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An investigation of candidate regions for association with Bipolar disorder

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Abstract

We performed a case control study of 1,000 cases and 1,028 controls on 1,509 markers, 1,139 of which were located in a 8 Mb region on chromosome 6 (105-113 Mb). This region has shown evidence of involvement in BP in a number of other studies. We find association between BP and two SNPs in the gene LACE1. SNP rs9486880 and rs11153113 (both have p-values of 2×10^{-5}). Both p-values are in the top 5% of the distribution derived from null simulations (p=0.02 and 0.01 respectively). LACE is a good candidate for BP; it is an ATPase. We genotyped 173 other markers in 17 other positional and/or functional loci but found no further evidence of association with BP.

Introduction

Bipolar disorder (BP) affects a person's mood, energy, and ability to function. It has a prevalence of about one percent. The severity of BP is often such that it will interfere with relationships and job performance, and in a significant number of individuals it can lead to suicide (Tondo et al, 2003). Full details of the symptoms can be found in the *Diagnostic and*

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Statistical Manual for Mental Disorders, fourth edition (DSM-IV) (American Psychiatric Association, 1994). The variable age of onset of the disorder and the difficulty of categorising its external manifestations make it difficult to diagnose (Schatzberg, 1998). Even when successfully identified, treatment is not always successful and there are no curative regimes.

The involvement of genes in the etiology of the BP is irrefutable. The heritability of the trait has been estimated in a number of different twin and adoption studies and appears to be between 60% and 85% (Cardno et al, 1999; Smoller and Finn, 2003; McGuffin et al, 2003). However, the underlying biological dysfunction is unknown. Identification of specific genes could provide more information about the neurobiology of the disorder and hence improve our ability to diagnose, treat and perhaps even cure BP in affected individuals. A great deal of work has been undertaken to achieve this aim (reviewed in: Baron, 2002; Craddock et al, 2005; Kato et al, 2005; Kato, 2007; Farmer et al, 2007).

Multiple candidate gene studies have been carried out although there is still no gene for which the functional effect on BP is unequivocal (Craddock and Sklar, 2009). Genes involved in serotonin, dopamine, and norepinephrine/noradrenaline pathways are good candidates (e.g. 5HTT, MAOA, and BDNF). Genes that show evidence of having an effect on schizophrenia, e.g. G72 and DISC1, have also been investigated because of the overlap with BP in terms of the genetic etiology.

Genome-wide linkage screens of BP have detected linkage to nearly every chromosome, in at least one study. These studies have been followed up by many linkage and association studies of the positional candidate regions. Some follow up studies have also been used to investigate more unusual inheritance patterns. For example, there is evidence that parent of origin effect is important in several chromosomal regions, including chromosome 18 (Mulle et al, 2007; Stine et al, 1995). A number of meta-analyses have also been completed including those by Segurado et al in 2003 and Badner and Gershon in 2002. In 2005, McQueen et al undertook a combined analysis of 11 linkage studies; the study included 5,179 individuals from 1,067 families and combined the raw genotype data. Chromosome 6 demonstrated the strongest evidence of linkage to the narrow definition of BP with a LOD score of 4.19 at position 115 cM. On the basis of this result we decided to investigate this region of chromosome 6 further. McQueen also found linkage to chromosome 8 at 151 cM (LOD 3.40) but this is with a broader definition of BP.

The evidence for the involvement of chromosome 6 in BP disorder in the McQueen paper appeared to be derived mainly from three studies: NIMH Wave 3 (Dick et al, 2003) with a LOD score of 3.6 for marker D6S1021 (114 cM 104.7 Mb); the cohort of Portuguese Island families (Pato et al, 2004) in which marker D6S1021 had an NPL score of 2.02; and the study by Liu et al (2003). Although the latter study does not report the details of their finding in this region, McQueen et al provide a plot of all the individual study results and a peak is evident in the region of interest. In further analysis of the NIMH Wave 3 study, a maternal parent of origin effect was uncovered as well as an interaction with 6p, a region previously linked to schizophrenia (Schulze et al, 2004). The Wellcome trust study (Bennett et al, 2002) that was included in the meta-analysis did not show any evidence in the first stage linkage analysis. But a follow-up study, with more markers and more individuals, demonstrated linkage with a LOD of 2.61 at marker D6S1021 (Lambert, 2005). A previous study of Danish families that was not included in McQueen's meta-analysis also reported a maximum LOD score of 3.8 for marker D6S1021 (Ewald et al, 2002). Furthermore, the other meta-analysis by Segurado (2003) showed suggestive though not significant linkage.

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Several genome-wide association scans (GWAS) have been undertaken (Baum et al, 2007; WTCCC, 2007; Sklar et al, 2008; Ferreira et al, 2008; Smith et al, 2009) and there is some suggestive evidence of association to chromosome 6 from some of these. Baum et al (2007) carried out a GWAS of BP using pooled DNA samples. They analyzed over 555,059 markers in two populations, one made up of 461 cases and 563 controls of European origin (the NIMH sample) and the other of 772 cases and 876 controls of German origin. The p-value of marker rs1327199 at position 112,382,053 bp (NCBI build 36) is 0.0008 which does not reach genome-wide significance but has a rank of 671 across the entire study of 555,059 markers in the NIMH sample. Marker rs1327199 is not associated in the German population.

Bipolar disorder was one of the seven common diseases studied by the Welcome Trust Case Control Consortium (WTCCC) (WTCCC, 2007). In that study only one marker (on chromosome 16) reached the criteria for genome-wide association. SNP rs9320174 at 107,092,101 bp (NCBI build 36) is ranked 182nd in the WTCCC GWAS (p-value 0.0000834). The studies by Ferreira et al (2008) and Sklar et al (2008) had some suggestive results in the region, more details of which are given in the discussion. The results from the Foundation for the National Institutes of Health Genetic Information Association Network (GAIN) initiative have been published recently. There is some sample overlap between this study and the study presented here but none of the SNPs on chromosome 6 have p-values which reach genome-wide significance (Smith et al 2009). Further information on individual markers is available through dGAP.

In recent months, a follow up of the McQueen study has been published (Fan et al, 2009). They genotyped 3,047 SNPs across a 23 Mb region of chromosome 6 in a case control sample (N = 530 cases, 534 controls) and a family-based sample (N = 256 nuclear families, 1,301 individuals). Their most significant result came from marker rs6938431 ($p = 6.72 \times 10^{-5}$, 110,852,299 bp – NCBI build 36) in the case-control sample with evidence of replication in an independent case control sample.

Despite the fact that not all studies provide evidence of the involvement of chromosome 6 in BP, a considerable number of them do. This provided additional motivation to assess evidence of association between BP and markers in a 8 Mb region on chromosome 6. We also investigated various other positional and functional loci.

Methods

Sample

The sample is made up of 1,000 cases and 1,028 controls of Caucasian ancestry. The cases were diagnosed as having either SAB (schizoaffective disorder) or BPI. The cases were recruited at 11 data collection sites by the Bipolar Consortium. Fifty-nine point five percent of the controls were male whereas 40.5% of the cases were male. The controls had a mean age of 52.9 (sd 17.7) and the cases had a mean age of 43.6 (sd 12.9). (The specific population and study characteristics are described in detail elsewhere—see Smith et al, 2009). They were interviewed with the Diagnostic Interview for Genetic Studies (Nurnberger et al, 1994), medical records were obtained, and final diagnosis was based on the current *APA Diagnostic and Statistical Manual*, 4th edition. Control subjects were collected separately through a volunteer panel and web-based psychiatric interview (available at www.nimhgenetics.org), using a grant awarded to Dr. Pablo Gejman and his collaborators (Sanders et al, 2008). Individuals had to respond negatively to the questions "Have you ever received treatment for, or been diagnosed with schizophrenia or schizoaffective disorder or bipolar disorder (manic-depression)", or "hearing voices others could not hear or believing things that others said were not true (such as that people were

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trying to harm you)". In addition, we excluded controls with a diagnosis of major depression and allowed only the presence of at most one depressive symptom.

Marker selection

We genotyped 1,509 markers, 1,139 in a 8 Mb region of chromosome 6 from 105,287,336 to 113,050,077 base pairs. One hundred and seventy three markers were chosen from 17 other regions that contain functional or positional candidates for BP. A combination of tagging methods and biology-based selection criteria were used to select SNPs in these regions. SNPs in coding regions were selected if they were reported by dbSNP build 126 to be genotyped and polymorphic (MAF > 0) in some population. We then used HapMap build 21 genotypes from the European American (CEU) sample to estimate minor allele frequencies and linkage disequilibrium (LD) coefficients for SNPs in the remaining regions. Tag SNPs were selected using the LD bin method of Hinds et al (2005) to select SNPs in the non-coding regions. Additionally, after tag SNPs were selected, any SNPs in 5′ UTR or 3′ UTR regions with a HapMap CEU MAF ≥ 10% were added. Further details of the 163 non-chromosome 6 SNPs that passed quality assessment are given in Table I. One hundred and ninety seven markers, a subset of the Illumina panel of Ancestrally Informative Markers in linkage equilibrium, were typed to assess population stratification.

Genotyping

One thousand, five hundred and nine markers were genotyped using the Illumina platform. Initial genotyping was carried out by Illumina using GoldenGate® Assay and BeadArray™ technology. Genomic DNA (50ng per ul) is biotinylated and immobilized on magnetic beads. The immobilized DNA is hybridized to the oligo pool containing three primers for each SNP locus to be queried. Two of these primers are allele specific, with their three prime bases defining the two alleles of the SNP locus, and one is designed to anneal 1 to 20 bases downstream of the allele specific primers. The specifically bound primers are extended using an enzyme specific for a correctly paired three prime base, and a ligase is used to join the extended product to the oligo bound downstream. Universal primer tails on the primers are used to PCR-amplify the extension-ligation products. The address tag incorporated into the downstream oligo allows the products to be captured onto the BeadArray™. The BeadArray™ has an average 30-fold redundancy for each bead type, or capture tag, represented in the array. A more detailed description of the process can be found at the Illumina website, www.illumina.com.

Quality control

Markers with low quality control scores were visually inspected and those with unclear cluster patterns were removed from the data set, as were monomorphic SNPs. One thousand, five hundred and nine markers were genotyped and 84 were removed in this first QC step. A further 57 markers were excluded from analysis: 34 with allele frequencies below 1%, 13 with HWE p-value of less than 0.001 in the controls, and 10 with missing call rates of 1% or greater. Call rates for all individuals were greater than 90%, with 99% of the individuals having a call rate of 99% or greater. This left 1,012 markers on chromosome 6, 163 candidate SNPs, and 193 markers for quality control.

Population Stratification

PLINK was used to investigate and adjust for population stratification (Purcell et al, 2007). We assessed whether stratification was present by determining λ—the median χ^2 score divided by its expected value of 0.445. We then performed multidimensional scaling of the identity by state (IBS) similarity matrix, and extracted the first dimension. Population stratification was controlled for by using this as a covariate in the regression analysis.

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Association analysis

Association analysis was performed using logistic regression model implemented in PLINK. As well as the covariate to control for population stratification we also included covariates to control for sex and age as these are significantly different between cases and controls. An additional model termed the genotypic test was applied, this has more power to detect non-additive effects. Empirical p-values were derived through permutation using PLINK. The option used corrects for multiple testing while controlling for the correlation structure between the SNPs.

Results

Population Stratification

Without correction, the λ for the total data set is 1.21. When the covariate derived from the IBS matrix is included in the model, the λ is 1.04.

Association analysis

In Figure 1, we graphically present the results from analysis of chromosome 6 using a model which assumes an additive mode of inheritance and includes a covariate to control for population stratification. SNPs rs9486880 (108,846,450 – NCBI build 36) and rs11153113 (108,863,061 – NCBI build 36) both had a p-value of 2×10^{-5}. These markers are in almost complete linkage disequilibrium (LD), with both r-squared and D' values of 1. Although none of the other markers near rs9486880 and rs11153113 have p-values less than 0.0001, results in the region are generally more significant than results elsewhere. There are 93 markers in a 0.8 Mb region and 34 have p-values below 0.05.

The p-values from the genotypic test were more significant, this could be because the effect of the SNP on BP is non-additive. The results for both models remained significant after permutation tests had been carried out. The cut-off for p-values in the top 5% of distribution from the null simulations was 6.6×10^{-5}. Further details can be found in Table II. No other markers had significant empirical p-values.

Discussion

This data provide suggestive evidence of association to two markers on chromosome 6. We were prompted to investigate this region as it provided the strongest support for linkage in the meta-analysis study by McQueen et al (2005).

The SNPs are in LACE1 (lactate elevation 1), a good candidate gene for bipolar illness. It appears to be an ATPase (as are other putative bipolar genes CACNA1C and P2RX4). This strengthens evidence that ion channelopathies may be involved in BP (Ferreira et al, 2008; WTCCC, 2007).

Our results show some concordance with the results from the other GWAS (see introduction for more information). We did not type rs1327199 the marker with a rank of 671 in the Baum et al study, but this SNP is only 23kb from rs7768046 (112,286,625 – NCBI build 36), which has a p-value of 0.004 in our study. We derived the LD from the HapMap data and the r^2 value between the two markers is only 0.036 (The International HapMap Consortium, 2005). The MAF of rs7768046 in the CEPH sample of the HapMap data is 37%. It is very much lower in the other populations and is in fact monomorphic in the YRI. The MAF for rs1327199 is 3% in the CEPH data and more common in the other samples, reaching 27% in the Chinese population. In the NIMH dataset the control frequency of

rs1327199 is 6% and the case frequency is 3%. It is possible that these two signals are pointing at the same source but this is by no means certain.

At a distance of one megabase away from our region there is a SNP with a rank of 182nd in the WTCCC GWAS (rs9320174) but it is not in LD with our top two markers ($r2 \leq 0.03$).

In the GWAS by Ferreira et al (2008), the genotypes for markers rs9486880 and rs11153113 were imputed. The association p-values were 0.018 and 0.033; not significant but not resounding negative. In a study by Sklar et al (2008) markers rs846951 (108,124,975) and rs7767017 (109,626,615) are either side of markers rs9486880 and rs11153113 and have p-values of 0.0004798 and 0.0005286, but they are not in LD with either marker rs9486880 or rs11153113.

Of the top 10 markers from the two primary datasets used in the fine mapping study by Fan et al, we only typed one, rs846950 (108,125,814). The p-value in our study was non-significant (p=0.8) whereas the p-value in their study was (0.0026). Different patterns of LD in the study populations may be what caused the association to be evident at different markers.

Although there is mounting evidence from the involvement of genes on chromosome 6 in BP there is inconsistency between the results from the different studies. There appears to be more consistent evidence from the linkage studies than the association studies. This could be explained by the genetic architecture of the disorder. It is possible that there are multiple causative variants in one region. Linkage studies have good power to detect regions like this but the LD pattern in the region would affect the ability of an association study to find them.

There are some differences in the phenotypes between the GWAS. Baum et al chose BP1 individuals whereas Sklar et al, Ferreira et al and the WTCCC chose a more relaxed phenotypic criteria which included BP2 individuals as well as those with schizoaffective disorder. Although the genetic influences for these disorders are expected to overlap, a change in the distribution of the different phenotypes could alter the power of the study to identify certain genes that are influential in one specific disorder or another.

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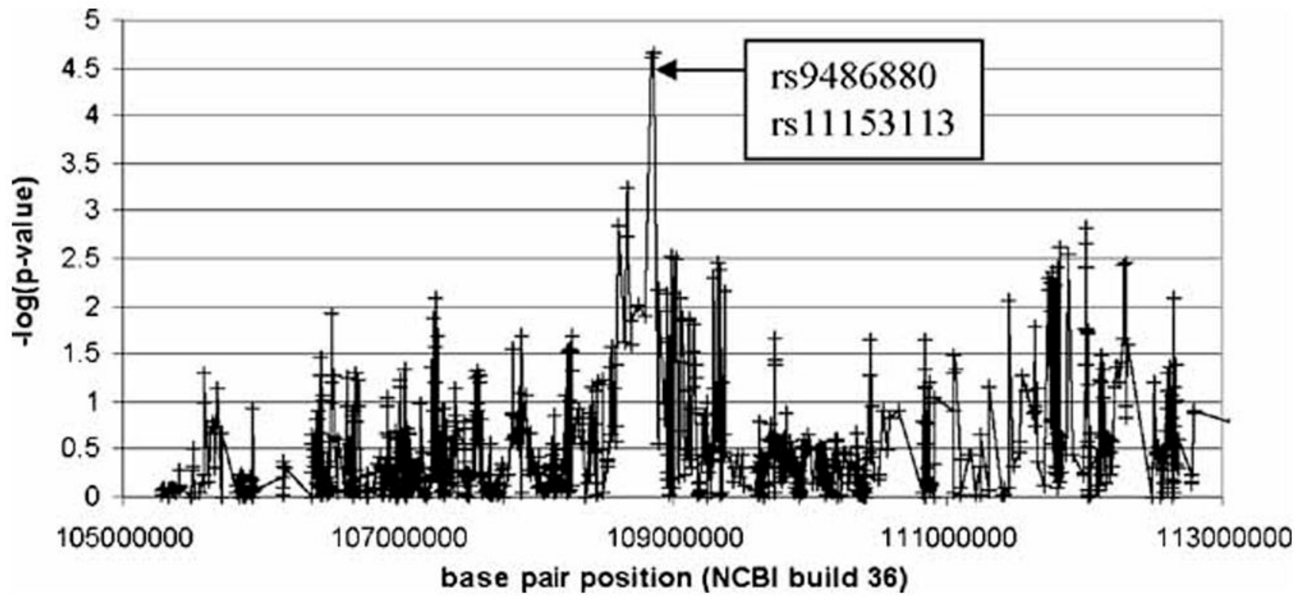

Figure 1.

Results from chromosome 6 markers. The −log 10 of the P-value from the logistic regression model assuming additive effects and including covariates to control for population stratification, sex and age is plotted against the base pair position.

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Table I

The number of SNPs in candidate genes on other chromosomes.

Chromosome	Gene	# SNPs
3	Dopamine receptor 3	3
6	dystrobrevin binding protein 1	3
7	Tachykinin 1	2
7	Cholinergic muscarinic 2 receptor	6
8	Chromosome 8 linkage (McQueen)	8
8	ZHX2	11
8	KCNQ3	18
8	ST3GAL1	68
11	brain-derived neurotrophic factor	4
12	Purinergic ligand-gated ion channel	7
12	12q24	8
15	Cholinergic receptor 3	1
16	Cyclic-AMP response element binding protein	3
17	protein phosphatase 1 regulatory (inhibitor) subunit 1B	3
19	circadian clock gene	2
21	transient receptor potential cation channel, subfamily M, member 2	3
22	adrenergic receptor kinase, beta 2	7
X	5-hydroxytryptamine (serotonin) receptor 2C	6

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Table II

Association results.

SNP	Alleles	Case/Control frequency	Additive + Sex + Age p-values (empirical p)	Genotypic p-values + Sex + Age (empirical p)
rs9486880	C/A	0.39/0.45	2.4×10^{-5} (0.02)	1.1×10^{-5} (0.002)
rs11153113	T/C	0.39/0.45	2.2×10^{-5} (0.01)	1.1×10^{-5} (0.002)