A Study of Subthreshold Hallucinatory Experiences and their Relationship to Genetic Liability for Schizophrenia

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ABSTRACT

Background

One of the hallmarks of schizophrenia is the presence of psychosis. However, subthreshold psychotic symptoms characterized by attenuated delusions and hallucinations also occur in healthy individuals from the general population. A body of evidence suggests that this phenomenon represents a continuum of schizophrenia, with severe and attenuated symptoms sharing a common genetic etiology. Hallucinations are one subthreshold psychotic symptom in which a clear continuum has been observed. The aim of this study is to assess if subthreshold hallucinatory experiences and schizophrenia share genetic liability.

Method

3,028 participants were administered the Launay-Slade Hallucination Scale (LSHS), which measures a predisposition to hallucinations, through Genes for Good, an online study of health and behavior. A genome-wide association study was conducted for subthreshold hallucinatory experiences. A polygenic risk score was then used to predict subthreshold hallucinatory experiences and assess the existence of a genetic correlation between the two.

Results

No reliable associations with hallucinatory experiences were found that reached genome-wide significance. None of the 124 previously established significantly associated schizophrenia risk variants were found to be significant after correcting for multiple testing. A polygenic risk score based on genetic vulnerability to schizophrenia was unable to successfully predict hallucinatory experiences with scores from the LSHS.

Conclusions

No substantial evidence was found to support the association between genetic liability for subclinical hallucinatory experiences and schizophrenia. The effect between subthreshold hallucinatory experiences and schizophrenia was too small to detect in our sample using a polygenic risk score.

INTRODUCTION

Schizophrenia is a severe neurodevelopmental disorder with lifetime morbid risk estimates around 1%. While the disorder prevalence may be low frequency, schizophrenia creates a disproportionately large human and economic cost, with a worldwide economic burden of $155.7 billion stemming from productivity and wage loss due to unemployment and premature death (Cloutier *et al*., 2016; Millier *et al*., 2014). No prevention methods exist for schizophrenia, and treatment is often only partially effective while causing severe side effects for many patients. Anti-psychotic medications have been available since the 1950s, however these medications have the highest non-adherence compared to medication for all other chronic diseases. This heavily contributes to relapse and suicide in psychotic patients (Lally & McCabe, 2015).

Despite this devastating impact on society, progress towards elucidating the specifics of genetic risk for schizophrenia has accelerated only recently. Decades of twin studies indicate that schizophrenia is up to 80% heritable, with early family studies suggesting that schizophrenia demonstrated polygenic inheritance patterns (Sullivan *et al*., 2003; Gottesman & Shields, 1967). More recent genome-wide association studies (GWAS) have supported these initial findings by identifying specific genetic variants associated with schizophrenia case status and further hypothesizing the existence of hundreds or thousands more variants (Purcell *et al*., 2009). The Psychiatric Genomics Consortium (PGC) has conducted the largest schizophrenia GWAS to date and identified 128 risk variants within 108 loci, 83 of which were novel significant associations with the disorder (Ripke *et al*., 2014).

While genetic risk plays a significant role in liability for schizophrenia, it is thought to be a combination of genetic predisposition, environmental factors, and the interaction between the

two that ultimately leads to the development of the disorder. The large range of proposed environmental factors and a polygenetic architecture posed difficulties for early researchers to model the disease, and led to the application of a threshold model that represents vulnerability to the development of schizophrenia (Gottesman & Shields, 1967). This model, called the liability threshold model, includes all possible genetic and environmental risk and protective factors that contribute in a combinatorial manner to the overall phenotype, producing a continuous distribution that ranges from normal to extreme. According to this model, schizophrenia is only observed once the liability has surpassed a given threshold. This multifactorial threshold model necessitates that individuals will exist below the threshold for diagnosis and therefore who do not develop the disorder, but who have a relatively high liability for schizophrenia.

In fact, it was observed in family studies that a higher than expected rate of attenuated psychotic behavior was observed in close relatives of those experiencing clinical psychosis. Based off of these observations, psychologist Sandor Rado proposed the schizotype, a genetic composition and environmental interaction that produced a set of personality traits and odd behavior (Sheen, 2004). A decade later, Paul Meehl expanded upon these ideas by arguing that a single gene, the schizogene, caused schizoptypy which he defined as the latent personality organization of attenuated symptoms of schizophrenia in the general population. It is then personality components, like anxiety and introversion, or environmental stressors that cause a schizotypal individual to develop a clinical psychotic disorder (Meehl, 1960; Kwapil & Barrantes-Vidal, 2015). These early ideas paired with more recent studies of subclinical populations have given rise to the fully dimensional approach in which schizotypy is considered a continuous and normal distribution of this personality of genetic vulnerability in which only the most extreme cases will result in a clinical disorder.

One of the central pillars of evidence for a shared causal mechanism between schizophrenia and subclinical psychosis is the high rate of schizoptypy in close relatives of schizophrenic patients. One study found not only do these family members exhibit subclinical psychotic behaviors, but these types of behaviors can also be predicted based off the symptoms of the clinically affected family member. Positive schizotypy was successfully predicted in relatives of patients with a non-affective psychotic disorder with the presence of positive psychotic symptoms (Fanous *et al*., 2001).

Further support for the idea of a psychosis continuum comes from the 2014 PGC schizophrenia analysis. Generally, the more genes that are involved in determining a trait, the more continuous the distribution of phenotype will be. A disorder with a minimum of 128 significant genetic risk variants is by definition polygenic, and thus would create a continuum of phenotypes. In addition to conducting a meta-analysis on schizophrenia, the PGC was also able to successfully predict schizophrenia case status based off the discovered risk variants, which is another indication the disorder must be highly polygenic in order for a wide range of variants to achieve success in predicting the existence of a trait.

Another source of genetic evidence for the schizophrenia continuum stems from a well-studied microdeletion on chromosome 22. 22q11.2 deletion syndrome is the single greatest genetic risk factor for developing schizophrenia, with approximately 1 out of 3 affected individuals developing schizophrenia or another psychotic disorder by early adulthood (Karayiorgou *et al*., 2010). This provides a useful opportunity to study genetic liability to schizophrenia, as this population carries a 25-fold increased risk of experiencing a form of psychosis. One study of subclinical psychosis in 22q11.2 patients found that 85% of the individuals experienced at least one subthreshold psychotic symptom whether it is a positive,

negative, or disorganized symptom. Thirty-three percent of patients reported experiencing perceptual abnormalities or hallucinations specifically (Tang *et al.,* 2014). These values are much larger than those that would be expected for the normal population.

The proposed schizophrenia spectrum is comprised of a heterogeneous array of symptoms all occurring with differing levels of severity across a spectrum of unaffected to high clinical relevance, within individuals at the same level of clinical relevance, and possibly within one individual over the course of the disorder. Due to this fact, psychotic experiences can be and often must be measured using a diverse variety of instruments. One of the most common methods is to administer questionnaires that measure subclinical psychotic experiences. This study utilized the Launay-Slade Hallucination Scale, a widely used questionnaire designed to measure a predisposition for hallucinatory experiences, one component of subclinical psychotic experiences (Launay & Slade, 1981). This instrument has been successfully used to measure hallucinatory experiences with nonclinical populations, psychiatric patients, and as a general measure for nonclinical psychosis (Vellante *et al*., 2012 ; Levitan *et al*., 1996; Mittal *et al*., 2013). Hallucinatory experiences measured on this scale are estimated to be 33% heritable (Hur *et al.,* 2012).

The aim of this study was to investigate the existence of a common genetic basis between subthreshold hallucinatory experiences and schizophrenia. To achieve this, a genome-wide association study using the Genes for Good responses to the Launay-Slade Hallucination Scale will be conducted in addition to a polygenic risk score that will be used to predict subclinical hallucinatory experiences based on a sum of risk alleles for schizophrenia determined by the PGC meta-analysis. A study with similar methods was conducted in 2014 with older PGC schizophrenia data in relation to a more general subclinical psychotic phenotype but was unable

to identify significant associations with subclinical psychosis or provide evidence of a genetic association between the two traits (Zammit *et al*., 2014). The present study aims to build upon previous work by using a more specific subclinical phenotype and using schizophrenia associated genetic variants that have since been discovered to evaluate one component of the proposed schizophrenia spectrum.

METHODS

Participants

Participants were collected from Genes for Good (GFG), an online genetic study of health and behavior at the University of Michigan. The study is conducted through social media using the Facebook App Platform where participants complete surveys and interactive tasks online that relate to health and behavior. Participation is open to anyone over 18 with a mailing address in the United States. The option to send in a saliva sample for genotyping is available to participants who complete a certain number of surveys. At the time of writing, over 26,026 people have participated in the study and over 6,610 DNA samples have been genotyped.

The present study took responses from 14,647 participants aged 18-70 who took the GFG Mental Health survey by January 2017. A subset of 3,028 Genes for Goods participants aged 19-70 (mean = 45.2, SD = 16.8) was included in the association analysis. This subset was selected from the total pool of survey participants based on European ancestry in addition to the availability of imputed genotyped data and demographic covariate data. A principal component analysis (PCA) was constructed and superimposed onto 1000 Genomes PCAs for comparison, and this was used to determine European ancestry.

Measures

Subthrehold psychotic experiences were quantified by calculating a sum of scored responses from an amended form of the Launay-Slade Hallucination Scale in which ten out of the twelve original items are reordered and positively coded.

Genotyping

DNA extraction and genotyping was performed at the University of Michigan Sequencing Core. All participants were genotyped on Illumina Human CoreExome bead chip array, which includes 250,000 common genetic variants to serve as a genotype imputation scaffold, 250,000 low frequency variants and rare variant custom content. Phasing was conducted using SHAPEIT (Delaneau, Marchini, & Zagury, 2012). Phased data was imputed to 1000 Genomes phase 3 using Minimac3 (Das *et al*. 2016) on an imputation webserver hosted at the University of Michigan (https://imputationserver.sph.umich.edu). Variants were filtered by imputation quality (Info score > 0.9) and by minor allele frequency (MAF > 0.001). 46,961,304 total sites were imputed.

Association Test

Single variant association tests were conducted with a fast linear mixed model score test using Rvtests (Zhan *et al*. 2016). Sex, age, age squared, and 10 genetic principal components were included as covariates in the analysis. 21,006,934 imputed variants were included in the analysis.

In total, 128 variants were identified as genome-wide significant in the Psychiatric Genomic Consortium's most recent meta-analysis of schizophrenia. In the present study, single variant tests will be done with the 128 PGC significant SNPs to see if any reach significance in the GFG sample. Chromosome X was not included in the present analysis, so the three PGC significant SNPs on chromosome X were not used. Additionally, the PGC used 1000 Genomes phase 1 as the reference panel for imputation, whereas the GFG genotypic data was imputed using 1000 Genomes phase 3. 1 PGC variant was not imputable on the 1000 Genomes phase 3 panel, and thus, only 124 out of the 128 variants will be used in the comparison.

Polygenic Risk Score

Polygenic risk score profiling is a technique that weights risk alleles from an independent association test according to their effect sizes, and then uses a sum of these risk variants and their respective weights to predict a trait in a target population. This method is incredibly useful as even when no significant associations are found, a genetic effect can still be shown (Dudbridge, 2013). The equation used for the polygenic risk score for an individual *i* for variants *j* through *n* is found below:

$$PRS_i = \sum_{j=1}^{n} \ln(\text{PGC } OR_{ij}) \times (no.\,of\ risk\ alleles_{ij})$$

The effect size in the present case is the log of the odds ratio taken from the PGC meta-analysis. This procedure is conducted including all SNPs with a *p*-value less than 5×10^{-8}. The same protocol is then repeated for *p*-value threshold increasing by an order of magnitude up to 5×10^{-1}, with more SNPs being included for each threshold. To account for SNPs in linkage disequilibrium, the PGC SNPs were pruned. Starting with the most significant SNP from the

PGC results, any SNPs 250 kilobases upstream and 250 kilobases downstream of the significant SNPs that had a linkage disequilibrium $r^2 > 0.01$ were removed. This was conducted for each significant PGC SNP in order of their significance.

RESULTS

The GFG Mental Health Questionnaire showed acceptable internal consistency with a Cronbach's alpha of 0.84. All items taken from the Launay-Slade Hallucination Scale and the mean responses are listed in Table 1. Scores from the scale were calculated by summing scored responses from each item. Possible scores range from 10-50, where 10 is strongly not endorsing any item and 50 is strongly endorsing each item. The average score in this sample was 20.6 (sd = 7.9). The 3,028 participants who were included in all analyses were 69.7% female with a mean age of 45.02. (sd= 16.76).

The Manhattan plot shown in Figure 1 includes all 21,006,934 SNPs included in the association analysis. One SNP, rs73525536 ($p= 6.3 \times 10^{-9}$) showed genome-wide association with subthreshold hallucinatory experiences. Figure 2 shows the quantile-quantile (Q-Q) plot for all 21,006,934 variants used in the association analysis. Overall, the plot shows acceptable variation from the expected *p*-values under the null hypothesis. The genomic control was 1.05.

Single variant tests were conducted on the GFG sample using 124 of the 128 significant schizophrenia variants from the PGC's 2014 meta-analysis. After correcting for only 128 genome-wide significant variants from the PGC paper, no SNPs were found to be significant ($p < 0.05/124 = 3.9 \times 10^{-4}$). A Q-Q plot for the 124 variants selected from the PGC analysis shown in Figure 3 shows some deviation from the expected values under the null hypothesis. Genomic control for all analyzed variants was 1.18.

Polygenic scores based on genetic risk for schizophrenia were not significantly correlated with scores on the Launay-Slade Hallucination Scale. The R^2 coefficients ranged from -0.03 to 0.001 with the $p < 0.5$ threshold showing the largest correlation.

DISCUSSION

This study aimed to examine the overlap between genetic liability for schizophrenia and subclinical hallucinatory experiences. This was done by comparing genome-wide association results of hallucination proneness to the results of the PGC schizophrenia GWAS. A polygenic risk score was then conducted using the PGC results to attempt to predict hallucinatory experience. Overall, no strong evidence was found to suggest that genetic variants associated with schizophrenia share a genetic etiology with subthreshold hallucinatory experiences. None of the 124 PGC significant SNPs were found to be significant in the GFG sample. However, the Q-Q plot in Figure 3 shows deviation from expectation under the null hypothesis with a genomic control of 1.18. Although no individual SNP showed significance, this suggests that the schizophrenia-associated variants are slightly more significantly associated with hallucinatory experiences than a non-associated trait would be. The results from the polygenic risk score show the correlation between the predicted level and the actual score of hallucinatory experiences was too small to be detected in the present analysis. One SNP, rs73525536, achieved genome-wide significance ($p < 5 \times 10^{-8}$, MAF = 0.013), however it is unlikely to be a reliable association. Variants in high linkage disequlibrium with this SNP did not show significance or even approach significance, as would be expected in a true association. Furthermore, this SNP is intergenic and not near any relevant protein coding genes, consistent with the assertion this is an undependable association. However, the null results are consistent with a similar study that was unable to

identify genetic associations with subclinical psychosis or able to predict subclinical psychosis through conducting a polygenic risk score with schizophrenia associated variants (Zammit *et al*., 2014). The aim of the present study was to provide evidence for association with hallucinatory experiences to support the larger idea that subclinical psychosis may be genetically continuous with schizophrenia. Thus a narrower phenotype and knowledge of the 83 novel schizophrenia associated variants that previous studies did not have access to was utilized, but no evidence of association could be produced.

One possible explanation for these results could be that subclinical psychosis has a lower suggested heritability than that of schizophrenia, and hallucinations have been suggested to show one of the lowest heritability estimates across positive, negative and cognitive symptoms of subclinical psychosis (Walter *et al*., 2016). Two other positive symptoms, grandiosity and paranoia, showed higher heritability estimates than that of hallucinatory experiences (Zavos *et al*., 2014). Hallucinations also show a much larger environmental etiological component than the other positive symptoms, with environmental factors such as childhood sexual trauma possessing a dose-response relationship with the quantity of hallucinations and lowering the age of onset of hallucinations in subclinical individuals (Larøi, 2012). These factors could make genetic associations with hallucinatory experiences more difficult to identify and require more power to do so. The sample size of 3,028 participants used in the GWAS provided limited power to detect associations for subclinical psychosis, however the polygenic risk score was not burdened by this limitation to the same degree, as the PGC discovery sample used had 79,845 individuals. This polygenic risk score had the power to detect a correlation of 0.05 with 80% power. This suggests that the effect of the correlation between genetic liability for schizophrenia and subthreshold hallucinatory experiences is smaller than 0.05.

This study has some important limitations that are necessary to consider. Genes for Good does not ask if a participant has ever been diagnosed with a clinical psychotic disorder, so there is no method to remove these individuals from our analysis of a non-clinical population. Additionally, the Launay-Slade Hallucination Scale was administered without an instruction to disregard hallucinatory experiences that occurred while under the influence of any drugs. Drugs acting on a wide spectrum of brain systems have been known to cause drug-induced psychosis but can also cause less severe psychotic like experiences (Murray *et al*., 2009;). The assumption made in this study is that a high score on the hallucination proneness scale is representative of a genetic predisposition to hallucinations. By grouping together participants with a genetic predisposition to hallucinate with participants who have experienced hallucinations due to environmental influences, identifying associated genetic variants becomes more difficult. More research is necessary in the area of drugs and the interactions with psychotic behavior, as the relationship and interactions are still somewhat unclear. For instance, GWAS results have suggested the possibility that a genetic predisposition for methamphetamine-induced psychosis exists, and that this genetic risk may be shared with the risk for schizophrenia (Murray *et al*., 2009; Ikeda *et al*., 2013*)*.

Subclinical psychotic experiences are generally first experienced during adolescence through early twenties (Zavos, 2014). The majority of the Genes for Good sample is older than adolescence; however, there is a subset of participants who have not passed the average age of onset for schizophrenia. Subclinical psychotic symptoms remain persistent in 20% of individuals that have experienced psychotic like experiences, and a clinical psychotic disorder is diagnosed in about 7% (Van Os & Reininghaus, 2016). This presents the possibility that the symptoms experienced by the youngest participants could be a part of the schizophrenia prodrome. If this

were the case, comparing the genetic liability to schizophrenia and the genetic liability to subclinical symptoms could be problematic, as our sample is no longer exclusively comprised of healthy individuals from the general population.

Despite these limitations, this study had the potential to identify specific risk variants associated with subthreshold hallucinatory experiences. The majority of the previous genetic research for hallucinations has been conducted with psychiatric or ultra-high-risk populations and not within the general population. Unaffected individuals are important for studying the continuum of hallucinations and psychosis, and the Genes for Good sample provides information not collected through hospitals or clinics. While genetic support is building for the idea of subclinical psychotic experiences such as hallucinations being located on the schizophrenia spectrum, it has mainly emerged through twin studies, estimates of heritability, and inheritance patterns. Specific overlapping genetic variants between the extreme and attenuated hallucinatory experiences have yet to be identified, something studies such as the present one seek to find. At the time of writing, this is the largest GWAS conducted specifically for subthreshold hallucinatory experiences. Once the next set of genotype data is released by Genes for Good, the sample size used will roughly double. This analysis will then have the ability to detect a correlation of 0.035 with 80% power between hallucinatory experiences and schizophrenia.

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Table 1: Mean endorsement of Launay-Slade Hallucination Scale Items in Genes for Good sample

Item	Mean (SD)	N
No matter how hard I try to concentrate, unrelated thoughts always creep in my mind.	3.3 (1.4)	3024
In my daydreams I can hear the sound of a tune almost as clearly as if I were actually listening to it.	2.9 (1.5)	3024
Sometimes my thoughts seem as real as actual events in my life.	2.5 (1.4)	3024
Sometimes a passing thought will seem so real that it frightens me.	2.2 (1.4)	3022
The sounds I hear in my daydreams are usually clear and distinct.	2.4 (1.4)	3023
The people in my daydreams seem so true to life that I sometimes think they are.	1.6 (1.1)	3024
I often hear a voice speaking my thoughts aloud.	1.7 (1.2)	3024
In the past I have had the experience of hearing a person's voice and then found that no one was there.	1.8 (1.3)	3022
On occasions I have seen a person's face in front of me when no one was in fact there.	1.3 (0.8)	3023
I have been troubled by hearing voices in my head.	1.2 (0.6)	3025
Average	**2.09 (0.7)**	

Note: SD = standard deviation, N= sample size

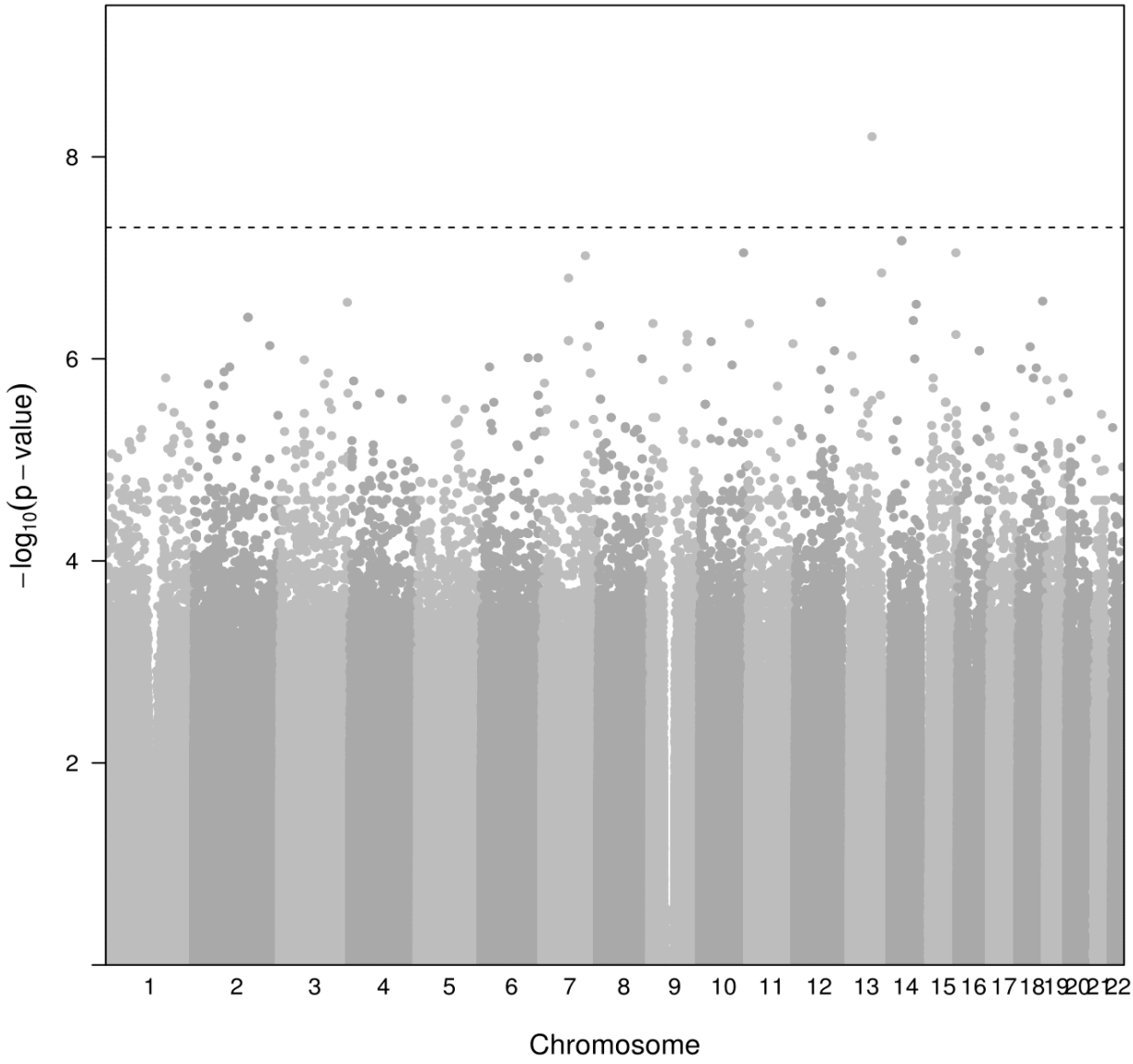

Figure 1. Manhattan plot of 21,006,934 variants analyzed in a genome-wide association study (GWAS) for subthreshold hallucinatory experiences in 2,038 participants from the Genes for Good sample. The dashed horizontal line marks the p-value threshold for significance ($p < 5 \times 10^{-8}$).

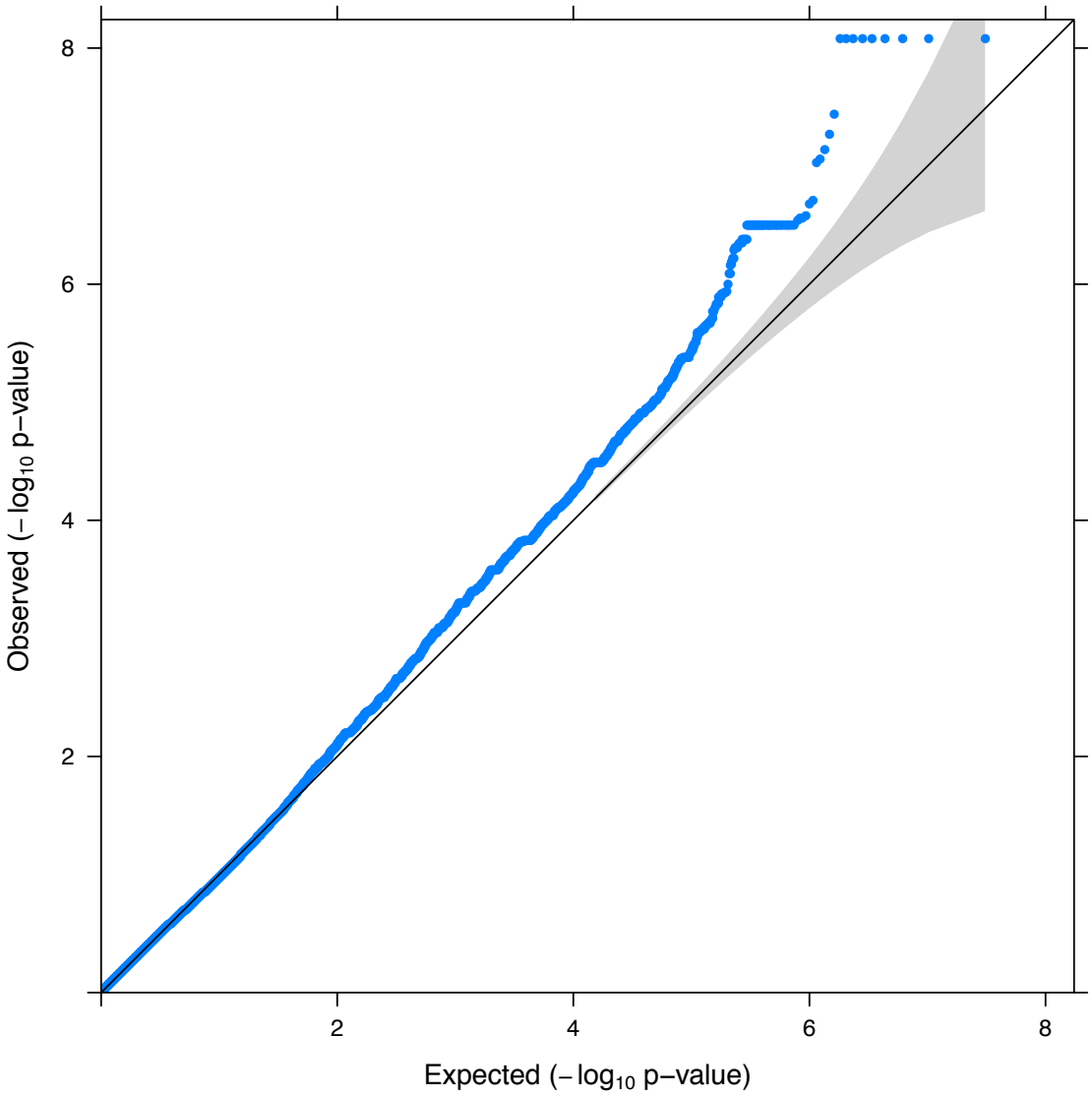

Figure 2. Q-Q plot of the p-values for all variants tested in the association test of subclinical psychotic experiences in a Genes for Good sample. The grey shaded region represents the 95% confidence interval under the null hypothesis. The genomic control (λ) was 1.05.

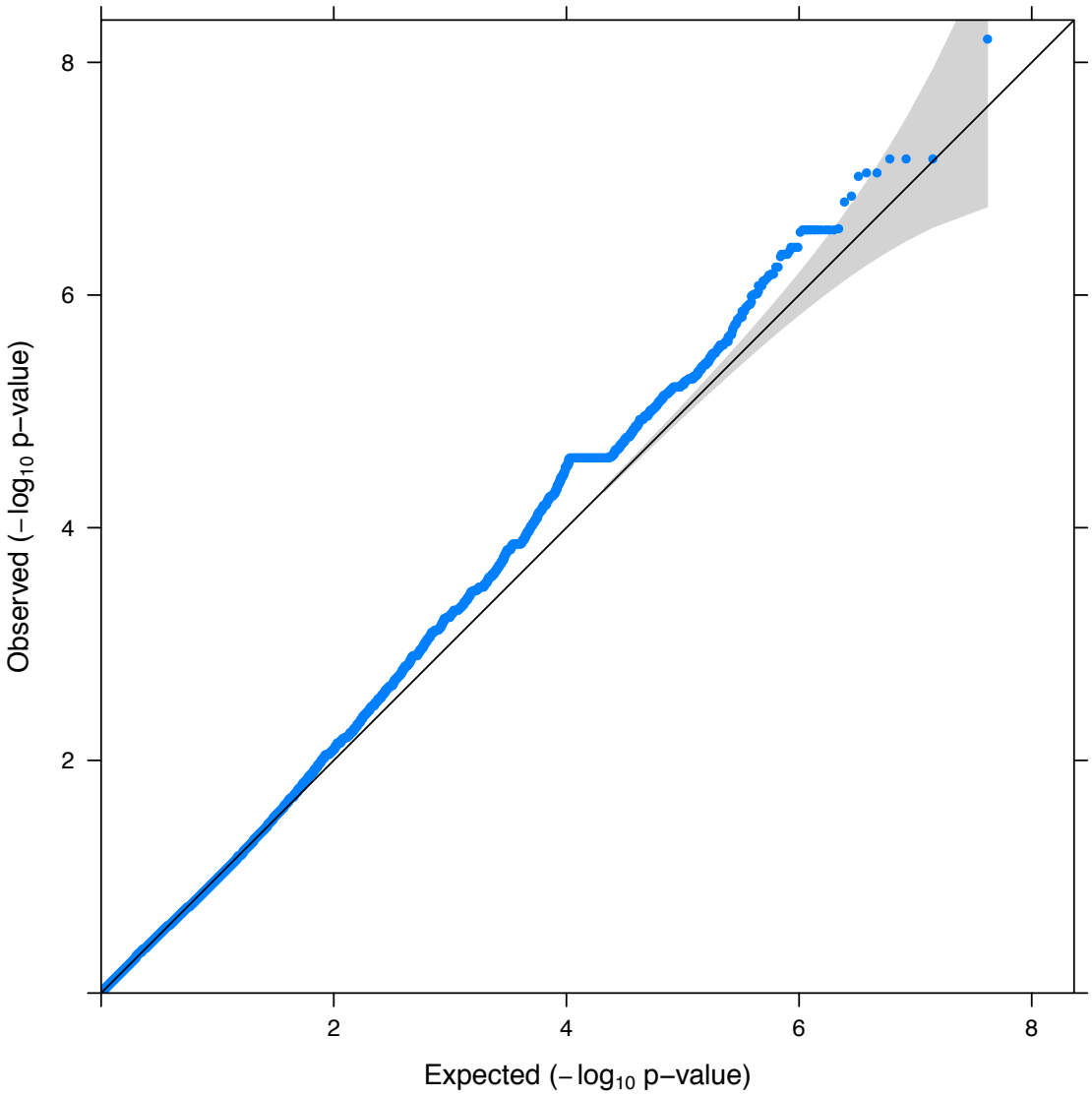

Figure 3. Q-Q plot of the 124 PGC significant variant p-values of subclinical psychotic experiences in a Genes for Good sample. The grey shaded region represents the 95% confidence interval under the null hypothesis. The genomic control (λ) was 1.18.