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Schizophrenia and Psychotic Spectrum Disorders

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Genetics of Schizophrenia 🔓

Introduction

Although it has been known for several decades that genetic factors play a major role in the etiology of schizophrenia, it has been only recently that the field has had the tools to probe the genetic architecture of the syndrome. As these tools have been applied to increasingly large samples of cases and controls to reveal DNA variations that occur more frequently among those with schizophrenia, one overriding conclusion has been reached: there is a humbling degree of complexity in the genetic foundations of schizophrenia. Risk for the disorder is now understood to be conferred by thousands of common single nucleotide variants, each of very small effect, as well as by thousands of larger mutations, each quite rare and of putatively larger effect (Purcell et al., 2014; Schizophrenia Working Group of the Psychiatric Genomics, 2014). This degree of genetic complexity is perhaps not surprising in view of the substantial heterogeneity in symptomology, course, treatment response, and other

clinical features of the syndrome (Cannon & Keller, 2006; Tan, Callicott, & Weinberger, 2008; Walton et al., 2013). Although many of the variants detected in genome-wide association studies implicate disruptions in certain biological pathways, including synaptic plasticity and immune function (Ohi et al., 2014; Schizophrenia Working Group of the Psychiatric Genomics, 2014), which are emphasized in current models of schizophrenia pathophysiology (Cannon, Kaprio, Lonnqvist, Huttunen, & Koskenvuo, 1998; Pogue-Geile & Yokley, 2010), only a tiny fraction of the risk-increasing variants have thus far been conclusively identified.

The goal of this chapter is to provide an overview of recent advances in the genetics of schizophrenia. We first consider the question of the magnitude of genetic involvement and the range of syndromes likely to share genetic influences in common with this syndrome. These issues are addressed from the perspective of genetic epidemiology, focusing primarily on studies of twins and nuclear families. We then turn to the molecular genetic basis of schizophrenia, highlighting findings of recent genome-wide association studies and discussing several challenges that the complexity of this syndrome raises for elucidating the full host of liability-conferring mutations. It is important to recognize that genes do not code for schizophrenia or any of its symptoms directly, but rather, indirectly, by impacting a number of biological signaling cascades and neural systems, which can be conceptualized as representing intermediate phenotypes or endophenotypes for schizophrenia (Cannon & Keller, 2006; Greenwood, Light, Swerdlow, Radant, & Braff, 2012; Tan et al., 2008; Toulopoulou et al., 2007). Apart from increasing sample sizes to facilitate mapping more variants associated with risk for schizophrenia, the next great challenge is revealing the links between risk-conferring mutations and disruptions in the brain systems underlying the expression of schizophrenia. These efforts will help to realize the promise of genetics to a personalized medicine approach in psychiatry: developing intervention targets based on knowledge of the mechanisms of abnormal gene action in particular cases.

Heritability: How "Genetic" Is Schizophrenia?

Heritability refers to the proportion of observed variance in a phenotype that is attributable to genetic influences. Schizophrenia's heritability has been estimated at about 80–85 percent in studies of monozygotic (MZ) and dizygotic (DZ) twins (Cannon et al., 1998; Cardno & Gottesman, 2000). MZ twin pairs share 100 percent of their genetic code, and DZ twin pairs on average share 50 percent—or approximately the same amount as any two siblings (Plomin, DeFries, & McClearn, 2008). In principle, the heritable component of a trait could be further subdivided into the component that is attributable to additive genetic influences and the component that is attributable to nonadditive or dominance genetic influences. Additive genetic variance emerges from the sum of allelic effects across multiple genes. Nonadditive genetic variance emerges in the presence of interactions between alleles, either

at the same locus (dominance effects) or different loci (epistatic effects). In twin modeling studies of schizophrenia, only additive genetic influences have been detected statistically. However, it is highly likely that twin studies to date have been too small to detect a measurable nonadditive component to heritability in the context of a robust additive component, leaving open the possibility that gene-gene interaction effects account for some share of the 80–85 percent heritability.

The remaining 15–20 percent of variance in schizophrenia is attributable to nongenetic factors. This nongenetic, or environmental, component could, in principle, be further subdivided into the part due to shared, or common, environmental influences and the part due to individual-specific environmental influences. Shared environmental influences include factors such as socioeconomic status and geographic location that hold for all members of a family (and equally so for members of twin pairs, whether MZ or DZ; Plomin, 2011). Twin modeling studies have not detected a measurable influence of shared family factors on risk for schizophrenia, though a small shared environmental component has been detected in some studies of nuclear families that include other types of kinships including half-siblings and adoptees (Lichtenstein et al., 2009). This means that the 15-20 percent of variance in schizophrenia due to non-genetic factors is primarily attributable to environmental effects specific to individuals. Such factors could include differential exposures to environmental pathogens (including drug abuse), head injuries, etc. Nevertheless, it is important to keep in mind that for the most part, environmental risk factors for schizophrenia are thought to be illness promoting only in the presence of predisposing genotypes (as in gene by environment interactions, denoted $g \times e$). The proportion of variance in schizophrenia attributable to $g \times e$ effects is not known. Such effects are currently grouped together (i.e., confounded) with the estimate for genetic effects in the case of $g \times e$ for shared environmental influences and with the estimate for nongenetic effects in the case of $g \times e$ for individual-specific environmental influences. Importantly, pre- and perinatal complications, such as maternal infection and fetal oxygen deprivation, which are among the most robust environmental risk factors for schizophrenia, probably contribute in a gene-dependent manner (Cannon et al., 2002; Mittal, Ellman, & Cannon, 2008). The higher heritability estimates for schizophrenia observed in twin studies (80–85 percent) than in some recent studies of nuclear families (65–70 percent) also suggests that environmental influences more likely be shared by co-twins in the same pregnancy (and in particular by MZ twins who are monochorionic) than by children from separate pregnancies, are major contributors to risk.

Genetic epidemiological methods have also been used to discern whether schizophrenia shares genetic risk factors in common with other psychiatric syndromes. Schizophrenia and bipolar disorder, while classically conceptualized as distinct syndromes according to Kraepelin, actually share a very high level of genetic overlap—on the order of 50–65

percent (Craddock, O'Donovan, & Owen, 2006; Lichtenstein et al., 2009; Purcell et al., 2009). Schizoaffective disorder has been found to also show high genetic correlations with both schizophrenia and bipolar disorder. Schizophrenia and bipolar disorder have both shared and syndrome-specific genetic inputs, but genetic contributions to schizoaffective disorder have been shown to entirely overlap with schizophrenia and bipolar disorder (Cardno, Rijsdijk, Sham, Murray, & McGuffin, 2014).

Molecular Genetics: What Genes Increase Risk for Schizophrenia?

Molecular genetic data—genetic information at the resolution of individual base pairs—has opened the field to investigate questions that could not be addressed by classic heritability studies. Heritability modeling can explain *how much* variance in incidence of schizophrenia is genetic, but not *what* genetic variants contribute. Molecular genetic studies are poised to uncover specific genetic variants that influence phenotypes. Any heritable phenotype in principle could be investigated, though molecular genetic techniques have mostly been leveraged to uncover variants increasing risk for syndromal or disease status. Exceptions to this include large-scale investigations of genetic influences on height (Yang et al., 2010) and IQ (Davies et al., 2011).

Some illnesses are genetically simple. Huntington's disease (HD) is caused by a mutation in a single gene, *huntingtin,* making it a Mendelian disorder. Mendelian disorders manifest in the presence of one copy of the disease-related variant. Assuming the individual lives through the period of risk for onset of disease, presence of the mutation is always associated with disease expression (100 percent sensitivity); absence is always associated with a lack of expression (100 percent specificity). Unlike HD, psychiatric illnesses are genetically complex. The current estimate of the number of independent single nucleotide polymorphisms (SNPs)— individual base-pair mutations—that contribute to schizophrenia is around 8,400 (Purcell et al., 2009; Schizophrenia Working Group of the Psychiatric Genomics, 2014). Each of these variants has a very small effect on risk for schizophrenia. Because of this, one would need many such variants to manifest schizophrenia as a phenotype. However, it is unknown how many such variants or in what configuration is required for schizophrenia. Furthermore, none of these variants may be specific to schizophrenia. Thus, ascertaining the genetic architecture of schizophrenia has introduced a variety of hurdles not initially anticipated by psychiatric geneticists.

Molecular genetic methods can classify and investigate genetic information in a variety of ways, including by type of mutation (e.g., deletion, duplication, translocation), frequency of mutation (i.e., common versus rare mutations), structural component (i.e., affecting promoter, exon, intron, etc.), gene, gene network (i.e., sets of genes that are functionally related), and chromosome, among many others (Heck et al., 2014; Hou & Zhao, 2013; Lee et al., 2012; Ohi et al., 2014; Purcell et al., 2014; Schork et al., 2013). These are some of the classifications psychiatric geneticists are currently using to organize the massive amount of genetic information available to discern how genetic variation might map onto neural function and behavior to promote or protect against disease.

Genetics of Schizophrenia

Recent work on the genetics of schizophrenia has revealed the importance of both common and rare genetic variants (Lee et al., 2012; Purcell et al., 2014; Stefansson et al., 2014; Szatkiewicz et al., 2014), enrichment of disease-promoting variants in the coding regions of genes (Schork et al., 2013), and specific involvement of a variety of genes associated with glutamate (Ayalew et al., 2012; Ohi et al., 2014) and GABA function (Wang, Liu, & Aragam, 2010), calcium and sodium channel expression (Cross-Disorder Group of the Psychiatric Genomics, 2013; Dickinson et al., 2014; Hertzberg, Katsel, Roussos, Haroutunian, & Domany, 2015; Ripke et al., 2013), immune function (Schizophrenia Working Group of the Psychiatric Genomics, 2014), and many other pathways hypothesized to be involved in the pathophysiology of schizophrenia.

Missing Heritability

Many of the first genetic disorders studied were Mendelian in nature, or much less genetically complex than mental illnesses such as schizophrenia (Diehl & Kendler, 1989). Huntington's disease is a good example, as is Alzheimer's disease, for which genotype at a locus in the gene APOE predicts 10–20 percent of the variance in prevalence (Bookheimer & Burggren, 2009). As recently as several decades ago, psychiatric geneticists were in pursuit of "the" schizophrenia gene or "schizogene," hoping that the genetic basis of schizophrenia would be analogous to that of Alzheimer's, which is also highly heritable, but non-Mendelian. Several mutations identified in pedigrees of families with high prevalence of schizophrenia seemed promising candidates for such a "schizogene," but ultimately each of these mutations had only modest effects in larger samples (e.g., DISC1; Sullivan, 2013). Such large mutations were present only in a small number of schizophrenia patients and had low specificity (i.e., also occurred in nonaffected family members), and different rare (but low penetrance) mutations were identified in different pedigrees (Stefansson et al., 2014; Szatkiewicz et al., 2014).

With the advent of genome sequencing came the opportunity to search more systematically for these disease-conferring variants. Genome-wide association studies (GWAS), the first of which investigated age-related macular degeneration (Klein et al., 2005), are designed to look for differences in allele frequencies as a function of a phenotype of interest, usually case status (i.e., patient versus nonpatient). These studies employ large samples of unrelated individuals, testing for an association between the phenotype and each of 500,000 to 2 million SNPs.

Originally, this type of study was expected to reveal all the genes that contributed to schizophrenia in relatively short order. However, even as sample sizes began growing from hundreds to thousands to tens of thousands of participants, often only a few genetic variants would meet the stringent significance thresholds required when conducting millions of statistical tests (Purcell et al., 2009; Ripke et al., 2013). Collectively, the identified pool of genome-wide significant variants accounted for less than 4 percent of the variance in case status—much less than the 65–80 percent heritability estimates from family and twin studies. This became known as the problem of "missing heritability."

Common Variant, Common Disease

There are billions of base pairs in the human genome. These are primarily composed of sequences held constant across all humans. A very small portion of this code varies between individuals and an even smaller percentage represents chunks of DNA or individual base pairs that vary commonly (i.e., the rare allele occurs in 1 percent or more of the population). These regions, and the polymorphisms in them, are "common variants" and are so-called because a substantial portion of a population (2 percent–50 percent, typically) carries a mutation at this genomic location. Common genetic variation is much easier to assess than rare variation, by virtue of its frequency in the population, but for the same reason typically has much smaller effects on phenotypes.

Several theories have emerged with possible explanations for the elusiveness of schizophrenia-related genes. One of the best developed is the common variant, common disease model (Reich & Lander, 2001). This model asserts that common genetic variation may contribute to psychopathology in addition to large, deleterious mutations, which are by virtue of their higher phenotypic impact, almost always rare at a population level. If thousands of common variants influence schizophrenia status, each contributing a very small increase in risk, this may explain the relatively low recurrence risk for schizophrenia (10 percent in offspring with one affected parent), while still accounting for the high heritability estimates (Cannon & Keller, 2006). As such, the CV/CD model posits that individual risk alleles for a psychiatric illness are distributed broadly in the general population. In this model, while any particular schizophrenia-related variant occurs at a high rate among unaffected individuals, those with and without the clinical phenotype differ in the aggregation of such risk variants, with affected individuals at the relative extreme of the underlying aggregated continuum of risk variants (Cannon & Keller, 2006).

Under this hypothesis—that common variants have small effect sizes, but together contribute substantial genetic risk for schizophrenia—two parallel lines of research emerged. The first was a push to increase sample size and thus increase statistical power to detect small effects. Over the last decade, the sample sizes in schizophrenia GWAS have grown from hundreds of individuals to close to 150,000 (Mah et al., 2006; Purcell et al., 2009; Ripke et al., 2013; Schizophrenia Working Group of the Psychiatric Genomics, 2014). The larger studies have had, as predicted, more success in identifying significant genetic variants associated with schizophrenia. As compared with early studies, which returned few significant hits, the largest study to date identified 108 genomic regions (Mah et al., 2006; Schizophrenia Working Group of the Psychiatric Genomics, 2014). However, even these 108 regions together only account for less than 4 percent of the variance in disease status.

Another line of research opted instead to lower the stringent p-value thresholds enforced by standard statistical rules. Purcell et al. (2009) suggested that many variants, even in extremely large samples, will still fail to cross the significance thresholds but will meet more nominal significance thresholds. He aggregated across thousands of nominally significant SNPs—most of which did not meet standard GWAS significance thresholds—to create a single, polygenic score approximating genetic risk for schizophrenia more broadly. These polygenic scores accounted for far more of the variance in disease status than any individual SNP and provided substantial evidence for the contribution of common variants to risk for schizophrenia (Purcell et al., 2009).

Other Genetic Risk Factors

Most common variants contributing to risk for schizophrenia have yet to be identified at genome-wide levels of significance (i.e., $p < 10^{-8}$). However, even if we had already mapped all the common risk variants, it is likely that much of the genetic variance would remain unexplained (Purcell et al., 2009). This portion, which has been estimated to be 30–50 percent of the variance in disease status, is due instead to rare mutations and epistatic effects (i.e., gene-gene interactions) (Schizophrenia Working Group of the Psychiatric Genomics, 2014).

The most frequently investigated form of rare mutation in schizophrenia is copy-number variation. Copy number variants (CNVs) are portions of the genome that are either duplicated or deleted. When these mutations occur in coding regions of the DNA, they can result in highly deleterious changes in function. One example is Down syndrome, which is caused by an additional copy of chromosome 21 and leads to profound intellectual disability. CNVs associated with schizophrenia are typically not as severe, though it is much harder to make general claims about the penetrance of rare variants, since very few individuals will have CNVs of the same length in the same genomic location and since most CNVs probably operate to increase risk against a non-zero background of common risk variants (Purcell et al., 2014; Stefansson et al., 2014; Szatkiewicz et al., 2014).

Additionally, risk-associated genes almost certainly do not increase risk strictly in an additive, linear way. Genes interact biologically—the exact patterns and systems of these interactions remain current avenues of inquiry. As such, their effects on phenotypic outcomes should be expected to interact statistically. Several examples of gene–gene interactions increasing risk for schizophrenia have been offered (e.g., Andreasen et al., 2012; Kang et al., 2011; Nicodemus et al., 2010), though this aspect of the field is still in its infancy.

Together, common variants, rare mutations, and epistatic effects between genes contribute to the substantial genetic component of schizophrenia. Environmental effects, along with gene–environment interactions also contribute to risk for schizophrenia. Although some risk-associating variants have been identified, the vast majority of the contributing genes remain to be uncovered. Advances in bioinformatics are expected to aid substantially in gene-finding efforts, and an improvement in phenotypic definition may also improve results.

Endophenotypes: How Do Genes Increase Risk for Schizophrenia?

Nearly all efforts to uncover the genetic factors relevant in schizophrenia, as well as all other psychiatric illnesses, have relied on case-control comparisons. Such studies by design can only detect genetic variants that tend to be present in cases and absent from controls. Thus, their success

relies on two assumptions: (1) that all cases will have similar genetic profiles, and (2) that individuals without schizophrenia will lack disease-related genetic variation. However, clinicians have long known that there is a great deal of heterogeneity within schizophrenia patients, which is almost certainly reflected at the gene level. Additionally, more recent work characterizing first-degree relatives of patients, as well as individuals with subsyndromal levels of psychotic symptoms, suggests genetic variants for schizophrenia are actually distributed among the general (nonaffected) population, as predicted by the CV/CD model (Cannon & Keller, 2006; Tan et al., 2008).

Gottesman and Shields (1972) suggested that schizophrenia, as defined at the syndromal level, may not be the optimal level at which to seek associations with genetics. Instead, they proposed an approach adapted from insect biology: the "endophenotype." In the insect literature, the term had been used to denote characteristics of grasshoppers that were not obvious and external (termed exophenotypes) but rather were microscopic or internal, requiring specialized measurement to discern. These endophenotypes were thought to explain behavioral variation in grasshoppers that could not be explained by exophenotypes. The authors used this term in the context of schizophrenia to refer to phenotypes associated with schizophrenia but that are not the disorder themselves, such as eye-movement abnormalities. These traits, more narrowly defined than the syndrome, were expected to involve fewer genes and, therefore, in a sense to be more proximal to the genetics of schizophrenia than the end state of the disorder itself. In other words, these traits were thought to be intermediate between the disease-promoting genetic variations and clinical syndrome (Gottesman & Gould, 2003).

Since the initial conceptualization of psychiatric endophenotypes, other terms are used to denote highly similar constructs, including intermediate phenotypes (Meyer-Lindenberg & Weinberger, 2006), biomarkers, subclinical traits, and vulnerability markers. Additionally, several components of the endophenotype concept have shifted since the term was initially applied in 1972. The notion that they cannot be directly observed but must be measured using specialized instruments is no longer central to their definition, as the field of endophenotypes has expanded to include self-reported, neuropsychological, and cognitive traits, along with neural and endocrinological markers.

The assumption that endophenotypes are less complex genetically than clinical syndromes has also not proven true. Some argue that endophenotypes are just as difficult to pin down genetically as disorders are, and the effect sizes of genetic loci on endophenotypes are no greater than on psychiatric disorders themselves (Flint & Munafò, 2007; Iacono, Vaidyanathan, Vrieze, & Malone, 2014). However, further refining of a particular endophenotype may aid in reducing complexity at the genetic level. Additionally, the endophenotype approach remains a fruitful way to identify elements of disorders that represent shared genetic variance with the disorder outcome. It also identifies traits that, if associated with the

disorder, do not only emerge symptomatically ("clinical phenotypes") but also are present earlier in life, so can be used as potential markers of liability prior to onset. These traits, in some cases, can also be more readily investigated in animal models.

Watershed Analogy of Endophenotypes

A useful way of conceptualizing the biological components of a complex phenotype such as schizophrenia is to imagine the clinical syndrome as the ultimate body of water in a watershed, the culmination of many distinct tributaries, streams, and rivers—endophenotypes at different levels of function—which flow into it (Cannon & Keller, 2006). In this analogy, thousands of genes individually contribute to hundreds of cell-signaling mechanisms (e.g., synaptic density in the prefrontal cortex), which underlie specific neural systems (e.g., working memory circuits) that, in turn, map onto primary clinical symptoms (e.g., cognitive deficits). Symptoms aggregate to form clinical syndromes like schizophrenia. Based on this framework, disruptions in any of these systems alone may not be enough to result in expression of the clinical syndrome, but the cumulative effects of many disruptions could. Thus, schizophrenia may be a collection of abnormal biological processes that impinge on an ultimate clinical phenotype. As such, examining each process individually may be more tractable than trying to connect thousands of genes to a complex set of symptoms, like schizophrenia, without any mechanisms in between (Cannon & Keller, 2006; Tan et al., 2008). Herein lies the most salient advantage of endophenotypes.

Endophenotypes include quantitative, heritable, phenotypic measures related to the disorder that varies dimensionally across the general population. If these phenotypes lie between the clinical syndrome and genes promoting the disease, they should be heritable (i.e., have some genetic basis) and be related to the development of the disease, rather than a secondary result of having the illness. Although mental disorders are currently defined categorically (an individual either does or does not have an illness), it is highly unlikely that the biological processes underlying these disorders are discrete (e.g., memory performance, synaptic density, receptor protein expression, etc., are all continuously varying phenomena). As such, endophenotypes should represent variation across the population. Additionally, there should be many endophenotypes for one complex disorder. Whereas early conceptualizations required that endophenotypes be specific to a single disorder, more recent findings demonstrate high rates of overlap in the genetic contribution to different disorders. This indicates instead that related disorders should share common endophenotypes (e.g., schizophrenia and bipolar disorder have substantial genetic and phenotypic overlap, so a subset of endophenotypes for one should be present in the other).

Many potential schizophrenia endophenotypes have been offered. Some of the first-identified endophenotypes included deficits in sustained attention deficit, working memory, and smooth-pursuit eye movement (Calkins, Curtis, Iacono, & Grove, 2004; Holzman, Proctor, & Hughes, 1973). One of the most reliable endophenotypes in schizophrenia—and most profound areas of cognitive impairment—is episodic memory (Greenwood et al., 2013; van Erp et al., 2008). Several other potential cognitive endophenotypes have been proposed, as well, including processing speed, set shifting, sequencing, verbal learning, spatial memory, general cognitive ability, and others (see Ohi et al., 2014; Snitz, MacDonald, & Carter, 2006 for a review).

A plethora of neural abnormalities, both gross and specific, have been reported in schizophrenia, including gray matter abnormalities in many brain regions (Mathew et al., 2014; Turner et al., 2012), reduced white matter integrity (Wheeler & Voineskos, 2014), and consistent findings of ventricular enlargement (Cannon et al., 1992). Specific aberrations in the prefrontal cortex, both structurally and functionally, have also been identified as endophenotypes, including structural abnormalities in polar and dorsolateral prefrontal regions (Cannon et al., 2002) and altered functional activity in the prefrontal cortex during performance of a working-memory and executive function tasks (Callicott et al., 2003; Owens et al., 2012).

Other endophenotypes have been proposed, including sensory processing and event related potential measures such as prepulse inhibition and P300 and P50 waves (Bramon et al., 2005; Bramon, Rabe-Hesketh, Sham, Murray, & Frangou, 2004), as well as traits such as coping style (Fortgang, Hultman, & Cannon, 2015) and impulsivity (Fortgang, Hultman, & Cannon). Locating endophenotypes will not only help us understand the nature of liability, but also will help with consistent detection and diagnosis of schizophrenia-spectrum disorders. Perhaps most importantly, it also represents the possibility of prevention of psychosis (Stone et al. 2005).

Liability-Threshold Model of Psychiatric Illness

If endophenotypes that underpin psychiatric illness vary dimensionally across the population, risk factors for those disorders should also be distributed in this manner. The relationship between aggregate risk and phenotypic severity (i.e., degree of a particular phenotype such as negative affect) represents the liability-threshold model (Cannon & Keller, 2006; Lee & Wray, 2013). Here, we would expect individuals who meet criteria for schizophrenia to fall on the extreme ends of the distributions of many related phenotypes, reflecting aggregation of risk at the tail end of the integrated distribution. However, individuals with varying degrees of risk, like relatives of patients who share genetic risk factors, or individuals with subclinical symptoms,

should fall higher on both risk and phenotypic severity relative to the population mean.

Consistent with this prediction, nonill siblings of patients with schizophrenia show moderate impairment—less than patients, but more than controls—on endophenotype measures (Tan et al., 2008). Siblings show similar phenotypic profiles neurocognitively, as well as neurologically, to patients with schizophrenia, though the impairments are attenuated in severity (e.g., Callicott et al., 2003; Iacono et al., 2014; van Scheltinga, Bakker, van Haren, Derks, Buizer-Voskamp, Boos, et al., 2013). Unaffected monozygotic twins also show more similarity to patients than dizygotic twins on endophenotype measures, further confirming the genetic component to the phenotypic overlap (van Erp et al., 2008). Finally, individuals that report subclinical symptoms or have related diagnoses (e.g., schizotypal personality disorder) show similar phenotypic and genetic profiles (Hazlett et al., 2015). These patterns support the view that genes confer risk for schizophrenia via these dimensional endophenotypes, thus giving advantage to testing those phenomena directly in searching for causal gene variants linked to schizophrenia.

Linking Genes to Endophenotypes to Schizophrenia

Many approaches have been used to link genes associated with schizophrenia to endophenotypes for schizophrenia. Consistent with the endophenotype approach, shared variance between schizophrenia and its neurocognitive endophenotypes is partially (up to 92 percent) accounted for by shared genetic variance (Toulopoulou et al., 2007). Similarly, candidate genes for schizophrenia identified through linkage studies, genome-wide association studies, and animal models of psychosis have been associated with many endophenotypes for schizophrenia, including measures of executive function, memory, prepulse inhibition, and others (Greenwood et al., 2012).

More widespread molecular genetic approaches have also been employed. Polygenic scores that approximate aggregate genetic risk for schizophrenia have been associated with symptoms of schizophrenia (Derks et al., 2012; Fanous et al., 2012), as well as other schizophrenia-related endophenotypes, including IQ (McIntosh et al., 2013; van Scheltinga, Bakker, van Haren, Derks, Buizer-Voskamp, Cahn, et al., 2013), structural MRI measures (van Scheltinga, Bakker, van Haren, Derks, Buizer-Voskamp, Boos, et al., 2013; Whalley et al., 2013), and working memory blood-oxygen-level-dependent (BOLD) activation (Walton et al., 2013). In these studies, higher genetic risk for schizophrenia is associated with lower performance or less robust neurophysiology. Finally, a few recent studies have identified sets of genes related to endophenotypes for schizophrenia, including general cognitive ability (Lencz et al., 2014), working memory (Heck et al., 2014), auditory verbal memory (Zheutlin et al.), and impulsivity (unpublished data), that also relate to schizophrenia case status. These represent the first attempts to use endophenotypes themselves to find schizophrenia-related genes, rather than using previously identified schizophrenia risk genes to predict variance on an endophenotype measure.

Future work testing for molecular evidence of shared etiology between putative endophenotypes and schizophrenia are poised to make substantial advances in our understanding of the genetics of the disorder. Comprehensive knowledge of those variants that predict a particular trait in the general population, as well as in patient samples, could offer insight into the genetic architecture of complex diseases like schizophrenia and help to identify specific genetic susceptibility for symptom clusters (e.g., gene pathways conferring risk for a particular cognitive impairment).

Conclusion

Although it has long been known that schizophrenia is highly genetic (Kallmann & Rypins, 1938), only recently have psychiatric geneticists started to identify genes that confer risk for illness, a process that has only just begun. Alongside work uncovering abnormalities at parallel levels of analysis including cellular signaling, neural circuit connectivity, and cognitive processes, gene-finding efforts in schizophrenia may help uncover the key neurobiological mechanisms disrupted in schizophrenia.

Heritability models using twin and family designs have quantified the genetic component of schizophrenia and discerned substantial genetic overlap with other psychiatric illnesses, along with many cognitive processes (Cannon et al., 1998; Craddock et al., 2006; Lichtenstein et al., 2009; Purcell et al., 2009; Toulopoulou et al., 2007). Molecular genetic techniques have uncovered the complexity of the genetic architecture of risk for schizophrenia, identifying over 100 impacted genes, with estimates of thousands more yet to be found (Purcell et al., 2009; Ripke et al., 2013; Schizophrenia Working Group of the Psychiatric Genomics, 2014). Of those, roughly half are likely to be common variants, each of very small effect, while the rest will be rare variants of larger impact. More advanced methods of parsing genetic information have identified systems of genes that are likely involved including those related to glutamate signaling, synaptic plasticity, and immune function, among other processes. Further advances in modeling complicated genetic effects will likely impact our understanding of schizophrenia genetics in the future.

Endophenotypes, which help bridge the biological gap between genes and behavior, will likely also advance understanding of the pathophysiology of schizophrenia. Burgeoning evidence of the dimensionality of clinical symptomology and those risk factors that underlie illness suggests that investigating biologically proximate aspects of disease (e.g., cognitive processes, abnormalities in brain maturation) will aid in uncovering disease-related mechanisms and risk factors. Already, many examples of the genetic overlap between risk for schizophrenia and related cognitive and neural measures have been reported (e.g., Callicott et al., 2003; Walton et al., 2013; Whalley et al., 2013). By ascertaining the mechanisms underlying impaired processes in schizophrenia, including the multitude of cognitive deficits, trouble with motivation, affect, and effort, as well as those systems related to the development of psychosis, it is the hope of the field that we can advance early detection and prevention, as well as develop new, more targeted treatments.

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