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Review

Specific and common genes implicated across major mental disorders: A review of meta-analysis studies☆

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ABSTRACT

Major efforts have been directed at family-based association and case–control studies to identify the involvement of candidate genes in the major disorders of mental health. What remains unknown is whether candidate genes are associated with multiple disorders via pleiotropic mechanisms, and/or if other genes are specific to susceptibility for individual disorders. Here we undertook a review of genes that have been identified in prior meta-analyses examining specific genes and specific mental disorders that have core disruptions to emotional and cognitive function and contribute most to burden of illness—major depressive disorder (MDD), anxiety disorders (AD, including panic disorder and obsessive compulsive disorder), schizophrenia (SZ) and bipolar disorder (BD) and attention deficit hyperactivity disorder (ADHD). A literature review was conducted up to end-March 2013 which included a total of 1519 meta-analyses across 157 studies reporting multiple genes implicated in one or more of the five disorders studied. A total of 134 genes (206 variants) were identified as significantly associated risk variants for MDD, AD, ADHD, SZ or BD. Null genetic effects were also reported for 195 genes (426 variants). 13 genetic variants were shared in common between two or more disorders (*APOE e4*, *ACE Ins/Del*, *BDNF Val66Met*, *COMT Val158Met*, *DAOA G72/G30 rs3918342*, *DAT1 40-bp*, *DRD4 48-bp*, *SLC6A4 5-HTTLPR*, *HTR1A C1019G*, *MTHR C677T*, *MTHR A1298C*, *SLC6A4 VNTR and TPH1 218A/C*) demonstrating evidence for pleiotrophy. Another 12 meta-analyses of GWAS studies of the same disorders were identified, with no overlap in genetic variants reported. This review highlights the progress that is being made in identifying shared and unique genetic mechanisms that contribute to the risk of developing several major psychiatric disorders, and identifies further steps for progress.

1. Introduction

As part of a concerted effort to understand the genetic contributions to major mental illness, many genetic association studies have been undertaken in the pursuit of specific genes implicated as risk factors in one or more mental illnesses. Neuropsychiatric disorders account for up to a quarter of all disability-adjusted life-years (Prince et al., 2007). Serious mental disorders that contribute the most to this global burden of disease affect both adults and children and include unipolar and bipolar affective disorders (Prince et al., 2007), schizophrenia (Prince et al., 2007), anxiety disorders such as panic disorder (Gore et al., 2011) and attention-deficit hyperactivity disorders (ADHD) (Belfer, 2008; Polanczyk et al., 2007).

The heritability (or proportion of variance due to genetic variation) of these serious mental disorders is significant, with lower limits of ~40% reported for major depressive and anxiety disorders, and increasing anywhere up to 60–90% for ADHD, schizophrenia or bipolar disorder (Burmeister et al., 2008). This high heritability led to the view that only a relatively small number of genes may underlie the genetic risk for these disorders, and these were typically sought via candidate gene studies; that is, genetic variants in genes

☆ *Note.* This work was mostly completed at the Brain Dynamics Centre at the University of Sydney. Justine Gatt has since moved to Neuroscience Research Australia with a dual position in the School of Psychology, UNSW.

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predicted to have a potential role in the illness and examined via a case–control or family-based association study. Many genetic variants have been identified and examined; some with consistency, but more often than not, with only small effects that fail replication (Chanock et al., 2007; Sullivan, 2007). This is unlike other medical conditions such as Parkinson's disease for which, despite its lower heritability, clear monogenic (single gene) causal risk factors have been clearly established (Burmeister et al., 2008). Therefore, there is a need to provide a synthesis of this data to guide future research activity.

What remains unknown is whether common genes via pleiotropic mechanisms are associated with psychiatric disorders that share similar symptomatology such as unipolar and bipolar affective disorders, or that are more prevalent during adulthood or childhood, or whether other genes are specific to susceptibility for individual disorders. Serious mental disorders are currently diagnosed and differentiated based on clinical symptoms, yet the genetic aetiology of these disorders is a topic of active debate. Genetic association and genome-wide association studies (GWAS) (Huang et al., 2010; Liu et al., 2011; Purcell et al., 2009; Smoller et al., 2013) suggest there is some degree of genetic overlap among specific disorders such as affective disorders and psychosis, but also specific genetic diversity. Genetic pleiotrophy, or the impact of one gene on multiple phenotypes, has been reported to account for 17% of the genes or 5% of the single nucleotide polymorphisms (SNPs) associated with complex traits (Serretti and Fabbri, 2013; Sivakumaran et al., 2011). Identification of such genes between disorders can help identify shared molecular pathways between the disorders.

Here, we provide a summary of all meta-analyses conducted to date of genetic association studies of the serious mental disorders contributing a large proportion of the burden of illness in adults and children, unipolar (MDD) and bipolar depression (BD), schizophrenia (SZ), anxiety disorder (AD) and attention-deficit hyperactivity disorder (ADHD). We have chosen this approach, a review of meta-analyses, as it provides an aggregate view of the strength of genetic findings to date, with analyses based on multiple original data sets, and the opportunity to compare information from older studies and combine them with newer, larger studies. Our review includes a focus on SNPs so that we can develop an understanding of the underlying molecular pathways (such as serotonergic, dopaminergic and glutamatergic pathways) in contributing to common and unique clinical symptoms. This is because SNPs are defined by specific changes to the nucleotide base and can be localized to a specific region within a single gene. We have not targeted other elements of genetic modulation such as CNVs or linkage variation because the information provided by these measures is often representative of more pervasive changes across multiple regions or genes and to date, there have been very few studies. For instance, copy-number variations (CNVs) involve changes to larger regions of the genome, ranging from 1000 nucleotide bases to several megabases in size, and linkage studies identify chromosomal regions that can span multiple genes cosegregating within a family. We did also however target meta-analyses of GWAS studies of these same disorders as a comparison. To date the focus has been on increasing sample size and power, and thus there are fewer independent GWAS studies that have been the subject of meta-analysis. The p value of GWAS is also usually very conservative due to multiple testing, which could potentially inflate the false-negative rate of variants with smaller effects due to reduced power.

2. Methods

We searched MEDLINE for all publications available up to end-March 2013 examining meta-analyses of genotypes in the five serious mental disorders. These meta-analyses determined significance at the $p < .05$ threshold. Our search terms were *meta-analysis*, *association study*, *gene*, *depression*, *depressive disorder*, *major depression*, *anxiety disorder*, *panic disorder*, *generalized anxiety disorder*, *phobic disorder*, *posttraumatic stress disorder*, *obsessive-compulsive disorder*, *attention deficit disorder with hyperactivity*, *schizophrenia*, *bipolar disorder*, *bipolar affective disorder*, *manic-depressive disorder*, *psychosis*, *psychotic disorders* or *manic depression*. A supplementary search for additional publications was performed using PUBMED using the same search terms with the limit of 'meta-analysis'. Meta-analytical studies included in our review were based on the following criteria: (a) published in a peer-reviewed journal in English; (b) reported on effects at the allelic or genotypic level; (c) provided unique estimates for unipolar major depression, anxiety disorder, ADHD, schizophrenia or bipolar disorder; (d) based on case–control or family-based studies; (e) based on two or more studies; (f) reported the risk allele and gene name; and (g) published before end-March 2013. Meta-analyses of GWAS data were also reviewed separately. We identified 12 GWAS meta-analyses studies to date, including 4 studies in MDD (Lee et al., 2012; Lewis et al., 2010; Shyn et al., 2011; Wray et al., 2012), 3 studies in SZ (Jia et al., 2012; Shi et al., 2009; Wang et al., 2012), 2 in ADHD (Ebejer et al., 2013; Neale et al., 2010), 1 in BD (Goes et al., 2012) and 1 in AD (Otowa et al., 2012). We also identified one other study that conducted a meta-analysis across GWAS data of SZ and BD patients combined (Wang et al., 2010).

3. Results

3.1. Distribution of genetic variants

A total of 157 studies or 1519 meta-analyses of multiple genes and/or multiple disorders were included in this review; of these, 378 meta-analyses confirmed significant effects for 134 genes (206 variants) across the range of disorders. Supplementary Table 1 summarizes genetic variants that were included in meta-analyses and contributed a significant effect ($p < .05$) to these meta-analyses. Information on sample ethnicity is provided as some studies reported multiple meta-analyses (sometimes with different results) when stratified by ethnic origin. As some meta-analyses included the same studies reported in other meta-analyses, this table includes a column called 'independent study' to reflect the largest and most recent independent meta-analysis study to date (indicated by '+'), with the other meta-analyses that include overlapping studies indicated by a dash (–) for the same genetic variant comparison, in the same ethnic group. The genetic variants that did not survive significance ($p > .05$) in the meta-analyses are reported in Supplementary Table 2. Null effects were found for 75% of total studies (1141 meta-analyses). Five percent of these null effects conflicted with significant effects reported in Supplementary Table 1 (53 out of 378 confirmed meta-analyses reported in Supplementary Table 1). Supplementary Table 3 provides a direct comparison of the significant findings with the studies showing a conflicting null result, and possible reasons for these discrepancies.

Of the total 1519 meta-analyses reviewed, the majority (63%, $n = 966$) focused on identifying genes in schizophrenia, of which 199 meta-analyses confirmed a significant gene effect for 50 genes (97 variants). The next disorder of focus was bipolar disorder at 17% ($n = 259$ meta-analyses) with 98 meta-analyses confirming 46 genes (65 variants); then MDD at 12% ($n = 177$ meta-analyses) with 43 meta-analyses confirming 27 genes (27 variants); then ADHD at 5% ($n = 81$) with 25 meta-analyses confirming 8 genes (11 variants); and finally anxiety disorders at 3% ($n = 36$) with 13 meta-analyses confirming 3 genes (6 variants).