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Pleiotropy and Cross-Disorder Genetics Among Psychiatric Disorders

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Abstract

Genome-wide analyses of common and rare genetic variation have documented the heritability of major psychiatric disorders, established their highly polygenic genetic architecture, and identified hundreds of contributing variants. In recent years, these studies have illuminated another key feature of the genetic basis of psychiatric disorders: the important role and pervasive nature of pleiotropy. It is now clear that a substantial fraction of genetic influences on psychopathology transcend clinical diagnostic boundaries. In this review, we summarize evidence in psychiatry for pleiotropy at multiple levels of analysis: from overall genome-wide correlation to biological pathways and down to the level of individual loci. We examine underlying mechanisms of observed pleiotropy including genetic effects on neurodevelopment, diverse actions of regulatory elements, mediated effects, and spurious associations of genomic variation with multiple phenotypes. We conclude with an exploration of the implications of pleiotropy for understanding the genetic basis of psychiatric disorders, informing nosology, and advancing the aims of precision psychiatry and genomic medicine.

Keywords

Pleiotropy; genetic correlation; psychiatric genetics; nosology; cross-disorder; precision psychiatry; GWAS

The organization and re-organization of psychopathology into syndromes and disorders has been an evolving project, beginning centuries ago and continuing to this day. The current

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prevailing classification or nosology of psychiatric disorders has its roots around the turn of the 20th century when a pantheon of (mostly European) authoritative figures proposed several major categories that were successively modified, sometimes discarded or combined, and ultimately reified in the International Classification of Diseases (ICD) and the Diagnostic and Statistical Manual of Mental Disorders (DSM). However, this nosology is, by design, “atheoretical”, eschewing etiologic accounts in favor of descriptive collections of symptoms. Though these disorders are presented as discrete entities with their own diagnostic criteria, there has been an ongoing debate about their validity. Family and genetic studies have played an important role in raising questions about the boundaries between our diagnostic categories and the degree to which they “carve nature at its joints” (1). In particular, evidence accumulated over decades of family and twin studies have shown that familial and heritable components commonly overlap between disorders(1).

Against this backdrop came advances in human genetics that have enabled examination of the genetic basis of disease at the level of DNA variation. A key theme emerging from recent genomic studies of complex traits and diseases is the widespread nature of pleiotropy (2, 3). Pleiotropy refers to the situation in which a genetic variant or gene has effects on more than one phenotype. In a recent GWAS spanning 558 traits, more than 90% of trait-associated loci (including more than 60% of genes) were found to be pleiotropic.(4) Here, we review the phenomenon of pleiotropy and cross-phenotype genetic effects on psychopathology, explore the potential mechanisms underlying shared genetic influences, highlight outstanding research questions, and consider implications for psychiatric genetics and nosology.

Genetic Overlap and Pleiotropy in Psychiatry

Well before it became possible to interrogate the genome at the level of DNA variation itself, family and twin studies began documenting overlap among psychiatric disorders (see (1) and (5) for review). In the past decade, characterizing such overlap at a molecular genetic level has become a major activity in the field of psychiatric genetics. The basis of this shared genetic vulnerability is generally attributed to the phenomenon of pleiotropy. However, pleiotropy can be considered at varying levels of analysis, from individual variants, to genes, loci that encompass multiple genes, biological pathways, and overall genome-wide correlation (Figure 1). Variant level pleiotropy has been observed for both common single nucleotide polymorphisms (SNPs) identified largely through GWAS and rare mutations assayed by exome and genome sequencing.

Because of regional linkage disequilibrium (LD), many, if not most, of the most statistically significant SNPs discovered by GWAS tag regions that encompass one or more true causal variants. As such, they are more accurately described as associated loci or regions. Fine-mapping studies are then required to narrow these regions to a credible set of variants that underlie the association signal (6). Rare copy number variants (CNVs), which may involve the deletion or duplication of large segments of DNA that encompass numerous genes, also pose challenges for identifying the causal variation within an associated region. Multiple causal variants within a gene may produce gene-level pleiotropy when, for example, each variant affects distinct phenotypes. Genes, in turn, participate in higher level networks or

pathways which can also contribute to multiple phenotypes. Finally, the aggregate pleiotropic effects of variant, gene, and pathways can produce genetic correlation between two or more phenotypes. In the sections that follow, we briefly summarize recent findings from genomic studies regarding pleiotropy and the shared genetic basis of psychiatric disorders.

Genetic Correlation Among Disorders.

In recent years, statistical methods to estimate SNP-based heritability have been extended to allow estimates of SNP-based genetic correlation (r_g) between phenotypes, a measure of the average effect of pleiotropy across all causal loci(7). In this paper, we use genetic correlation as an index of polygenic overlap between phenotypes, though it has been noted that genetic correlation may underestimate the magnitude of overlap when the direction of causal variant effects on the phenotypes are mixed, and methods are available to address this (8). In the first large-scale analysis of genetic correlation between psychiatric disorders, the Cross Disorder Workgroup of the Psychiatric Genomics Consortium (PGC-CDG) examined five major psychiatric disorders (autism spectrum disorder, ASD; attention deficit/hyperactivity disorder, ADHD; bipolar disorder, BD; major depressive disorder, MDD; and schizophrenia, SCZ) and found substantial evidence of genetic overlap (9). The strongest genetic correlation was observed between BD and SCZ (r_g=0.68), but significant correlations were also found between MDD and SCZ (0.43), BD (0.47), and ADHD (0.37), respectively and between SCZ and ASD (0.16). Regarding the strong genetic overlap between BD and SCZ, an analysis using causal mixture modeling indicated that 75% of the causal common variants influencing the two disorders are shared (8). Analyses of post-mortem cortical transcriptomic profiles among these disorders (with alcoholism substituting for ADHD) have shown that patterns of shared gene expression closely correlated (r = 0.79) with pairwise genetic correlations. (10) The Brainstorm Consortium (11) estimated pairwise r_g for 25 brain disorders (psychiatric and neurologic) as well as related quantitative traits. Significant genetic correlations were observed for psychiatric disorders (especially among ADHD, MDD, BD, anxiety disorders, and SCZ) while little overlap was seen among neurologic disorders (including stroke, epilepsies, multiple sclerosis, Parkinson disease and migraine). Interestingly, none of the neurologic disorders were significantly genetically correlated with the psychiatric disorders with the exception of migraine, supporting the clinical distinction between psychiatric and neurologic disease.

A more recent PGC-CDG analysis spanning eight psychiatric disorders (12) expanded our understanding of genomic relationships by applying genomic structural equation modeling (13), which can model multivariate genetic associations among phenotypes. The findings revealed three correlated genomic factors that together accounted for more than 50% of the genetic variation underlying these disorders. The first factor comprised disorders characterized by compulsive/perfectionistic behaviors, specifically anorexia nervosa (AN), obsessive-compulsive disorder (OCD), and, to a lesser extent, Tourette syndrome (TS). Mood and psychotic disorders (MDD, BD, and SCZ) loaded most strongly on a second factor while the third factor encompassed three early-onset neurodevelopmental disorders (ASD, ADHD, TS) as well as MDD. These results illustrate how modeling disorder relationships using common variant genomic data can provide insights into the underlying

structure of psychopathology that could inform a more bottom-up reconceptualization of psychiatric nosology.

Genetic correlation and polygenic risk score (PRS) analyses have also revealed genomic overlap between psychiatric disorders and other biomedical traits and disorders. A notable example is the finding of significant negative genetic correlations between AN and a range of metabolic phenotypes, including obesity, type II diabetes, leptin, fasting insulin and insulin resistance (14). These results have suggested a reconceptualization of AN as a disorder with both neurobiologic and metabolic etiology. Other work has shown significant genetic overlap between SCZ and immune-mediated diseases (15) and between depression and cardiovascular disease (16, 17).

Network and Pathway Pleiotropy.

Genetic correlation analyses can estimate the overall magnitude of genetic sharing between phenotypes, but they do not address the biological basis of the overlap. Network and pathway analyses take us a level down from aggregate genomic effects to identify which biological or functional pathways contribute. These analyses typically take as inputs variant-level association results, partition them into biologically-relevant gene sets, and then ask which gene sets or pathways are enriched among GWAS signals. A broad-spectrum role for genes involved in calcium channel signaling was first documented in the PGC-CDG analysis of five disorders in which this pathway was implicated across ASD, ADHD, MDD, BD and SCZ(9). The PGC Network and Pathway Analysis subgroup expanded on this work and found 49 pathways with evidence of association across BD, MDD, and SCZ (18). Clustering of these pathways revealed three biological themes: histone methylation, synaptic biology, and immune and neurotrophic pathways. In the larger PGC-CDG analysis of eight disorders (12), pleiotropic loci were significantly enriched in pathways related to neurodevelopment as well as glutamate receptor signaling and voltage-gated calcium channel signaling.

Transcriptomic analyses of postmortem gene expression have also revealed shared and distinct gene networks across multiple psychiatric disorders (19). For example, genes involved in glial cell differentiation (predominantly expressed in astrocytes) were upregulated in ASD, BD, and SCZ while expression of neuronal gene sets involved in synaptic function were down-regulated across these disorders(10). Another analysis (20) identified gene expression profiles shared across these three disorders including those involved in synaptic function, nervous system development, lipid signaling, and posttranslational protein modification. To date, the results of these studies have been somewhat inconsistent, and it can be difficult to determine whether gene expression differences are causal or secondary to disease states.

The complex, interconnected nature of gene regulatory networks led Boyle, Pritchard and colleagues(21) to propose an “omnigenic model” of complex traits. In this model, the genetic architecture of many diseases involves variations in a limited set of “core” genes as well as a much larger component from “peripheral” genes that are connected to the core genes through regulatory pathways. In what they refer to as “network pleiotropy”, “virtually any variant with regulatory effects in a given tissue is likely to have (weak) effects on all diseases that are modulated through that tissue.” The model predicts that these indirect

effects may contribute to genetic correlations among disease phenotypes, though others have challenged the distinction between core and peripheral genes(22).

Pleiotropic Effects of Copy Number Variants.

CNVs have convincingly shown cross-disorder effects for a range of neurodevelopmental disorders (NDDs). These pleiotropic CNVs tend to be rare (frequency < 0.5%) and occur *de novo* (ie, not inherited) but their effect sizes are substantially larger than those seen with individual SNPs (23). Most of the CNVs associated with SCZ are also associated other NDDs, particularly ASD and intellectual disability (ID) or developmental delays (DD), though the frequency and penetrance of these CNVs tend to be greater for ASD/ID/DD than for SCZ(24). Specific CNVs associated with ASD or SCZ have also been associated with TS, ADHD, and OCD(25–27). The cross-disorder risk associated with CNVs may be due to altered dosage of multiple genes encompassed by deletions or duplications. In the case of 22q11 deletions and duplications, accumulating evidence indicates that the spectrum of phenotypic effects depends on copy number dosage and deletion size.(28–31) Occasionally, the pathogenic effect of rare CNVs can be localized to a specific gene. For example, deletions of 2p16.3 that specifically disrupt *NRXN1,* a pre-synaptic adhesion protein involved in synaptogenesis and synaptic transmission, have been associated with ID/DD, ASD, ADHD, SCZ, epilepsy, and TS (32).

Gene, Locus and Variant Pleiotropy.

GWAS have identified a growing number of common variants associated with more than one neuropsychiatric disorder. In the most comprehensive analysis to date, the PGC-CDG (12), reported a GWAS meta-analysis comprising 727,126 individuals across 8 disorders (ASD, ADHD, TS, AN, OCD, MDD, BD, and SCZ). A total of 109 independent pleiotropic loci were identified including 23 that showed evidence of association with four or more disorders. The most highly pleiotropic locus was observed at the netrin-1 receptor gene *DCC*, a master regulator of white matter projections that plays a key role in axonal guidance during neuronal development (33) and in the maturation of mesolimbic dopaminergic connections to the prefrontal cortex during adolescence (34). Functional genomic analyses showed that the pleiotropic loci map to genes that, on average, show heightened expression beginning in the second prenatal trimester and are enriched in frontal cortical neurons, particularly glutamatergic neurons. Of note, cross-disorder analyses have also provided evidence for loci that appear to have relatively disorder-specific effects and presumably account for the incomplete genetic correlations among psychiatric disorders (12, 35–38). For instance, a GWAS of SCZ vs. BD cases identified several disorder-specific loci and found enrichment of genes involved in potassium ion response as a differentiating genetic mechanism between these two highly genetically correlated disorders (35) Also of note, FMRP-targets and genes implicated in excessive synaptic pruning have thus far been more convincingly linked to SCZ than to BD (39, 40).

Rare variant association studies have also revealed pleiotropic effects of specific mutations, especially for ASD and other NDDs. Indeed, a recent overview noted that “to date, no genes have been identified that, when mutated, confer only ASD risk and no risk for ID or other NDDs.” (41) Exome-sequencing has shown that rare protein-truncating variants are

associated with ASD, ADHD, ID, but also SCZ and BD (42, 43). *MAP1A*, a gene involved in the organization of neuronal microtubules, was significantly associated with ASD and ADHD in a pooled analysis of all cases.(43) In addition, exome sequencing of parent-child trios with OCD found significant overlap between genes harboring *de novo* damaging mutations in OCD with those previously found to contribute to TS and ASD (44). Rare variants in genes involved in chromatin function have also demonstrated pleiotropic effects on psychopathology, presumably due to the widespread regulatory role of chromatin remodeling on gene expression. For example, disruptions (by rare point mutations, translocations, and structural deletions) of *MBD5*, a gene involved in heterochromatin and epigenetic regulation, have been associated with ASD/ID/DD as well as a broad range of phenotypes including anxiety and BD (45). In addition, rare loss-of-function (LOF) mutations in *SETD1A*, a histone methylatransferase, have been associated with SCZ, ASD, and other NDDs (46), while LOF mutations in *CHD8*, a regulator of chromatin remodeling, have been associated with syndromic NDDs, including ASD and ID (47).

Genetic Influences on Transdiagnostic Phenotypes.

Genetic influences on psychiatric disorders also share genetic determinants with dimensional psychological and neurocognitive traits that transcend diagnostic boundaries. In some cases, these findings support the hypothesis that categorically-defined disorders represent the extremes of quantitative traits and subthreshold symptoms that are seen across the spectrum of “normal” variation (48, 49). For example, common variants and *de novo* rare variants affecting ASD are also associated with typical variation in the population in social and communication ability (50). CNVs known to be pathogenic for NDDs (including ASD and SCZ) are also associated with cognitive deficits among individuals unaffected with neuropsychiatric disorders (51), and a greater burden of these CNVs have been observed among adults with a history of psychotic experiences in the absence of psychiatric disorders (52). Similarly, polygenic risk for SCZ is associated with social cognitive and neurocognitive traits in healthy individuals (53) and common variant liability to ADHD is associated with variation in extraversion (54) and subthreshold ADHD symptoms (55). A large scale GWAS meta-analysis of neuroticism, a personality trait indexing negative affectivity, found substantial genetic correlations with anxiety disorders ($r_g = 0.82$) and depression (.68) but also significant correlations with ASD and SCZ (56). Other studies have found significant genetic overlap between psychiatric disorders and a range of structural and functional neuroimaging phenotypes (57). Overall, these studies suggest that the boundaries between disorder and normal variation are indistinct.

Phenomewide Effects of Psychiatric Risk Loci.

Now that GWAS have been extensively applied across virtually all domains of biomedicine, it has become relatively straightforward to examine (by simple look-up) the pleiotropic effects of loci that have been implicated in psychiatric disorders. The NHGRI-EBI GWAS Catalog(58) comprises nearly 200,000 associations across a broad landscape of complex traits and reveals numerous instances in which loci convincingly associated with neuropsychiatric phenotypes are also associated with other biomedical traits and diseases. For example, a coding missense variant (rs13107325 C>T, A391T) in the manganese transporter *SLC639A8* is strongly associated with SCZ but has also shown genome-wide

significant association with an array of other traits and disorders from blood pressure and lipid levels to alcohol consumption, Crohn's disease and others.(59) The highly pleiotropic nature of this variant is likely related to its effect on regulating levels of manganese, a co-factor for glycosylation enzymes that in turn affect a vast assortment of cellular pathways (60)

The availability of large-scale biobanks linking electronic health records (EHRs) and genomic data, have recently enabled phenome-wide association studies (PheWAS) (61). In contrast to GWAS which involves an unbiased search across the genome for variants associated with a specific phenotype, PheWAS involves an unbiased search across the phenome for phenotypes associated with a specific variant (or group of variants). Thus, PheWAS is effectively a search for pleiotropy that leverages the availability of broad phenotypic data such as those now available in biobanks and population registers. A growing number of studies have taken a PheWAS approach to examine the phenotypic spectrum of psychiatric risk variants, mostly focused on PRS. (62–66) For example, PheWAS in the UK Biobank have found associations between MDD PRS and a range of biological and psychological traits including cardiovascular disease, celiac disease, sleep disorders, white matter microstructure, and neuroticism.(66, 67)

Potential Mechanisms underlying Shared Genetic Influences

The observation that a genetic variant is associated with multiple phenotypes can be due to a number of phenomena(2). In this section, we discuss potential mechanisms of observed pleiotropy that can drive shared genetic risk associations across complex traits (depicted in Figure 2).

Type I. Biological Pleiotropy

Biological pleiotropy (also known as horizontal pleiotropy) refers to the scenario in which a causal variant or a gene produces direct biological effects on more than one phenotype (2). Here we define two subtypes of biological pleiotropy: single-gene pleiotropy and multi-gene regulatory pleiotropy (Figure 2A). The major distinguishing feature of the two subtypes is whether causal risk variants, either residing in coding or non-coding regions, directly affect a single gene (i.e., single-gene pleiotropy) or multiple genes simultaneously (i.e., multi-gene regulatory pleiotropy).

Single-gene pleiotropy

Causal risk variants may affect multiple traits through the action of a *single* target gene with multifarious effects (Figure 2A(a)). There are a number of non-mutually exclusive scenarios under which gene pleiotropy may occur; a gene may perform multiple, distinct molecular functions, participate in multiple independent biological pathways or cellular processes, or be expressed in multiple organs, tissues or spatiotemporal contexts, each affecting distinctive traits. In addition, a single gene can have diverse biological roles by encoding multiple protein isoforms – that is, protein products that differ in structure and function. Various regulatory mechanisms, including alternative splicing, RNA editing, or post-transcriptional modifications, enable this diversity of gene-to-protein mapping (68). Of note, more than

94% of human genes encode protein isoforms, and alternative splicing is particularly widespread in the nervous system (69).

Figure 3 depicts four exemplar mechanisms of single-gene pleiotropy related to psychiatric disorders (See Supplement for an expanded discussion). *NRXN1* encodes multiple isoforms with differential effects on psychiatric and neurocognitive symptoms (Figure 3A) and has been associated through common and rare variant studies with NDDs including ASD, ID and SCZ(70–72), with suggestive associations reported for ADHD, TS, OCD, and BD (reviewed in (73, 74)). The transcription factor *TFC4* acts as a "master regulator" of diverse downstream transcription factors and their target genes.(Figure 3B) Common variants in *TCF4* have been associated with SCZ and MDD, while rare damaging mutations have been linked with PittHopkins syndrome, ID, SCZ, ASD, and MDD (75–79). A third example is *DCC,* the most pleiotropic locus in the recent PGC-CDG analysis of eight psychiatric disorders (Figure 3C). Through its interaction with netrin-1, a key molecule essential for axon guidance (80), *DCC* plays a fundamental role in establishing white matter connections in diverse brain regions across critical developmental windows. Finally, *RBFOX1*, a highly conserved RNA-binding protein, appears to have diverse neurobiologic effects by regulating tissue-specific alternative splicing of genes important for neuronal development and excitability (81, 82) and has been associated with numerous childhood- and adult-onset neuropsychiatric disorders and related traits.(12, 58, 83–89). (Figure 3D).

Multi-Gene Regulatory Pleiotropy

Pleiotropy may also occur when a causal variant directly alters the expression of *multiple* genes, each of which may underlie the change of distinct phenotypes.(Figure 2A(b)). More than 90% of loci identified in GWAS localize to non-coding regions (90), which include a broad spectrum of regulatory elements. Many of these regulatory elements, including enhancers, silencers, insulators, and cis-eQTLs govern the dynamic control of spatiotemporal gene expression, and in many cases, are shared by multiple genes in a given region (91). "Super-enhancers", large clusters of enhancers occupying an extended range of genomic regions(92), can regulate expression of functionally related genes *en masse.* Variation around the super-enhancer region around *RERE* has been associated with SCZ, MDD, AN, ASD, and TS (12). Regulatory pleiotropy can also result from genetic effects on chromosome conformation (93). Through three-dimensional looping, distal non-coding regulatory elements up to several megabases away from gene promoters can interact and modulate expression of target genes. For example, a variant upstream of protocadherin cell adhesion (PCDH) gene clusters on chromosome 5, important in neurodevelopment, affects expression of multiple protocadherin genes which have been associated with SCZ and MDD (12, 56).

Type II. Mediated pleiotropy

Mediated pleiotropy (also known as "vertical pleiotropy") occurs when a variant exerts a direct influence on one trait, which itself has a causal effect on a second trait. (2) A statistical association between the variant and both traits may be detected, but the variant's effect on the second trait may only be mediated through the first trait. A familiar example of

mediated pleiotropy is the observation that variants affecting low-density lipoprotein (LDL) levels are secondarily associated with coronary artery disease (94).

Several mediation-analysis approaches have been developed to estimate the relative proportions of direct and indirect genetic effects in the presence of pleiotropy (95–97). In recent years, Mendelian randomization (MR) methods have been widely used to examine putative causal relationships between an exposure (X) and an outcome (Y) using one or more genetic variants (G) as instrumental variables. The MR approach is based on the fact that alleles are randomly allocated at conception and has three core assumptions (98): (1) G is robustly associated with X, (2) G is not associated with any confounder (U) of the X-Y relationship, and (3) G is independent of Y conditioning on X and U. When these assumptions are met, the causal effect of X on Y can be estimated as the ratio of G-Y effect to G-X effect. In a sense, then, MR can be thought of as a test of mediated pleiotropy in addition to its role in testing causal exposure-outcome effects.

MR has been used to examine several hypotheses about causal effects on mental illness. For example, several MR studies have investigated the long-debated causal relationship between cannabis use and schizophrenia, with mixed results (99). Surprisingly, stronger evidence has been reported for a causal influence of schizophrenia risk on cannabis use than effects in the other direction (99). MR analysis has also been applied to biological “exposures” with evidence, for example, that low C-reactive protein levels are causally related to SCZ risk (100, 101). Findings from such MR studies may help identify modifiable factors for targeted prevention and intervention, though the mechanisms underlying mediated pleiotropy are often unknown.

Type III. Spurious pleiotropy

Finally, apparent pleiotropic associations may arise due to various artefacts in study design or limitations in defining risk genotypes and phenotypes, creating “*spurious pleiotropy*” (2). In essence, spurious pleiotropy can result from a kind of misclassification at either the genomic or phenotypic level.

At the genomic level, spurious pleiotropy may occur when an associated region encompasses multiple causal variants or genes that are in strong LD. In this case, variants or genes affecting different phenotypes through independent biological mechanisms may appear to be a single associated “pleiotropic” locus. In their genome-wide survey of pleiotropy, Watanabe and colleagues (4) found that the MHC region, where more than 300 genes are tightly clustered in long-ranged LD blocks, was associated with more than 200 phenotypes across 23 phenotypic domains. However, in-depth investigation using fine-mapping and colocalization analysis identified more than a third of these associations as false positives. Improved methods of fine-mapping and incorporation of functional annotation and gene-expression data will help further sift through spurious pleiotropic signals in regions of high LD.

Phenotypic misclassification, a well-known phenomenon in psychiatric diagnosis, can also induce spurious pleiotropy. For example, if a sufficient proportion of cases of BD are

misdiagnosed as MDD, a GWAS of the two disorders could inflate evidence for genetic correlation and loci associated with both disorders. However, while simulations have shown that diagnostic misclassification can induce spurious genetic correlation, misclassification rates would need to be unrealistically high to account for the magnitude of genetic overlap that has been found in GWAS analyses (11). A variant of the misclassification problem can occur when there is unrecognized comorbidity of phenotypes, either due incomplete phenotyping or induced by ascertainment bias (102). For example, if cases of one disorder are enriched for comorbidity with a second disorder, ignoring this comorbidity could result in biased estimates of genetic correlation between the two disorders. Finally, the selection of controls could also drive spurious pleiotropy. The use of shared controls is not uncommon in GWAS of multiple phenotypes, and failure to account for these in statistical analysis can bias estimates of genetic overlap. In addition, recent simulations demonstrate that the use of both unscreened controls and “super-normal” controls (screened to exclude multiple related phenotypes) can upwardly bias genetic correlations, especially between disorders that are common.(103) Minimizing the possibility of spurious pleiotropy in cross-disorder studies requires careful and broad-based phenotypic assessment to limit misclassification (ideally including longitudinal measures that can account for instability of phenotypic presentations) and the selection of controls screened to only exclude the target disorders.

Implications for understanding the genetic basis of psychiatric disorders.

We have learned that some genes and pathways may have pleiotropic effects on psychopathology by impacting neurodevelopment. For example, rare CNVs that have broad neuropsychiatric effects appear to disrupt neurodevelopment in fundamental ways that confer risk for multiple NDDs. Common variants with highly pleiotropic effects also appear to act in part by modulating neurodevelopmental processes and the establishment of brain circuitry that may create a relatively pluripotent vulnerability to mental illness beginning in prenatal periods.(12) The differentiation of this vulnerability into the more distinct syndromes that we recognize clinically may then involve additional sets of common and rare variations and environmental factors, possibly mediated by epigenetic effects. In addition, as reviewed earlier, other pleiotropic genes may act through effects on broad regulatory networks that amplify their cross-disorder effects. It is likely that, as sample sizes and functional genomic resources expand, we will see more and more evidence of interconnections among genomic contributions to psychiatric and other disorders owing to their extreme polygenicity(3). Indeed, the evidence to date may simply represent the initial scaffolding upon which we will build a more comprehensive view of the genomic map of the human phenome in which psychiatric disorders represent one component of a highly networked structure.

Implications for psychiatric nosology.

The current systems for classifying psychiatric disorders (the ICD and DSM) have relied on the consensus of experts and historical traditions for grouping symptoms into syndromes. The evolving database of genetic relationships and pleiotropic genes reviewed here has revealed surprising degrees of shared biology among these syndromes. Incorporating these insights into our understanding of psychopathology encourages the possibility of

constructing a more bottom-up classification of psychiatric disorders. For example, the recent findings of the PGC-CDG indicate that certain constellations of disorders load on different correlated genomic factors. It is important to note, however, that the discovery of shared genetic or other biological risk factors does not by itself entail that clinical categories are collapsible. Psychiatric disorders, are defined not only by their genetic boundaries but also by their symptoms, course, age of onset, and a variety of other features(1). The complexity and multifactorial etiology of psychiatric disorders make it unlikely that specific genetic "signatures" will, by themselves, be found to define and distinguish neuropsychiatric syndromes. Nevertheless, genetic relationships can reasonably inform future efforts to build classifications that are more closely tied to etiology. In addition, as the power of genetic studies grows, we may be able to dissect the heterogeneity of disorders and discern subtypes that are more genetically homogeneous. Overall, then, the lumping and splitting of psychiatric disorders is likely to continue, but the hope is that it will be increasingly grounded in evidence-based biological insights.

Genetic data can also provide evidence for a more dimensional conceptualization of clinical syndromes. Genomic influences on psychiatric disorders appear to be largely continuous with subsyndromal symptoms and with dimensional components of disorder (e.g. neurocognition and social cognition), supporting a view of disorders as extremes of a distribution of quantitative traits. Again, however, incorporating these insights into a diagnostic system is not straightforward; for example, clinical decisions about when treatment is warranted may still require the demarcation of (somewhat arbitrary) thresholds. On the other hand, a greater emphasis on quantitative traits may justify their status as viable treatment targets as is the case in other areas of medicine (e,g, blood pressure and lipid levels in cardiovascular medicine).

Implications for genetic counseling and genomic medicine.

The pleiotropic nature of many genetic variations is also relevant for the implementation of genomic medicine. For example, a genomic work-up including chromosomal microarray analysis and exome sequencing has been recommended as standard of care for idiopathic ASD (104). As we have seen, however, many rare CNVs and mutations associated with ASD are also associated with other NDDs and with SCZ. The expanding database of pleiotropic associations may thus complicate genetic counseling for individuals and families carrying such genetic risk factors. Some have also argued for more routine genetic testing for large-effect CNVs in adult-onset disorders. For example, 22q11 deletions carry a substantial risk of SCZ (~25–30%) even though they are found in a small minority of cases (~1%) (105). Routine genetic testing for 22q11 CNVs has been advocated for patients with SCZ because it can have implications for reproductive decision-making, cascade screening, and because patients and families also find value in having an explanation for the illnesses they are suffering from.(106) However, individuals carrying 22q11 deletions are also at risk for a range of psychiatric disorders (including ASD, ADHD, ID, anxiety disorders, and mood disorders) as well as subsyndromal cognitive and psychiatric impairments (107, 108). Thus, genetic counseling for these individuals may need to include risk estimates and communication for a broad range of disorders.

Implications for precision psychiatry and therapeutic development

The emerging paradigm of precision medicine has been defined as “an approach to disease treatment and prevention that seeks to maximize effectiveness by taking into account individual variability in genes, environment, and lifestyle.” (109) Several fields of medicine have already had success in this effort, with particular emphasis in two directions. The first has been the use of genetic and genomic information to guide the development of novel drug targets for cancers, hyperlipidemia, and cystic fibrosis (110). Second, there has been growing interest in the use of PRS to stratify risk and treatment strategies based on individual genetic risk profiles, especially in cardiovascular disease and oncology (111). In both of these efforts--drug development and risk stratification--pleiotropy may have important implications for the application of precision medicine.

In the case of drug development, identifying pleiotropic variants may help define the spectrum of therapeutic and adverse drug effects. For example, Diogo and colleagues (112) conducted a PheWAS of 25 variants associated with common diseases and putative drug targets in prior GWAS and supported by additional biological evidence. Examining 1683 disease phenotypes, they identified phenotypic associations that either validated suspected drug targets or predicted likely adverse drug effects. The finding that specific genes or loci have pleiotropic effects on a range of psychiatric disorders could mean that treatments targeting the biology of such genes would have broad-spectrum therapeutic effects. At the same time, several loci have now been shown to have opposite directional pleiotropic effects —increasing the risk of one psychiatric disorder while lowering the risk of others (12, 37). In these instances, treatments based on modulating these gene products for one disorder could have unintended adverse consequences on another disorder.

With regard to PRS-based stratification, PheWAS have also identified pleiotropic associations that might impact risk prediction in healthcare systems For example, in a recent analysis by the PsycheMERGE consortium leveraging electronic health record-linked biobanks (63), a SCZ PRS was associated with SCZ as well as an array of psychiatric disorders and medical phenotypes. To the extent that PRS become relevant to risk prediction, such pleiotropic effects may create challenges for risk assessment and communication. At the same time, pleiotropy can be leveraged to improve the power and accuracy of polygenic risk prediction for a given disorder by incorporating SNP effects from traits genetically correlated with the target disorder (113).

Conclusions

Just as genetic studies have demonstrated that essentially all psychiatric disorders are heritable, research over the past decade has taught us that virtually all of these disorders have some degree of genetic overlap with other phenotypes. However, we are only beginning to understand the details of how these phenotypes are related, the molecular mechanisms of cross-phenotype correlations, and the implications of pleiotropy for precision and genomic medicine. Progress in this area will benefit from the increasing availability of large-scale genomic and phenotypic databases, advances in statistical methods, improved functional annotation of the genome, and the application of newer cellular model systems and genome

editing technologies that can be used to dissect the biological basis of pleiotropy. A host of questions are high on the research agenda. How do variants confer broad vs. more phenotype specific effects? Which cross-phenotype associations reflect biological, mediated, or spurious pleiotropy? How exactly can cross-disorder genomic relationships inform psychiatric nosology? The answers to these and other questions are certain to deepen our understanding of mental illness and improve the prospects for precision psychiatry.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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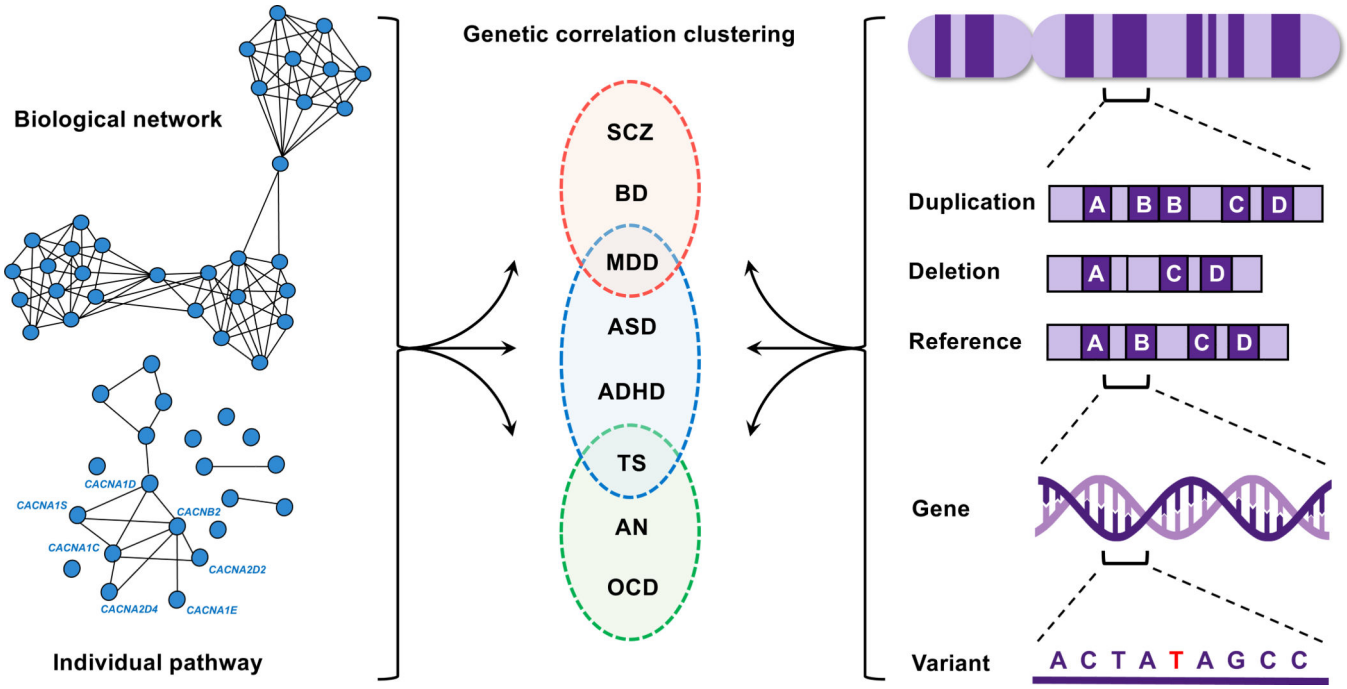

Figure 1. Widespread pleiotropy among psychiatric disorders at different levels of genomic analysis.

Center panel: Pleiotropy has been estimated at the genome-wide scale as genetic correlation among psychiatric disorders. (e.g., r_g = 0.68 between SCZ and BD). Decomposition of the genetic correlation matrix for eight psychiatric disorders revealed a three-factor structure, comprising compulsive/perfectionistic behaviors (AN, OCD, and TS), mood and psychotic disorders (SCZ, BIP, MD), and early-onset NDDs (TS, ASD, ADHD, and MDD). *Left panel:* Multiple genes can form biological pathways, and individual pathways can cluster into more complicated networks. Analyses leveraging these aggregated genetic effects have identified specific pathways (e.g., calcium channel signaling and glutamate receptor signaling) enriched for loci affecting several psychiatric conditions. *Right panel:* Individual pleiotropic loci include copy number variants (CNVs) implicated in a range of NDDs (e.g., 22q11 deletions). Finally, a growing catalog of specific genes and single nucleotide variants have shown pleiotropic effects in common and rare variant association studies (e.g., association of *CACNA1C* with BD, SCZ, and ASD).

SCZ: schizophrenia; BD: bipolar disorder; MDD: major depressive disorder; ASD: autism spectrum disorder; ADHD: attention-deficit/hyperactivity disorder; TS: Tourette syndrome; AN: anorexia nervosa; OCD: obsessive compulsive disorder

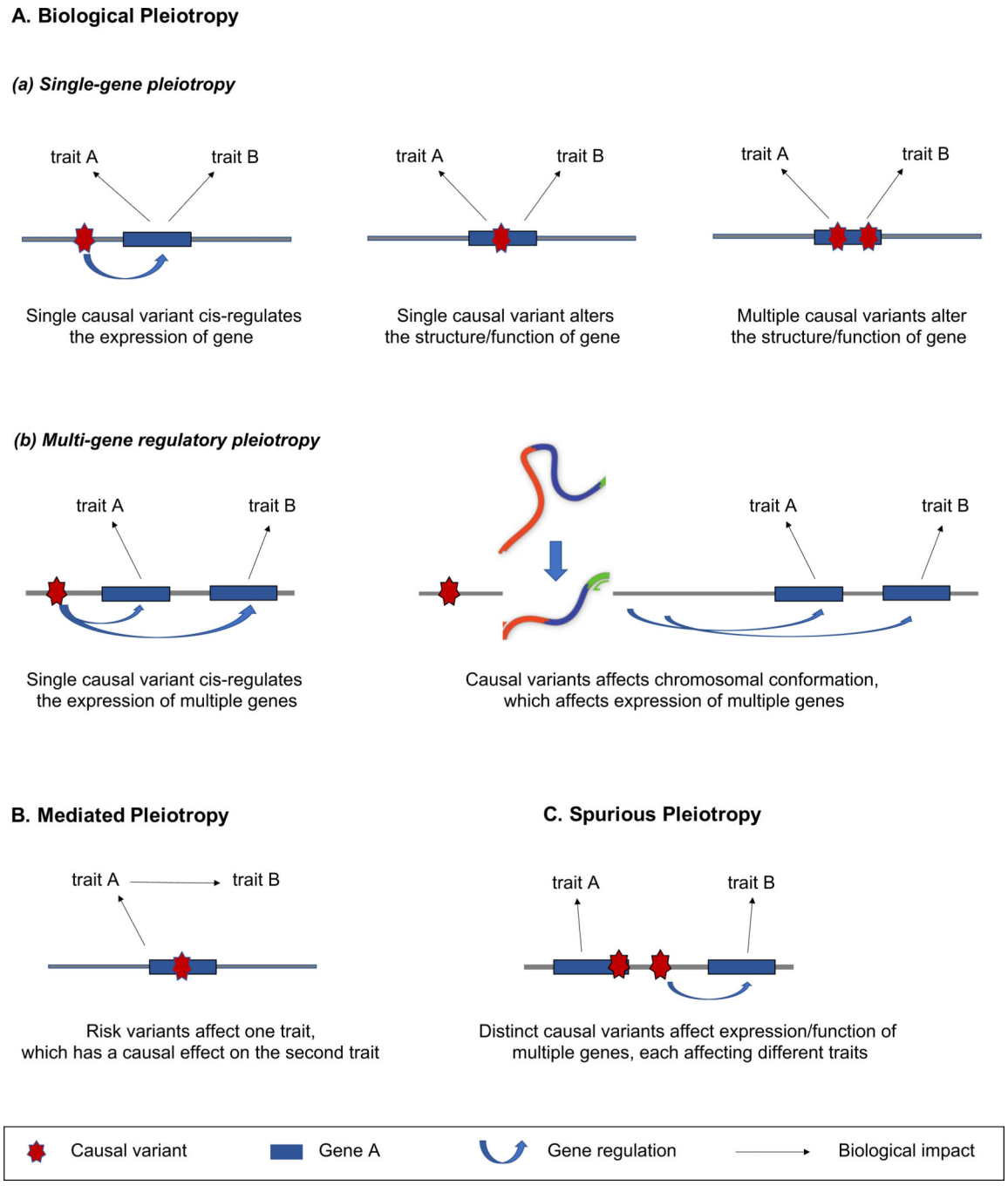

Figure 2. Pleiotropic mechanisms underlying cross-phenotype associations.

We define three classses of pleiotropic mechanisms: biological pleiotropy, mediated pleiotropy, and spurious pleiotropy. (A) Biological pleiotropy include (a) single-gene pleiotropy where causal variants, residing in coding or non-coding regions, affects the function/activity/expression of a single gene that influences more than one trait; and (b) multi-gene regulatory pleiotropy where non-coding causal variants affect the expression of multiple genes simultaneously, each of which may underlie distinct traits. (B) Mediated pleiotropy refers to the situation in which a causal variant influences one trait which in turn

causes phenotypic changes in a second trait. (C) Spurious pleiotropy describes situations when cross-trait associations occur due to various artefacts or limitations in study design.

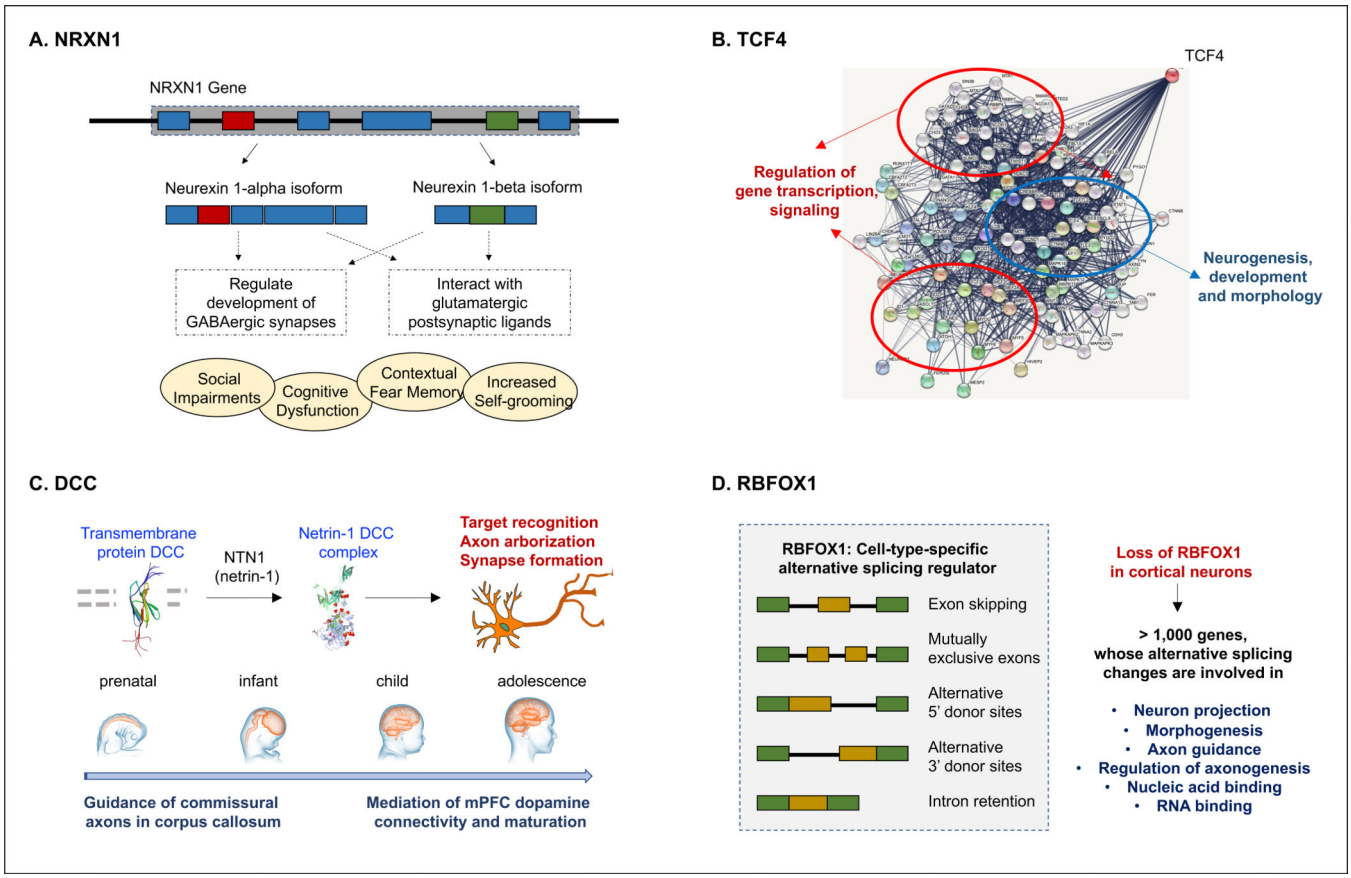

Figure 3. Examples of single-gene pleiotropy associated with psychiatric disorders.

A) Figure 3. Examples of single-gene pleiotropy associated with psychiatric disorders. A) Cell adhesion protein NRXN1 produces distinct protein isoforms, each may affect distinct brain circuits, behavioral systems, and psychiatric disorders. (B) Transcription factor TCF4 regulates more than 5% brain-expressed genes, many of which are key players in brain gene transcription, signaling, and neurodevelopment. (C) DCC is a master regulator that governs axon guidance during early neurodevelopment and mediation of mPFC dopamine connectivity during adolescence. (D) RBFOX1 encodes a cell-type-specific alternative splicing regulator that plays an essential role for neural development and excitability.