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Neuropsychiatric illnesses have a hereditary component.

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ABSTRACT
Neuropsychiatric diseases are multifaceted syndromes with poorly understood neurological underpinnings. We have made substantial progress in our understanding of the genetic architecture of these disorders and the genetic loci involved in recent years. This review article discusses previous attempts to identify susceptibility genes for neuropsychiatric disorders, as well as recent progress made through genome-wide association studies, copy number variation analyses, and exome sequencing, and how these findings can help neuroscientists better understand these disorders.

INTRODUCTION

Schizophrenia (SZ), bipolar disorder (BD), major depressive disorder (MDD), and attention deficit hyperactivity disorder (ADHD) are all frequent neuropsychiatric illnesses that can be quite severe. They are not characterised by apparent neuropathology, and the underlying molecular mechanisms are largely unknown. It is known, however, that the majority of neuropsychiatric illnesses are at least partly heritable, and it has long been hoped that the discovery of susceptibility genes could provide much-needed insights into their molecular aetiology, potentially leading to more successfulltreatments. In the last decade, technological advancements in genome analysis, along with enormous sample numbers, have resulted in considerable gains in our understanding of the genetic architecture of major neuropsychiatric illnesses and the genes that cause them. This article will discuss previous attempts to identify susceptibility genes for various diseases, recent breakthroughs in the area, and future directions, as well as how these findings can improve neuroscience research.

Neuropsychiatric diseases are heritable

For almost a century, it has been recognised that mental disease may run in families. Twin studies, which compare the rate of trait sharing between monozygotic, or identical, twins (who share all of their genetic variability) and dizygotic twins (who share some of their genetic variability), can be used to determine how much of this is due to genetic factors rather than familial environment (who share half of their genetic variability on average). Due to the assumption that environmental effects are largely the same for monozygotic and dizygotic twins, the difference in trait concordance between the two types of twins can be used to estimate the trait's 'heritability,' or the proportion of trait variance (or disease liability) that is due to genetic factors. Due to the assumption that environmental effects are largely the same for monozygotic and dizygotic twins, the difference in trait concordance between the two types of twins can be used to estimate the trait's 'heritability,' or the proportion of trait variance (or disease liability) that is due to genetic factors. Most neuropsychiatric illnesses have a significant hereditary component, according to twin studies: heritability for SZ, BD, and ADHD is between 75 and 80 percent.MDD, on the other hand, has a lower but still significant heritability of 40%. Various well-replicated findings provide a solid empirical framework for investigations aimed at identifying genetic variations that increase the risk of these illnesses.

Studies on genetic linkage

Genetic linkage was one of the first methods for discovering genetic risk loci for psychiatric diseases. Linkage studies are usually done in big families with multiple members who are sick, and they are based on the assumption that genetic markers within a few million nucleotide bases of a disease allele are more likely to be inherited with it. Within a family, co-segregation of the disease with a certain marker allele implicates the chromosomal region where the marker is placed in the condition. Linkage studies are best suited for Mendelian diseases with one or a few genetic loci exerting a strong effect on risk, with considerable

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success in locating the Huntington's disease gene and those producing Alzheimer's disease early onset variants. However, despite decades of effort, linkage studies have failed to reliably identify risk loci for prevalent neuropsychiatric illnesses, showing that the genetic contribution to these disorders does not follow simple monogenic or oligogenic models.

Approaches to cytogenetics that have been around for a long time

Searching for large chromosomal abnormalities in affected people was another early method for investigating genetic origins of neuropsychiatric illnesses. Approximately 7% of autism sufferers have cytogenetic abnormalities. However, neuropsychiatric illnesses with a less evident developmental origin are infrequent. The most important finding in this regard is a balanced t(1;11)(q42; q14) translocation affecting the DISC1 gene in a large Scottish family, which co-segregates with numerous psychiatric symptoms (including SZ, BD, and MDD).Despite the fact that the discovery of DISC1 sparked a flood of neuroscience research, there is no solid evidence that DISC1 is a risk gene for neuropsychiatric disorder outside of the original family.

Studies on candidate genes and their associations

The third main way to risk gene discovery is by association; the goal here is to find susceptibility variants that aren't sufficient to cause the condition on their own, and so avoid detection by linkage. The 'case–control' study, in which the frequency of individual DNA variations is compared between people with and without the ailment, is the most prevalent design. Ignoring technical errors and poor study design, significant case–control differences in allele or genotype distributions suggest either direct effects of the associated allele on susceptibility to the disorder (e.g. by changing amino acid sequence or gene expression) or a population-wide correlation between such a risk allele and the assayed variant (a phenomenon known as 'linkage disequilibrium'). Due to technological limitations, early research had to confine themselves to a small number of variants within candidate genes that were chosen based on their known biological functions (e.g. genes involved in dopamine function as candidates for SZ). Although there are numerous reports of candidate gene association in the literature, none of them are sufficiently reproducible to be deemed reliable. In retrospect, the tiny effects on susceptibility that are now known to characterise frequent risk alleles, the low probability that any picked candidate allele is a true risk allele, and limited sample sizes can all be blamed for the lack of consistency.

Genome-wide association studies (GWAS)

In the early 2000s, the introduction of genotyping arrays made it possible to genotype 100,000s of DNA variants, often known as single-nucleotide polymorphisms (SNPs), in a significant number of people at a low cost. At the same time, better understanding of linkage disequilibrium patterns in the human genome allowed scientists to infer (or'impute') genotypes at millions of other SNPs, capturing the majority of common DNA variation (i.e. variants with population allele frequencies > 5%) in each person's genome.As a result, genome-wide association studies (GWAS) of neuropsychiatric illnesses became conceivable. The large sample size and coverage effectively address the main limitations of candidate gene approaches (bias towards existing hypotheses, low probability of selecting a true risk allele from the millions present in the genome, low statistical power from small sample sizes) and thus allow comprehensive and unbiased genome assessments that may provide new insights into biology.It is now apparent that frequent DNA variants in the general population each confer only a minor increase in the risk of neuropsychiatric diseases (odds ratios of related variants typically 1.1). To identify them at a significance threshold that controls for testing millions of DNA variations (based on 1 million independent tests in a thorough GWAS, the generally recognised threshold for 'genome-wide significance' is P 5 108), very high sample sizes are necessary. GWAS, on the other hand, have shown to be an extremely useful technique for discovering these common genetic risk factors for complex diseases as sample sizes have expanded.International collaborative efforts, particularly the Psychiatric Genomics Consortium, have accelerated progress in psychiatric genetics (PGC). SZ has had the most success to date, with a landmark study encompassing 36,989 patients and 113,075 controls revealing 108 distinct risk loci with genome-wide relevance.Previous candidate genes involved in glutamate (GRIN2A, GRM3, GRIA1, and SRR) and dopamine (DRD2) function, as well as calcium channel signalling (CACNA1 C, CACNB2, and CACNA1 L) and other unique biological processes, have all been implicated with the aetiology of SZ. A meta-analysis encompassing an additional 11,260 SZ cases and 24,542 controls has discovered 50 new SZ risk loci with genome-

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wide significance. While GWAS can reveal genetic risk loci, additional functional studies are usually needed to confidently identify the susceptibility genes that reside within them. The great majority of frequent risk mutations for neuropsychiatric diseases appear to modify regulatory areas of the genome (e.g. binding sites for transcription factors) that are hundreds of kilobases (kb) away from the genes they regulate. Furthermore, linkage disequilibrium makes distinguishing between functional risk variations and variants that are correlated with them challenging, resulting in association signals that frequently span many genes.Furthermore, linkage disequilibrium makes distinguishing between functional risk variations and variants that are correlated with them challenging, resulting in association signals that frequently span many genes. The association between SZ and a broad region at the major histocompatibility complex (MHC) locus on chromosome 6 has been shown to partly reflect structural variation at the complement component 4 (C4) gene locus, resulting in increased C4A expression; for example, functional interrogation of GWAS risk loci has already yielded important insights; for example, the association between SZ and a broad region at the MHC locus on chromosome 6 has been shown to partly reflect. Using chromosome conformation capture technologies, long-range interactions between regulatory elements and their target gene(s) can also be explored. (Because regulatory elements are often cell-specific, a lot of study has gone into mapping and characterising them in diverse tissues, cell types, and developmental stages, including the human brain.These tools may be used to prioritise functional variations that underpin GWAS signals as well as assess which cell types they are most likely to be active in. When studying the biological activities of susceptibility genes for neuropsychiatric illnesses, neuroscientists should use these findings in order to focus on the relevant gene transcripts, brain areas, cell types, and developmental stages.

Pleiotropy and polygenic risk scores

Since the beginning of GWAS, it has been clear that common risk loci for psychiatric disorders that have been identified at genome-wide levels of significance are only the 'tip of the iceberg,' with thousands of other variants conferring weak effects on risk falling short of this stringent significance threshold. The International Schizophrenia Consortium (2009) provided the first evidence for the highly polygenic nature of psychiatric disorders, in which the summation into a 'polygenic risk score' of thousands of DNA variants exhibiting at least minimal association with SZ was found to account for a significant proportion of the risk in an independent SZ sample.The amount of liability captured by polygenic risk scores is a function of the GWAS discovery sample size and the liability to disorders captured by SNPs on genotyping arrays, which is typically between 30% and 50% of the heritability. The approach provides the first quantitative biomarker of genetic liability that can be applied to any individual independent of psychiatric status, despite the fact that the information content and predictive power of polygenic risk scores are not diagnostically useful. The availability of such a biomarker has a variety of potential applications in neuroscience, including testing the validity of intermediate cognitive, behavioural, and neuroanatomical phenotypes for these conditions. However, the most widely used application of polygenic risk scores to far has been in determining the genetic link between neuropsychiatric illnesses.

Polygenic risk for SZ was found to be related with risk for BD, but not non-psychiatric diseases, in the first study (International Schizophrenia Consortium, 2009), indicating a genetic overlap between the two disorders. Following research employing risk scores and other polygenic approaches have clearly proven significant genetic sharing across a wide range of psychiatric diseases.SZ, for example, shares a shared variation contribution with ADHD, MDD, autistic spectrum disorder, obsessive-compulsive disorder, and anorexia nervosa, in addition to BD. Common genetic variation has provided clear evidence for pleiotropic effects in psychiatry, while uncommon genetic variation has shown similar results. As we'll see later, uncommon mutations that increase the chance of SZ also increase the risk of other neurodevelopmental diseases, and cognitive function is often impacted even in people who don't have a clinical condition (Kendall et al., 2017; Stefansson et al., 2014). Pleiotropy should be considered by neuroscientists when evaluating human endophenotype investigations and modelling mutations in animal and cellular systems (O'Donovan and Owen, 2016).

Variants in copy number

The genetic architecture of neuropsychiatric illnesses now contains uncommon variants that could have a substantially bigger impact on risk, in addition to common variants with a moderate effect. Since the 1990s, it has been

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recognised that patients with velocardiofacial (or DiGeorge) syndrome, a disorder caused by significant deletions on chromosome 22q11.2, had a high risk of SZ (Murphy et al., 1999). These deletions, which affect about one in every 4000 newborns and often affect at least 40 genes, are now recognised as the disorder's earliest copy number variants (CNVs). CNVs, which are commonly characterised as deletions, duplications, or insertions bigger than 1 kb, are significantly more common in the human genome than previously thought, thanks to the discovery of genotyping arrays. Rare (population frequencies 1%) or de novo CNVs occur at a rate more than double that of controls in patients with autism and SZ, according to genome-wide CNV studies.

Exome sequencing

The last ten years have seen significant advancements in sequencing technology, allowing for faster and more cost-effective searches for uncommon DNA variants (such as point mutations) that are not detected by existing SNP genotyping arrays. To present, research on mental populations has mostly concentrated on sequencing the exome, which is the 1% of the genome that encodes proteins (i.e. coding exons). This strategy is expected to provide three benefits: Exonic mutations, for starters, point to specific genes (cf. GWAS). Second, the effects of premature stop codon mutations on gene function may be predicted to a significant extent. Third, specific coding alterations that are rare or de novo, like rare CNVs, can have a big impact on risk. Rare coding mutations are particularly appealing to neuroscientists looking to produce new ideas because of these advantages.Each person has one germline exonic de novo mutation on average. People with intellectual disabilities/developmental delays have a higher de novo rate than those with autism spectrum disorder. Exome sequencing studies have revealed an increased abundance of very raredisruptive coding mutations in SZ, which are spread across many genes and evidence that such variants contribute to BD. The rarity of individual mutations, as well as their wide dispersion, has necessitated the use of very large sample numbers to identify specific genes, similar to pathogenic CNVs. This approach has yielded for autism spectrum disorder (De Rubeis et al., 2014; Sanders et al., 2015), and it is now yielding for SZ, where a recent analysis of exome sequencing from 4264 SZ cases, 9343 controls, and 1077 SZ parent–proband trios revealed a genome-wide significant association between the disorder and rare loss-of-function variants in the SETD1A gene, which encodes a histone methyltransfer. As we progress toward whole genome sequencing in neuropsychiatric illnesses, higher sample sizes and a better understanding of non-coding areas of the genome will be necessary.

Pathway analyses

Given the difficulty of identifying individual genes in neuropsychiatric illnesses, testing the extent to which identified risk variants converge on established biological processes is a complementary and possibly extremely revealing method. CNVs linked to SZ, for example, have been found to be enriched for genes encoding components of the NMDA and GABAA receptor complexes. Pathway analyses of minor de novo mutations detected in patients by exome sequencing and of common variation revealed using GWAS, which show specific enrichment at gene loci producing post-synaptic proteins, indicate the relevance of synaptic processes in SZ. Genes involved in histone methylation pathways were found to be enriched for genetic correlations with all three disorders in a pathway analysis of GWAS data for SZ, BD, and MDD.Genes involved in histone methylation pathways were found to be enriched for genetic correlations with all three diseases, especially BD, in a pathway analysis of GWAS data for SZ, BD, and MDD. A better understanding of the genes influenced by genetic risk variation, as well as their biological functions, will certainly enhance future pathway analysis.

CONCLUSION

In recent years, significant progress has been made in our understanding of the genetics of prevalent neuropsychiatric illnesses for which neuronal leads have proven elusive. It is now known that these illnesses are highly polygenic, involving thousands of common and rare genetic variants that, when combined with environmental risk factors, increase a person’s odds of getting them. Many of these risk variations appear to be shared among neuropsychiatric diseases as well.Both common and unusual genetic risk loci for neuropsychiatric illnesses have been found with high confidence as sample sizes have expanded. GWAS-identified associations between neuropsychiatric illnesses and common variations appear to be mostly due to regulatory genetic variation, which may operate on specific gene transcripts, in certain cell types, and at various

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developmental stages. Rare and de novo CNVs and exonic mutations that might result in hemizygous loss of gene function may impart higher impacts on risk for specific neuropsychiatric disorders, particularly those with evident neurodevelopmental aspects. Many additional genetic risk loci for neuropsychiatric illnesses will be discovered in the coming years, thanks to larger sample numbers and extensive genotyping by whole genome sequencing.Translating these findings into a better understanding of the molecular, cellular, and neurophysiological mechanisms that underpin neuropsychiatric disorders would necessitate the collaboration of scientists from several fields of neuroscience.

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