CANDIDATE GENE SCORING TO PREDICT BROAD ADOLESCENT PSYCHOPATHOLOGY

BY

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THESIS

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ABSTRACT

Candidate gene effects consistently fail to replicate. However, because it is now known that most genetic effects are incredibly minute, samples of the size typically employed in psychological research were undoubtedly too small to detect the effects of individual candidate genes. In addition, research showing strong genetic correlation among mental disorders suggests data on multiple disorders and their symptoms is the most appropriate for uncovering the etiology of mental illness. That is, single gene, single disorder studies are underpowered. We tested whether the combined effect of 121 candidate genes was sufficient to predict psychopathology in a sample of 343 adolescents. A genetic risk score was created with highly precise effect estimates from a genome-wide association study (GWAS) on 337,199 people. To maximize the strength of this score, we used transdiagnostic p-factor model scores as our measure of psychopathology. The genetic risk scores failed to predict in our sample and were dwarfed by age and gender effects, mirroring the genes' weak and mostly non-significant results in the GWAS. Our results are most consistent with the view that the candidate gene approach is obsolete. However, modern molecular genetics studies like GWAS currently lack detailed, thorough phenotype measurement. Future work should focus on developing high quality, deeply phenotyped data currently lacking in large consortia efforts.

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CHAPTER 1: INTRODUCTION

Due to its prevalence and persistent nature, mental illness is estimated to have the greatest disability burden of all diseases types worldwide, with major depressive disorder (MDD) individually ranking #5 out of 291 conditions included in the Global Burden of Disease Study (Murray et al., 2013). In any given year, 1 in 5 people meet criteria for diagnosis of a mental disorder (Steel et al., 2014). Given the substantial cost to society mental illness imposes, increasing public interest surrounds the issue. In 2013, then-president Obama launched the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative and hosted a National Conference on Mental Health. Still, successful treatment of psychopathology lags, and diagnosis remains thoroughly descriptivist. In an effort to steer research toward biological mechanisms, the National Institute of Mental Health (NIMH) implemented the Research and Domain Criteria (RDoC).

A component of RDoc concerns how genes influence psychology and behavior. Behavior genetics traditionally incorporates twin and family studies and, more recently, molecular genetic studies. Both approaches can estimate the degree to which traits are influenced by genes: twin studies by comparing the similarity of identical twins to that of fraternal twins and molecular genetic studies by correlating specific mutations with traits. In terms of mental disorders, this generally means examining rates of psychopathological morbidity in twin pairs and comparing the genotypes of clinical patients with those of unaffected individuals. If identical twins are diagnosed with the same disorder more often than fraternal twins are, we have evidence of genetic influence. If some mutations are more common in patients of that disorder, we have evidence that those mutations are in part responsible for that genetic influence.

According to twin studies, approximately 50% of the variation in all measured human traits, and 46% of the variation in all psychiatric traits, can be attributed to genetics (Polderman et al., 2015). Molecular genetics generally provides lower estimates, purportedly due to current limitations in the technology and inadequate sample sizes (Yang et al., 2015). Molecular genetic estimates have increased with time, the development of new methodologies, and sample size (Speed et al., 2017).

Sample size is a key issue in the history of molecular behavior genetics. Another key issue is the complex, correlated architecture of psychopathology. As would be expected with a predominance of comorbidity, genetic correlation among psychiatric illnesses abounds. Molecular genetic estimates place the genetic correlation between Bipolar I (BP1) and Schizophrenia (SCZ) at r = .68. Even MDD, which does not have a history of being phenotypically associated with SCZ, exhibits a moderate genetic correlation with it at r = .43 (Lee et al., 2013). Specifying traits that are closest to biological reality is the first step to uncovering genetic influences on psychopathology.

The Structure of Psychopathology

Correlated dimensions, not categories.

It has become increasingly apparent to researchers and clinicians alike that the complex structure of mental illness is not well captured by a categorical diagnostic system like that of the DSM, and that it would be bettered served by continuous dimensions. Mental disorders are simultaneously too narrow and too broad in scope, with rampant comorbidity and symptom heterogeneity the norm rather than the exception.

The prototypical example of disorder comorbidity is depression and anxiety. Around 60% of depressed participants in a US representative epidemiological study of mental health had at least one comorbid anxiety disorder (Kessler, Chiu, Demler, Merikangas, & Walters, 2005). The

murkiness of the boundary between depression and anxiety is even more apparent at the symptom level. Over 95% of depressed patients experience at least one anxiety symptom, and up to 65% of anxious patients experience low mood (Hranov, 2007).

As for the contrasting issue of symptom heterogeneity, schizophrenia has long been recognized as being comprised of several disparate symptoms that may not be shared even among several patients. There have been several attempts to create subtypes of schizophrenia based on the nature, severity, and onset of the symptoms such as the distinction between the paranoid, catatonic, and disorganized. Apart from the division between negative and positive symptoms, such subtyping approaches have fallen out of favor, but the issue of symptom heterogeneity remains (Keller, Fischer, & Carpenter, 2011).

Another consequence of the current arrangement is the paradoxical pairing of diagnostic instability with symptom stability. Patients often drift from diagnosis to diagnosis while by and large experiencing the same symptoms and responding similarly to identical treatments (Kotov et al., 2017). In addition, due to the arbitrary thresholds for diagnosis and without a formal dimension of severity, subclinical presentations are ignored and severe cases are not adequately tagged. This is in opposition to other areas of medicine, which fluidly combine severity dimensions with categorical diagnoses (Carragher, Krueger, Eaton, & Slade, 2015). Arranging symptoms on dimensions ameliorates these shortcomings and clarifies the relationships between disorders and between symptoms.

The structure of psychopathology is hierarchical.

Evidence has converged around hierarchical structures of psychopathology that account not only for the comorbidity of closely-linked disorders but also among all forms of psychopathology. Though some models retain DSM categories by using latent class analysis or

some hybrid categorical/dimensional modelling, continuous, symptom-based measures predominate and offer the strongest level of prediction. (Kotov et al., 2017). Through covariance-based methods – principally, factor analysis – clusters of correlated symptoms can be organized into overarching dimensions. In these frameworks, disorders are understood as specific combinations of symptoms and/or as profiles with varying scores on the dimensions.

The latest of these hierarchical models is the Hierarchical Taxonomy of Psychopathology (HiTOP; Kotov et al., 2017) which expands Caspi and colleagues' (2014) P-factor model. The P-factor model and HiTOP go beyond the widely accepted and successful internalizing/externalizing dichotomy by establishing "superspectra" that refer to a general liability for mental illness. Just as there is a "g factor" for general intelligence, there is a "p factor" for psychopathology, argued Caspi and colleagues (2014).

Below this all-encompassing psychopathology superspectrum exist narrower spectra: internalizing, externalizing, and thought disorder (Figure 1). Internalizing refers to a tendency to direct negative feelings and behaviors toward the self. Disorders that could be classified as internalizing or which have substantial internalizing components include: MDD, Generalized Anxiety Disorder (GAD), Obsessive Compulsive Disorder (OCD), Post-traumatic Stress Disorder PTSD, and Anorexia Nervosa (AN). Externalizing, on the other hand, refers to a tendency to direct the negativity outward. Disorders that could be classified as externalizing or which have substantial externalizing components include: Attention Deficit Hyperactivity Disorder (ADHD), the Substance Use Disorders (SUDs), Oppositional Defiant Disorder (ODD), Conduct Disorder (CD), Antisocial Personality Disorder (ASPD), and Intermittent Explosive Disorder (IED). The thought disorder spectrum, comprised of psychotic symptoms experienced

in schizophrenia and related disorders, is also well-replicated (Kotov et al., 2017) but does not emerge as clearly in adolescent samples due to the later age of onset for psychotic disorders.

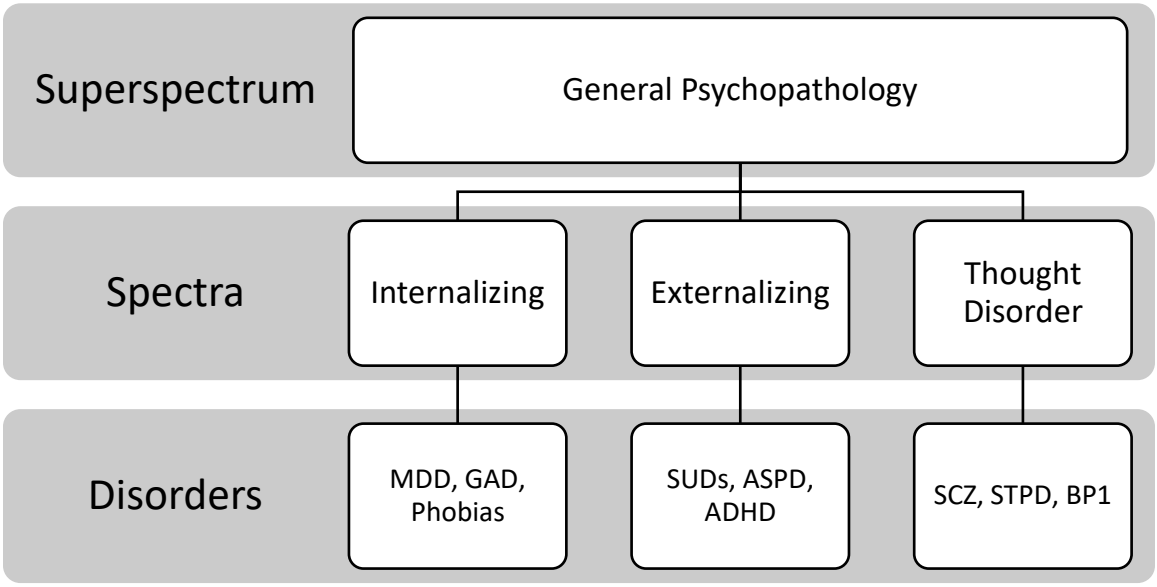

Figure 1 **The P-factor Model in HiTOP terminology. For simplicity, symptomology spread across spectra, such as BP1's manic psychosis, are not pictured.**

Though DSM disorders are abandoned in HiTOP, they can be interpreted in the same way as they are in other hierarchical models - as combinations of different symptoms across the spectra (Figure 1). Some disorders fit more neatly within a single spectrum than others. The most characteristic symptoms of MDD, for example, spread across multiple subfactors of internalizing such as distress and negative affectivity, but they all fall within internalizing. Bipolar I, in contrast, has both substantial affective and thought disorder components due in part to manic psychosis.

The meaning of the P-factor and superspectra.

HiTOP, P-factor, and other hierarchical models describe and predict psychopathology with greater accuracy than the traditional categorical approach, but what the spectra and

superspectra actually mean etiologically is an area of ongoing research. The authors of HiTOP attest that the spectra and superspectra are meaningful units of analysis that are more useful than DSM diagnoses for understanding genetic contributions to psychopathology (Kotov et al., 2017). However, there are three alternative explanations that fit the data to varying degrees.

The most conservative explanation dismisses the spectra as being artifactual, perhaps due to common method bias or symptom mislabeling. For example, attention problems in a child may be mistaken for intellectual disability or a patient may over-lump their symptoms together because they misinterpret survey questions. In both cases, artificial correlations between symptoms and disorders would be observed. This argument is contradicted by agreement between studies that use various designs, measurements, and samples (Kotov et al., 2017). Notably, clinician ratings of their patients' symptoms also reproduce the P-factor structure, even though they are trained in the DSM (Morey, Krueger, & Skodol, 2013).

A related line of argument disputes the interpretation of the statistics: principally, that correlational studies cannot demonstrate causality, and, therefore, that factors are better understood as summaries, not causes, of their subfactors. Caspi and colleagues (2014) themselves asked in their paper, "Is p merely a statistical *reductio ad absurdum* or is it real and meaningful?" (p. 132). Wood, Gardner, and Harms (2015) discussed the limitations of covariance-based methods used in non-experimental, cross-sectional studies. Longitudinal and twin designs get closer to causality, but an additional problem remains: superordinate factors are always estimated more accurately than their components. For personality inventories, facets by definition have fewer items than the factors they comprise; for psychopathology, a grouping of disorders necessarily contains more cases than any one disorder. Modeled effects will be most

strongly tied to factors. Even if the causal direction is in fact reversed, the subfactors will look like noise.

The most popular argument against shared genetic etiology is the causal or temporal hypothesis that related disorders cause one another. For instance, anxiety and depression can appear to occur cyclically (Hranov, 2007). This hypothesis has not been ruled out as of yet, necessitating more longitudinal studies. Some have found that disorders are more fine grained in adolescence and that comorbidity increases with age, the opposite of what would be expected with a general, transdiagnostic cause (Hranov, 2007). Even with the g factor for general intelligence, debate persists around whether it should be understood as a cause or as a consequence of events during development.

Finally, the genetic etiology perspective serves as the basis for this study and most behavior genetics investigations of psychopathology. Though behavior genetics is not incompatible with the developmental hypothesis, it is increasingly assumed that genes primarily contribute to psychopathology generally (or transdiagnostically) rather than specifically for any one disorder. That is, genetic effects are expected to have the greatest prevalence and strength at the spectra and superspectra levels – e.g. with the p-factor and/or internalizing instead of MDD. Twin and family studies have borne this out for over a decade. For example, when multiple externalizing disorders are analyzed together in a twin study design, the estimated proportion of externalizing behavior variance due to genetics (i.e. heritability) is maximized at the level of the entire externalizing spectrum – specifically up to 84% (Young, Stallings, Corley, Krauter, & Hewitt, 2000), which is up to 50 percentage points higher than estimates for individual disorders (Hicks, Krueger, Iacono, McGue, & Patrick, 2004).

With such powerful genetic effects on psychopathology, one might expect that the genetic architecture involved would be fairly simple once comorbidity is handled as a given with a small set of easily identifiable genes responsible. That scenario, while attractive, is far removed from the truth. The genotypic structure of psychopathology is infinitely more complex than the already complicated phenotypic structure, with many more moving pieces that demand of researchers ever greater care with measurement and sampling.

The Traditional Candidate Gene Approach

Before modern sequencing technology, focusing on individual genes like *5-HTTLPR-S* and *MAOA-L* was a necessity, as genotyping more than a handful of genetic variants was time intensive and cost-prohibitive. "Candidate genes" with the strongest theoretical support were included. Though genotyping many millions more genetic variants is comparatively less expensive and time consuming today, candidate genes studies are still attractive to many because they presumably allow for a closer interrogation of biological mechanism than would be feasible in large, atheoretical approaches like genome-wide association studies (GWASs) in which mutations at millions of individual points along the As,Ts,Cs and Gs of the genetic code are correlated with a trait (as described in-depth below). Unsurprisingly, just how reasonable it is to sift through so many single nucleotide polymorphisms (SNPs) is questioned.

Unfortunately, the candidate gene approach has fallen out of favor due to rampant replication failures and unreliable effect size estimates in the literature. Many researchers suspect the same methodological problems plaguing other areas of psychological science - namely, the file drawer effect, selective reporting of data, and low statistical power (Dick et al., 2015; Duncan & Keller, 2011; Duncan, 2014). Negative results appear to have been suppressed, and small sample size studies were vulnerable to false positives and poor effect estimates. For example, (Duncan & Keller, 2011) meta-analyzed the candidate-gene-by-environment literature

and found that effect sizes were negatively correlated with sample size and time of publication. In other words, the landmark studies first establishing the GxE effect used small samples and later studies with larger samples failed to replicate. They also found that GxE reports often used misspecified interaction models, such that an unknown proportion of apparent GxE effects may be better explained by interactions between covariates and environmental conditions – no gene effects necessary.

The widespread suspicion surrounding candidate genes is supported by a recent failed replication attempt on the main effects of popular candidate genes on SUDs and externalizing disorders (Samek et al., 2016). By virtue of its 3,487-person sample size, this study had a 97% chance of detecting effects that are but a fraction of the size estimated by candidate gene meta-analyses – yet not one candidate gene replicated. In other words, Samek and colleagues (2016) had a near-certainty of detecting the effects claimed by the literature, and they did not find any.

Rare variants can theoretically surpass the minute effects of common mutations/alleles (Gibson, 2012). Natural selection keeps them at a low frequency in the population because they are deleterious - e.g. the mutations that cause achondroplasia dwarfism, *G1138A* and *G1138C* polymorphisms of fibroblast growth factor receptor 3 (*FGFR3*) gene. However, classic candidate genes are neither rare nor technically "genes" at all. They are instead common alleles found in a large proportion of the healthy population. Candidate gene selection was inspired by research in which gene function was tremendously compromised or altered, including "gene knockout" experiments or rare genetic disorders such as Brunner's Syndrome (Brunner et al., 1993). Despite this, only one common polymorphism of many in a gene would be selected to represent the entire gene, and they were necessarily common variants to make finding participants feasible. The *MAOA-L*, *5-HTTLPR-S*, *DRD4-L*, and *DRD2 Taq1A* risk alleles are variants readily found in

large portions of the population. The most common *MAOA-L* polymorphism is carried by 30% of Caucasian men (Raine, 2014). Candidate genes would be more accurately dubbed "candidate alleles", and the effects of common alleles are small.

The Infinitesimal Model and GWAS

If candidate gene effects do exist, they are almost certainly much smaller and require larger sample sizes. In 1919, R.A Fisher demonstrated mathematically that normally distributed traits could not possibly arise from mendelian patterns of inheritance but instead from the combined, infinitesimally small effects of many genetic variants (Fisher, 1919). Dubbed the "infinitesimal model", this insight by Fisher has been confirmed by GWASs. In a GWAS of over 250,000 people, 697 single nucleotide polymorphisms (SNPs) identified as significantly associated with human height together accounted for only 20% of the variability in height attributable to genes (Yang et al., 2010). Psychological and behavioral traits show even greater polygenicity (Okbay et al., 2016), so much so that polygenicity has been dubbed a "law" of behavior genetics (Chabris, Lee, Cesarini, Benjamin, & Laibson, 2015). With so many genes working together in concert, GWAS is in fact better equipped for uncovering biological mechanisms than candidate gene studies are.

GWASs simultaneously analyze millions of genetic variants, specifically SNPs, in a single study. If the DNA double helix can be thought of as a ladder when unwound and laid flat, the individual rungs on that ladder are single nucleotides. One way that this ladder can differ between individuals is by a change at the level of one individual rung. Where one person may have adenine (A) at a particular rung, another may have guanine (G) in the same place. Because it is one rung, it is a single nucleotide and, because it varies among members of a population, it is a polymorphism (having "multiple forms"). These are the polymorphisms investigated in a GWAS, SNPs. The most common design in psychiatric GWASs is case control, which examine

the frequency of SNP alleles in cases relative to controls through logistic regression. Alleles that have an odds ratio greater than 1 for being a case are tagged as risk alleles. GWASs on psychological traits that are measured as normal, continuous variables employ linear regression models. Allele correlations between the SNP and the trait use Pearson's *r*, which ranges from -1 to 1; the higher the absolute value of the number, the greater the association. If, say, the A allele in the previous example is significantly more common among SCZ patients than the G allele, we can say that the SNP is linked to SCZ and that A is the risk allele.

An important procedure in GWAS is the control of population stratification. Population stratification refers to the presence of different allele frequencies in ancestry groups that arises through selection-neutral processes like genetic drift in geographically distant populations (Novembre et al., 2008). Spurious associations can be found when ancestry-stratified alleles that have code for non-behavioral traits (e.g. skin, eye color, height) tag disparities between ancestry groups that are the result of purely social processes. For example, a GWAS on income and educational attainment in the United States would identify SNPs causing white skin as significant predictors if ancestry was not accounted for.

The Basic Template of a GWAS:

1. Genotype hundreds of thousands or millions of SNPs in tens of thousands of unrelated individuals.
2. Perform quality control on the calls the SNP arrays provide to ensure accuracy.
3. Impute millions of SNPs based on the patterns observed in the sequenced SNPs.
4. Record how many of each allele each person has at each SNP. Since SNPs are predominantly bi-allelic (having only 2 common alleles), these will either be 0 for

individuals who did not inherit the "counted" allele of either parent, 1 for those that received one copy from a parent, and 2 for those that received a copy of the counted allele from both parents.

5. Perform a regression analysis in which these allele counts are correlated with the trait of interest and important covariates like age and sex are controlled for. The most important covariate to control for is ancestry as measured by genotyping to avoid confounding population stratification.
6. Identify SNPs associated with the outcome that are statistically significant after a Bonferroni multiple testing correction for 1 million tests at $p = 5 \times 10^{-8}$.

Constrained by minute effect sizes and a severe multiple testing correction, extremely large samples are a necessity. After the aforementioned GIANT Consortium, closing the gap in the prediction of human height required an additional 2,593 SNPs and around 550,000 more people (Yengo et al., 2018). Given that GWAS is currently restricted to SNPs and no other form of mutation such as copy number variants (CNVs), this level of prediction is nonetheless impressive. Sample size is not the only road to statistical power, however.

Current Study

Largely because common variant effects are so small, many GWAS researchers combine effects across them using poly-genic risk scores, or GRSs (International Schizophrenia Consortium, 2009). For each SNP, the number of risk alleles (0 homozygous non-risk, 1 heterozygous, 2 homozygous risk) an individual has is multiplied by the regression weight found in a previous "training" sample, and the resulting values for all of the SNPs are then summed (Dudbridge, 2013). The equation for GRSs is as follows:

$$(SNP_1 minor\ alleles, i.e.\ 0/1/2\ * \beta_1) + (SNP_2 minor\ alleles * \beta_2) + \ldots + (SNP_i minor\ alleles * \beta_i) \quad (1)$$

For example, a SNP with a weight of 0.3 would have a value of 2 × 0.3 = 0.6 for homozygotes of the risk allele, 1 × 0.3 = 0.3 for heterozygotes, and 0 × 0.3 = 0 for homozygotes of the non-risk allele. Two SNPs with identical combinations of allele number & weight would sum to 1.2, 0.6, and 0, respectively. Therefore, the more risk alleles an individual has across SNPs and the greater the effect of those alleles, the more likely it is that the person will score highly on the trait at hand.

By combining the effects of candidate genes in a GRS, we can possibly detect effects sizes below those estimated by the extant candidate gene literature. Candidate genes may in fact be predictive of psychopathology but less so than previously believed.

We applied the GRS method to 121 candidate "gene" SNPs (listed in Appendix) to predict psychopathology in the Gene, Environment, Mood study (Snyder, Young, & Hankin, 2017). Weights for the GRSs were obtained from GWASs on neuroticism, anxiety, and risk-taking (Churchhouse & Neale, 2017).

CHAPTER 2: METHOD

Training Sample

Scoring weights were obtained from Churchhouse & Neale (2017) who conducted a 10.8 million SNP GWASs on data from the UK Biobank. The UK Biobank is a public repository of medical and genetic data on a representative sample of 500,000 men and women aged 40-69 from the UK. After they implemented quality control measures, data from 337,199 UK Biobank participants remained for their study (see Table 1 for trait-specific sample sizes). Three measures of psychopathology - neuroticism, worrying, and risk-taking - had three corresponding factor scores in GEM: general psychopathology, internalizing, and externalizing, respectively. In the bifactor model of psychopathology created by Caspi and colleagues (2014) that Snyder and colleagues (2017) used in the GEM testing sample, neuroticism no longer correlated with internalizing once the general psychopathology "p-factor" is accounted for, but anxiety does. Therefore, we used the worrying/anxious feelings GWAS for the internalizing factor. Regressions on all nine combinations of UKB traits and GEM factor scores were conducted for thoroughness, however. Height was incorporated as a negative control.

Table 1

Sample Sizes Available for Each Trait out of Combined Total

UKB Measure	Sample Size	Corresponding GEM Factor
Neuroticism	274,108	P-factor
Worrying/Anxious feelings	328,717	Internalizing
Risk-taking	325,821	Externalizing
Standing height	336,474	Negative Control

Target Sample

The target sample consisted of female (55.5%) and male adolescents aged 9-19 from the Gene, Environment Mood longitudinal study (Snyder et al., 2017). To limit multiple testing

liability, we restricted testing to the factor scores estimated in the GEM sample at Time 2, in consideration of consistent evidence of heritability of psychopathology increasing with age during adolescence (Bergen, Gardner, & Kendler, 2007) and evidence of homotypic continuity increasing with age for the internalizing factor within this sample (Snyder et al. 2017). On average, participants were 13.58 years old (SD = 2.37, range = 9.3–17.5) at T1 and 15.07 years old (SD = 2.36, range = 10.7–19.1) at T2.

Data on 121 SNPs from 343 participants were included in the final analysis. From the original sample of 571 participants, 228 participants were removed for missing genotypes on more than 12 SNPs (~10%). 23 SNPs were dropped from the original 144 SNPs. 7 were unavailable in our training sample, and 5 had a high degree of missingness (>40% of genotypes). 11 with ambiguous strands (i.e. A\T, T\A, C\G, G\C) were dropped for having minor allele frequencies between .35 and .50, which made them impossible to confidently verify using the 1000 Genome estimates. Psychopathology in the GEM sample consisted of factor scores for general psychopathology (the "p-factor"; Caspi et al., 2014), internalizing, and externalizing in GEM (see Snyder et al., 2017 for details on their p-factor model).

Polygenic Risk Scores and Statistical Analyses

GRSs for each participant were calculated by multiplying the number of risk alleles per SNP (0,1,2) with the corresponding UKB regression coefficient, summed over all SNPs. No p-value threshold was used for SNP inclusion in the scores such that all 121 SNPs contributed to the GRSs regardless of their p-values in the UKB.

Where β_T is the association between a UKB phenotype GRS (neuroticism, worry, or risk taking) and its target phenotype (p-factor, internalizing, or externalizing, respectively); β_{NT} is the

association(s) between a GRS and any of its non-target phenotypes; and β_0 is the association(s) between a negative control GRS for height and any of the PIE phenotypes:

- If $\beta_T > 0$, aggregate genetic risk from the set of included candidate genes predicts the target phenotype.
- If $\beta_{NT} \neq 0$, then the genetic risk is not specific to the target phenotype.
- If $\beta_0 \neq 0$, the negative control (height) has failed, implying that estimates are biased (e.g. by unmeasured population stratification).

We regressed each of the three PIE factors on each GRS, including age, gender, and dummy-coded participant race/ethnicity as covariates:

$$\{P, I, E\} = b_i\, GRS_i + b_{age} age + b_{gender} gender + b_{race} race + e_i i \quad (2)$$

Significance of the association between each of the GRS_i and the p-factor, internalizing, and externalizing scores was evaluated by significance of the bi term. Multiple testing correction took into account the likely intercorrelation among behavioral GRSs. That is, it was understood that the prediction weights were likely not independent, and therefore that the effective number of independent tests would be lower than nine, the number of GRSs tested. We applied as a correction (Nyholt, 2014) method of accounting for non-independence of multiple tests:

$$\alpha = 0.05 \div \left[\left(1 + (M_{DV} - 1) \left(1 - \left(\frac{Var(\lambda_{DV})}{M_{DV}} \right) \right) \right) * \left(1 + (M_{IV} - 1) \left(1 - \left(\frac{Var(\lambda_{IV})}{M_{IV}} \right) \right) \right) \right] \quad (3)$$

Where M_{DV} is the number of dependent variables (here, the p-factor, internalizing, and externalizing); M_{IV} is the number of target (i.e. non-control) GRSs used as independent variables (here, neuroticism, worry, and risk taking); $Var(\lambda_{DV})$ and $Var(\lambda_{IV})$ are the variances for the eigenvalues obtained from a correlation matrix of the dependent or independent variables,

respectively. For example, if the variables are entirely independent, then $Var(\lambda) = 0$ and $\alpha = 0.05 \div (3 \times 3) = 0.0056$; if the PIE factors are entirely independent and the GRSs are perfectly correlated, then $Var(\lambda_{IV}) = M_{IV}$ and $\alpha = 0.05 \div (3 \times 1) = 0.017$).

CHAPTER 3: RESULTS

Primary Analyses

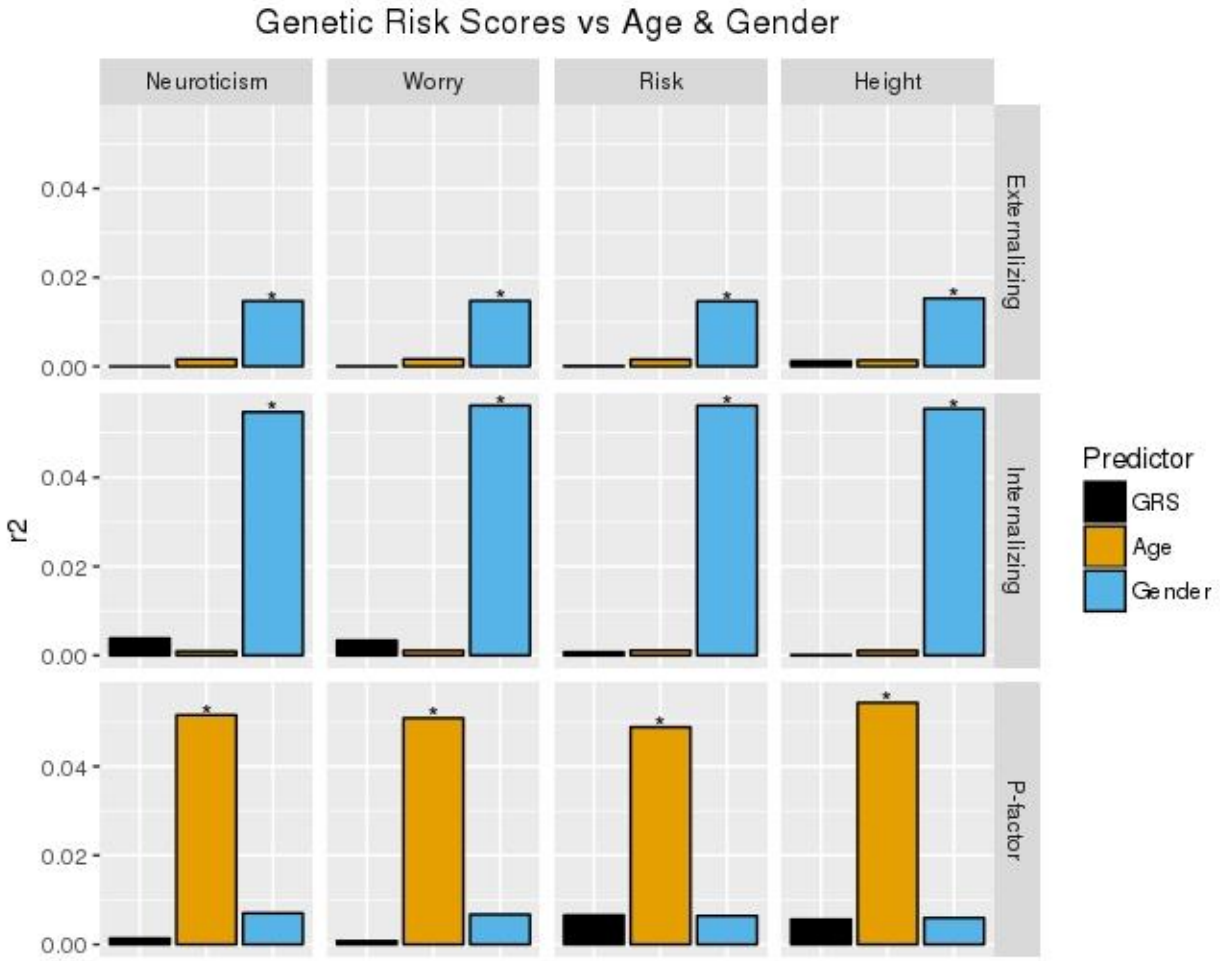

Figure 2. **Comparison of the four GRSs' prediction of psychopathology in GEM.**

None of the GRSs reached statistical significance before or after multiple test correction in any of the models (all $p > 0.05$). Gender was a significant predictor in all internalizing (all $p < 1.46 \times 10^{-5}$) and externalizing (all $p < .0267$) models, and age was a significant predictor in all p-factor models (all $p < 4.04 \times 10^{-5}$). Substantial correlation was observed between the neuroticism, worry, risk-taking, and height GRSs (Table 2), which accounts for the remarkable similarity of the regression results across all models. Oddly, both neuroticism and worry were more strongly correlated with height than with risk-taking.

Table 2

Correlation matrix for all variables across all 12 models (incl. control)

Variable	1	2	3	4	5	6	7	8
1. GEM P-factor	—							
2. GEM Internalizing	0.12	—						
3. GEM Externalizing	0.33	-0.34	—					
4. Neuroticism GRS	-0.03	-0.07	0.01	—				
5. Worry GRS	-0.04	-0.05	0.00	0.87	—			
6. Risk-taking GRS	-0.10	-0.02	-0.02	0.42	0.34	—		
7. Height GRS	-0.05	0.02	0.03	-0.62	-0.67	-0.42	—	
8. Age	0.23	-0.04	0.04	0.03	-0.02	-0.06	0.09	—

Secondary Analysis: Performance of Candidate SNPs in the UKB

Though we did not find evidence for the GRSs having a significant effect on psychopathology, the GEM sample may have been underpowered to detect the true effects of the SNPs, as their magnitudes may be more typical of GWAS. To determine the prediction strength of the candidate SNPs in a large, well-powered GWAS, we referred to the GWASs on the UKB.

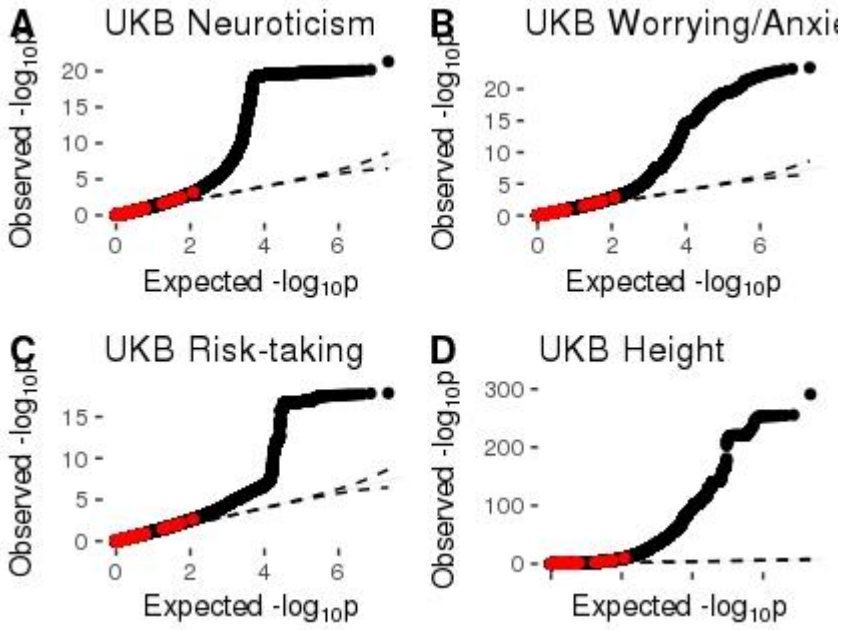

Figure 3. **QQ plots of -log10 p-values for 10 million SNPs available in the UKB data.** P-values for the candidate SNPs are in red.

Five candidate SNPs reached the genome-wide significance threshold ($p < 5\times 10^{-8}$) in the UKB GWAS on neuroticism: rs878886, rs1876828, rs242924, rs110402, rs2715148 (Appendix). Of these, rs878886 and rs1876828 were also significant predictors of worrying/anxiety and height. Compared to the best performing candidate SNP, p-values were lower for 1,809 SNPs in neuroticism, 5,976 in worrying/anxiety, 1,367 in risk-taking, and 68,589 in height (Figure 3).

CHAPTER 4: DISCUSSION

None of the genetic risk scores were significant predictors of psychopathology in the GEM sample. With 343 participants, we had 80% power to detect Pearson correlations of 0.155 magnitude after multiple testing correction. The combined effect of 121 candidate genes was insufficient, only amounting to a maximum of r = -.10 between the neuroticism GRS and internalizing. The candidate genes also showed poor performance in the larger UKB training samples, of which the smallest (N = 274,108) had 80% power to detect correlations of r = 0.012 at the genome-wide significance level of 5×10^{-8}. Only 5 candidate SNPs were genome-wide significant in the neuroticism GWAS, and they were surpassed by thousands of other SNPs. Two of the five were also significant predictors of height. This means that the 121 candidate genes we tested were not strong, much less uniquely strong, predictors of psychopathology.

As can be seen in Figure 2, substantial correlation between the candidate GRSs was observed. While intercorrelation among the psychopathology measures (neuroticism, worry, risk-taking) might be expected, the strong correlation with height was surprising. This may indicate that the effect estimates are biased by unmeasured population stratification within the GEM sample. The population frequencies of candidate genes differ between ancestry groups that are inadequately labeled with self-reported race. Just like other candidate gene studies, we cannot test for the possibility of population stratification in our sample because of the absence of sufficient genome-wide data needed to estimate genetic ancestry (Novembre et al., 2008).

Alternately, the genetic contribution of these candidate genes to psychopathology may be pleiotropic (pleion “more” and tropos “way” in Greek), with some of these candidate SNPs in particular bearing wide-ranging effects on body size as well as mental health. The two SNPs

shared by the neuroticism, worry, and height GWASs as significant predictors - rs878886 and rs1876828 - lie within the corticotropin-releasing hormone receptor 1 (*CRHR1*) gene. Corticotropin-releasing hormone (CRH) is a stress hormone of the HPA axis that is implicated in anxiety disorders, but CRH also affects appetite and metabolism (Laryea, Arnett, & Muglia, 2012) which could in turn influence height.

Our results indicate that researchers should look elsewhere for strong genetic predictors of psychopathology. Our use of SNPs does not rule out the potential role of rare variants within these genes, but the common variants used previously in research should be regarded with caution. Future GWAS research should employ GWAS-sized samples to explore the possibility of weaker but useful effects than could be detected with our sample size. Ideally, these would be in studies as "well-phenotyped" as GEM in which thorough, validated measures are used and participants are followed over time. Such work would capitalize on the advantages smaller studies have over large consortia, providing the beneficial properties researchers sought from candidate gene studies without ignoring the biological reality of polygenicity.

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APPENDIX: LIST OF THE 121 CANDIDATE GENE SNPs

Table 3
The 121 Candidate SNPs Analyzed and their Betas in the UKB

rsid	Allele	Frequency	Neuroticism	Worry	Risk-taking	Height
rs878886	G	10.69%	0.0949*	0.008*	0.0019	-0.013*
rs1876828	T	60.36%	0.0949*	0.008*	0.0019	-0.013*
rs242924	G	37.07%	-0.0509*	-0.0044	-0.0015	0.0047
rs110402	G	37.30%	-0.0508*	-0.0043	-0.0014	0.0045
rs7209436	C	33.60%	-0.0498*	-0.0043	-0.0013	0.0046
rs2715148	A	31.58%	0.0475*	0.0043	0.0018	-0.0020
rs1800497	A	54.30%	0.057*	0.0032	0.0023	0.0009
rs13438494	T	28.50%	0.0461*	0.0045	0.0018	-0.0022
rs2522833	C	41.48%	0.0458*	0.0042	0.0014	-0.0005
rs6265	T	19.54%	0.0329	0.0060	-0.0057	0.0049
rs4757138	A	24.62%	-0.0282	-0.0028	0.0037	-0.0135*
rs242939	C	5.88%	0.0517	0.0045	0.0008	-0.0128
rs12884323	C	35.98%	-0.0246	0.0004	-0.0013	0.0007
rs5522	C	8.84%	0.0365	0.0027	0.0007	-0.0004
rs35369693	C	69.07%	-0.0435	-0.0005	-0.0007	0.0023
rs33933482	A	58.48%	-0.0317	-0.0005	-0.0006	0.0034
rs265974	G	42.48%	0.0186	0.0015	0.0013	-0.0045
rs2020934	A	37.06%	-0.0166	-0.0009	0.0002	-0.0116*
rs53576	A	35.01%	-0.0176	-0.0004	0.0022	0.0007
rs237897	A	27.75%	-0.0163	-0.0009	0.0026	0.0003
rs594242	C	12.73%	0.0189	0.0024	-0.0006	-0.0026
rs1800796	C	10.70%	-0.0369	-0.0036	0.0006	0.0094
rs1824024	C	28.85%	0.0156	0.0016	-0.0019	-0.0015
rs17110489	C	53.38%	-0.0165	-0.0044	0.0004	-0.0015
rs1959813	C	29.08%	-0.0146	0.0007	-0.0026	0.0019
rs17486278	C	47.60%	0.0153	0.0018	-0.0038	-0.0028
rs904467	A	57.86%	0.0169	0.0012	0.0004	-0.0021
rs4448731	C	39.73%	-0.0142	-0.0007	-0.0020	0.0024
rs3007105	T	39.46%	0.0143	-0.0007	0.0030	-0.0022
rs10496417	A	25.52%	0.0143	-0.0002	-0.0009	-0.0025
rs4792887	T	63.65%	-0.0244	-0.0024	-0.0009	0.0142*
rs16969968	A	52.74%	0.0146	0.0018	-0.0038	-0.0028
rs4675690	T	38.51%	-0.0136	-0.0033	0.0018	0.0005
rs4583306	G	39.11%	0.0132	-0.0004	0.0006	0.0071
rs7940188	C	4.51%	-0.1839	-0.0275	-0.0110	0.0425
rs3794808	C	37.33%	0.0129	-0.0003	0.0002	0.008*
rs12291063	C	67.38%	-0.1772	-0.0284	-0.0096	0.0432

Table 3
The 121 Candidate SNPs Analyzed and their Betas in the UKB (cont.)

rs2020936	G	16.20%	0.0159	0.0011	0.0020	0.0009
rs3764352	C	24.48%	0.0152	0.0022	0.0009	0.0040
rs165599	A	27.27%	0.0135	-0.0026	0.0040	0.0041
rs4570625	T	51.95%	-0.0151	-0.0042	-0.0007	0.0005
rs3750344	C	59.91%	0.0164	0.0030	0.0020	-0.0010
rs907094	G	24.55%	0.0149	0.0022	0.0009	0.0040
rs12443955	G	20.21%	0.0127	-0.0005	-0.0002	0.0022
rs6354	G	14.38%	0.0139	0.0011	0.0016	0.0010
rs854560	T	49.85%	-0.0114	-0.0009	-0.0017	-0.0008
rs140700	T	65.90%	-0.0189	-0.0013	-0.0021	-0.0006
rs140701	T	36.81%	0.0110	-0.0006	0.0004	0.0074
rs16965628	C	63.93%	-0.0222	-0.0032	-0.0018	-0.0041
rs1042173	C	36.17%	0.0104	0.0004	0.0000	0.0093*
rs6869645	T	67.29%	-0.0219	-0.0013	-0.0013	0.0031
rs2061174	G	27.38%	0.0104	0.0003	-0.0019	-0.0024
rs6314	A	65.32%	-0.0169	0.0003	-0.0017	0.0039
rs643627	C	49.62%	0.0106	0.0016	0.0000	0.0019
rs28536160	C	56.29%	0.0251	0.0015	-0.0067	-0.0037
rs7569963	A	52.18%	0.0099	0.0026	-0.0024	0.0035
rs1801260	G	51.35%	-0.0098	-0.0005	0.0011	0.0000
rs11174811	A	63.60%	-0.0121	-0.0043	0.0001	0.0018
rs35608965	C	67.36%	0.0230	0.0015	-0.0064	-0.0039
rs1800795	C	48.43%	-0.0085	0.0000	0.0006	0.0059
rs806368	C	55.55%	-0.0102	0.0001	-0.0008	-0.0015
rs4680	A	38.62%	-0.0081	-0.0027	0.0024	0.0035
rs6196	G	62.11%	-0.0107	-0.0024	-0.0007	0.0074
rs4633	T	37.97%	-0.0081	-0.0026	0.0023	0.0033
rs12635797	T	59.93%	0.0131	0.0028	-0.0007	0.0004
rs279858	C	43.47%	-0.0077	0.0018	-0.0055	-0.0041
rs2230912	G	61.69%	-0.0102	0.0004	0.0012	-0.0018
rs279871	C	43.10%	-0.0076	0.0018	-0.0054	-0.0041
rs1587097	T	66.20%	-0.0113	-0.0051	0.0009	0.0000
rs578776	G	44.89%	-0.0078	-0.0019	0.0039	0.0029
rs7766029	C	38.32%	-0.0067	-0.0020	0.0009	-0.0004
rs2268493	C	55.66%	-0.0071	0.0005	0.0024	-0.0020
rs569207	T	50.89%	-0.0074	-0.0026	0.0038	0.0018
rs1799913	T	44.78%	-0.0063	-0.0015	0.0020	0.0122*
rs2267717	A	59.21%	-0.0100	-0.0011	-0.0028	0.0077
rs662	T	44.25%	0.0067	-0.0003	0.0007	-0.0023
rs41423247	C	49.85%	0.0062	-0.0007	0.0005	0.0068

Table 3
The 121 Candidate SNPs Analyzed and their Betas in the UKB (cont.)

rs7933505	A	45.38%	-0.0061	-0.0014	0.0020	0.0124*
rs1562027	A	22.93%	0.0066	0.0020	-0.0005	0.0044
rs1360780	T	22.31%	0.0064	0.0046	-0.0019	0.0006
rs12273539	T	67.21%	-0.0730	-0.0188	-0.0060	0.0331
rs7594560	C	61.81%	0.0081	0.0005	0.0003	0.0003
rs13355613	T	57.73%	-0.0064	-0.0014	0.0004	0.0048
rs737865	G	51.94%	0.0059	0.0004	-0.0017	-0.0028
rs1801133	A	50.90%	-0.0056	0.0018	0.0000	-0.0002
rs3800373	C	22.31%	0.0056	0.0047	-0.0011	0.0022
rs9470080	T	24.48%	0.0053	0.0048	-0.0028	0.0016
rs1799971	G	60.95%	0.0074	0.0046	-0.0025	0.0029
rs2270007	G	11.24%	0.0066	0.0006	0.0015	-0.0074
rs40184	T	39.87%	-0.0048	-0.0008	0.0003	0.0019
rs9380526	C	23.07%	0.0050	0.0048	-0.0029	0.0015
rs9534511	T	32.54%	0.0045	0.0008	-0.0011	-0.0026
rs2709376	T	4.60%	0.0129	0.0052	-0.0014	0.0040
rs2395634	A	22.67%	0.0047	0.0043	-0.0017	0.0010
rs6311	T	39.24%	0.0043	0.0010	-0.0009	-0.0022
rs2304672	C	6.04%	0.0077	-0.0035	0.0011	0.0023
rs9296158	A	23.47%	0.0044	0.0044	-0.0017	0.0010
rs497068	G	29.51%	0.0040	-0.0022	0.0050	0.0043
rs6198	C	61.14%	0.0054	0.0010	-0.0011	0.0102
rs6190	T	70.81%	0.0116	0.0052	-0.0057	0.0057
rs16147	T	32.91%	-0.0037	-0.0003	0.0007	0.0054
rs2963238	G	31.50%	-0.0038	0.0008	-0.0006	-0.0059
rs1819741	C	49.41%	-0.0040	-0.0008	-0.0016	0.0009
rs7997012	A	23.79%	-0.0034	-0.0009	0.0002	-0.0029
rs4606	G	48.81%	-0.0038	-0.0008	-0.0016	0.0008
rs27048	T	42.67%	-0.0034	0.0010	0.0015	0.0000
rs4234955	G	24.48%	-0.0036	0.0000	0.0008	0.0000
rs4251417	T	66.49%	0.0052	0.0014	0.0020	-0.0132*
rs429358	C	62.61%	-0.0034	0.0033	-0.0003	0.0024
rs10482672	A	60.55%	0.0036	0.0003	-0.0017	-0.0049
rs324389	T	47.90%	0.0024	-0.0001	-0.0026	-0.0017
rs548583	A	29.79%	0.0021	-0.0023	0.0053	0.0038
rs1013940	G	67.66%	-0.0034	-0.0009	-0.0006	0.0013
rs2254298	A	15.02%	-0.0026	0.0012	0.0006	-0.0025
rs1490453	A	58.35%	-0.0016	-0.0009	-0.0013	0.0006
rs2253206	G	34.87%	-0.0011	-0.0008	0.0022	-0.0041
rs6330	A	44.86%	0.0007	0.0012	-0.0005	0.0073

Table 3
The 121 Candidate SNPs Analyzed and their Betas in the UKB (cont.)

rs33976516	G	67.26%	-0.0020	-0.0002	-0.0064	-0.0018
rs9534496	C	13.20%	0.0007	-0.0006	-0.0005	-0.0009
rs2020942	T	49.85%	0.0005	0.0015	0.0008	-0.0061
rs1611115	T	16.27%	-0.0002	-0.0007	-0.0004	0.0005

* denotes significance at the $p < 5 \times 10^{-8}$ genome-wide significance level