent loci in around 4,500 cases. Two loci exceeded genome-wide significance (Table 3). Similarly, a sign test between the discovery and follow-up results was highly significant, again suggesting insufficient power. [59]

In BIP, the genome-wide significant association at *CACNA1C* (α subunit of the L-type voltage-gated calcium channel) deserves specific comment given its mechanistic implications. Indeed, multiple voltage gated calcium channel subunits were among the top 34 loci followed up in the BIP GWAS. Calcium channels regulate neuronal excitability (already a treatment target for BIP) and multiple brain functions including long term potentiation and synaptic plasticity. Combined analysis of the PGC BIP and SCZ samples strengthened the association in the *CACNA1C* region. Further, results from SGENE+ [60]

implicate *NRGN* (neurogranin) which may act as a calcium sensor. [61] Therefore, detailed investigation of brain calcium biology is warranted for both BIP and SCZ.

For SCZ, the strongest association is in the extended MHC region (chr6:27–33 Mb). The evidence for association is compelling but high gene density and exceptionally high linkage disequilibrium complicate the identification of specific sequence variation. Although tempting to propose that the association supports long-standing hypotheses concerning roles in SCZ for intra-uterine infection, autoimmunity, or even synaptic pruning (in which MHC genes play a role), this lack of precision renders such propositions speculative.

A novel association for SCZ is in Ensembl gene *RP11-490G2.1* which encodes the primary transcript for miR-137 (*MIR137*). [62] Supporting the hypothesis that this association implicates *MIR137*, predicted targets of miR-137 were significantly enriched for smaller GWAS p-values ($p<0.01$), and four of the genes that achieved genome-wide significance contain verified miR-137 binding sites. [63] miR-137 is a key regulator of neuronal development with roles in neurogenesis and maturation [64,65] and is highly expressed at synapses in the cortex and hippocampus. [66] Future studies of networks regulated by miR-137 offer the possibility of insights into SCZ pathophysiology.

GWAS of BIP and SCZ have been predominantly based on subjects of European ancestry, but there are increasing reports from other world ancestries. [67,68] Although those findings do not yet provide additional pathophysiological insights, it is worth noting that a chr8 locus found in an East Asian sample [67] has support in the PGC dataset, suggesting that planned mega-analyses across world populations will be informative.

Some of the most intriguing findings for SCZ and BIP are from large sets of genetic markers (Box 3). [69] There are now replicated data that vulnerability to SCZ is influenced by common genetic variation in hundreds of different loci, and this vulnerability partially overlaps that for BIP. [69] Indeed, the large-scale impact of large numbers of common variants may be a general feature of human complex traits [70–77]

Autism Spectrum Disorders (ASD)

Rare variation

For ASD there is a notably strong *prima facie* case for there being a a cardinal role for rare variation. Karyotyping studies suggested that on the order of 5% of ASD cases have one of a large number of rare but relatively gross chromosomal abnormalities. [14,78] In addition, ASD has been noted as a comorbid feature of >100 single gene, Mendelian medical genetic syndromes, [79] although the penetrance and confidence of the clinical associations are variable. Indeed, ASD mutations with very high penetrance are exceptional (i.e., Rett syndrome mutations in *MECP2* and *CDKL5*), and Mendelian diseases enriched for ASD have far less than complete penetrance (e.g., Fragile X syndrome and tuberous sclerosis). [78]

Analysis of SV has been a major focus in ASD research (Table 2, Figure S1). Implicated loci to date are generally rare and potent risk factors but incompletely penetrant and not specific to ASD. As these large events impact the dosages of many genes, biological insight has been slow to emerge; however, pathway analyses of genes within SV do implicate

neuronal processes of etiological relevance. [45–47] Large SVs are present in 5–10% of ASD cases, and the number of ASD SVs could total 130–234. [80] There is also consistent evidence for increased SV burden in ASD. [49,80–82] For example, 5.8% of ASD probands had ≥1 rare *de novo* SV versus 1.7% of their unaffected siblings (OR=3.5), and this difference was more pronounced for SV that intersected genes. [80] The 16p11.2 SV associated with ASD and SCZ has been termed a "mirror image" SV since the deletion and duplication are associated with increased and reduced head and body size. However, it is difficult to understand the clinical features of ASD and SCZ as mirror images and, more importantly, ASD is associated with both 16p11.2 deletions and duplications.

ASD is the first psychiatric disorder for which exome sequencing using substantial numbers of samples has been published. Three recent papers describe the results from exome sequencing of ~600 trios, and identify roles for *de novo* exonic mutations in *SCN2A*, *KATNAL2*, and *CHD8* in the pathogenesis of ASD. [83–85] Intriguingly, all three studies noted an increased rate of *de novo* exonic mutations in older parents (with the mutations generally being of paternal origin), [83–85] and pathway analyses reported in two of the studies found that genes containing *de novo* exonic variation were more closely connected in reference to protein-protein interaction databases. [83,84] Additional sequencing studies are in progress.

However, a central finding from these papers was that only a minority of cases had a *de novo* putatively functional variant, suggesting that this class of genetic variation is unlikely fully to explain the clinical entity of ASD. Indeed, estimates from *de novo* exonic mutations (similar to those from SV data) suggest that ASD is highly polygenic (estimates ranged from 400–1000 genes). [84,85] Importantly, a hypothetical model of ASD caused by rare but fully penetrant mutations in 100 different genes could be confidently rejected. [83]

Common variation

Evaluation of rare SV and exonic variation in ASD is particularly advanced. In contrast, evaluation of common variation is far more limited (Figure 1a) and the published GWAS for ASD are small by current standards. [86–89] It is currently not possible to discern or dismiss a role for common genetic variation in risk for ASD. In our opinion, GWAS with larger samples are needed for ASD, given that detailed studies of rare variation currently explain a fraction of risk and that common variation plays a clear role in other psychiatric disorders. Indeed, there were few confident findings for GWAS of SCZ when the sample sizes were similar to those now available for ASD. Additional support for our recommendation for more GWAS is provided by Voineagu *et al.* who identified a gene expression module that had attenuated expression in post-mortem brain samples of individuals with ASD and which also had enrichment for GWAS signals. [90]

Alcohol and Nicotine Dependence (ALC & NIC)

ALC and NIC are complex conditions to study, given the requirement for ingestion of a psychoactive substance and cohort effects due to temporal and geographic variation in the availability of ethanol and nicotine. Many investigators focus on ALC and NIC, which are clinically salient but multi-component syndromes. [91] As part of the TAG consortium, [92] we determined that the components of the Fagerstrom Test for Nicotine Dependence (a measure

of NIC) had heritabilities ranging from relatively high to near zero with important common environmental effects. Other investigators evaluated self-reported lifetime maximum use of ethanol (grams/day) or nicotine (cigarettes per day), and such continuous measures of consumption are often available for secondary analysis of samples studied for other diseases.

For ALC, the published GWAS are small and no large-scale meta-analysis has been conducted. [93–97] In our opinion, there are clear needs for a high-quality meta-analysis and to increase the number of samples with GWAS data – particularly given that risk profile analysis (Box 3) suggested that larger samples would yield more associations. [97] For alcohol consumption, GWAS in East Asian samples confirmed the role of *ALDH2*, [98,99] and *AUTS2* was implicated in alcohol consumption in European subjects. [100] Using a candidate gene approach, the association of *ADH1B* with ALC and alcohol consumption was extended to European ancestry subjects. [101]

For NIC, a field-wide meta-analysis is also needed. For smoking behavior, large meta-analyses have been conducted. [92,102,103] The strongest finding is an association of smoking quantity with a cluster of nicotinic receptor genes (*CHRNA5-CHRNA3-CHRNB4*) with an effect size corresponding to one cigarette per day, and there may be several independent associations. [104] Associations to this region have also bee reported for lung cancer. [105,106] A recent study showed that *Chrna5* null mice had higher nicotine intake due to loss of an inhibitory effect on brain reward systems. [107]

Major Depressive Disorder (MDD)

The PGC GWAS mega-analysis of 9,240 MDD cases and 9,519 controls (replication in 6,783 MDD cases) revealed no findings of genome-wide significance. [108] These null results are intriguing as almost all other published GWAS with N>11,000 for any disease has found at least one genome-wide significant finding. The most likely reasons for these results are particularly high heterogeneity of MDD and insufficient power arising from its lower heritability. [108] There are few published data on SV although one study found increased SV burden in MDD cases versus controls (OR=1.31). [109]

A provocative finding from 2003 was that risk for MDD might be influenced by a gene-environment interaction with genetic variation near the serotonin transporter. [110] Meta-analyses have supported [111,112] and not supported [113,114] this finding. This association did not replicate in an independent but similar study from the same geographic region, casting particular doubt on the reported association. [115]

Other disorders (ADHD and AN)

The published GWAS for ADHD [116] and AN [117] are small, but larger samples are in progress (e.g., by the Wellcome Trust Case-Control Consortium for AN). Given low power, no conclusions about common variation can be made. In ADHD, increased SV burden has been reported (OR=2.1), [118,119] an effect higher in ADHD cases with MR (OR=5.7). [118] Pathway analysis in ADHD found association signals enriched in the same GO categories also overrepresented for large SV. [120] The weak signals in ADHD GWAS are not randomly distributed but index the same pathophysiological pathways as rare SV. Thus, it appears that

the reason no common variants have yet confidently been implicated in ADHD by GWAS is lack of power, not lack of variants to be found.

What is the Emerging Picture

Knowledge of psychiatric genetics is vastly greater than it was five years ago. Specifically, there are now multiple high-confidence SV (Table 2), rare exonic variants (currently only for ASD, AD, and ALC), and an increasing number of robustly significant and replicated common variants (Table 3). The data support multiple novel biological hypotheses (for example, cholesterol metabolism and the innate immune response in AD, a network involving miR-137 for SCZ, calcium signaling for BIP and SCZ, and chromatin remodeling for ASD) and reinforce previous hypotheses such as synaptic biology for SCZ and ASD).

Genetic architecture

These results also provide insights into genetic architecture that are critical for planning more complete attempts at the genetic dissection of these major public health conditions; now we can make informed predictions about the types of future studies that can increase understanding in order to generate well-grounded biological hypotheses.

For several disorders, there are now data to replace the interminable debate about the fundamental nature of these illnesses. [121] These occasionally vociferous debates [70] have generally been of an “either/or” nature: psychiatric disorders as collections of Mendelian-like, single gene disorders (multiple rare variant models) “versus” psychiatric disorders are caused by many common variants of small effects (common disease/common variant models). [15,122] Although we were initially agnostic [123] we now believe that the data support both positions.

For disorders with sufficient data (AD, BIP, and SCZ), the results are consistent with an allelic spectrum and an etiological role for both rare and common variation. As an example, Figure 1b synthesizes current knowledge of SCZ as an empirical allelic spectrum map compared to a conceptual schematic from a 2008 review in this journal. [10] There are no known Mendelian variants, and power analyses can exclude common variants of modest effect (genotypic relative risk > 1.5 for allele frequencies > 0.1). There are multiple SVs that are rare, strong, but non-specific risk factors (Table 2), and 17 common variant associations of subtle effects (Table 3). There is an important component arising from common variation in hundreds of different loci (Box 3), and larger sample sizes are likely to convert many of these to genome-wide significance. The frequency region between 0.001–0.05 is under investigation by studies evaluating exon variation, and more should be known in 2012–2013. This allelic spectrum map might well be replicated for other psychiatric disorders should larger studies of both rare, uncommon, and common variation be achieved.

Hypothesized genetic architectures consisting entirely of rare variants are inconsistent with the data for AD, ASD, BIP, and SCZ (as well as for multiple other complex biomedical diseases). [70–77] The Procrustean theory that common variant signals inevitably reflect “synthetic associations” [124] to rare, high penetrance mutations is not credible. [77,125–127]

Psychiatric disorders are polygenic. The evidence is strong that many genes are involved in the etiology of AD (currently evidence of rare exonic, rare SV, and common variation), ALC (currently evidence of common variation), ASD (currently evidence of *de novo* exonic variation and SV), BIP (currently evidence of common variation), NIC (currently evidence of common variation), and SCZ (currently evidence of rare SV and common variation). Projections for ASD and SCZ suggest that variation at hundreds of different genes will ultimately be shown to be involved. [58,80,85] There are statistical hints that ADHD and MDD might also be polygenic.

Polygenicity may be a general feature of complex biomedical diseases. [128,129] Common variant SNP effects have been estimated to explain large proportions of the phenotypic heritability for a wide range of diseases: BIP and SCZ; [69,130] T1DM, T2DM, Crohn's disease, rheumatoid arthritis, celiac disease, and coronary artery disease; [70,77] and continuous traits (height, intelligence, and body mass). [70,131,132] These results are consistent with suggestions that the "missing heritability" [133] is merely hidden. [132]

As discussed further below, currently we do not now possess a comprehensive enumeration of loci associated with any psychiatric disorder (i.e., the "parts list"), regardless of where genetic variation might lie in the allelic spectrum-effect size space.

Implications and Future Directions

Why these successes matter

As other commentators have written, [70,128,134,135] and as we argued in early 2009, [123] the proximal purpose of genetic studies is to gain insight into biology. This goal is crucial for psychiatric disorders as so little is known about pathophysiology, and as highly publicized but ultimately false leads have occurred. For this primary goal, there have been unequivocal successes for many psychiatric disorders. This crucial point is sometimes overlooked: the knowledge base in psychiatric genetics is vastly greater than five years ago, and the rate of change is unprecedented in the history of the field.

What about clinical utility? So-called personalized medicine has been touted as the critical yardstick against which to measure the success of genetic studies. We believe clinical utility is the ultimate goal, but an inappropriate proximal goal. Still, there are a number of findings whose clinical significance should be evaluated. For example, SV testing is often part of the clinical evaluation of ASD, and careful evaluation of its utility in psychosis is warranted. As another example, Dr Roy Perlis and colleagues are evaluating the "repurposing" of isradipine (an approved antihypertensive that interacts with the protein product of *CACNA1C*) for the treatment of BIP. It is possible that risk profile scores, SV burden, or rare variant burden could have clinical utility. If these assess latent liability, they might be useful in selected clinical scenarios (e.g., predicting which patients require aggressive treatment in the psychosis prodrome). [136]

The polygenicity of psychiatric disorders poses intriguing difficulties: how can these many genes be coherently tied together? A parsimonious hypothesis is that the polygenic basis of a psychiatric disorder is manifest in the regulation or function of one or more known or novel

pathways. Genetic variation at many different loci could introduce numerous slight alterations that result in a pathway that is insufficiently robust in response to an environmental insult or that leads to an inappropriate developmental program. [137] Risk for a complex psychiatric disorder could be conferred by the emergent properties of the pathway itself rather than any single component. For SCZ, this conceptualization is supported by the risk profile findings for SCZ, and by the miR-137 results that hint at an underlying regulatory network. For ASD, typical patterns of cortical gene expression in frontal and temporal cortex have been found to be attenuated in ASD cases compared to controls, and an empirically-derived gene expression module that is under-expressed in ASD was found to be enriched for known ASD susceptibility genes and genetic association signals. [90]

Alternative modes of investigation, such as network medicine, are needed to further our understanding of the roles of pathways in complex biological traits. [138] If polygenicity is indeed fundamental to complex psychiatric disorders and if some psychiatric disorders eventually prove to be pathway diseases, [137] then we need to confront this directly and to develop innovative methods. Developing such methods is more constructive and more likely to advance our understanding of these devastating diseases than raging against nature for not delivering common diseases in simpler Mendelian units.

Indeed, if one or more psychiatric disorders eventually prove to be pathway diseases, there could be clinical benefit. We conjecture that it might be considerably easier to coax an existing but dysfunctional biological pathway into the normal range than to replace components broken by Mendelian mutations. Moreover, in an era where many drug companies have moved away from drug development for psychiatric disorders, [139] the ability to measure such a hypothetical pathway in an appropriate cellular system could enable chemical biology screens of existing and novel compounds as well as the evaluation of the rational use of multiple compounds simultaneously.

Implications for strategy

A comprehensive portrait of genetic architecture does not now exist for any psychiatric disorder. Gaining more complete knowledge of the “parts list” for each disorder - the specific loci etiologically involved plus the identity, frequency, and impact of genetic variation at each locus - would be of exceptional importance. Such an enumeration would catalyze an array of specific, targeted and nuanced scientific studies. For example, such studies might lead to elucidation of biological mechanisms between the genotype and psychiatric phenotype, enablement of cell-based chemical biology and pharmacological screening, evaluation of gene action over developmental time, addressing the critical roles of gene-gene and gene-environment interactions, understanding the role played by epigenetic modifications, evaluation of disease prediction models, and so forth.

This is an attainable goal. The genomic search space is large but finite and so, in theory, elucidating the parts list for a psychiatric disorder could be achieved. Based on the evidence to date, thorough and well-powered genomic evaluations across the allelic spectrum are needed. We believe that a balanced portfolio of genomic assessments is required, as there are clear roles for common variation, SV, rare variation, and de novo variation for most disorders. Most discoveries in psychiatric genetics to date are from GWAS and SV

evaluation (both often based on the use of GWAS chips), and larger and more comprehensive GWAS and SV studies are highly likely to increase knowledge. [135] It is possible to provide realistic estimates of power and to predict the number of new associations for each increment in sample size [128,129,140] (e.g., predictions have been made for GWAS and SV in 50,000 SCZ cases and 50,000 controls [140]). Based on the recent ASD studies, sequencing directed at rare and *de novo* variation will have a role in a balanced portfolio of approaches. [83–85] Indeed, with improvements in accuracy, coverage, and pricing, it is possible that sequencing could evolve into the technology of choice for genotyping all major classes of genetic variation.

Such a series of studies would be costly, so a critical challenge is funding. These costs deserve to be placed in context of the public health implications of these disorders and, historically, psychiatric research has ben underfunded in comparison to public health impact (with the possible exception of AD). [141–144] For example, the lifetime cost per person with SCZ is on the order of $US 1.4 million: [145] if this program of research were eventually able to prevent only several dozen cases, it would likely prove to be cost-effective.

Continued cooperation—The successful study of any type of genetic variation in complex biomedical diseases requires very large sample sizes as a means to cut the Gordian knot posed by genetic architecture, etiological complexity, and phenotypic uncertainty. To achieve this end, there have been multiple meta-analysis [146,147] consortia in psychiatric genetics, of which the Psychiatric Genomics Consortium (http://pgc.unc.edu) is the largest and most encompassing. [123,148,149] Indeed, a GWAS co-authorship network graph demonstrates the high connectedness of researchers in the field (Figure S2).

An initial concern regarding GWAS meta-analysis was that increased signal from combining multiple samples would be negated by “noise” due to inter-site differences. This theoretical concern has not been borne out in practice, as illustrated above with the examples in SCZ, [58] BIP, [59] smoking behavior, [92] alcohol consumption, [100] and AD. [35,36] These meta-analyses are designed to identify risk or protective loci that have relatively similar effects across populations and that are not particularly sensitive to sample-specific factors. For example, T2DM and breast cancer loci identified in European samples tend to replicate in samples of East Asian ancestry. [150,151] It is possible that some genetic variants associated with phenotype risk are only found in certain population groups and are missed in meta-analysis; however, conclusive identification of such loci is likely to be challenging unless the effect sizes are relatively large.

Statistical rigor—In our opinion, a key ingredient of progress in psychiatric genetics has been uncompromising statistical rigor. Genomic technologies routinely posit 10^5–10^8 hypotheses, and false positives are a serious concern. For some investigators, suggestive statistical evidence combined with intriguing biology is sufficient. However, we fear that any benefit from relaxing statistical standards will be outweighed by the negative consequences of false positive claims.

This issue is particularly salient for exonic variation. Humans carry a huge pool of phenotypically-neutral background variation that adds noise to genetic analyses (for

example, each person has ~100 loss-of-function variants, most of which are rare in a population), [152,153] and the presence of such variation complicates identification of disease-relevant variants. Thus, owing to chance, a researcher would expect to find a functional exonic mutation – possibly in a gene with intriguing biology – in one case sample and none of their control samples. More quantitatively, if 1% of cases are caused by fully penetrant mutations in a single gene with no background confounding variation, then observing 10 deleterious mutations in 1,000 cases and 0 in 1,000 controls would not stand out in test statistics from 20,000 genes. More realistic scenarios (including locus heterogeneity, incomplete penetrance, and background variation) will substantially erode the signal. The published results for ASD [83–85] and unpublished data on SCZ suggest these issues will be important and underscore the need for sequencing studies to have the same emphasis on statistical rigor and large sample sizes that has enabled GWAS to realize success for multiple psychiatric disorders. [154]

Psychiatric genetics is not “post-genomic”

In psychiatric genetics, we are at the end of the beginning, not the beginning of the end. Remarkably, in a field characterized by a checkered history and few confident etiological clues, the genetics knowledge base has advanced considerably during the past five years, and results to date contain clear indications that further study will yield greater insight. Elucidation of the genetic architectures of psychiatric disorders is an attainable goal with existing technologies (albeit both costly and cost-effective). Few predictions are perfectly safe, but we would argue that genetics is a particularly good bet for psychiatry.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary

Note. This is a placeholder, will be completed prior to publication

Genome-wide association	an unbiased genome screen unrelated cases and appropriately matched controls or parent-affected child trios. The dominant technology has been individual genotyping using highly multiplexed SNP arrays

Genome-wide linkage	a type of unbiased genome screen based on multiplex pedigrees. Genotyping approaches have included restriction fragment length polymorphisms, microsatellites, and SNP arrays. After adjustment for multiple comparisons, the signal is the co-segregation of a genotype with a disease phenotype within the pedigrees
Multiplex pedigree	a family constellation containing more than one affected individual
Polygenic	“many genes”, with no implications about the frequencies, modes of action, or effect sizes of any relevant genetic variation
Risk profile	defined in Box 3
Simplex pedigree	a family constellation containing one affected individual
Karyotyping	
Structural variation	

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Figure 1a

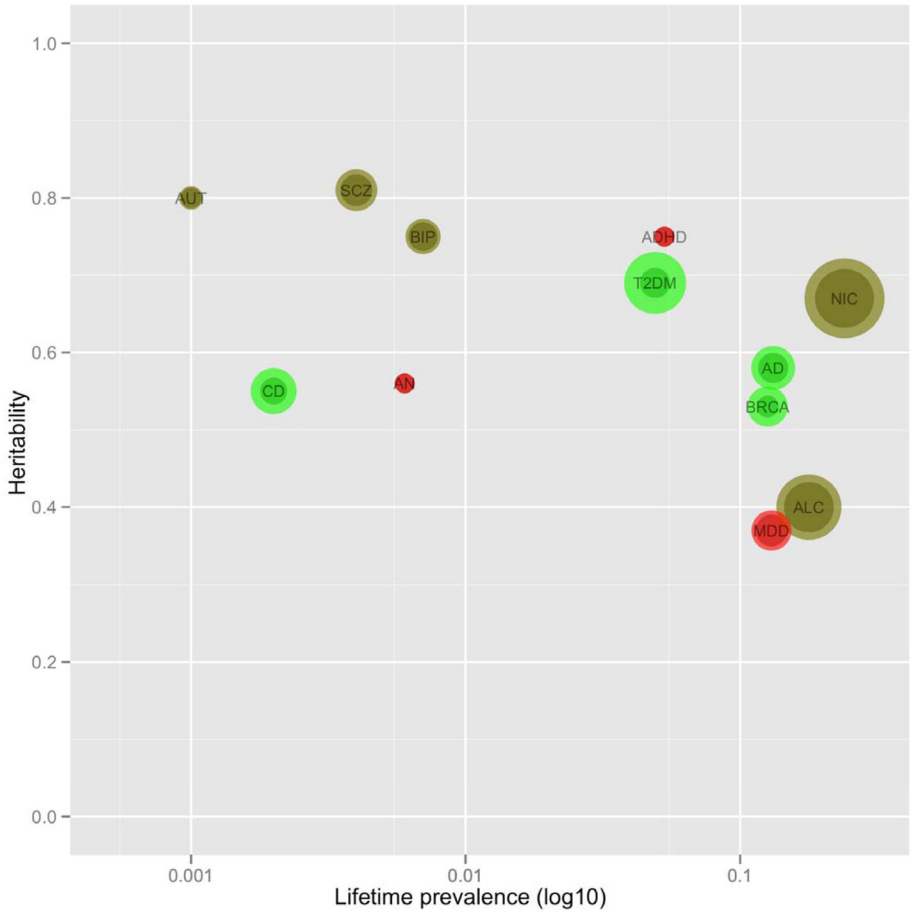

Figure 1b

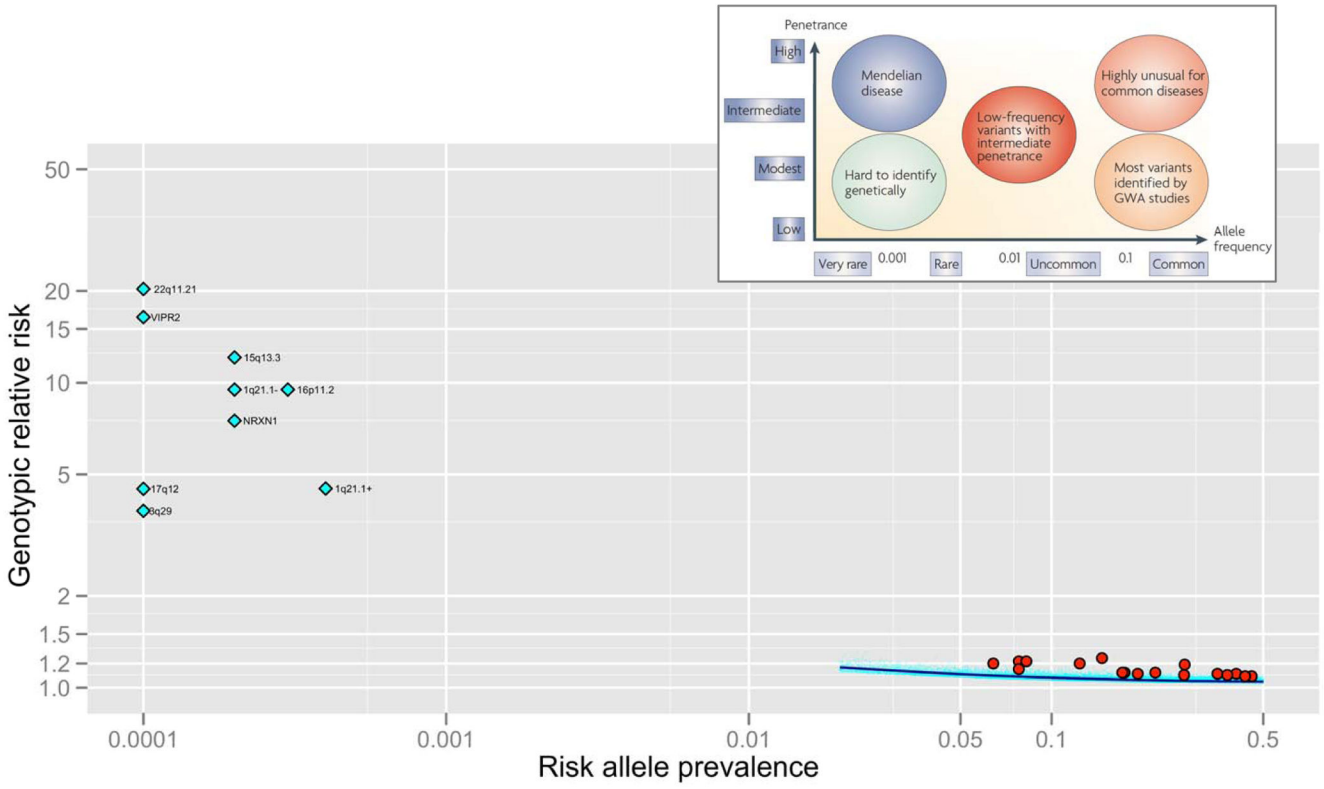

Figure 1. Results pertaining to genetic architecture

(a) Plot of heritability by $\log_{10}$ lifetime prevalence for nine psychiatric disorders considered in this review plus three complex diseases for which genetic dissection has been particularly successful (Tables 1 and S1). Each disorder is plotted by as heritability by lifetime prevalence. Color indicates qualitative success in identifying etiological genetic variation (green=notably successful, khaki=some successes, red=minimal or no clear success to date). The bubble sizes are proportional to the numbers of cases studied in GWAS (the smaller circle indicating discovery N_{case} and the larger circle the total N_{case} for discovery plus replication samples). Abbreviations: ADHD=attention-deficit hyperactivity disorder, ALC=alcohol dependence, AD=Alzheimer's disease, AN=anorexia nervosa, ASD=autism, BIP=bipolar disorder, BRCA=breast cancer, CD=Crohn's disease, MDD=major depressive disorder, NIC=nicotine usage (maximum cigarettes per day), SCZ=schizophrenia, and T2DM=type 2 diabetes mellitus.

(b) Allelic spectrum of SCZ. The inset is a conceptual schematic from a 2008 *Nature Genetics* review. [10] The lower part of the figure depicts empirical results for SCZ. The x-axis is $\log_{10}$(AF) in controls. The y-axis is the point estimate for genotypic relative risk (GRR, $\log_{10}$). For clarity, confidence intervals are not shown. There are no known Mendelian variants for SCZ (AF $\ll$ 0.0001, GRR $\gg$ 50). There are no known common variants (AF > 0.05) with GRR > 1.5, and these can be excluded with > 99% statistical power. Nine SVs associated with SCZ are shown as light blue diamonds (Table 2, 1q21.1- is the deletion and 1q21.1+ is the duplication). If AF in controls was 0, AF was set to 0.0001.

These SVs do not have a corresponding region in the inset. Seventeen common variants have been associated with SCZ (red circles, Table 3). SNPs contributing to the PGC SCZ risk profile score [58] (21,171 autosomal SNPs with $P_T < 0.1$, Box 3***, panel b***) are shown in light blue dots with a lowess smoother in dark blue.

Table 1

Defining features of nine psychiatric disorders ‡

Abbrev.	Name	Life prev	Heritability	Essential characteristics	Notable feature
AD	Alzheimer's disease	0.132	0.58	Dementia, defining neuropathology	Of the top 10 causes of death in the US, AD alone has increasing mortality
ADHD	Attention-deficit hyperactivity disorder	0.053	0.75	Persistent inattention, hyperactivity, impulsivity	Costs estimated at ~$US 100×10^9/year
ALC	Alcohol dependence	0.178	0.57	Persistent ethanol use despite tolerance, withdrawal, dysfunction	Most expensive psychiatric disorder (total costs exceed $US 225×10^9/year)
AN	Anorexia nervosa	0.006	0.56	Dangerously low weight from self-starvation	Notably high standardized mortality ratio
ASD	Autism spectrum disorder	0.001	0.80	Markedly abnormal social interaction and communication beginning before age 3	Huge range of function, from people requiring complete daily care to exceptional occupational achievement
BIP	Bipolar disorder	0.007	0.75	Manic-depressive illness, episodes of mania usually with MDD	As a group, nearly as disabling as SCZ
MDD	Major depressive disorder	0.130	0.37	Unipolar depression, marked and persistent dysphoria with physical/cognitive symptoms	Ranks #1 in burden of disease in world
NIC	Nicotine dependence	0.240	0.67	Persistent nicotine use with physical dependence (usually cigarettes)	Major preventable risk factor for many diseases
SCZ	Schizophrenia	0.004	0.81	Long-standing delusions and hallucinations	Life expectancy decreased by 12–15 years

‡ Most of these definitions are made more restrictive by requiring persistence over time (e.g., the criteria for SCZ require ≥6 months of symptoms), significant impairment, and presence across multiple different contexts. See Table S1 for more detail. Additional sources are references [1,2,181–183].

Table 2

Structural variation associated with psychiatric disorders.

SV	Location (mb)	Genes	Type	Disorder	$Freq_{case}$	$Freq_{control}$	OR	P	Citation	Other associations
1q21.1	chr1:145.0–148.0	34	Deletion	SCZ	0.0018	0.0002	9.5	8×10^{-6}	184	DD, MR, micro-/macrocephaly, dysmorphia, epilepsy, cataract, cardiac defects, possibly ASD, [185] Thrombocytopenia-Absent Radius syn [48,158,184–188]
			Duplication	SCZ	0.0013	0.0004	4.5	0.02	184	
2p16.3	chr2:50.1–51.2	*NRXN1*	Deletion	ASD				0.004	80	DD, MR, epilepsy, Pitt-Hopkins-like syndrome-2
		exons	Deletion	SCZ	0.0018	0.0002	7.5	1×10^{-6}	184	
3q29	chr3:195.7–197.3	19	Deletion	SCZ	0.0010	0.0	3.8	4×10^{-4}	184	DD, MR, possibly ASD
7q11.23	chr7:72.7–74.1	25	Duplication	ASD	0.0011			0.003	80	DD, MR. Deletion: Williams–Beuren syndrome
7q36.3	chr7:158.8–158.9	*VIPR2*	Duplication	SCZ	0.0024	0.0001	16.4	4×10^{-5}	44,184	-
15q11.2	chr15:23.6–28.4	70	Duplication	ASD	0.0018			4×10^{-9}	80	DD, MR, Prader-Wili/Angelman syndromes [188]
15q13.3	chr15:30.9–33.5	12	Duplication	ADHD	0.0125	0.0061	2.1	2×10^{-4}	119	
			Duplication	ASD	0.0013			2×10^{-5}	80	
			Deletion	SCZ	0.0019	0.0002	12.1	7×10^{-7}	184	DD, MR, epilepsy [188,189]
16p13.11	chr16:15.4–16.3	8	Duplication	ADHD	0.0164	0.0009	13.9	8×10^{-4}	118	Deletion: DD, epilepsy [188,189]
16p11.2	chr16:29.5–30.2	29	Deletion	ASD	0.0037			5×10^{-29}	80	DD, MR, epilepsy, macrocephaly, obesity [190,191]
			Duplication	ASD	0.0013			2×10^{-5}	80	DD, MR, epilepsy, microcephaly, low BMI [190,191]
			Duplication	SCZ	0.0031	0.0003	9.5	3×10^{-8}	184	
17q12	chr17:34.8–36.2	18	Deletion	ASD	0.0017	0.0	6.12	9×10^{-4}	192	
			Deletion	SCZ	0.0006	0.0	4.49	3×10^{-4}		
22q11.21	chr22:18.7–21.8	53	Del or dup	ASD	0.0013			0.002	80	
			Deletion	SCZ	0.0031	0.0	20.3	7×10^{-13}	184	DD, MR, velocardiofacial-DiGeorge syndrome

Locations are NCBI Build 37/UCSC hg19. The positions of these SV are denoted in Figure S1 with yellow circles. For succinctness, the citations refer to the most comprehensive study rather than an initial report. Genes refers to UCSC knownGenes. OR=odds ratio. DD=developmental delay, MR=mental retardation, BMI=body mass index.

Table 3

GWAS findings for psychiatric disorders.

Phenotype	SNP	Location	Discovery GWAS	Largest meta-analysis	P value	OR	Nearest gene
AD	rs3818361	chr1:207784968	2018/5324[34]	<19870/39846[35]	3.7×10^{-14}	1.18	*CR1*
AD	rs744373	chr2:127894615	3006/14642[193]	<19870/39846[35]	2.6×10^{-14}	1.17	*BIN1*
AD	rs9349407	chr6:47453378	8309/7366[36]	18762/29827[36]	8.6×10^{-9}	1.11	*CD2AP*
AD	rs11767557	chr7:143109139	8309/7366[36]	18762/35597[36]	6.0×10^{-10}	1.11	*EPHA1*
AD	rs11136000	chr8:27464519	3941/7848[33]	8371/26965[193]	1.6×10^{-16}	1.18	*CLU*
AD	rs610932	chr11:59939307	6688/13251[35]	>19000/38000[35]	1.2×10^{-16}	1.10	*MS4A* cluster
AD	rs3851179	chr11:85868640	3941/7849[33]	8371/26966[193]	3.2×10^{-12}	1.15	*PICALM*
AD	rs3764650	chr19:1046520	5509/11531[35]	>17000/34000[35]	5.0×10^{-21}	1.23	*ABCA7*
AD	rs2075650	chr19:45395619	-	8371/26966[193]	1×10^{-295}	2.53	*APOE, TOMM40*
AD	rs3865444	chr19:51727962	8309/7366[36]	18762/29827[36]	1.6×10^{-9}	1.10	*CD33*
ALCcon	rs1229984	chr4:100239319	-[101]	-	1.3×10^{-11}	-	*ADH1B*
ALCcon	rs6943555	chr7:69806023	-[100]	-	4.1×10^{-9}	-	*AUTS2*
ALCcon	rs671	chr12:112241766	-[99]	-	3×10^{-211}	-	*ALDH2*
BIP	rs12576775	chr11:79077193	7481/9251[59]	11974/51793[59]	4.4×10^{-8}	1.14	*ODZ4*
BIP	rs4765913	chr12:2419896	7481/9250[59]	11974/51792[59]	1.5×10^{-8}	1.14	*CACNA1C*
BIP	rs1064395	chr19:19361735	682/1300[194]	8441/35362[194]	2.1×10^{-9}	1.17	*NCAN*
NDsc	rs3025343	chr9:136478355	41,278[92]	64,924[92]	3.6×10^{-8}	1.13	*DBH*
NDcon	rs1329650	chr10:93348120	38,181[92]	73,853[92]	5.7×10^{-10}	-	*LOC100188947*
NDint	rs6265	chr11:27679916	74,035[92]	143,023[92]	1.8×10^{-8}	0.94	*BDNF*
NDcon	rs1051730	chr15:78894339	38,181[92]	73,853[92]	2.8×10^{-73}	-	*CHRNA3*
NDcon	rs3733829	chr19:41310571	38,181[92]	73,853[92]	1.0×10^{-8}	-	*EGLN2, CYP2A6*
SCZ	rs1625579	chr1:98502934	9394/12462[58]	17839/33859[58]	1.6×10^{-11}	1.12	*MIR137*
SCZ	rs2312147	chr2:58222928	-	18206/42536[195]	1.9×10^{-9}	1.09	*VRK2*
SCZ	rs1344706	chr2:185778428	479/2937[174]	18945/38675[196]	2.5×10^{-11}	1.10	*ZNF804A*
SCZ	rs17662626	chr2:193984621	9394/12463[58]	17839/33860[58]	4.6×10^{-8}	1.20	*PCGEM1*

Phenotype	SNP	Location	Discovery GWAS	Largest meta-analysis	P value	OR	Nearest gene
SCZ	rs13211507	chr6:28257377	3322/3587[69]	18206/42536[195]	1.4×10^{-13}	1.22	*MHC*
SCZ	rs7004635	chr8:3360967	9394/12465[58]	17839/33862[58]	2.7×10^{-8}	1.10	*MMP16*
SCZ	rs10503253	chr8:4180844	9394/12464[58]	17839/33861[58]	4.1×10^{-8}	1.11	*CSMD1*
SCZ	rs16887244	chr8:38031345	3750/6468[67]	8133/11007[67]	1.3×10^{-10}	1.19	*LSM1*
SCZ	rs7914558	chr10:104775908	9394/12466[58]	17839/33863[58]	1.8×10^{-9}	1.10	*CNNM2*
SCZ	rs11191580	chr10:104906211	9394/12467[58]	17839/33864[58]	1.1×10^{-8}	1.15	*NT5C2*
SCZ	rs11819869	chr11:46560680	1169/3714[197]	3738/7802[197]	3.9×10^{-9}	1.25	*AMBRA1*
SCZ	rs12807809	chr11:124606285	-	18206/42536[195]	2.8×10^{-9}	1.12	*NRGN*
SCZ	rs12966547	chr18:52752017	9394/12468[58]	17839/33865[58]	2.6×10^{-10}	1.09	*CCDC68*
SCZ	rs9960767	chr18:53155002	-	18206/42537[195]	4.2×10^{-9}	1.20	*TCF4*
SCZ+BIP	rs1344706	chr2:185778428	479/2937[174]	21274/38675[196]	4.1×10^{-13}	1.11	*ZNF804A*
SCZ+BIP	rs2239547	chr3:52855229	9394/12471[58]	16374/14046[58]	7.8×10^{-9}	1.12	*ITIH3-ITIH4*
SCZ+BIP	rs10994359	chr10:62222107	9394/12470[58]	16374/14045[58]	2.4×10^{-8}	1.22	*ANK3*
SCZ+BIP	rs4765905	chr12:2349584	9394/12469[58]	16374/14044	7.0×10^{-9}	1.11	*CACNA1C*

Table 3 focuses on results achieving genome-wide significance in large samples. We use a significance threshold of 5×10^{-8} (reference [198]). Most associations achieving this level of significance are secure but some may ultimately prove not to be. Included are SNPs with $p < 5\times10^{-8}$ that were evaluated in samples of a minimum of around 10,000 cases and 10,000 controls. Discovery sample sizes reflect the primary samples for which full GWAS were conducted. In most cases, discovery P values were $> 5\times10^{-8}$ but met a threshold (typically 1×10^{-5}) for inclusion in replication efforts. In some instances, simultaneous publications based upon overlapping samples were considered "discovery". Where this occurred, providing samples of roughly equivalent sizes, the most significant primary GWAS findings are given; otherwise, the largest discovery samples are favored. For many studies, it was not possible to extract the exact sample size used for each locus so the sample sizes above are approximate. P-values and ORs are from the meta-analysis with the largest sample sizes. If two meta-analyses based on overlapping samples reported similar results, the "discovery" study is cited. The genes nearest each locus are provided but etiological variants are generally unknown, and it remains likely that some of the associations do not alter the function of the designated genes (e.g., *ITIH3-ITIH4* where multiple correlated SNPs span many genes, and *TCF4-CCDC68* where statistically independent associations occur in *TCF4* and closer to *CCDC68*). In the *TCF4-CCDC68* example, it may be that both associations point to the same functional element but, it is also possible that independent etiological variants occur in adjacent genes.

For the SCZ loci attributed to Steinberg et al., [195] no discovery sample size is listed because the initial P values were modest and, as the authors conducted multiple follow-up analyses, there is no obvious discovery sample. At the MHC, the International Schizophrenia Consortium [69] is designated discovery as it was the only primary GWAS for which genome-wide significance at the MHC was obtained. Steinberg et al. is cited for the meta-analysis at the MHC as it reported the most significant MHC association. [195] The most significant SNP at the MHC across the two studies is not identical, and the one listed is that from Steinberg et al. Multiple statistically independent SNPs have been reported at the MHC. [58,186] We note that genome-wide significance had been reported in BIP for *ANK3*[199] but not in a larger mega-analysis including the same samples. [59] Others have reported genome-wide significance for composite phenotype studies of *ITIH3-ITIH4*[200] (but see reference [201]) and *CACNA1C* [202] but in samples smaller than required for inclusion in the above table.

ALCcon means alcohol consumption. The rs671 association was in East Asian samples. The *ADH1B* locus was also associated with ALC.

NDcon means nicotine consumption (as maximal cigarettes per day, continuous). NDinit means smoking initiation (ever versus never began smoking). NDsc means smoking cessation (whether regular smokers had quite at time of interview).