



A decade in psychiatric GWAS research

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Abstract

After more than 10 years of accumulated efforts, genome-wide association studies (GWAS) have led to many findings, most of which have been deposited into the GWAS Catalog. Between GWAS's inception and March 2017, the GWAS Catalog has collected 2429 studies, 1818 phenotypes, and 28,462 associated SNPs. We reclassified the psychology-related phenotypes into 217 reclassified phenotypes, which accounted for 514 studies and 7052 SNPs. In total, 1223 of the SNPs reached genome-wide significance. Of these, 147 were replicated for the same psychological trait in different studies. Another 305 SNPs were replicated within one original study. The SNPs rs2075650 and rs4420638 were linked to the most replications within a single reclassified phenotype or very similar reclassified phenotypes; both were associated with Alzheimer's disease (AD). Schizophrenia was associated with 74 within-phenotype SNPs reported in independent studies. Alzheimer's disease and schizophrenia were both linked to some physical phenotypes, including cholesterol and body mass index, through common GWAS signals. Alzheimer's disease also shared risk SNPs with age-related phenotypes such as age-related macular degeneration and longevity. Smoking-related SNPs were linked to lung cancer and respiratory function. Alcohol-related SNPs were associated with cardiovascular and digestive system phenotypes and disorders. Two separate studies also identified a shared risk SNP for bipolar disorder and educational attainment. This review revealed a list of reproducible SNPs worthy of future functional investigation. Additionally, by identifying SNPs associated with multiple phenotypes, we illustrated the importance of studying the relationships among phenotypes to resolve the nature of their causal links. The insights within this review will hopefully pave the way for future evidence-based genetic studies.

Introduction

The GWAS Catalog is a comprehensive database that archives genome-wide association studies (GWAS) investigating associations between single-nucleotide polymorphisms (SNPs) and a variety of phenotypes, ranging from psychiatric disorders, to physical disorders, to other medical, physical, and psychological traits. GWAS feature data-driven, fairly objective designs and often use relatively

large sample sizes, making them better-powered and less biased than most candidate-gene studies.

Motivation behind this review

The year 2017 marks the 10-year anniversary of psychiatric GWAS. While the first GWAS recorded by the GWAS Catalog was published in 2005 on the topic of age-related macular degeneration, a GWAS in the field of psychiatry was not published until a WTCCC-funded study in 2007. This study examined seven diseases, including bipolar disorder [1].

Since then, genotyping costs have dropped dramatically and GWAS have become an essential step on the path towards uncovering genetic factors of phenotypes. Research concerning psychiatric disorders and relevant traits have accounted for a significant share of the accumulated GWAS findings and will be the focus of this review. Such findings are often selectively and mistakenly interpreted by the media, the public, clinicians, patients, and even some investigators in related fields. We feel the obligation to

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provide a scholastic, holistic, and stringent summary of the GWAS data. In doing this, we have identified SNPs that have been repeatedly reported in association with the same disorder and that should thus bear better confidence. We also hope to uncover hidden connections between disorders or traits by highlighting genomic regions that could be associated with multiple conditions, something that can only be done by collecting results from many different studies and reviewing them together.

Candidate genes have been studied for several decades in psychiatry. They have mostly included small sample sizes and have often been underpowered. Some frequently studied genes have been included in meta-analyses combining a large collection of studies. However, such meta-analyses have thus far reported disappointing results. Candidate genes have been found to be non-reproducible or insignificant upon further scrutiny, as in the case of two meta-analyses on bipolar disorder and schizophrenia candidate genes [2, 3]. This article, therefore, focuses on GWAS signals. That being said, as GWAS produce more findings, it will likely be increasingly useful to compare results of candidate genes with GWAS signals. Furthermore, there will be a greater quantity of robust data from which to make more informed decisions about good candidate genes.

It should be noted that, as writing this summary requires some arbitrary decisions regarding inclusion criteria for disorders and traits and grouping of phenotypes, the reported results are somewhat swayed by bias. Its parameters should thus be refined and improved in future reviews.

Data

The data in this summary includes all studies recorded by the GWAS Catalog (<https://www.ebi.ac.uk/gwas/>) as of the date of download (March 30, 2017); the most recent study in the data set was published on October 31st, 2016. The data set includes literature sources, phenotype information, p -values, and identified SNPs, among many other pieces of data.

GWAS utilize stringent significance thresholds as a result of the multiple testing correction needed to account for millions of SNPs on the human genome. While the GWAS Catalog collected SNPs associated with p -values as large as 1×10^{-5} (with the exception of one result, which was linked to 2×10^{-5}), the commonly used cut-off for genome-wide significance is typically $p = 2 \times 10^{-8}$ or 5×10^{-8} .

The GWAS Catalog, as of the date of download, included a total of 2429 studies, 1818 phenotypes, and 28,462 SNPs. In order to redirect the focus of the analysis to psychiatry, we limited the set of phenotypes to a list of 217

Table 1 Number of total and genome-wide significant SNPs in the entire GWAS Catalog and within the reclassified phenotypes

	Total # of SNPs # of Genome-wide significant SNPs # of Replicated SNPs		
Entire GWAS Catalog	28,462	8740	–
Reclassified psychology-related/behavioral/cognitive phenotypes	7052	1223	Total of 452, including 147 (replicated across studies) + 305 (replicated in the same study)

Also listed are the SNPs found in more than one study that reached genome-wide significance in at least one of the studies (Supplementary Table 2a) and those which were significant for multiple samples within the same study but were not listed in Supplementary Table 2a for that phenotype (Supplementary Table 2b).

reclassified phenotypes, many of which are also directly related to psychiatric illness (Supplementary Table 1). In addition to retaining many phenotypes from the initial data set, we added some broader phenotypes that combined similar traits in order to make parsing and comparison easier and more efficient. While many of the reclassified phenotypes are explicitly psychological in nature, we also included phenotypes that are not classically psychological but are likely related to or correlated with mental functioning. A total of 514 studies and 7052 unique SNPs remained after phenotype reclassification and filtering. Out of these, 1223 SNPs reached genome-wide significance. Of these, 453 SNPs were reproduced in some capacity (see section on reproducibility and Table 1).

Finally, the data set included a broad range of samples. The paper with the smallest sample size among the psychiatry-related studies was a study on clozapine-induced cytotoxicity that used 90 European ancestry lymphoblast cell lines [4]. The largest sample size included samples from 549,935 individuals as part of a study on depression, neuroticism, and subjective well-being [5].

Reproducibility

As in any other scientific discipline, reproducibility is a critical indication of the strength of genetic findings. Here, we identified SNPs that have been associated with the same reclassified disorder or trait in two or more studies (if a significant association was found for a very similar phenotype at that SNP, that phenotype was also included). If the specific risk allele for the SNPs of interest were reported consistently for each study, we also included the allele (denoted by a hyphen and the base letter following the name of the SNP). We excluded non-identical reclassified “compound phenotypes” (phenotypes that are a combination of multiple disorders or traits) if they only matched with reclassified phenotypes that were part of the compound. For example, if the only reclassified phenotypes found to be significant for a SNP were schizophrenia and the compound phenotype “autism, bipolar disorder, or schizophrenia,” then the SNP was not considered to be replicated. However, a SNP found to be related to the phenotype psychosis and mood in two different studies would be considered replicated. Furthermore, we required at least one of the findings corresponding to the phenotype and SNP to reach genome-wide significance ($p \leq 2 \times 10^{-8}$). All further replicated findings for the same SNP and the same or very similar reclassified phenotype met the catalog’s p -value cut-off of $p \leq 2 \times 10^{-5}$. In Supplementary Table 2a, we listed the 147 SNPs meeting the above criteria (excluding replication samples within a single paper) for reclassified phenotypes. Supplementary Table 2b lists 305 SNPs that were

significantly replicated in samples within a single paper but were not listed in Supplementary Table 2a for that/those phenotype(s).

We consider the 147 SNPs reported by two or more separate publications arguably more reliable than the 305 SNPs replicated by the same publications, so our discussion focuses on the former. The SNPs rs2075650 and rs4420638 were linked to the most replications within a single reclassified phenotype. Both are associated with AD and cognitive decline, also brain eQTL (Supplementary Table 2a).

rs2075650 is located in an intron of the *TOMM40* gene, a mitochondria membrane protein. It is a brain eQTL SNP for the gene *PPMIN* and many other genes (though not for *APOE4* or *TOMM40*). The G-allele for rs2075650 was reported to confer an odds ratio of two in a small case–control study [6]. This SNP is also associated with hippocampal atrophy. However, there is a question as to whether it carries an independent AD risk. One study posits that rs2075650’s relationship with AD is more attributable to its modest linkage disequilibrium with rs429358 [7]. rs429358 is on the fourth exon of *APOE* and, along with rs7412, determines the *APOE* haplotype, where the variant $\epsilon 4$ is the strongest risk factor for AD. rs429358 was associated with AD in three studies (Supplementary Table 2a). The SNP rs4420638 is located downstream of the *APOC1* gene. rs4420638’s association with AD could also be related to its linkage disequilibrium with rs429358 and so is likely also not an entirely independent risk locus [8, 9]. rs4420638 is a brain eQTL SNP for non-*APOE* genes, according to BRAINEAC. The often complex relationships among GWAS signal linkage disequilibrium and the link between GWAS signals and brain eQTL may merit further investigation to clarify issues of causality.

Narcolepsy and nicotine-related phenotypes were also linked to highly replicated SNPs. They were associated with the SNPs rs1154155 [10–13] and rs1051730 [14–17], respectively, each in four different studies. rs1154155 is mapped to the downstream region of *TRAJ10*, a gene in the TRAJ (T cell receptor alpha joining) gene cluster. rs1154155 is an eQTL SNP for mir208a in white matter. rs1051730 is a coding synonymous variant in *CHRNA3* but is also an eQTL SNP for *CHRNA5* in brain. Both *CHRNA3* and *CHRNA5* are strong candidates for nicotine dependence.

Schizophrenia was the disease with by far the largest number of SNPs replicated within-phenotype—74—though many of these replications came from the same two studies, which shared samples [18, 19]. Educational attainment accounted for eight replicated SNPs, and Alzheimer’s disease was associated with 21 replicated SNPs.

While, at face value, the aforementioned findings could suggest strong genetic underpinnings of Alzheimer’s

disease and schizophrenia, it should be noted that some topics have been given more attention than others. For example, the search term “GWAS Alzheimer’s disease” returns about four times as many results in Google Scholar as “GWAS educational attainment.”

The fact that some studies drew from the same samples as other studies must also be taken into account. For example, only four publications from two research groups (from the Netherlands and the UK) have studied educational attainment in GWAS [20–23], and many of the samples from the four studies either were shared or came from the same biobank. Because recruiting huge samples is difficult, it is common for consortia to publish several studies on the same continuously growing sample. Thus, not all of the SNPs we recorded should be considered independently replicated. Going forward, it will be important for researchers to be cognizant of the limited validity of many reported GWAS findings.

Table 1 summarizes the quantity of SNPs according to criteria of significance, phenotype class, and replication status.

Reproduced GWAS signals as brain eQTL

We entered the 147 reproduced GWAS signals into the UK Brain Expression Consortium’s (UKBEC) expression quantitative trait loci (eQTL) database (<http://www.braineac.org/>). Among the 147 SNPs, a total of 88 SNPs (60%) exceeded the threshold cut-off required to reach significance ($0.05/147$ replicated SNPs = 3.4×10^{-4} , see Supplementary Table 2a). Of these, the SNP rs17693963 (associated with schizophrenia, bipolar disorder, or schizoaffective disorder [24, 25]) was the strongest brain eQTL and was most significantly associated with expression of the gene *ZNF389* in white matter ($p = 2.8 \times 10^{-10}$), among other brain regions. GTEx data also reported rs17693963 as an eQTL SNP in many tissues (including brain) and as being associated with several genes. The second most significant brain eQTL was rs727428 (associated with sex hormones and androgen levels [26, 27]). This SNP was most strongly associated with *TNFSF13*, *TNFSF12-13*, and *TNFSF12* in temporal cortex ($p = 2.1 \times 10^{-9}$) and cerebellum ($p = 4.7 \times 10^{-9}$).

Cross-phenotype analysis

GWAS can help draw attention to psychiatric disorders and other intermediate phenotypes that may share genomic risk factors. The literature with the greatest impact on this topic has largely pointed to overall shared genetics between schizophrenia and other psychiatric conditions, perhaps most notably bipolar disorder, intellectual disability, and autism spectrum disorder, based on polygenic risk scores

and shared rare variants [19, 28–30]. In this analysis, we again focused on individual SNPs recorded in the GWAS Catalog, which primarily includes common variants. For cases in which phenotypes were redundant, they were sometimes summarized or combined (e.g., “hematocrit” and “red blood cell traits,” when linked to the same SNP, were condensed to “red blood cell traits”).

We identified the SNPs and SNP risk alleles mapped to distinct phenotypes (e.g., excluding matches between single phenotypes and compound phenotypes encapsulating that phenotype and excluding very similar phenotypes). The cross-phenotype analysis required a more stringent threshold cut-off than the reproducibility analysis because, unlike in the case of reproducibility, this analysis needed to account for all examined phenotypes. We thus required that the associations for all phenotypes reach genome-wide significance ($p \leq 2 \times 10^{-8}$).

Because our focus is on psychiatry, we only summarized findings concerning SNPs linked to at least one psychological, behavioral, or cognitive trait, though we also included all significant findings for non-psychological/behavioral/cognitive phenotypes that were associated with the same SNPs. The SNPs associated with multiple phenotypes are plotted in a network in Fig. 1.

Addictive behavior and substance use

Many significant SNPs were mapped to the use of various substances, a phenotype category that has been measured in both controls and those affected by addiction. Four SNPs were associated with both nicotine-related phenotypes and phenotypes related to respiration. rs1051730 was linked to smoking behavior [15–17] and nicotine dependence [14] (combined into “nicotine-related phenotypes”), post bronchodilator FEV1, post bronchodilator FEV1/FVC ratio, pre bronchodilator FEV1, pre bronchodilator FEV1/FVC ratio, and lung cancer [31, 32, 34]; rs2036527 was related to smoking behavior [33], post bronchodilator FEV1, post bronchodilator FEV1/FVC ratio, pre bronchodilator FEV1, and pre bronchodilator FEV1/FVC ratio [34]; rs34684276-A was associated with post bronchodilator FEV1, post bronchodilator FEV1/FVC ratio [34], and nicotine dependence [35]; and rs56113850-T was associated with nicotine metabolite ratio in current smokers [36], local histogram emphysema pattern [37], post bronchodilator FEV1, and post bronchodilator FEV1/FVC ratio [34]. While these connections between smoking and respiratory phenotypes are meaningful, there exists the strong possibility that respiratory changes are the product of smoking and that these SNPs are not organic genetic causes of lung cancer.

Additionally, rs6265 was associated with both body mass index [38] and smoking behavior [15].

physical consequences of excessive substance use or indicate common genetic predispositions. Surprisingly, there were no significant associations between substance use phenotypes and psychiatric disorders that are frequently comorbid with substance abuse.

Educational attainment

Findings pertaining to educational attainment also appeared multiple times in cross-phenotype analysis. The term “educational attainment” had multiple implications. For example, “educational attainment” could indicate years of education or performance on a reasoning task, which are quite distinct from each other. rs10761741-T has been identified as a SNP risk allele for vascular endothelial growth factor levels [82] and years of education [20]. In the case of the former, the T allele at this locus seemed to indicate greater epinephrine-induced platelet aggregation and higher circulating VEGF levels. Serum VEGF levels have been reported as being associated with prefrontal cortex volume in schizophrenia patients [83]. Therefore, there is a possibility that this SNP might be related to educational attainment as a result of its contribution to brain structure.

rs2456973 was associated with vitiligo [84], a skin disorder, and educational attainment [20]. There is no obvious genetic connection between the two phenomena so far.

One meta-analysis reported rs12193446-A as the strongest SNP risk allele for refractive error \times education interaction [85]. Another study also revealed rs12193446-A as the SNP allele most strongly determining ocular axial length [86]. Similarly, a study of a rural population in India reported a positive correlation between ocular axial length and education; the same result was found in two other studies—one with a Chinese population and one with an elderly White population [87–89].

The SNP rs12553324 was found to be associated with level of educational attainment [23] and, in a separate study, was also identified as an area of interest for bipolar disorder [90]. Glahn et al., in a non-genetic 2006 study predating both of the former, found that bipolar patients had fewer years of educational attainment [91]. On the contrary, when measuring academic achievement in terms of performance rather than years in school, MacCabe et al. found somewhat mixed results [92]. While there was a relationship between bipolar disorder and low grades, there was also a very increased rate of eventual bipolar disorder diagnosis amongst those with high grades, compared to those with average grades. A genetic study reported a positive genetic correlation, achieved through linkage disequilibrium score regression, between bipolar disorder and years of education [93]. One paper studying polygenic risk score results, which represent combined contribution of many common SNPs to risk, found that high risk score of bipolar disorder and

schizophrenia are predictive of high educational attainment [94]. There appears to be a relationship between bipolar disorder and educational attainment; the specific nature of this link should be further studied.

Alzheimer’s disease

Several studies mapped common SNPs to Alzheimer’s disease and many other phenotypes [7, 9, 58, 65–67, 95–143]. More than one SNP was mapped to both Alzheimer’s disease and each of the following traits:

- Verbal declarative memory
- Cingulate cortical amyloid beta load (covariate in one study)
- C-reactive protein
- Longevity
- Cholesterol
- Cognitive decline
- Age-related macular degeneration
- Triglycerides

Given that both Alzheimer’s disease and these phenotypes are largely related to aging, the findings are not surprising. Inflammation, as it relates to Alzheimer’s, could also be an interesting further topic of study because of inflammation’s link to C-reactive protein.

Schizophrenia

Schizophrenia-focused GWAS findings also attained cross-phenotype significance. In particular, rs13107325-T was linked to schizophrenia [18], as well as to body mass index [112, 144, 145], HDL cholesterol [66, 67], blood pressure [146, 147], and N-terminal pro b-type natriuretic peptide in acute coronary syndrome [148]. Some of these findings are congruent with research that has found higher rates of cardiovascular diseases in schizophrenia [149, 150]. rs8042374 was associated with schizophrenia [18, 19] and lung cancer [151], a finding that is not incredibly surprising given the high rates of smoking in schizophrenics [152].

While some SNPs associated with both schizophrenia only and cohorts with schizophrenia and other disorders (e.g., autism, bipolar disorder) were excluded from the results due to the complications of linking a compound trait to a single finding, the high volume of SNPs associated with such combined effects suggests heretofore uncovered genetic commonalities between schizophrenia and other psychiatric disorders. Although polygenic analysis indicates that bipolar disorder and schizophrenia share genetic risk factors, they did not share any significant individual SNP associations according to our analysis. This may be related to imbalance in sample sizes. Schizophrenia GWAS

typically have much larger sample sizes than bipolar disorder GWAS. Still, there was some evidence for shared GWAS signals between the two disorders. For example, the SNP rs1006737 in the *CACNA1C* gene was linked to schizophrenia, with a p of 5×10^{-12} , but with bipolar disorder at $p = 7 \times 10^{-8}$ [153, 154]. Thus, the bipolar association did not meet the significance threshold for our analysis. However, both schizophrenia and bipolar disorder were associated with several different SNPs reaching genome-wide significance in *CACNA1C* [18, 19, 153, 155].

Supplementary Table 3 summarizes the cross-phenotype SNPs and their associated phenotypes, with the phenotypes that were later transformed into reclassified phenotypes listed under the name of the reclassified phenotype.

Limitations of the current review

We acknowledge that there are many areas of GWAS that were not deeply addressed within this paper. In writing this review, we relied primarily on the data as it was presented in the GWAS Catalog. Certain statistical parameters such as effect size could not be easily summarized and compared, as not all studies used the same criteria. Also, as the GWAS Catalog includes only GWAS, our analysis did not take candidate gene studies into account, meaning that our points of comparison were not exhaustive.

The present review is intended to serve as a broad summary and analysis of psychiatric GWAS. We believe that future studies and reviews that approach GWAS from a different angle or that focus on finer statistical details, even going so far as to scrutinize raw data from individuals, could lead to interesting and important findings.

More validation is needed

As shown in Table 1, fewer than half of the psychological genome-wide-significant associations have been validated, either in an independent study or in a replication sample. Because of the possibility of false discovery, the likelihood of a GWAS signal being a true marker of the tested phenotype holds fairly limited promise prior to replication.

Heterogeneity issues across studies

Any discrepancies between individual studies must be taken into consideration as confounding variables. For example, studies included a broad range of sample sizes, some of which only included a single racial or ethnic group; these studies should be replicated with different populations. It should also be noted that some studies drew from the same consortia, meaning that many samples likely shared participants. Additionally, some of the papers in the database

were meta-analyses of other GWAS, which created another opportunity for sample overlaps.

Differentiating causal associations from indirect correlational relationships

In assessing the data, it is important to beware of tempting but potentially false causal conclusions. For example, rs1051730 was mapped to smoking and some related physical conditions, including lung cancer. In order to find evidence that the listed physical health risks are governed by the same genomic regions (rather than just being a result of smoking behavior), it would be important to compare smokers to non-smokers, a variable that was not stringently controlled with respect to the loci of interest.

Despite these caveats, the relationships drawn between non-pathological phenotypes and psychiatric disorders is an important area of study. The findings linking the two types of traits promote the idea that physical phenotypes may eventually be able to serve as valid biomarkers of psychopathology. Going forward, it will be important to make efforts to distinguish between shared genetic roots and phenotypes that co-occur but which are not the results of a common genetic cause.

Conclusion

GWAS research has yielded many discoveries in both psychiatry and physical pathology. Further research and improvement in big data parsing methods will be an imperative part of fully legitimizing the field, but there already exist strong bases for forming theories about genome-wide associations.

Most psychiatric disorders appear to share specific risk loci with physical disorders or phenotypes instead of other behavioral, psychological, or cognitive traits. This could perhaps be because many psychiatric disorders are characterized by a rather wide assortment of sub-phenotypes, some of which may be linked to different biological phenotypes. Perhaps most notably, GWAS research on substance use has led to many associations with physical traits, which may harbor implications for addiction research.

Future directions

Revealing the functionality of GWAS-associated SNPs and resolving the causal nature of the relationship between SNPs and their associated traits should be one of the major objectives of post-GWAS conducted in the coming years. The CRISPR/Cas9 editing of risk alleles in induced pluripotent stem cells (iPSC) [156], as well as gene knockdown

and knockout studies, promise to bring exciting new insights to the discipline of GWAS.

The study of genetic relationships between various phenotypes is a vast new field of research with possibilities that will only increase as the rate of research accelerates and the GWAS database grows. Such research is giving us a new perspective on the etiology and pathology of disorders.

GWAS, while still in its infancy, has led to a prodigious quantity of publications and areas of study. We hope the insights gleaned in this investigation will help to guide future research in psychiatric genomics by highlighting worthwhile areas of investigation, ultimately enhancing our understanding of psychiatric disorders.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest

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