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A genome-wide association study of seasonal pattern mania identifies *NF1A* as a possible susceptibility gene for bipolar disorder

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Abstract

Objective: The use of subphenotypes may be an effective approach for genetic studies of complex diseases. Manic episodes with a seasonal pattern may distinguish phenotypic subgroups of bipolar subjects that may also differ genetically.

Method: We have performed a genome-wide association study using GAIN genotype data from the Bipolar Genome Study (BiGS) and bipolar subjects that were categorized as having either seasonal or non-seasonal patterned manic episodes.

Results: A bipolar case-only analysis identified three genomic regions that differed between seasonal and non-seasonal patterned manic episodes of bipolar subjects. The most significant association was for rs41350144, which lies within an intron of *NF1A* gene on 1p31 (P=3.08 × 10^{-7}, OR=2.27). Haplotype construction using flanking three SNPs (rs41453448, rs1125777, and rs12568010) spanning 7549 bp showed a more significant association (P=2.12 × 10^{-7}, OR=0.4).

Conclusions: These data suggest that genetic variants in the *NF1A* gene region may predispose to seasonal patterned of mania in bipolar disorder.

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Contributors

H.J.L., H.G.W. and T.A.G. take responsibility for the association analyses and the general integrity of the data. J.R.K. and D.F.K. participated in particular aspects of study design. Members of the BiGS consortium were responsible for subject collection and genotyping. All authors were responsible for reviewing and approving the final manuscript.

Conflict of interest

H.J.L., H.G.W., T.A.G., D.F.K., and J.R.K. have no competing financial interests in relation to the work described.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2012.07.032.

Keywords

Seasonal pattern; Bipolar disorder; Genome-wide association

1. Introduction

Bipolar disorder (BD), also known as manic-depressive illness, has a lifetime prevalence of approximately 5–6.4% in the general population (Akiskal et al., 2000; Judd and Akiskal, 2003), although the lifetime prevalence of bipolar I disorder (BPI) is around 1%. Family, twin, and adoption studies suggest heritability estimates of 60–80% for BDI (Tsuang and Faraone, 1990). Although BD is highly heritable, the identification of specific genetic variations has yielded limited findings (Baum et al., 2008a, 2008b, Sklar et al., 2008, 2011, Wellcome Trust Case Control Consortium, 2007, Smith et al., 2011). Creating subgroups of patients with BD according to clinical subphenotypes has been suggested as a possible approach for further genetic studies in BD (McQueen et al., 2005).

Circadian rhythm dysfunction is hypothesized to play a role in the pathophysiology of BD (Kripke et al., 2009; Jones, 2001; Mansour et al., 2005; McClung, 2007; Wehr et al., 1983; McCarthy et al., 2012). BD patients usually demonstrate circadian rhythm-related symptoms, including a periodicity of manic-depressive episodes, diurnal variation of mood, and sleep disturbance, such as sleeplessness during mania and insomnia or hypersomnia during depression. Sleep disturbances may be caused by circadian dysfunctions in BD and may promote emotion dysregulation (Harvey et al., 2006). However, the causal relationship between sleep disturbance and emotional problems may be bidirectional (Dahl, 2004). Furthermore, sleep disturbances are very common symptoms in psychiatric illness, and most mood episodes heighten sleep problems. While it is difficult to distinguish core circadian disturbance as a subphenotype from the complex mood disorder symptomatology, a seasonal pattern of manic episodes is a more clearly recognizable sub-phenotype of circadian dysfunction in BD.

Seasonal pattern in mood disorders has been well recognized since ancient times when Hippocrates described the correlation between season and the precipitation of manic episodes in BD. Many studies have since revealed that BD patients have more manic episodes during the spring and summer (Barbini et al., 1995; Parker and Walter, 1982; Takei et al., 1992; Volpe and Del Porto, 2006; Lee et al., 2007; Mulder et al., 1990; Sayer et al., 1991). Although a positive association between the photoperiod and BD mania has been reported in some studies BDI patients (Lee et al., 2002), others have not found an association (Silverstone et al., 1995; Whitney et al., 1999). Despite these contradictory findings, there seems to be some evidence for a higher prevalence of manic BD episodes in the spring and summer months. Seasonality in mood disorder was reported associated with a family history for mood disorders (Brambilla et al., 2012) and self-reported seasonal mood changes were reported to be heritable in a twin study (Jang et al., 1997).

These observations suggest that seasonal pattern subtypes of mania may represent genetically distinct subtypes of BD. We explored this hypothesis in a genomewide association (GWA) analysis of seasonal pattern mania *vs.* non-seasonal mania in BDI

subjects and controls of European ancestry genotyped as part of Genetic Association Information Network (GAIN) by the Bipolar Genome Study (BiGS).

2. Methods

2.1. Subject ascertainment

For genotyping as part of the Bipolar Genome Study (BiGS), BDI subjects were selected from those collected by the NIMH Genetics Initiative for bipolar disorder in five waves at 11 sites across the United States as described elsewhere in detail (Smith et al., 2009). Recruitment for waves 1–2 consisted of extended multiplex families with a BDI proband, waves 3–4 included families with a BDI proband and at least one other sibling with BDI or schizoaffective disorder, bipolar type, whereas Wave 5 consisted of unrelated BDI cases. All subjects provided written informed consent according to the local IRB protocols and were interviewed using the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994). Information was obtained from other family informants and medical records and reviewed along with the interview by a panel of experienced clinicians to obtain a final best-estimate diagnosis. The complete DIGS interview, which includes over 2000 questions with detailed information regarding manic and depressive episodes, is available for these subjects.

Control subjects were selected from those ascertained through a NIMH-supported contract mechanism between Dr. Pablo Gejman and Knowledge Networks, Inc. All subjects donated a blood sample and were given a medical questionnaire. The selected controls were matched for gender and ethnicity with the BD cases, and all control subjects who endorsed a history of BD, psychosis, or recurrent major depression were excluded from our study.

2.2. Genotyping and cleaning

The initial sample was genotyped at the Broad Institute as part of the Genetic Association Information Network (GAIN) using the Affymetrix 6.0 (1M SNP) array. A total of 1001 BD cases, 1033 controls, and 724,067 SNPs were available for analysis following an extensive QC process (Smith et al., 2009) to eliminate individuals with >10% missing data and SNPs with poor allele clustering, >10% missing data, duplicate errors, minor allele frequencies (MAFs) <0.05, and Hardy–Weinberg equilibrium $p<10^{-6}$. The second sample was similarly genotyped at the Translational Genomics Institute (TGEN) and underwent a comparable QC process that resulted in 1190 BD cases, 401 controls, and 728,187 SNPs available for analysis. An additional round of QC performed on the merged GAIN and TGEN samples resulted in 703,012 passing SNPs.

2.3. Phenotypes

Phenotypes were derived from the Phenome Database, which compiles data across the DIGS 2, 3, and 4 to arrive at a common set of variables for each subject in the sample (Potash et al., 2007). As a part of the DIGS interview, BD subjects were queried, "*Do your episodes (mania/hypomania) tend to begin in any particular season?*" Subjects who answered 'Spring' or 'Summer' were categorized as BD with seasonal patterned mania and subjects who answered 'no pattern' were categorized as BD with non-seasonal patterned

mania. Those who answered ‘Fall’, ‘Winter’, or ‘Unknown’ or who endorsed more than one season were categorized as missing because their patterns may be not related to circadian response to increased light exposure during Spring or Summer. It may be an instead related to other social factors such as anniversary reactions during other seasons. There were 392 BD subjects in the seasonal mania (SM) group and 930 subjects in the non-seasonal mania (NSM) group.

2.4. Association analyses

To assess genetic factors contributing to seasonal patterned mania, we first performed a case-only analysis of SM *vs.* NSM. In order to differentiate those genetic factors that are unique to seasonal patterned mania, as opposed to those that may modify the expression of mania in BD, the SM group was compared to controls in a secondary analysis. A similar analysis was performed for NSM. All association analyses were performed using logistic regression in PLINK (Purcell et al., 2007) with covariate adjustment for sex. Label-switching permutations were performed to assess the empirical significance of the results, since spurious results may result from a sampling bias through the selection of a small subset of individuals.

2.5. Linkage disequilibrium analysis

Linkage disequilibrium (LD) among SNPs were obtained by D' and r2 using Haploview with default parameters and HapMap CEU+TSI (R2). (Barrett et al., 2005) The proxy SNPs with regional recombination rates were assessed by using SNAP and 1000 Genomes Pilot 1 data (Johnson et al., 2008).

2.6. SNP imputation

The genotypes for missing markers in a dataset can be confidently inferred by LD and the correlation between genotypes in a reference data set. Association tests of genotyped markers should show similar levels of association compared with imputed markers. Missing SNPs were imputed using the expectation–maximization (E–M) algorithm in PLINK and the HapMap CEU r23a reference panel. The imputed SNPs were used for the functional enrichment analysis.

2.7. Functional enrichment analysis

Gene ontology analysis was performed on the gene sets harboring the identified SNPs (P<0.005) using DAVID software (Huang et al., 2009a, 2009b). The enriched gene functions with more than five genes were identified from the SM *vs.* NSM, SM *vs.* control, and NSM *vs.* control analyses, respectively.

3. Results

We performed a primary GWA of SM *vs.* NSM to identify SNPs associated with seasonal patterns of manic episodes. As shown in Fig. 1, we identified 28 associated SNPs with $P < 10^{-4}$ in this case-only analysis, the most significant of which was rs41350144 (OR=2.27) with a P value of 3.08×10^{-7} (permuted P=1.0×10^{-6}). This SNP is located within an intron of the gene encoding nuclear factor 1/*A* (*NF1A)* on chromosome 1p31.

As shown in Table 1, we identified a total of three genomic regions of interest (ROIs) on chromosomes 1p31, 6q24, and 7p15, defined as regions containing at least two SNPs with $P < 10^{-4}$ and adequate support for association (i.e., $P < 10^{-3}$) from surrounding SNPs within 100 kb. As detailed in Fig. 2A, support for the 1p31 region came from a total of six SNPs spanning 16 kb, many of which exhibited high levels of LD with the most significant SNP, rs41350144. For the second ROI, shown in Fig. 2B, a peak *P* value of 2.04×10^{-5} (OR=1.934, permuted $P=1.4 \times 10^{-5}$) was observed for a SNP (rs1415913) within an intron of the *AK097143* gene on 6q24, and *P* values of $< 10^{-4}$ were observed for three other SNPs. The third ROI, detailed in Fig. 2C, was identified through rs864745, an intronic SNP within the *JAZF1* gene on 7p15, which yielded a peak *P* value of 2.44×10^{-5} (OR=0.54). An additional four SNPs with *P* values of $< 10^{-4}$ (i.e., rs10274928, rs849141, rs537124, rs552707) were observed in this region.

All of those ROIs are located within or near blocks of high LD which were calculated from Hapmap version 3 (R2, CEU TSI) by Haploview (Fig. 2). This may be an indication of the functional significance of these regions. To exclude the possible effect of the linkage within each of the ROI regions, we performed conditional analyses with the most significant SNPs in each ROI (rs41350144, rs1415913, and rs864745, respectively), but none of those ROI SNPs are significant (data not shown), indicating the dependent association of the SNPs to the strongest SNP.

Next, we further sought whether the haplotype construction improve the statistical significance of the SNPs. Before analysis, linkage disequilibrium-based SNP pruning was applied by calculating variance inflation factor (VIF) using PLINK. VIF is $1/(1 - R^2)$ where R^2 is the multiple correlation coefficient for a SNP being regressed on all other SNPs simultaneously. After pruning the SNPs in the *NF1A* gene region with VIF threshold 2, a total of 66 out of 116 SNPs were remained. The haplotypes were constructed with the pruned SNPs using sliding window specification of 2–6 flanking SNPs. As shown in Table 2, this revealed that the haplotype comprising three adjacent SNPs (rs41453448, rs1125777, and rs12568010) spanning 7,549 bp has an even more significant association to this region with a *P* value of 2.12×10^{-7} (OR=0.4), although was not the individual *P*-values of each SNP (rs41453448, $P=0.018$; rs1125777, $P=1.76 \times 10^{-6}$; rs12568010, $P=0.4465$).

The analyses comparing the SM and NSM groups with controls identified 28 and 72 SNPs, respectively, with $P < 10^{-4}$ (see Supplemental Table 1). The most significant association in the SM *vs.* control analysis was for rs2245641 on chromosome 9p22 (OR=1.90, $P=2.21 \times 10^{-6}$, permuted $P=2.00 \times 10^{-6}$). Of the SNPs identified in the SM *vs.* control analysis, the five SNPs (i.e., rs41350144, rs7556462, rs12692570, rs537124, and rs552707) overlapped with those observed in the SM *vs.* NSM with $P < 10^{-4}$, and two of these are located within the *NF1A* gene.

The most significant association in the NSM *vs.* control analysis was rs3750552 (OR=1.68, $P=4.74 \times 10^{-6}$, permuted $P=3.00 \times 10^{-6}$) which is located near the phosphoglucomutase 5 gene (*PGM5)* on chromosome 9q21. Other SNPs within the ROIs identified in the SM *vs.* NSM analysis were more moderately associated ($P < 0.05$) in the analyses comparing SM and NSM with controls.

To determine whether the associated SNPs showed enrichment in certain functional pathways, we imputed the data using genotypes from the publicly available CEU HapMap dataset (r23a). Gene Ontology functions were identified for all genes containing SNPs associated with $P < 0.005$, as shown in Table 3. The SM *vs.* NSM analysis showed an enrichment of both adhesion and development-related pathways. In the SM *vs.* control analysis, an enrichment of apoptosis-related functions was observed in addition to enrichment of development and adhesion pathways. Development-related gene functions were also significantly enriched in the NSM *vs.* control analysis. This may suggest that altered functions of adhesion or development-related pathways contribute to the expression of seasonal patterns of manic episodes.

4. Discussion

Previous studies have suggested that BD has a strong genetic component, and several GWA studies have been performed to identify the genes contributing to BD susceptibility. However, there has been little consistency among the individual GWA studies. For example, the Wellcome Trust Case Control Consortium (2007) reported an association on chromosome 16p12 (P=6.3 × 10^{-8}). Baum et al., 2008a, 2008b found evidence that *DGKH* was associated with BD in a combined GWAS sample (P=1.5 × 10^{-8}). Sklar et al. (2008) identified *MYO5B* as being associated with BD. Smith et al. (2009) found an association to the region Xq27.1 in a European American BD sample (P=1.6 × 10^{-6}) and to *DPY19L3* in an African American sample (P = 1.5 × 10^{-6}). Very recently, Sklar et al. (2011) confirmed genome-wide significant evidence of association for *CACNA1C* and identified a new intronic variant in *ODZ4* in combined GWAS sample. However, none of these findings reaches the 5 × 10^{-8} threshold for statistical significance in a GWA study. One reason for the lack of success in elucidating the inherited risk may be due to genetic heterogeneity of BD.

We have hypothesized that clinical subphenotypes of BD may identify more homogeneous subsets of patients that can be studied with increased power to detect genetic variation (Potash et al., 2007). Our analyses of seasonal patterned mania identified *NF1A* as a possible susceptibility for BD in an analysis of SM *vs.* NSM. Associations to SNPs within this gene were also prominent in the analysis of SM *vs.* control, whereas much lower association signals were observed for this region in the NSM *vs.* control analysis, suggesting that this gene may be a specific regulator of seasonality in mania.

There are several limitations to our study. First, we do not have access to an independent sample in which to replicate our findings. Second, the evaluation of seasonal pattern of manic episodes was dependent on patients' memory. This retrospective approach has a risk of recall bias. Third, the sample sizes of SM and NSM were small and may not have been sufficient to detect the smaller genetic effects. Taking these limitations into account, further investigations with larger samples and more valid seasonality evaluations are needed.

Recently, several meta-analyses have been performed in the hope that increasing the sample size will lead to increased statistical power. Scott et al. (2009) reported a meta-analysis of three studies (NIMH/Pritzker, GlaxoSmithKline Research & Development, and WTCCC) with a combined sample 3683 non-overlapping cases and 14507 extended controls and

>2.3 million genotyped and imputed SNPs. Three chromosomal regions with *P* values of approximately 10^{-7} were identified: 1p31.1 (no known genes), 3p21 (425 known genes), and 5q15 (*MCTP1*). Among three regions, strongest evidence of association was observed for rs472913 (OR=1.18, $P=2.0 \times 10^{-7}$), which is 500 kb from the closest known gene, *NF1A* on chromosome1p31.3. This same gene gave the strongest signal for association with seasonal manic in our sample. Interestingly, in a recent meta-analysis combining the GAIN and TGEN samples described herein with the WTCCC sample (Smith et al., 2011), one of the top hits for BD was rs2989476 (OR=1.16, 3.07×10^{-6}), which is located near *NF1A*. These two meta-analyses, which overlap to some degree in terms of subjects, suggest that *NF1A* may be a susceptibility gene for BD or at least a certain subgroup of BD. Our results suggest that perhaps this subgroup is seasonal patterned mania.

The *NF1A* (nuclear factor *1*/*A*) gene is involved in cellular transcription and DNA replication, and its haploinsufficiency is associated with a central nervous system malformation syndrome, as well as ureteral and renal defects (Lu et al., 2007). In a transgenic mouse experiment, the *NF1A* knock out mouse was reported to show abnormal emotion/affect behavior (Le-Niculescu et al., 2009). Recent GWA studies suggest the involvement of *NF1A* in celiac disease (Dubois et al., 2010), ventricular depolarization (Sotoodehnia et al., 2010), and serum uric acid levels (Wei et al., 2011). In a recent GWAS, Wei et al. (2011) reported that *NF1A* has an important epistatic effect with *SLC2A9* on serum uric acid levels. Interestingly, a recent paper reported increased uric acid levels in drug-naïve subjects with a first manic episode of BD (Salvadore et al., 2010). A randomized, placebo-controlled trial showed that the purinergic modulator allopurinol, a xanthine oxidase inhibitor, was effective in treating acute mania when used adjunctively with lithium (Machado-Vieira et al., 2008). Furthermore, seasonal variation in serum uric acid levels has been reported to be the highest during summer (Murciano Revert et al., 2000), and gout attacks showed a higher frequency peak in spring (Gallerani et al., 1999).

NF1A is involved with a number of genes thought to participate in BP pathology. First, it inhibits transcription of the thyroid stimulating hormone β subunit (Kim et al., 2010), which is thought to be a key link by which photoperiodic control of melatonin influences pars tuberalis control of gonadotropin-releasing hormone (GNRH), a key pituitary hormone, and perhaps other aspects of hypothalamic function (Dardente et al., 2010; Masumoto et al., 2010) Second, *NF1A* directly regulates expression of GNRH, though it may not be the most active form of NF1 at the GNRH promoter (Givens et al., 2004; Miller, 2008). Third, *NF1A* directly regulates transcription of growth hormone (Norquay et al., 2003), the glucocorticoid receptor (Mukhopadhyay et al., 2001), and the testosterone receptor (Lin et al., 2006), all of which may play parts in the physiology of mania. Fourth, *NF1A* in combination with SP1 influences expression of the 5HT3 receptor, which may be involved in mood (Bedford et al., 1998), and may be associated with suicide in schizophrenia (Garbett et al., 2008). Taken together, these findings provide evidence to suggest a role for *NF1A* in BD and perhaps seasonal mania, which may be a useful as a subphenotype for BD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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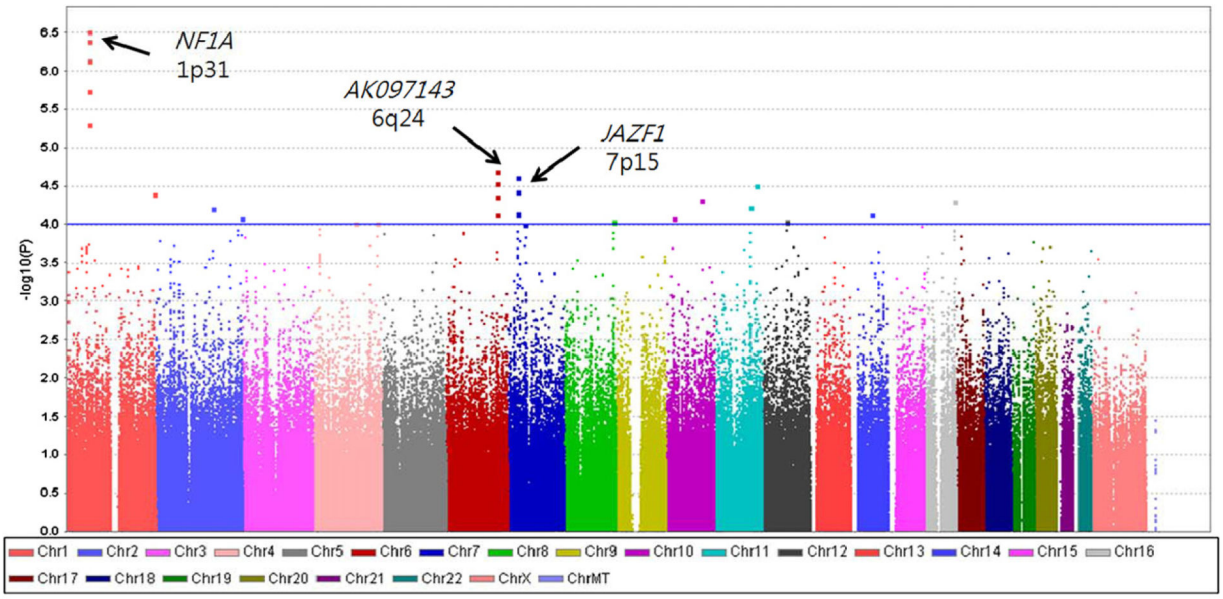

Fig. 1.

Results of the genome-wide association analysis of SM *vs.* NSM. Manhattan plot shows the chromosomal view of the—log *P* values of SNPs. The three genes *NF1A*, *AK097143, JAZF1* located in the ROIs are as indicated (arrows).

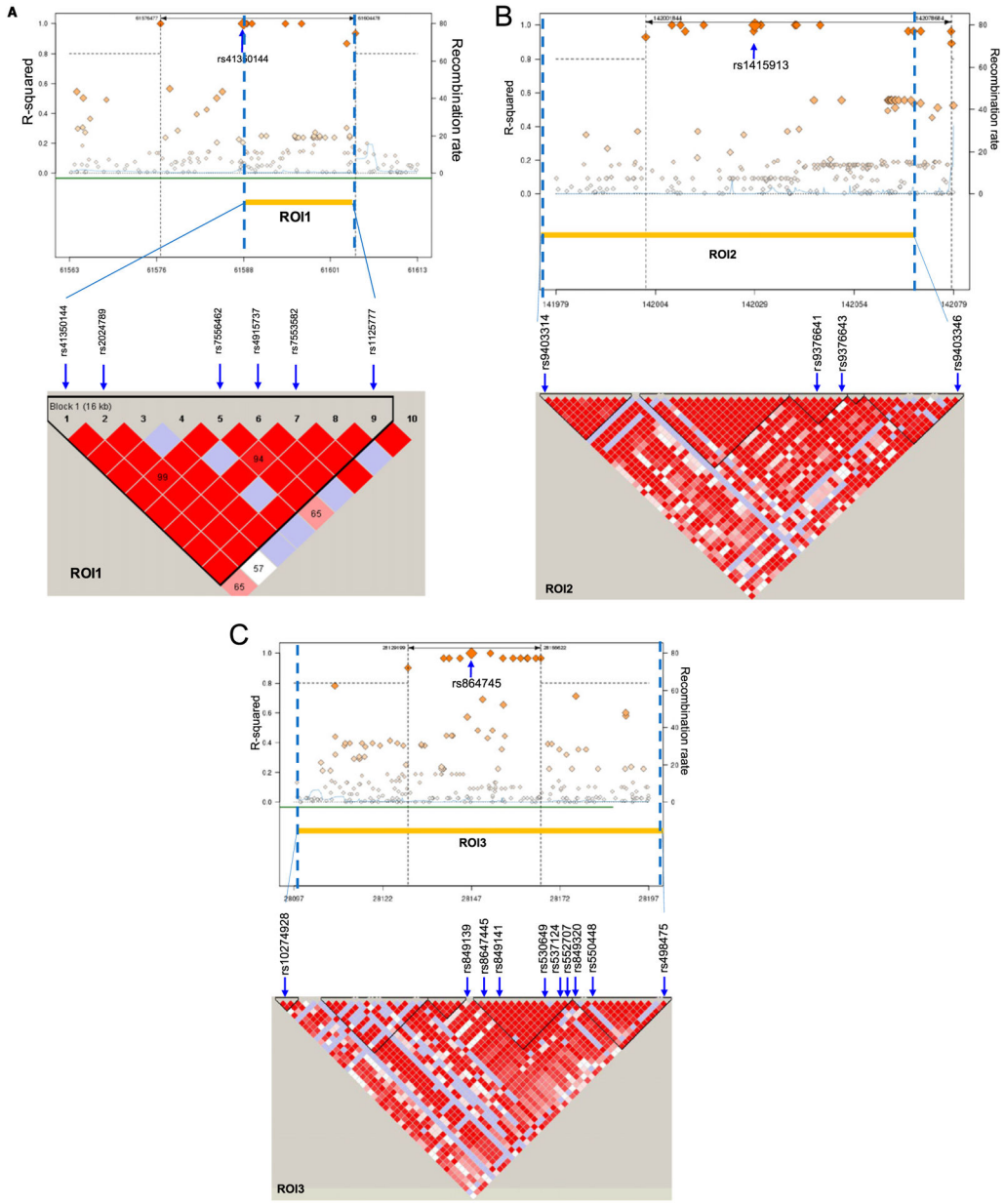

Fig. 2.

Haplotype association plots for the three ROIs in the SM *vs.* NSM analysis. Proxy SNPs with regional recombination rates in the three ROI are shown as determined from SNAP with HapMap 1000 Genomes Pilot 1 data ((A)–(C), top). The regional LDs around the three ROIs are shown by Haploview using CEU+TSI r2 data ((A)–(C), bottom). The D' scores for each paired SNP are indicated with color scheme. The recombination rate (pale blue line), the lowest *P*-value SNP (the biggest diamond mark), and ROI span (dotted vertical line) are indicated.

Table 1

Regions of Interest (ROI) with enriched association in the SM *vs.* NSM analysis.

	Position	SNP ID	Allele	Minor Allele Freq (MAF)	Odd Ratio (OR)	Confidence Interval (CI)	*P*-value	Permuted *P*	Gene
ROI1	chr1:61588387	rs41350144	T	0.477	2.269	1.66 – 3.11	3.08×10^{-7}	1.00×10^{-6}	*NFIA*
	chr1:61589589	rs2024789	C	0.476	2.202	0.27 – 0.72	7.24×10^{-7}	2.00×10^{-6}	*NFIA*
	chr1:61594407	rs7556462	C	0.477	2.264	1.61 – 3.01	4.06×10^{-7}	1.00×10^{-6}	*NFIA*
	chr1:61594871	rs4915737	G	0.131	0.374	1.65 – 3.11	1.80×10^{-4}	1.04×10^{-4}	*NFIA*
	chr1:61596963	rs7553582	C	0.199	0.3662	0.22 −0.63	4.93×10^{-6}	4.00×10^{-6}	*NFIA*
	chr1:61604478	rs1125777	T	0.472	2.142	0.24 – 0.56	1.77×10^{-6}	3.00×10^{-6}	*NFIA*
ROI2	chr6:141873044	rs9403314	T	0.315	0.5243	0.37 – 0.73	2.27×10^{-4}	2.55×10^{-4}	-
	chr6:142016408	rs9376641	A	0.335	1.839	1.41 – 2.59	7.34×10^{-5}	6.33×10^{-5}	*AK097I43*
	chr6:142029277	rs1415913	G	0.335	1.934	1.48 – 2.73	2.04×10^{-5}	1.40×10^{-5}	*AK097I43*
	chr6:142030807	rs9376643	T	0.334	1.868	1.43 – 2.62	4.23×10^{-5}	$2.80\text{E} \times 10^{-5}$	*AK097I43*
	chr6:142067836	rs9403346	T	0.334	1.9	1.46 – 2.68	2.92×10^{-5}	2.00×10^{-5}	*AK097I43*
ROI3	chr7:28104718	rs6971086	G	0.266	0.5477	0.39 – 0.77	4.51×10^{-4}	3.77×10^{-4}	*JAZFI*
	chr7:28108613	rs10274928	A	0.470	0.5328	0.39 – 0.73	7.25×10^{-5}	4.53×10^{-5}	*JAZFI*
	chr7:28145921	rs849139	C	0.366	0.537	0.39 – 0.75	2.04×10^{-4}	1.3×10^{-4}	*JAZFI*
	chr7:28147081	rs864745	T	0.488	0.5114	0.37 – 0.7	2.44×10^{-5}	2.10×10^{-5}	*JAZFI*
	chr7:28151616	rs849141	A	0.280	0.4931	0.35 – 0.7	7.06×10^{-5}	3.30×10^{-5}	*JAZFI*
	chr7:28156074	rs1635853	T	0.408	0.5421	0.39 – 0.74	1.53×10^{-4}	1.06×10^{-4}	*JAZFI*
	chr7:28168955	rs530649	G	0.1369	0.4221	0.27 – 0.67	2.55×10^{-4}	1.71×10^{-4}	*JAZFI*
	chr7:28169667	rs537124	C	0.284	0.4815	0.34 – 0.68	3.75×10^{-5}	2.70×10^{-5}	*JAZFI*
	chr7:28171828	rs552707	T	0.284	0.4815	0.34 – 0.68	3.75×10^{-5}	2.70×10^{-5}	*JAZFI*
	chr7:28175361	rs849320	T	0.137	0.4276	0.27 – 0.68	2.70×10^{-4}	2.34×10^{-4}	*JAZFI*
	chr7:28195567	rs550448	G	0.137	0.3987	0.25 – 0.64	1.20×10^{-4}	7.20×10^{-5}	*JAZFI*
	chr7:28222765	rs498475	G	0.368	0.5876	0.43 – 0.8	6.68×10^{-4}	6.35×10^{-4}	*AK293540*

Table 2

Haplotype analysis of the ROI1(1p31) region.

CHR	BP1	BP2	SPAN	SNP1	SNP2	HAPLOTYPE	OR	P*
1	61596977	61604526	7549	rs41453448	rs12568010	GCA	0.427	2.12E-07
1	61604478	61604526	48	rs1125777	rs12568010	*CA*	0.428	2.30E - 07
1	61592660	61594407	1747	rs17121983	rs7556462	CC	2.26	4.06E - 07
1	61592660	61594871	2211	rs17121983	rs4915737	CCC	2.26	4.06E - 07
1	61594407	61594871	464	rs7556462	rs4915737	CC	2.26	4.11E-07
1	61588942	61594407	5465	rs2364467	rs7556462	GCC	2.2	8.99E - 07

*The haplotypes with *P*-value < 10^{-6} are shown.

Table 3

The enriched gene functions in the group comparison.

GO terms	*P*-values		
	SM *vs.* NSM	SM *vs.* CTL	M *vs.* CTL
Development			
GO:0048858—cell projection morphogenesis	0.0264	0.0020	0.0002
GO:0032990—cell part morphogenesis	0.0331	0.0029	0.0003
GO:0000902—cell morphogenesis	0.0748	0.0081	0.0006
GO:0030030—cell projection organization	0.0028	0.0001	0.0009
GO:0048812—neuron projection morphogenesis	0.0898	0.0142	0.0014
GO:0032989—cellular component morphogenesis	0.1236	0.0095	0.0022
GO:0031175—neuron projection development	0.0791	0.0078	0.0025
GO:0048667—cell morphogenesis involved in neuron differentiation	0.0837	0.0127	0.0034
GO:0035295—tube development	0.2151	0.3199	0.0051
GO:0007409—axonogenesis	0.1489	0.0506	0.0052
GO:0048666—neuron development	0.0261	0.0008	0.0123
GO:0051130—positive regulation of cellular component organization	0.0049	0.3319	0.4061
GO:0060537—muscle tissue development	0.0353	0.0012	0.5534
GO:0003001—generation of a signal involved in cell-cell signaling	0.0349	0.0087	0.5871
GO:0050808—synapse organization	0.0117	0.0089	0.7599
GO:0014706—striated muscle tissue development	0.0945	0.0009	0.7642
GO:0007517—muscle organ development	0.0010	0.0005	0.8687
GO:0030182—neuron differentiation	0.0542	0.0022	0.0256
Adhesion			
GO:0022610—biological adhesion	0.0029	0.0008	0.0202
GO:0007155—cell adhesion	0.0029	0.0008	0.0205
Apoptosis			
GO:0043065—positive regulation of apoptosis	0.5950	0.0092	0.2917
GO:0043068—positive regulation of programmed cell death	0.6018	0.0097	0.2984
Others			
GO:0050804—regulation of synaptic transmission	0.1353	0.0078	0.8252

GO terms	*P*-values		
	SM *vs.* NSM	**SM *vs.* CTL**	**M *vs.* CTL**
GO:0044057—regulation of system process	0.0147	0.0022	0.9754
GO:0035023—regulation of Rho protein signal transduction	0.0557	0.0011	0.1950
GO:0016192—vesicle-mediated transport	0.0407	0.0097	0.3495