Association Between Sodium- and Potassium-Activated Adenosine Triphosphatase α Isoforms and Bipolar Disorders

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Background: The sodium- and potassium-activated adenosine triphosphatase (Na^+, K^+-ATPase) is a major plasma membrane transporter for sodium and potassium. We recently suggested that bipolar disorders (BD) may be associated with alterations in brain Na^+, K^+-ATPase. We further conjectured that the differences in Na^+, K^+-ATPase in BD patients could result partially from genetic variations in Na^+, K^+-ATPase α isoforms.

Methods: To test our hypothesis, we undertook a comprehensive study of 13 tagged single nucleotide polymorphisms (SNPs) across the three genes of the brain α isoforms of Na^+, K^+- ATPase (*ATP1A1*, *ATP1A2,* and *ATP1A3,* which encode the three α isoforms, α1, α2, and α3, respectively) identified using HapMap data and the Haploview algorithm. Altogether, 126 subjects diagnosed with BD from 118 families were genotyped (parents and affected siblings). Both individual SNPs and haplotypes were tested for association using family-based association tests as provided in the UNPHASED and PBAT set of programs.

Results: Significant nominal association with BD was observed for six single SNPs (α1: rs11805078; α2: rs2070704, rs1016732, rs2854248, and rs2295623; α3: rs919390) in the three genes of Na^+, K^+-ATPase α isoforms. Haplotype analysis of the α2 isoform (*ATP1A2* gene) showed a significant association with two loci haplotypes with BD (rs2295623: rs2070704; global p value = .0198, following a permutation test).

Conclusions: This study demonstrates for the first time that genetic variations in Na^+, K^+-ATPase are associated with BD, suggesting a role of this enzyme in the etiology of this disease.

Key Words: Affective disorders, bipolar disorders, family-based study, genetic association, Na^+, K^+-ATPase, SNPs

Bipolar disorder (BD) is characterized by profound mood symptoms that include episodes of mania, hypomania, and depression (1). Family and twin studies provide strong evidence for a contribution of genetic variation to the risk for BP (2,3). Heritability of BD has been estimated to be as high as 80% (4,5). Bipolar disorder is a complex heritable disease; thus, a large number of genes may be involved in its etiology. Indeed, numerous candidate genes for BD have been examined in case-control association studies (1,6).

ATP1A1, *ATP1A2,* and *ATP1A3* are a group of genes that code for the catalytic subunit of the sodium- and potassium-activated adenosine triphosphatase (Na^+, K^+-ATPase) enzyme, present in the plasma membrane of all eukaryotic cells. The enzyme hydrolyzes adenosine triphosphate (ATP) and uses the free energy to drive the transport of potassium into the cell and sodium out of the cell (for a review, see 7). In addition to pumping ions, Na^+, K^+-ATPase is engaged in the assembly of multiple protein complexes into functional microdomains that transmit signals to different intracellular compartments (for a review, see 8). Clearly, disturbance in Na^+, K^+-ATPase density and/or activity could have significant implications on brain function. The Na^+, K^+-ATPase is an oligomer composed of three polypeptides, the α, β, and FXYD subunits. Thus far, four α, three β, and seven FXYD isoform subunits have been identified (9). The α subunit is a multi-spanning membrane protein that is responsible for the catalytic and transport properties of the enzyme and contains the binding sites for the cations, ATP, and digitalis steroids (10,11). The three isoforms, α1, α2, and α3, are present in brain tissue (12). Whereas neurons are the principal source of the α3 polypeptide, glial cells preferentially express α2 (12,13).

The possible involvement of Na^+, K^+-ATPase in BD was suggested more than 50 years ago (14,15). Bipolar disorder has consistently been associated with abnormalities in the Na^+, K^+-ATPase activity in erythrocytes (16–18). Meta-analysis of erythrocyte Na^+, K^+-ATPase activity in bipolar illness found a significant mood-state related decrease in the enzyme activity in both manic and BD patients when compared with euthymic bipolar patients but not when ill patients were compared with normal control subjects (18). Furthermore, Na^+, K^+-ATPase density was significantly lower in BD patients than in major depressed and schizophrenic patients (19,20). Recently, Chetcuti *et al.* (21) have demonstrated a reduction in brain Na^+, K^+-ATPase α1 isoform expression in mice treated with the mood stabilizer lithium. In addition, the levels of digitalis-like compounds, the endogenous inhibitors of the Na^+, K^+-ATPase, in the parietal cortex of BD patients were significantly higher than in normal individuals and depressed patients (19). Potential associations between the *ATP1A1*, *ATP1A2,* and *ATP1A3* genes and BD have been examined only in a few studies that found evidence for

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Table 1. Primers Used in Genotyping of *ATP1A1*, *ATP1A2*, and *ATP1A3* Tagged SNPs

Gene	First PCR Primers	SNP	Second PCR Primer Extensions
ATP1A1	F: GCTGCTGGGTGGTAGTTAGC	rs757578	$(T)_8$ GGGGATTAAAATGTGGG
	R: GCACAGGCTTCCTTGTTAGC		
	F: CCTGAGCAAAGGGATTTTTG	rs850602	TTACTAGTTCCTTTGTGA
	R: CCAAGGACAAAGCACGAACT		
	F: GGTGAAGCTATGGGCAAGAC	rs11805078	$(T)_{27}$ TTGTAAGTGGGGGTAAAA
	R: TCACGGATTCTCTCTGAGCA		
ATP1A2	F: CAAGCCTGCACAAGCATAAA	rs1016732	$(T)_6$ GGGCTTCACGGAGGAAGA
	R: GTCCTGCATCTCAGCTAGGG		
	F: TGCCCCTATTCCTTTACCTT	rs2753267	$(T)_{24}$ AAGCTCCTCAAGGGCAG
	R: CCATATTGCATTGGAATCCT		
	F: TCATTGTCACTGGCTGCTTC	rs2854248	TTCTGTCAGCTCCCAGGC
	R: ATTAGGTGCTGGCATGGAAA		
	F: GCACATACGCTCAGAACCAA	rs11265329	$(T)_{12}$ GGGCCTCGCTGCCCCCTT
	R: CAGAGGGCACAGGTTTCAGT	rs16831388	$(T)_{12}$ CTGGGTTCTAGAGATAA
	F: GCTTTGGCTCACCTATCCTG	rs2295623	$(T)_{21}$ CTGGGAGCCACAAGGCAC
	R: CTCCATTGCTATGGGTGTCC		
	F: GGACTTGTCTCCCAGTCGAG	rs2070704	$(T)_{30}$ AGGGTTGGCTTGGCAGTG
	R: GGGAACTTCTCCACCCTGAT		
ATP1A3	F: CCTTGCCTGTCTCTCTCCAT	rs919390	CCATCTCTTCCCCGTCCC
	R: GCGGCAGGAGATAGTGGA		
	F: GAGGTTCTGGAGGCCTGAC	rs2217342	$(T)_{21}$ CTCCAAGGGGTTGTCGTG
	R: TGTGATCTCCAGGCACACAG		
	F: GGTGACAAATGTGCATCAGC	rs8107107	$(T)_{24}$ GAAACAAGGTGTGCCGTG
	R: GATCCGAGACCCTGTCTCAA		

ATP1A1, *ATP1A2*, and *ATP1A3* encode for the α1, α2, and α3 isoforms of the Na^+, K^+-ATPase, respectively. The conditions for the different PCR reactions are described in the Method and Materials section.

Na^+, K^+-ATPase, sodium- and potassium-activated adenosine triphosphatase; PCR, polymerase chain reaction; SNP, single-nucleotide polymorphism.

association between a dinucleotide microsatellite polymorphism within the *ATP1A3* gene and BD (2,22).

The fundamental role of Na^+, K^+-ATPase in brain function and the suggested function for this enzyme in the pathophysiology of BD led us to examine polymorphism within genes encoding this enzyme and their association with BD. We undertook a comprehensive study of 13 tagged single nucleotide polymorphisms (SNPs) across the entire three gene regions of the α subunit using HapMap (http://hapmap.org) data and the Haploview (http://www.broad.mit.edu/mpg/haploview) algorithm. Altogether, 126 subjects diagnosed with BD from 118 families were genotyped and both individual SNPs and haplotypes were tested for association with the disease.

Methods and Materials

Participants

Altogether, 126 subjects (Palestinian Arabs) with BD (73 men and 53 women) and their parents (88 mothers and 88

Table 2. Position of All Tagged SNP Sites and Their Relation to Exon-Intron Boundaries of the Three α Subunits Genes of Na^+, K^+-ATPase

	Gene	rs Number	SNP	Position	Location
1	*ATP1A1*	rs757578	C/T	116725838	Intron 1
2		rs850602	C/G	116722475	Intron 1
3		rs11805078	C/T	116719908	Intron 1
1	*ATP1A2*	rs1016732	A/G	158353592	Intron 1
2		rs2753267	A/G	158358745	Intron 3
3		rs2854248	A/T	158360551	Intron 5
4		rs11265329	C/T	158362070	Intron 7
5		rs16831388	A/G	158362249	Intron 7
6		rs2295623	A/C	158363939	Intron 7
7		rs2070704	A/G	158378762	3′ UTR
1	*ATP1A3*	rs919390	C/G	47162890	3′ UTR
2		rs8107107	C/T	47169150	Intron 16
3		rs2217342	G/T	47181356	Intron 1

SNP locations are based on a comprehensive study of all 13 tagged SNPs across the entire three genes regions of the α subunit using HapMap data and the Haploview algorithm.

Na^+, K^+-ATPase, sodium- and potassium-activated adenosine triphosphatase; SNP, single-nucleotide polymorphism; UTR, untranslated region.

fathers) and unaffected siblings (19) were recruited. In total, 118 families, out of which 22 families had two or more children diagnosed with BD, were included in the research group. Exclusion criteria included absence of both parents and non-Palestinian ancestry (two generations). All patients were interviewed by two experienced psychiatrists using the Structured Clinical Interview for DSM Disorders (SCID) interview and diagnosis as BD was assigned according to DSM-IV criteria. One hundred twenty subjects were bipolar I and 6 patients were bipolar II. Cumulative years of illness were 7.2 ± .744 (1–28 years). The average number of hospitalizations was 4.9 ± .53 (1–24 episodes). The DNA of these patients had been examined previously for association with chromosome 22, particularly with microsatellite marker D22S278 (22q12) (23). The protocol for the experiments was approved by the local hospital Helsinki committee (Kemal Psychiatric Hospital, Bethlehem).

Genotyping

DNA was extracted by Master Pure Kit (Epicentre, Madison, Wisconsin). Single nucleotide polymorphisms were identified by searching through the public Single Nucleotide Polymorphism database (dbSNP) (http://www.ncbi.nlm.nih.gov/SNP/). Altogether, 16 tagged SNPs were identified across the gene regions of *ATP1A1*, *ATP1A2*, and *ATP1A3* (36.94 kilobase pairs [kbp], 27.83 kbp, and 27.64 kbp, respectively) by Haploview (http://www.broad.mit.edu/mpg/haploview) (24).

Genotyping of all SNPs was performed using the SNaPshot Methods (Applied BioSystems, Foster City, California). This method relies on the extension of a primer immediately adjacent to the SNP using fluorescently labeled dideoxynucleotide triphosphates (ddNTPs). The fluorescently labeled extension primers were then visualized by electrophoresis on a capillary ABI PRISM 310 automated sequencer (Applied Biosystems, Foster City, California). Amplification of the Na^+, K^+-ATPase was

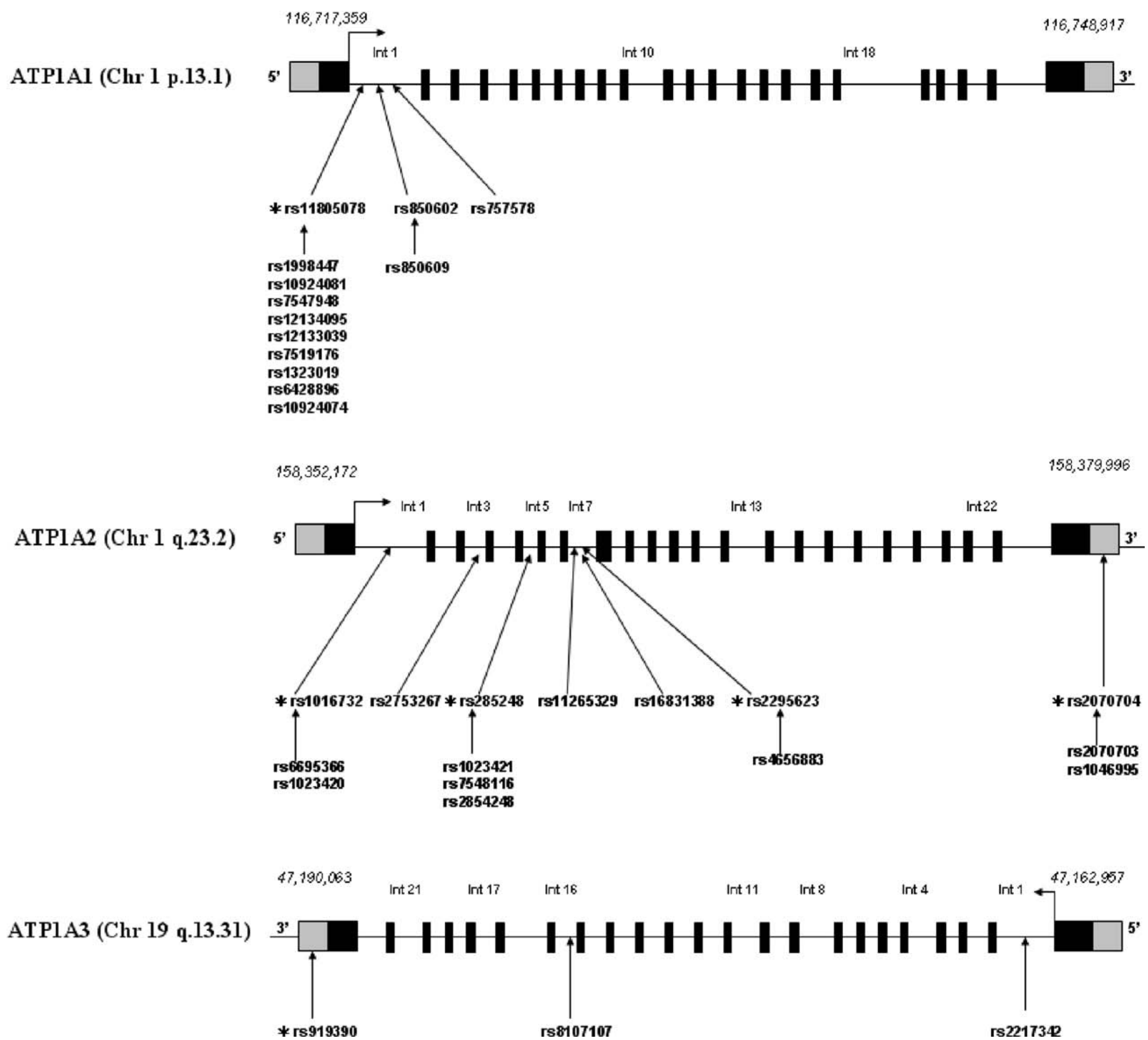

Figure 1. Genomic structures and locations of SNP sites for *ATP1A1*, *ATP1A2,* and *ATP1A3* genes. The arrows indicates the direction of transcription and the transcription start site of each gene. Exons are denoted by black, with untranslated regions in gray. The locations of the tagging SNPs used in this study are shown below the gene, and their IDs correspond to those given in Table 2. The single tagging SNPs, which are significantly associated with BD ($p < .005$), are marked with asterisks. SNPs that are in linkage disequilibrium to the tagging SNPs are listed. The statistical analyses are described in the Methods and Materials section. BD, bipolar disorder; LD, linkage disequilibrium; SNP, single nucleotide polymorphism.

achieved using the pairs of primers as described in Table 1. Polymeric chain reaction (PCR) cycling conditions in the SNaPshot Method were as follows: samples were heated at 94°C for 5 min and followed by 35 cycles of 94°C (30 sec), 55°C (30 sec), and 72°C (90 sec) and final extension step of 72°C for 5 min. After the first PCR cycle, the PCR products were cleaned with ExoSAP (USB, Cleveland, Ohio) at 37°C for 30 min and then at 80°C for 15 min. The conditions for the second PCR were as follows: 96°C (10 sec), 50°C (5 sec), and 50°C (30 sec) for 25 cycles. The second PCR products were cleaned using shrimp alkaline phosphatase (SAP) initially at 37°C for 1 hour followed by 72°C for 15 min.

The extension primers for SNaPshot Method are shown in Table 1. In the case of Mendelian error, the genotyping for the entire family was rechecked and if the error persisted the genotyping for that SNP was not included in the analysis. The overall Mendelian error rate following our double check procedure was $<$ .5%.

PBAT (Helix Tree)

The PBAT software package provides a unique set of tools for complex family-based association analysis at a genome-wide level (25–27). PBAT can handle nuclear families with missing parental genotypes, extended pedigrees with missing genotypic information, analysis of single nucleotide polymorphisms, haplotype analysis, quantitative traits, multivariate/longitudinal data, and time-to-onset phenotypes. The data analysis can be adjusted for covariates and gene/environment interactions. The multivariate family-based association test (MFBAT) provided for in the PBAT-Helix Tree (http://www.goldenhelix.com/pharmhelixtreefeatures.html) is a set of programs (25,26) using family-based association test generalized estimating equations (FBAT-GEE). In the current investigation, we used MFBAT to examine the association between single SNPs and three genes of α subunits of Na^+, K^+-ATPase and BD in few genetics models as additive, dominant, recessive, and heterozygote. The detailed description of the PBAT models used in the present study was explained previously (28,29).

Other Statistical Methods

We used the logistic-based variant of the transmission disequilibrium test (TDT), the so-called extended transmission disequilibrium test (ETDT) (30), to assess association (and linkage) without the confounding effect of population stratification. The TDT, in its simplest version, compares, for one allele, the number of times this allele is transmitted with the number of times this allele is not transmitted to an affected offspring. Note that only heterozygous parents are informative. This approach can be extended to haplotypes. The various tests are implemented in the latest version (3.0.9) of UNPHASED (http://www.rfcgr.mrc.ac.uk/~fdudbrid/software/unphased/). UNPHASED (31) is a suite of programs for association analysis of multilocus haplotypes from unphased genotype data.

Correction for Multiple Testing

We used the permutation test option as provided in PBAT single SNPs and UNPHASED (haplotypes) to avoid spurious results and correct for multiple testing. Permutation test correction was performed using 1000 iterations (random permutations).

Results

We first tested single SNPs in each gene for association with BD using PBAT. Three SNPs in *ATP1A2* gene were not included in the analysis: one SNP was not in Hardy-Weinberg equilibrium (rs10797059) and two SNPs were not informative (rs12077973, rs12723123) due to low heterozygosis. Three tagging SNPs were tested for association with BD in *ATP1A1*, seven SNPs in *ATP1A2,* and three SNPs in *ATP1A3*. The position of SNPs assayed in the genes and their location along the Na^+, K^+-ATPase genomic region and their relationship to the exon/intron boundaries of the gene are shown in Table 2 and Figure 1. The SNPs in *ATP1A1* are all localized close to exon 1 intron 1 boundary, while in *ATP1A2* they are distributed along the entire gene. In *ATP1A3* gene, the SNPs are located in intron 1, intron 16, and 3' untranslated region (UTR). The graph and linkage disequilibrium (LD) values for single SNPs were

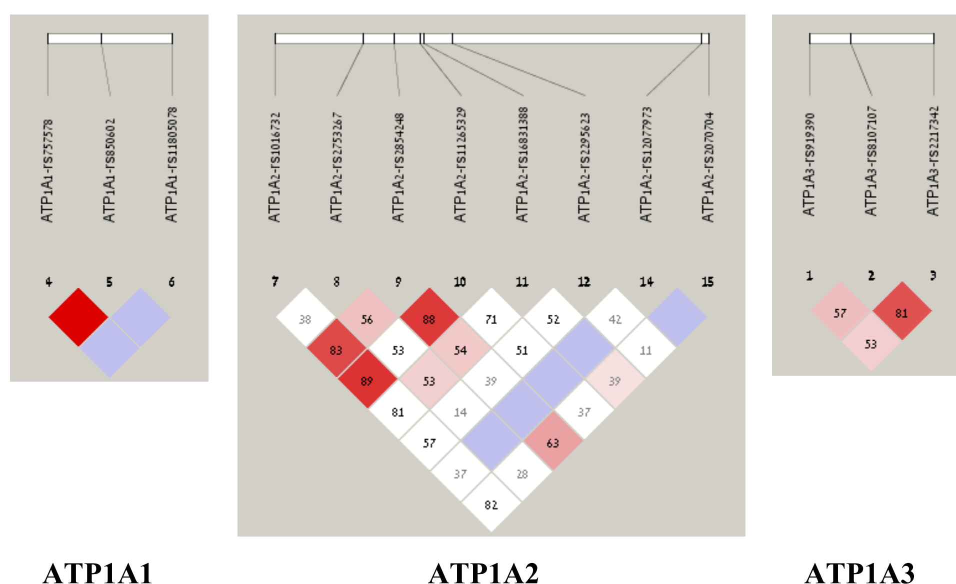

Figure 2. Marker-to-marker D′ relation of the SNPs of the three α subunit genes of Na^+, K^+-ATPase. All the SNPs in this investigation are tagged SNPs, therefore the LD values are low between them and there is no haplotype blocks. The LD values were computed using Haploview (http://www.broad.mit.edu/mpg/haploview/) (24). LD, linkage disequilibrium; Na^+, K^+-ATPase, sodium- and potassium-activated adenosine triphosphatase; SNP, single nucleotide polymorphism.

Table 3. Single Tagging SNPs Association Between the Three α Isoforms of Na^+, K^+-ATPase and BD

Gene	rs Number	Allele	Number of Informative Family	Frequency	Model	*p* Value (FBAT)	Heritability Direction
ATP1A1	rs11805078	C	11	.915	additive	.0184 (.013)	n
		T	11	.084	additive	.0184	p
	rs1016732	G	40	.835	additive	.0393 (.09)	n
		A	40	.165	additive	.0393	p
		G	11	.835	dominant	.006 (.536)	n
		A	11	.164	recessive	.0066 (.007)	p
	rs2854248	T	38	.563	dominant	.0110 (.54)	p
		A	38	.436	recessive	.0110 (.006)	n
		T	57	.563	heterozygote	.0031 (.003)	p
		A	57	.436	heterozygote	.0031	p
ATP1A2	rs2295623	A	25	.166	dominant	.0208 (.026)	n
		C	25	.833	recessive	.0208 (.032)	p
		C	25	.833	heterozygote	.0014 (.9)	n
		A	25	.166	heterozygote	.0014	n
	rs2070704	A	35	.75	additive	.0236 (.019)	p
		G	35	.244	additive	.0236	n
		G	35	.245	dominant	.0158 (.028)	n
		A	35	.755	recessive	.0158	p
		A	35	.755	heterozygote	.022 (.045)	n
		G	35	.244	heterozygote	.022	n
ATP1A3	rs919390	G	53	.429	additive	.0163 (.021)	p
		C	53	.570	additive	.0163	n
		C	36	.570	dominant	.0268 (.18)	n
		G	36	.429	recessive	.0268 (.023)	p

All the single SNPs were examined in genetics model of PBAT: additive model, dominant, recessive, and heterozygote. The table depicts the 6 significant SNPs associated with BD, along the three genes that encode the three α isoforms of Na^+, K^+-ATPase, out of the 13 tagging SNPs tested. The *p* value in parentheses indicates the *p* value after permutation test (1000 permutations).

BD, bipolar disorder; FBAT, family-based association test; n, negative heritage (under transmitted); Na^+, K^+-ATPase, sodium- and potassium-activated adenosine triphosphatase; p, positive heritage (overtransmitted); SNP, single-nucleotide polymorphism.

computed using Haploview (http://www.broad.mit.edu/mpg/haploview/) (24) and are shown in Figure 2.

Single SNP association in the three genes encoding the individual isoforms of the Na^+, K^+- ATPase with BD are summarized in Table 3. One SNP in *ATP1A1* (rs11805078), four SNPs in *ATP1A2* (rs2070704, rs1016732, rs2854248, and rs2295623), and one SNP in *ATP1A3* (rs919390) were in nominal association with BD (Table 3). All the single SNPs were examined in genetics models of PBAT program: additive model, dominate, recessive, and heterozygote (Table 3) (28,29). Following permutation tests, at least one genetic model remained significant for all of the examined SNPs. The SNP in α1 isoform of the Na^+, K^+- ATPase (rs11805078) was significantly associated with BD only in the additive mode (p = .018). The four SNPs in the α2 isoform of the Na^+, K^+-ATPase and the single SNP in the α3 isoform were significantly associated with BD in several genetics models (see Table 3 for details). The locations of the tagging SNPs significantly associated with BD are marked with asterisks in Figure 1.

We next proceeded to a multimarker association analysis using UNPHASED and its convenient sliding window approach. Consecutive SNPs comprising haplotypes of increasing length (from two to three SNPs along the *ATP1A1* and *ATP1A3* genes and two to seven SNPs along the *ATP1A2* gene) were examined for association with BD. One haplotype block in the *ATP1A2* gene (rs2070704–rs2295623) was significantly associated with BD after permutation test (p = .0198, Table 4).

Discussion

The activity of Na^+, K^+-ATPase is the major determinant of Na^+ and K^+ gradients across cellular plasma membrane, which establishes directly the electrical potential on the plasma membrane (for a review, see 7). Consequently, the density and activity of Na^+, K^+-ATPase are critically important parameters determining many cellular functions and it is plausible that changes in its function may lead to pathological states (32–34). In the nervous system, Na^+, K^+-ATPase activity

Table 4. Individual Haplotype in *ATP1A2* Gene Significantly Associated with BD

Window	rs2295623	rs2070704	Case	Control	Chi-Square	*p* Value	*p* Permutation
1 Locus		A	126	164	5.923	.015	.01
		G	36	30	5.923	.015	
2 Loci	C	A	104.5	138.1	4.4	.035	.0198
	A	**G**	10.49	4.127	8.27	.004	

SNPs and haplotype in the *ATP1A2* gene were tested for association with BD using UNPHASED and its convenient sliding window approach. The significant overtransmitted alleles for single SNPs are marked by grey.

BD, bipolar disorder; SNP, single nucleotide polymorphism.

facilitates the generation of action potentials (35) and affects neurotransmitter release (36,37) and reuptake (38), which are crucial to neuronal function. Thus, changes in Na^+, K^+-ATPase activity due to genetic alterations may lead to aberrant neuronal function and central nervous system (CNS) pathology. Recent studies have documented that mutations in α2 isoform of Na^+, K^+-ATPase are responsible for familial hemiplegic migraine type 2 (39) and mutations in α3 isoforms are involved in rapid-onset dystonia parkinsonism (40).

Previous studies have introduced the hypothesis that brain Na^+, K^+-ATPase is involved in the etiology of BD (19,36,37,41). Only a few studies have examined association between genes encoding Na^+, K^+-ATPase and BD. Mynett-Johnson *et al.* (2) showed evidence for an allelic association between a dinucleotide repeat polymorphism within the gene encoding the α3 subunit of Na^+, K^+-ATPase and BD, which was not replicated in an Amish population (22). An additional study (42) examined the association of excess CAG repeats in the ATPase β1 subunit gene (*ATP1B1*) and found no association with BD (43).

The present study demonstrated for the first time an association between tagging SNPs in Na^+, K^+-ATPase and BD. Significant association was observed between six single tagging SNPs in each of the three genes of α subunits of Na^+, K^+-ATPase with BD. These tagging SNPs are all located in introns or the 3′ UTR region and their functional significance remains to be elucidated.

A recent review depicts all the linkage and association studies of genes with BD (6). More than 300 genes have been repeatedly linked with BD, out of which more than 25 are involved with transport activities and more than 30 in intracellular signaling processes. Thus, our findings are consistent with and strengthen the notion that changes in transport or signaling process confer risk for BD. Other additional genome-wide association studies of bipolar disorder have identified a large number of SNPs associated with the disease (1,5). None of these chromosomal regions corresponds to any of the genes examined in the current investigation.

Genetic variations in intronic regions may influence transcription, as has been shown in numerous studies (for review, see 44). Using bioinformatics tools (Geomantic program–Mat inspector Release professional 7.7.3 [Genomaticx Software GmbH Company, Munich, Germany]), we have found that two of the SNPs that are significantly associated with BD (rs919390 and rs11805078) are close to regions encoding transcription factors, suggesting possible functional significance: the single tagging SNP in the α3 subunit (rs919390), which is largely expressed in neural cells (12), is located close to the 15 base pair (bp) consensuses sequence of activator protein 2 factors (AP2F). It is tempting to speculate that this SNP may be involved in alterations in the expression of AP2F (45) and engaged in the etiology of BD. In addition, the single tagging SNP in α1 subunit (rs11805078) is 7 bp downstream and 5 bp upstream to the consensuses sequence of myelin transcription factor 1 (Myt1). Myelin transcription factor 1 influences the development of oligodendrocyte progenitor cell proliferation, differentiation, and myelin gene transcription in human CNS (46).

Haplotype analysis demonstrated significant association to BD in the gene that encodes the α2 subunit of Na^+, K^+-ATPase at two loci (rs2070704–rs2295623). The single SNP rs2070704 contributed the strongest association with BD, when allele G is overtransmitted to BD patients. Interestingly, changes in α2 isoform associated to BD have been previously documented, demonstrating a reduction in this isoform in temporal cortex samples of BD patients as compared with normal control subjects (47). These results are clearly only provisional and need to be replicated in an independent sample, preferably a different ethnic group, to reduce the possibility of false-positive findings. The conundrum of false-positive results in association studies and the nature of tentative knowledge are extensively discussed in an article by Sullivan (48).

One of the limitations of the current study is that we were unable to examine the effect of continuous variables (number of hospitalizations, age of onset) on the association as possible confounding factors between these SNPs and affected status. The information for these variables was available only for some of the patients, and PBAT was unable to compute the interaction between the continuous variable and affected status for this smaller sample size.

In summary, this study demonstrates for the first time that genetic variations in tagging SNPs in the three genes of α isoforms of Na^+, K^+-ATPase are associated with BD and suggest the role of this enzyme in the etiology of BD. Future studies of expression, sequencing, and activity measurements of the Na^+, K^+-ATPase in BD patients are needed to understand the role of this crucial enzyme in the pathology of this disorder.

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