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Genome-Wide Significant Localization for Working and Spatial Memory: Identifying Genes for Psychosis Using Models of Cognition

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Abstract

It is well established that risk for developing psychosis is largely mediated by the influence of genes, but identifying precisely which genes underlie that risk has been problematic. Focusing on endophenotypes, rather than illness risk, is one solution to this problem. Impaired cognition is a well-established endophenotype of psychosis. Here we aimed to characterize the genetic architecture of cognition using phenotypically detailed models as opposed to relying on general IQ or individual neuropsychological measures. In so doing we hoped to identify genes that mediate cognitive ability which might also contribute to psychosis risk. Hierarchical factor models of genetically clustered cognitive traits were subjected to linkage analysis followed by QTL region-specific association analyses in a sample of 1,269 Mexican American individuals from extended pedigrees. We identified four genome wide significant QTLs, two for working and two for spatial memory, and a number of plausible and interesting candidate genes. The creation of detailed models of cognition seemingly enhanced the power to detect genetic effects on cognition and provided a number of possible candidate genes for psychosis.

Keywords

schizophrenia; genetics; cognition; GWAS; linkage

Introduction

Genetic factors are important for developing a psychotic disorder, the heritability for schizophrenia and bipolar disorder, the two most common psychotic illnesses, are both above 0.80 (Sullivan et al., 2003; McGuffin et al., 2003). While recent genome-wide association studies have successfully localized a number of statically significant risk loci, these findings only explain a fraction of the genetic variance associated with psychotic illnesses. A complementary approach for identifying psychosis risk genes is to use focus on endophenotype (Gottesman and Gould, 2003), heritable non-diagnostic measures that are genetically related to the illness. Comprehensive neuropsychological research has established cognitive impairment as an intrinsic feature of psychosis (Reichenberg and Harvey, 2007). Impairments are evident in numerous cognitive domains but one of the most consistently reported is in memory, particularly in working and spatial memory (Park and Holzman, 1992; Heinrichs and Zakzanis, 1998; Lee and Park, 2005; Glahn et al., 2003; Glahn et al., 2006). Cognition, and more specifically memory, has utility as an endophenotype of psychosis. There is substantial overlap between the genetic factors that mediate psychosis risk and those that mediate both general cognition and working memory ability (Toulopoulou et al., 2007; Toulopoulou et al., 2010; Owens et al., 2011). Plus, there are clear familial effects such that unaffected relatives exhibit spatial memory impairment that is intermediate between that of affected probands and healthy controls (Glahn et al., 2010; Glahn et al., 2007a; Bora et al., 2009; Hoff et al., 2005; Sitskoorn et al., 2004). Therefore, isolating genes for memory may be a fruitful approach for identifying psychosis risk genes.

Despite high heritability estimates for cognition and general intelligence (which vary between 50–80%), multiple attempts to isolate specific causative genes have been met with difficulty (Deary, 2012). The reasons for this are twofold. Firstly, the high heritability estimates reported for intelligence reflect the overall cumulative genetic effect on a trait but do not reveal the subtle complexities therein or the specific composition and architecture of the underlying causal genes (Almasy, 2003). Secondly there is substantial phenotypic complexity associated with intelligence which has been largely overlooked in molecular genetic studies, with most gene discovery studies focusing instead on measures of general IQ or individual neuropsychological tasks (Deary et al., 2009). Over a century of rigorous investigation into the sources of individual variation in cognitive ability has resulted in a consensus that the structure of cognition is best described as a three-tier taxonomy. This taxonomy is characterized by a general, or 'g', factor that subsumes several strongly and positively correlated cognitive domains onto which load individual neuropsychological tasks (Carroll, 1993). Typically, *g* accounts for over half of individual differences in cognitive ability but individual cognitive domains also reflect domain-specific abilities (Plomin and Spinath, 2002). This view is largely consistent with findings from cognitive neuroscience that suggest that specific domains are associated with relatively distinct brain circuits (Lenartowicz et al., 2010). This line of thought suggests that identifying genes that influence distinct cognitive domains may be more tractable than finding genes for general intelligence (van der Sluis et al., 2010), particularly given that a domain-specific approach is essentially

a multivariate one and so it remains statistically more powerful than univariate analyses of individual neuropsychological tasks (Bearden and Freimer, 2006).

We report on linkage and association analyses for cognitive domains derived from neuropsychological measures in a sample of 1,269 individuals from large extended pedigrees. The aim of this study was to characterize in detail the genetic basis of cognition and in so doing, isolate potential risk genes for psychosis. We implemented an approach whereby individual traits were genetically clustered (versus the more conventional approach utilizing phenotype clustering) to create phenotypically detailed and genetically informed models of cognition including both a *g* factor and specific cognitive domains. These factors were then included in linkage and association analyses to reveal a series of genomic regions for distinct aspects of cognition.

Methods

Participants

The sample comprised 1,269 Mexican American individuals from extended pedigrees (75 families, average size 16.28 people, range = 2–131) as well as 58 spouses with no biological relationship to other individuals in the study. The sample was 63% female and had a mean age of 44.78 (SD = 15.19; range = 18–97). Individuals in this San Antonio Family Study cohort have actively participated in research for over 18 years and were randomly selected from the community with the constraints that they are of Mexican American ancestry, part of a large family, and live within the San Antonio region (see (Olvera et al., 2011) for recruitment details). The Mini International Psychiatric Interview (MINI-Plus) was administered to all individuals. The prevalence of psychiatric disorders in the present sample are as follows: Lifetime Depression (33%), Recurrent Depression (18%), Anxiety Disorders (19%), (Hypo)Mania (2%), Dysthymia (0.5%), Alcohol Disorders (32%), Substance Disorders (13%), Schizoaffective Disorder (0.7%), Schizophrenia (0.5%).

All participants provided written informed consent before participating in any aspect of the study.

Neuropsychological Assessment

As part of the “Genetics of Brain Structure and Function” protocol, each participant was required to complete a 90-minute neuropsychological test battery consisting of standard and computerized measures (Glahn et al., 2010; Glahn et al., 2007b). Eighteen neurocognitive variables were derived from thirteen separate neuropsychological tests, including measures of attention, executive processing, working memory, declarative memory, language processing, intelligence and emotional processing (see Table 1). In addition, the vocabulary and matrix reasoning subtests of the WASI were administered and a formal IQ measure was derived. Subjects were tested in their choice of language, of the entire sample 9% were tested in Spanish and the remainder were tested in English.

Data Analysis

Genotyping

Subjects were genotyped for approximately one million SNPs using Illumina HumanHap550v3, HumanExon510Sv1, Human1Mv1 and Human1M-Duov3 BeadChips, according to the Illumina Infinium protocol (Illumina, San Diego, CA). SNP loci were checked for Mendelian consistency utilizing SimWalk2 (Sobel and Lange, 1996). SNPs or samples exhibiting high calling rate failures or requiring excessive blanking (i.e., if <95% of the genotypes are retained) were eliminated from analyses. Missing genotypes were imputed according to Mendelian laws based on available pedigree data using MERLIN (Abecasis et al., 2002). Maximum likelihood techniques, accounting for pedigree structure, were used to estimate allelic frequencies (Boehnke, 1991). Estimates of allelic frequencies were formally tested and found to be in Hardy-Weinberg equilibrium. For linkage analyses, multipoint identity-by-descent (IBD) matrices were calculated based on 28,387 SNPs selected from the 1M GWAS panel as follows. Using genotypes for 345 founders, SNPs on each chromosome were selected to be at least 1kb apart, MAF $\geq$ 5%, and LD within a 100kb sliding window not exceeding $|\rho| = 0.15$. The resulting selection averaged 7–8 SNPs/centimorgan. For each centimorgan location in the genome, multipoint IBD probability matrices were calculated using a stochastic Markov Chain Monte Carlo procedure implemented in the computer package, LOKI (Heath, 1997).

Quantitative Genetic Analyses

All genetic analyses were performed in SOLAR (Almasy and Blangero, 1998). SOLAR implements a maximum likelihood variance decomposition to determine the contribution of genes and environmental influence to a trait by modeling the covariance among family members as a function of genetic proximity. The genetic contribution to a trait is represented by the heritability, or h^2 , index. First, univariate variance decomposition analysis was applied to all individual neuropsychological variables and any trait with a $h^2 < 0.20$ was dropped from subsequent analyses. All traits were normalized using an inverse Gaussian transformation. Age, age², sex, testing language and the presence of major depressive disorder or an anxiety disorder were included as covariates and the residuals were retained for later analysis. Second, bivariate analysis was applied to all pairs of variables where the phenotypic covariance between two traits was decomposed into its genetic and environmental constituents to determine the extent they are influenced by shared genetic effects (e.g. genetic correlation).

Cognitive Modeling Analysis

Hierarchical cluster analysis, as implemented in R (R Development Core Team, 2011), was applied to the estimated genetic correlation matrix (described above) to establish groups of genetically related cognitive traits. Traits that share the greatest degree of genetic overlap were clustered together in domain-specific factors. First, the genetic correlation matrix was converted into a matrix of dissimilarity scores by subtracting the absolute value of each correlation from 1. Agglomerative clustering was then applied to this matrix of distance scores. This method of clustering begins with n clusters where each cluster represents a single item then, at each step, two clusters are fused together in accordance with the distance

values. This analysis was interpreted using a dendrogram plot where similar traits are on the same limb of the tree and distinctly different traits are placed on other limbs (Crawley, 2007).

The resultant clusters of traits were then fit as confirmatory factor models using Mplus (Muthén and Muthén, 2011). This analysis was applied to the residuals from the univariate genetic analysis (where the effects of age, sex and testing language were covaried). To appropriately estimate standard errors and X^2 statistics, family structure was taken into account using the *cluster* command in Mplus. Each factor model was assessed in terms of both model fit and the strength and significance of the factor loadings. Typically a significant X^2 is suggestive of poor model fit. However given the large sample size, less weight was attributed to this index (Kline, 2005). The included model fit estimates were as follows: X^2 , RMSEA, CFI, TLI and SRMR. For RMSEA a value which is below .05 is considered excellent fit. For CFI and TLI a value greater than .90 is indicative of good fit and of .95 excellent fit. For SRMR a value below .10 is considered a good fit. Once a factor model was established factor scores were derived for each individual participant and saved for subsequent analysis.

Two model types were fitted to the cognitive data. Both models included domain specific and general factors but the relationships between the factors differed in each model. First, a hierarchical model was fit. This model assumed that the individual cognitive domains represent highly correlated facets of general intelligence, or *g*. Second, a non-hierarchical bi-factor model where the overlap between individual cognitive tests is captured by a *g* factor along with specific uncorrelated factors which represent domain-specific cognitive abilities independent of *g* (Holzinger and Swineford, 1937).

Linkage and Genome Wide Association Analyses

Quantitative trait linkage analysis was performed to localize specific chromosomal locations influencing cognitive factors (Almasy and Blangero, 1998). Model parameters were estimated using maximum likelihood. The hypothesis of significant linkage was assessed by comparing the likelihood of a classical additive polygenic model with that of a model allowing for both a polygenic component and a variance component due to linkage at a specific chromosomal location (as evidenced by the location-specific identity-by-descent probability matrix). The LOD score, given by the log10 of the ratio of the likelihoods of the linkage and the polygenic model, served as the test statistic for linkage. Genome-wide thresholds for linkage evidence were computed with correction for both the number of loci tested per genome and the effective number of traits. Briefly, using a method derived from (Feingold et. al., 1993), genome-wide p-value thresholds were computed as a function of the average marker density (linkage SNPs per centiMorgan) and the mean recombination frequency given the complexity of the specific pedigrees used in this study; these p-values were then converted to LOD scores. In our case, a LOD of 1.69 is required for suggestive significance (likely to happen by chance less than once in a genome-wide scan) and a LOD of 2.9 is required for genome-wide significance. These thresholds per linkage scan were further penalized for the effective number of traits, calculated using the method outlined by Cheverud (2001). (Simply dividing by the total number of traits would be over-conservative

to the extent that they are correlated.) Applying this method to the genetic correlations between the factor scores reveals that we have 3.86 effective traits. Any region demonstrating potential pleiotropic effects (i.e., linkage to multiple traits) was further investigated using bivariate linkage (Almasy et al., 1997). The null hypothesis of linkage of a particular locus to *both* traits was tested against the alternative of linkage to neither by comparing the likelihoods of the relevant nested models; this joint test can be more powerful than the respective univariate tests if the traits are genetically correlated. The $\ln(\text{likelihood ratio})$ statistic for this test is distributed as a mixture of 1 and 2 df chi-squares (Self and Liang, 1987); this p-value is converted to a 1 df equivalent LOD for ease of comparison to the univariate linkage tests.

Any genomic region meeting genome-wide significance for linkage was further assessed using association analysis of the cognitive trait and the genetic variants encapsulated by the linkage peak; association models included both the fixed effect of the focal SNP and the random effects of local and polygenic heritability (Blangero, 1993). Statistical significance levels were established according to the effective number of tested variants given the linkage disequilibrium (LD) structure in the region (Moskvina and Schmidt, 2008). In more detail the pairwise genotypic correlations are calculated in an effort to establish the effective number of independent tests carried out during association analysis. The Moskvina and Schmidt (2008) method, is considered a conservative method and entails computing the eigenvalues of the genotypic correlation matrix. A corrected p-value is obtained from a Bonferroni correction based on the nominal alpha ($= 0.05$) and the total number of independent tests.

Results

Genetic Analysis of Cognitive Measures

Heritability estimates for individual cognitive measures are shown in Table 1. All cognitive traits were found to be moderately to strongly heritable. The estimated pair-wise phenotypic and genetic correlations are shown in Table S1. Phenotypic correlations are predominantly moderate to strong, of which a substantial amount is due to genetic overlap.

Cognitive Factor Models

Figure 1 shows the results of the hierarchical cluster analysis applied to the genetic correlation matrix. Four main clusters emerged from the data including: Verbal Memory, Working Memory, Spatial Memory, and Executive Function.

A model including the four clusters plus a g factor was fit to the neuropsychological data (see Figure 2A). The fit of this model was good, X^2 was significant ($X^2_{99} = 343.850, p < .001$) but other fit indices suggested that the model was a good fit (RMSEA = .049 (95% CI = .044 – .055, $p = .579$), CFI = .950, TLI = .940, SRMR = .042). All factor loadings were significant at the $p < .001$ level.

This model was re-specified as a bi-factor model where the g factor and memory factors were forced to be completely orthogonal (see Figure 2B). The executive factor was dropped as when measures from this factor were allowed to load on g , the loadings exceeded 1,

suggesting multicollinearity between these measures and g . The model fit the data well, X^2 was significant ($X^2_{25} = 58.873, p < .01$) but other fit indices suggested that the model was a good fit (RMSEA = .036 (95%CI = .024 – .048, $p = .977$), CFI = .991, TLI = .984, SRMR = .023). All factor loadings were significant at the $p < .001$ level.

Linkage Analysis

QTL localization results are summarized by the maximum LOD scores observed for each factor in the hierarchical and non-hierarchical models as shown in Table 2. For the general cognition model, one factor exhibited genome-wide significant QTLs and the remaining factors showed suggestive significance. For working memory two clear linkage peaks emerged on chromosome 8, one at ~89 cM (LOD = 3.298, adjusted $p = 0.007$) and the other at ~142 cM (LOD = 4.239, adjusted $p = 0.072$) which suggests that there are QTLs associated with working memory at chromosomal locations 8q21.11–13 and 8q24.22 respectively (see Figure 3A). The verbal memory (LOD = 2.028) and spatial memory (LOD = 2.693) factors also showed suggestive significance at chromosomal locations 22q.11.21 and 7q36.1, respectively.

When the memory factors of the hierarchical model were re-specified as a bi-factor model one factor exhibited a genome-wide significant QTL. The best univariate score for spatial memory was found on chromosome 17 at ~94cM (LOD = 3.763, adjusted $p = 0.023$) and a second linkage peak for spatial memory was found on chromosome 17 at ~117cM (LOD = 3.503, adjusted $p = 0.065$) suggesting QTLs for spatial memory at 17q22–24.2 and 17q25.1–3, respectively (see Figure 3B).

Inspection of Figure 3A strongly suggests pleiotropy where regions of chromosome 8 appear to be implicated in all aspects of cognition to some degree. Bivariate linkage analysis was employed over chromosome 8 to investigate these potential pleiotropic effects. Table 3 shows the results of the bivariate linkage analysis and the pleiotropy tests, both the bivariate LOD scores, all of which exceed the critical value of 2.9, and the pleiotropy tests suggest that there is complete pleiotropy on chromosome 8 between working memory and the other cognitive domains in the general cognition model in the region of 8q24.22.

QTL-specific Association Analysis

Association analysis was conducted for all genetic variants under each genome-wide significant QTL (see Table 4). For the working memory factor taken from the general cognition model, there were two significant QTLs on chromosome 8. For the first QTL, two variants met the adjusted significance level of 2.8×10^{-5} (total number of SNPs = 3549, effective number of SNPs = 1833). The first SNP rs2467774 is located at 80,675,246 bp which is 999 bp downstream of the gene *HEY1* (*hairy/enhancer-of-split related with YRPW motif 1*) and had a p -value of 1.1×10^{-5} ; the second SNP rs723686 at 80,661,733 bp, was 13,513 bp downstream of *HEY1* and had a p -value of 1.2×10^{-5} (see Figure 4).

For the spatial memory factor taken from the bi-factor model there were two significant QTLs on chromosome 17. For the first QTL, two variants met the adjusted significance level of 5.3×10^{-5} (total number of SNPs = 1927, effective number of SNPs = 960). The first SNP

rs9907597 is located at 59,435,497 bp within the gene *BCAS3* (*breast carcinoma amplified sequence 3*) and had a p -value of 2.9×10^{-5} ; the second SNP rs12162165 is located at 58,582,538 bp within the gene *APPBP2* (*amyloid beta precursor protein (cytoplasmic tail) binding protein 2*) and had a p -value of 4.2×10^{-5} (see Figure 5A). For the second QTL on chromosome 17, one variant met the adjusted significance level of 4.9×10^{-5} (total number of SNPs = 1775, effective number of SNPs = 1038). The SNP rs1867467 is located at 74,959,497 bp, 13,026 bp downstream of the gene *MGAT5B* (*mannosyl (alpha-1,6)-glycoprotein beta-1,6-N-acetyl-glucosaminyltransferase, isozyme B*) and had a p -value of 4.2×10^{-5} (see Figure 5B).

Replication within the PGC schizophrenia data

Of the SNPs shown to be associated with cognition in the present manuscript one shows a significant association with schizophrenia risk in the GWA study published by the Psychiatric Genetics Consortium (PGC; Ripke et al, 2011). We checked the strength of association between the four SNPs shown to be associated with memory with schizophrenia risk using the Riopili (<http://www.broadinstitute.org/mpg/ricopili/>) database. Because we tested five SNPs a Bonferroni corrected α of 0.0100 was required. The SNP rs723686 on chromosome 8, which was significantly associated with working memory ability, also showed an association with schizophrenia risk ($p = 0.00728$; see Figure S1).

Discussion

Dissecting the genetic architecture of psychotic illnesses has been met with limited success when using diagnostic classification alone (Sullivan, 2005). This has led many in the field to focus instead on endophenotypes (Gottesman and Gould, 2003). In the present manuscript we used detailed phenotypic models of cognition to localize genetic influences on working and spatial memory in the hope that those genetic influences might have utility as candidates for future work in the field of psychiatric genetics. A hierarchical model revealed two QTLs on chromosome 8 (8q21.11–13 and 8q24.22) for working memory and showed pleiotropy with other cognitive domains while a bi-factor model revealed two QTLs on chromosome 17 (17q22–23.2 and 17q25.1) for spatial memory. Association analysis conducted in the region of those QTLs revealed five variants that were significantly associated with memory ability and of these, rs723686, showed an association with schizophrenia risk in the PGC data ($p = 0.00728$; see Figure S1).

Cognitive impairment meets the criteria, as outlined by Gottesman and Gould (2003), for being an endophenotype of psychosis. Impairment is associated with psychosis in the population and is state-independent (Reichenberg and Harvey, 2007), it is heritable (Deary, 2012), and finally cognitive impairment and psychosis co-segregate within families (Toulopoulou et al., 2007; Toulopoulou et al., 2010; Owens et al., 2011; Glahn et al., 2010; Glahn et al., 2007a; Bora et al., 2009; Hoff et al., 2005; Sitskoorn et al., 2004). While the prevailing approach in psychiatric genetics has been to search for genes that directly influence illness risk, diagnostic status is relatively distal from the underlying causal physiological mechanism. In contrast an approach centered on endophenotypes shifts the focus from illness risk to allied phenotypes, or biomarkers, of the illness in the hope that the

genetic architecture will be relatively less complex and thus easier to disentangle. Moreover, because endophenotypes vary within the normal population they are amenable to study in samples without focus on a specific illness. Of course cognitive ability is normally distributed and as a consequence cognitive dysfunction is widespread in the population. It is not the assertion of the present paper that psychosis explains normal variation in cognition. However, the strategy of focusing on normal variation has been successfully applied to the study of many complex diseases including heart disease (Kathiresan et al., 2009), obesity (Willer et al., 2009), diabetes (Cai et al., 2004), hypertension (Cho et al., 2009), osteoporosis (Kiel et al., 2007) and depression (Glahn et al., 2012).

Previous research has consistently implicated the chromosomal region 8q21.13, which captures the two variants (rs2467774 and rs723686) shown to be associated with working memory in the present study, in psychosis risk. Genome-wide linkage studies have found suggestive associations between this region and bipolar risk in adolescents (Doyle et al., 2010) and adults (Kerner et al., 2007), and DNA-methylation changes in this region are associated with major psychosis in adults (Mill et al., 2008). Members of the *HEY* gene family have been identified as mediators of psychotic-illness risk either directly or through well characterized dopamine pathway genes (Middleton et al., 2004; Fuke et al., 2005). Finally, structural variation in the region 8q21.3 is associated with autism risk which is interesting given the large amount of genetic overlap between psychosis and autism risk (Gilman et al., 2012; Marshall et al., 2008).

Association analysis at 8q21.13 with working memory revealed two common variants associated with the *HEY1* gene, one 999 base pairs downstream (rs2467774) and the other ~13,000 base pairs downstream (rs723686). *HEY1* is a transcription target of *Notch* and makes up part of the hairy and enhancer of split (*HES*) and Hairy/Enhancer-of-split-related with YRPW-like motif (*HEY* also called *HERP*) gene families (Bray and Bernard, 2010). These are basic helix-loop-helix genes which are highly expressed in the developing brain where they maintain neural precursor cells, mediating neurogenesis and differentiation during neurodevelopment (Kokubo et al., 1999; Leimeister et al., 1999; Sakamoto et al., 2003). This gene family continues to be expressed in the adult brain and is involved in neurogenesis throughout the lifespan (Stump et al., 2002; Elliott et al., 2001). *Notch* receptors are primarily activated by two ligand types, Delta and Jagged, with activation resulting in intramembrane cleavage of the *Notch* receptor where the intracellular domain (NICD) replaces transcriptional co-repressors with activators that in turn trigger expression of *HEY* and *HES* genes via the transcription factor RBPJ κ (Fischer and Gessler, 2007). The *Notch* signaling pathway has previously been implicated in memory (Costa et al., 2005). For example, in drosophila with a mutant form of *Notch* that specifically affects the intracellular domain necessary for transcription, formation of long-term memory is impaired (Ge et al., 2004). Similarly, mice with heterozygous mutations in RBPJ κ exhibit deficits in spatial memory (Costa et al., 2003).

Notch signaling has also been implicated in Alzheimer's disease, a neurological disorder with a devastating impact on memory and increased production and accumulation of amyloid β -protein in brain (Selkoe, 2001). Although Notch involvement is typically associated with presenilin-dependent γ -secretase activity, recent research has shown an

association between *HEY1* over-expression and reduced amyloid β metabolism (De Strooper et al., 1999; Leal et al., 2012). This ties in neatly with the significant association for spatial memory and the gene *APPBP2* (variant rs12162165) located at 17q23.2, which is functionally associated with the processing of amyloid precursor protein (Nagase et al., 1996). Overall, these results are interesting because while Notch (and amyloid β) has been implicated in memory in animal models and in humans affected by neurological illness such as Alzheimer's, this is the first time that this association has been paper to highlight the potential importance of *HEY1* in this context.

Association was seen between spatial memory and *BCAS3* at 17q23.2, a gene which is amplified and over-expressed in breast cancers and is moderately expressed in the brain (Barlund et al., 2002). Relatively little is known about the function of the protein beyond its involvement in breast cancer and there are no known homologs (Gururaj et al., 2006). Structural abnormalities in the genomic region 17q32.2 have been associated with mild to moderate developmental delay and microcephaly in a handful of case studies (Ballif et al., 2010; Nimmakayalu et al., 2011). In addition, we found evidence for association with an intergenic SNP (~13kb downstream of *MGAT5B*) and spatial memory. Although it is unlikely that this variant directly influences gene expression, our current understanding of how genetic regulation is controlled is limited. Epigenetic factors, such as DNA methylation, histone modification and non-coding RNA influence gene regulation in ways that we do not currently comprehend. The identification of variation in intergenic regions, which may influence phenotypes such as spatial memory, may represent an as yet unknown spectrum of variants that regulate gene or protein expression. Suffice to say that given the strong link between the working memory QTL and psychosis, this region on chromosome 17 might be of particular interest in future psychosis research. A possible link between breast cancer and both bipolar disorder and schizophrenia risk may exist, such that there is strong genetic competition between the disorders where cancer causes over-proliferation of cells and psychosis putatively causes cell death as is described by Rzhetsky and colleagues (Rzhetsky et al., 2007). Interestingly, the breast cancer drug tamoxifen has been shown to be effective in the treatment of bipolar (Kulkarni et al., 2006; Amrollahi et al., 2011).

This study shows that by using detailed phenotypic models of cognition it is possible to localize genetic influences on memory. Furthermore it is possible that modeling the data in this way has contributed to the literature showing that the chromosomal region 8q21.13 is important for psychosis risk and furthermore highlights *HEY1* as being of particular interest within this region. The present study demonstrates that one SNP, located 13kb upstream of *HEY1*, shows an association with working memory and also shows an association with schizophrenia risk in the PGC sample. Identifying these genetic influences was made possible by focusing on QTLs that influence cognitive domains rather than on *g* or general intelligence. The genetic signal for *g* was weaker than for the cognitive domains and in fact, the bi-factor model shows that a genetic signal for spatial memory only emerged when the variance associated with general cognition was removed from the individual domains and modeled as a separate factor. Moreover, given that bivariate linkage demonstrated pleiotropy between working memory and the other cognitive domains including *g* these findings

suggest that focusing on cognitive domains may in fact be an effective strategy for isolating genes for general intelligence.

An interesting feature of the present population is that they are of non-Caucasian origins. This is interesting because the findings, at least for one SNP identified to be associated with working memory, appears to be generalizable to the Caucasian population employed by the PGC. However, one potential limitation of the sample used in the present study is that, because it has been randomly ascertained from the general population, it is subject to common mental illness. However, anxiety and depression were included as covariates and neither alcohol nor substance use disorders co-varied significantly with the working or spatial memory factors which showed significant linkage in the present study and moreover their inclusion did not change either the linkage or association results. However, education and socioeconomic influences were not co-varied for in the present study and this should be remembered as a potential weakness of the present study.

In summary, the linkage and association findings presented in this manuscript highlight the use of detailed phenotypic models for finding genes for cognition and in so doing these findings contribute to the literature showing that the chromosomal region 8q21.13, and more specifically *HEY1*, is important for psychosis risk. This suggests a new methodology for identifying genes for cognition as an endophenotype of psychosis, one which attempts to model cognitive domains taking into account both phenotypic and genetic factors, thus maximizing their potential as endophenotypes for mental ill-health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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FIG. 1.

Dendrogram of the cluster analysis which depicts four clusters: verbal memory (red), working memory (yellow), executive function (blue) and spatial memory (green).

FIG. 2.

Statistical modelling of the cognitive data. A: The three-tier hierarchical general cognition model. B: The bifactor general memory model.

FIG. 3.

Linkage analysis. A: Chromosome 8 multipoint plot for all factors taken from the general cognition model where working memory exhibited two genome-wide significant QTLs. B: Chromosome 17 multipoint plot for all factors taken from the general memory model where spatial memory exhibited two genomewide.

FIG. 4.

QTL-specific association analysis for the first genomewide significant QTL region associated with the working memory factor on chromosome 8.

FIG. 5.

QTL-specific association analysis for the first (A) and second (B) genome-wide significant QTL regions associated with the spatial memory factor on chromosome 17.

Table 1

Description and heritability of cognitive traits.

Trait	Primary Dependent Measure	h^2	Standard Error	p-value
Digit Symbol Correct	No. of correctly identified digit-symbol pairs in 90 sec	0.55	0.059	3.88×10^{-27}
Letter Number Sequencing	No. of correctly recalled number-letter strings in numerical and alphabetical order	0.55	0.060	4.57×10^{-26}
Trails B	Time needed to connect alternating letters and numbers	0.55	0.066	8.99×10^{-23}
Letter Fluency	No. of words, beginning with specific letter, generated in 60 sec	0.54	0.059	1.23×10^{-26}
Facial Memory	No. of faces recognized during the Penn Face Memory Test	0.52	0.068	3.96×10^{-20}
Digit Span Backwards	No. of correctly recalled digit strings in reverse order of presentation	0.48	0.066	2.56×10^{-18}
Digit Span Forwards	No. of correctly recalled digit strings in their original order of presentation	0.48	0.060	1.61×10^{-20}
Digit Symbol Memory	No. of correctly remembered digit-symbol pairs upon task completion	0.42	0.066	7.64×10^{-15}
CVLT Learn	No. of items recalled during 5 exposures of 16-word list of CVLT	0.40	0.064	2.80×10^{-14}
CVLT Delay	No. of list items recalled after 20-min delay	0.37	0.059	1.42×10^{-14}
PCET Correct	No. of correctly matched shapes on PCET	0.37	0.056	2.72×10^{-16}
Category Fluency	No. of animal names generated in 60 sec	0.36	0.065	1.91×10^{-12}
Emotion Recognition	No. of emotions correctly identified	0.33	0.067	8.96×10^{-10}
CPT False Alarms	No. of false alarms during 6-min identical pairs CPT	0.30	0.066	8.13×10^{-9}
CPT Hits	No. of hits during 6-min identical pairs CPT	0.30	0.064	1.14×10^{-8}
Trails A	Time needed to connect letters in ascending order	0.29	0.063	1.16×10^{-8}
SCAP	No. of correct responses on a spatial delayed response test	0.27	0.063	1.00×10^{-7}
CVLT Semantic	Proximal recall of semantically related list items during 5 repeated exposures of 16-word list	0.22	0.056	7.00×10^{-7}

Abbreviations: CPT, Continuous Performance Test; CVLT, California Verbal Learning Test; PCET, Penn Conditional Exclusion Test

Table 2

Heritability and top LOD scores for all factors derived from the two factor models.

Model	Factor	h^2	Standard Error	p -value	LOD	Chrom	Loc	Location
General Cognition Hierarchical Model	Verbal Memory	.48	.070	4.06×10^{-15}	2.208	22	7	22q11.21
	Working Memory	.66	.058	1.25×10^{-32}	4.239	8	142	8q24.22
	Spatial Memory	.63	.0623	4.07×10^{-26}	3.298	8	89	8q21.11
	Executive Function	.65	.059	2.86×10^{-30}	2.693	7	164	7q36.1
	General Cognition	.68	.058	1.16×10^{-32}	2.709	12	107	12q22
General Memory Bi-factor Model	Verbal Memory	.27	.071	6.40×10^{-06}	1.711	22	7	22q11.21
	Working Memory	.42	.064	1.15×10^{-14}	1.790	18	121	18q23
	Spatial Memory	.21	.071	1.48×10^{-04}	3.763	17	94	17q23.2
	General Memory	.62	.056	9.59×10^{-33}	3.341	17	117	17q25.1
					2.593	8	92	8q21.13

Table 3

Results of the bivariate linkage analysis.

Phenotype	Bivariate LOD	Chrom	Loc	X ²	p
General Cognition	3.1687	8	142	19.07	6.30 × 10 ⁻⁰⁶
Executive Function	3.1988	8	142	18.46	8.65 × 10 ⁻⁰⁶
Spatial Memory	3.1468	8	142	15.99	3.19 × 10 ⁻⁰⁵
Verbal Memory	3.2332	8	142	12.82	1.71 × 10 ⁻⁰⁴

Table 4

Estimates of X^2 , size and direction of effect and variance explained for significant SNPs from the QTL-specific association analysis.

SNP	X^2	<i>p-value</i>	β	Variance Explained
rs2467774	19.37	0.000011	-0.22	0.024
rs723686	19.18	0.000012	-0.20	0.022
rs9907597	17.51	0.000029	0.19	0.019
rs12162165	16.77	0.000042	0.21	0.018
rs1867467	16.78	0.000042	0.19	0.016