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Identification of rare non-synonymous variants in *SYNE1/CPG2* in bipolar affective disorder

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Abstract

Bipolar affective disorder (BPD) is a severe mood disorder with a prevalence of ~1.5% in the population. The pathogenesis of BPD is poorly understood; however, a strong heritable component has been identified. Previous genome wide association studies (GWAS) have indicated a region on 6q25, coding for the *SYNE1* gene, which increases disease susceptibility. *SYNE1* encodes the synaptic nuclear envelope protein-1, nesprin-1. A brain specific splice variant of *SYNE1, CPG2* encoding candidate plasticity gene 2, has been identified. The intronic single nucleotide polymorphism (SNP) with the strongest genome-wide significant association in BPD, rs9371601, is present in both *SYNE1* and *CPG2*. We screened 937 BPD samples for genetic variation in *SYNE1* exons 14-33, which covers the *CPG2* region, using high resolution melt analysis. In addition, we screened two regions of increased transcriptional activity, one of them proposed to be the *CPG2* promoter region. We identified six non-synonymous and six synonymous variants. We genotyped three rare non-synonymous variants, rs374866393, rs148346599, and rs200629713, in a total of 1,099 BPD samples and 1,056 controls. Burden analysis of these rare variants did not show a significant association with BPD. However, nine patients are compound heterozygotes for variants in *SYNE1/CPG2* suggesting that rare coding variants may contribute significantly to the complex genetic architecture underlying BPD. Imputation analysis in our own whole genome sequencing sample of 99 BPD individuals identified an additional eight risk variants in the *CPG2* region of *SYNE1*.

Keywords

Genetics; *SYNE1*; synaptic nuclear envelope protein-1; *CPG2*; bipolar affective disorder; depressive disorder; genome-wide association study/GWAS; genetic predisposition to disease; genotype; single nucleotide polymorphism

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Introduction

Bipolar affective disorder (BPD) is a severe mood disorder characterised by episodes of mania and depression and has a lifetime risk of up to 1.5 % (Merikangas et al., 2011). Heritability estimates for BPD range between 79-83 % (Barnett and Smoller, 2009; Kendler et al., 1996; Kieseppa et al., 2004; McGuffin et al., 2003) and twin studies have found concordance rates of 40-70 % for monozygotic twins (Burmeister et al., 2008). Relatives of individuals with BPD are at increased risk for other psychiatric diseases such as schizophrenia and major depression, with which BPD shares phenotypic similarities (Craddock et al., 2005). Linkage studies have suggested evidence for linkage between genetic markers and BPD on several chromosomal regions (Badner and Gershon, 2002; Buttenschon et al., 2010; Greenwood et al., 2012; Hamshere et al., 2005; Lambert et al., 2005; McQueen et al., 2005; Segurado et al., 2003). Fine mapping of BPD genes using tests of linkage disequilibrium has been advanced by the HapMap consortium (Ceulemans et al., 2011; International HapMap Consortium, 2003; Song et al., 2010). Candidate gene studies have implicated several genes (Craddock and Forty, 2006), although replication of findings has been slow (Chen et al., 2011; Dizier et al., 2012; Seifuddin et al., 2012). No single causal genetic variant of BPD has been identified. However, there are many genes of major effect that seem to harbour variation that may increase susceptibility to BPD. Large samples sizes required to establish consistency of results and genome-wide association studies (GWAS) have presented significant evidence for several areas of association (Cichon et al., 2011; Djurovic et al., 2010; Ferreira et al., 2008; Gonzalez et al., 2014; Lencz et al., 2013; Muhleisen et al., 2014; Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011; Seifuddin et al., 2013; Sklar et al., 2011; Xu et al., 2014; Yosifova et al., 2011). There is replicated evidence for genome-wide significant association in the ankyrin-3 (or ankyrin-G), *ANK3*, and the voltage-dependent L type calcium channel alpha 1C subunit, *CACNA1C*, genes in BPD (Dedman et al., 2012; Erk et al., 2014; Fiorentino et al., 2014; Gonzalez et al., 2013; Green et al., 2013b; Lett et al., 2011; Schulze et al., 2009; Scott et al., 2009; Smith et al., 2009; Takata et al., 2011; Tesli et al., 2011; Zhang et al., 2013).

Linkage analysis identified association in the chromosome 6q25 region with susceptibility to schizophrenia in a small study (Lindholm et al., 2001) and autism (Philippe et al., 1999). One of the genes in this locus is *SYNE1*, encoding synaptic nuclear envelope protein-1 (also known as enaptin or nesprin-1). The *SYNE1* single nucleotide polymorphism (SNP) rs9371601, located in intron 16, passed the genome-wide significance threshold ($P < 5.0x10^{-8}$) in large BPD GWAS (Ferreira et al., 2008; Sklar et al., 2011), followed by later replications (Green et al., 2013a; Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011; Xu et al., 2014). However, this SNP has subsequently been shown to be only nominally significantly associated with BPD at $P = 2.72x10^{-4}$ in the largest GWAS to date of 9,784 BPD patients and 30,471 controls (Hou et al., 2016). Nesprin-1 has been suggested to play several roles in cytoplasmic nuclear positioning, inner nuclear envelop function and Golgi structure maintenance (Gough et al., 2003). Nesprin-1 is an exceptionally large spectrin family member and is expressed in a range of tissues, including the central nervous system. Expression of nesprin-1 is greatest in the cell bodies of Purkinje cells and in olivary body neurons of the lower brainstem. Mutations in *SYNE1* lead to rare Mendelian

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phenotypes such as autosomal recessive arthrogryposis and autosomal recessive cerebellar ataxia 1 or ARCA1 (Attali et al., 2009; Dupre et al., 1993; Gros-Louis et al., 2007). Furthermore, SNPs in *SYNE1* have previously been noted in a meta-analysis of genome-wide association data of BPD and major depressive disorder (Liu et al., 2011).

Like *SYNE1*, the *ANK*3 gene has been repeatedly implicated by GWAS to specifically increase susceptibility to BPD (Ferreira et al., 2008; Shinozaki and Potash, 2014; Sklar et al., 2011). Among a list of 180 genes, both *SYNE1* and *ANK3* were implicated in CNS development, neural projections, synaptic transmission, various cytoplasmic organelles and cellular processes and contributed to 20-30% of the genetic load across six major neuropsychiatric disorders-attention deficit hyperactivity disorder, anxiety disorders, autistic spectrum disorders, BPD, major depressive disorder, and schizophrenia (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Lotan et al., 2014). Both the ankyrin-G and nesprin-1 proteins contain a highly conserved spectrin binding domain, which is suggested to link proteins to the spectrin actin cytoskeleton. Nesprin-1 has been implicated to play a role in the function of ankyrin-G (Devarajan et al., 1996; Yang et al., 2007). However, no evidence for ankyrinG and nesprin-1 protein interaction has been shown to date.

The top GWAS *SYNE1* SNP, rs9371601, was not found to be associated with structural brain alterations in BPD (Tesli et al., 2013). The strongest non-synonymous SNP in *SYNE1*, rs214976, associated with BPD is also present in the candidate plasticity gene 2, *CPG2,* a brain specific splice variant of exons 16 to 33 of *SYNE1*, which was first characterised in the rat (Cottrell et al., 2004). *CPG2* encodes a protein present exclusively in the post-synaptic endocytotic zone of excitatory synapses and is up-regulated by kainite-induced seizures in rat hippocampus dentate gyrus (Cottrell et al., 2004; Nedivi et al., 1996; Nedivi et al., 1993). In this paper, we present data from a *SYNE1/CPG2* gene scan in BPD.

Here, we have screened *SYNE1* exons 14 – 33 for variants in BPD samples using high resolution melt (HRM) analysis, a polymerase chain reaction (PCR)-based method for identifying DNA sequence variations by detecting changes in the melting of DNA duplexes. Human *CPG2/SYNE1* cDNA sequence alignments with the human genome include an additional two *SYNE1* exons (14 and 15), which were screened. In addition, the putative promoter region of *CPG2* in intron 14 of *SYNE1* and a potentially retained *CPG2* intron corresponding to *SYNE1* intron 33 (Cottrell et al., 2004) were also screened for polymorphisms. Non-synonymous variants were subsequently genotyped in the University College London, UCL, BPD case control sample.

Methods

UCL clinical sampling

The UCL BPD cohort consists of 1,099 individuals. These were sampled in two cohorts. The first cohort (UCL1) comprised 506 bipolar I cases (Ferreira et al., 2008; Sklar et al., 2011) while the second cohort (UCL2) comprised 409 bipolar I (69%) and 184 bipolar II cases (Dedman et al., 2012). Among the UCL1 BPD cases were 143 with comorbid alcohol-dependence syndrome (ADS) according to Research Diagnostic Criteria (RDC) (Lydall et

al., 2011). All UCL bipolar cases were interviewed by a psychiatrist using the lifetime version of the Schedule for Affective Disorders and Schizophrenia-Lifetime Version (SADS-L) schedule (Spitzer and Endicott, 1977), rated with the 90-item Operational Criteria Checklist (OPCRIT) (McGuffin et al., 1991) and met diagnostic criteria for bipolar disorder according to RDC (Spitzer et al., 1978). The sample of 1,056 normal controls comprised 672 screened controls who were interviewed with the initial clinical screening questions of the SADS-L and selected on the basis of not having a family history of schizophrenia, alcohol dependence or BPD, for having no past or present personal history of any RDC-defined mental disorder, and were not heavy drinkers; plus 384 unscreened British normal volunteers provided by European Collection of Animal Cell Cultures (ECACC). All cases and controls were selected to be of UK or Irish ancestry as described previously (Datta et al., 2010). UK National Health Service multicenter and local research ethics approvals were obtained and signed informed consent was given by all subjects. Genomic DNA was obtained from frozen whole blood samples for cases and controls in UCL1 and from saliva samples for the cases in UCL2. DNA was extracted for all samples using methods we have published previously (Pereira et al., 2011) and quantified with PicoGreen (Invitrogen, Paisley, UK) by fluorimetry.

High resolution melt curve screening

937 BPD samples from UCL1 and UCL2 cohorts were scanned using HRM. Primers to amplify exons 14 to 33 within *SYNE1*, as well as for the putative *CPG2* promoter region on *SYNE1* intron 33 and a region of increased transcriptional activity on *SYNE1* intron 14 can be seen in supplementary eTable 1. Mutation screening was performed using either Sensixmix HRM reagents (Bioline, London, UK), Accumelt HRM SuperMix (Quanta Biosciences, Maryland, USA) and Lightscanner Master Mix (BioFire Diagnostics, Inc., Utah, USA) with the Roche LightCycler 480. Optimal HRM amplification conditions for each primer pair can be seen in supplementary eTable 1.

Sequencing

Samples that displayed altered or shifted HRM melt curve profiles were selected for sequencing. Sequencing was performed using the Big Dye terminator v3.1 Cycle Sequencing kit (Applied Biosystems, Warrington, UK) on an ABI 3730xl DNA Analyzer (Applied Biosystems) and analysed with the Staden Package (Staden, 1996).

Genotyping and association analysis

To determine whether potentially aetiological non-synonymous variants in *SYNE1* increase susceptibility to BPD, fluorescent allele-specific PCR (KASPar) (LGC Genomics, Hoddesdon, UK) genotyping assays were designed. The three *SYNE1* variants identified by HRM, rs374866393, rs148346599, and rs200629713, were KASPar genotyped on a LightCycler 480 RealTime PCR System (Roche, Burgess Hill, UK) in all 1,099 UCL1 and UCL2 BPD and control samples. Quality control to confirm the reproducibility of genotypes was performed as described previously (Dedman et al., 2012). All these data were analysed to confirm Hardy–Weinberg equilibrium (HWE). Genotypic and allelic associations as well as burden analysis for rare single nucleotide variants were determined using Fisher's exact tests. Significance values shown for all analyses are uncorrected for multiple testing and a cut-off significance value of $P < 0.05$ was used.

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Data analysis

Bioinformatic analysis to predict the effect of non-synonymous variants on the function of *SYNE1* and the proposed *CPG2* region was carried out using the UCSC genome browser (http://genome.ucsc.edu/), Polyphen-2 (http://genetics.bwh.harvard.edu/pph2/index.shtml) (Adzhubei et al., 2010) and SIFT BLink (http://sift.jcvi.org/www/SIFT_BLink_submit.html) (Kumar et al., 2009). The protein reference for SIFT used was gi:220675590. The effect of a synonymous mutation on the exon was predicted using Gen script Rare Codon Analysis (http://www.genscript.com/cgi-bin/tools/rare_codon_analysis). The codon adaptation index is a measure of synonymous codon usage bias where higher values indicate a higher proportion of the most abundant codons and possibly a higher chance of expression (Sharp and Li, 1987). Project Hope (http://www.cmbi.ru.nl/hope/input) was accessed to analyse protein structure of the mutations in *CPG2* (Venselaar et al., 2010).

1000 Genomes Phase3 data (1000 Genomes Project Consortium, 2010) was used alongside our own BPD whole-genome sequencing reference panel from 99 individuals (Fiorentino et al., 2014) to impute additional significantly associated variants in the *CPG2* region of *SYNE1* from the UCL Psychiatric Genomics Consortium 1 BPD samples (Sklar et al., 2008). Imputation analysis was performed using IMPUTE2 (Howie et al., 2011; Howie et al., 2009) and association analysis was carried out using SNPTEST version 2.5.1 using the frequentist association test (Marchini and Howie, 2010). The Ensembl Variant Effect Predictor (VEP) (McLaren, 2010) was used to predict the functional consequences of known and unknown variants and regulatory region variants were analysed in the ENCODE data (ENCODE Project Consortium, 2011). In our modest sample size the frequency of non-synonymous SNPs likely to affect protein function were summed across the cases and controls in a burden analysis to assess the overall impact of rare mutations in the gene (Knight et al., 2009).

Results

High resolution melt curve screening for variants

Common SNP detection—Following HRM analysis, several differently shaped melt curves were detected in *SYNE1* (Table 1). Two SNPs, rs4343926 and rs4331993, were found in the untranslated region between *SYNE1* exon 14 and *SYNE1* exon 15. It should be noted that rs4331993 occurred only in combination with rs4343926. Several samples with an abnormal melting profile were sequenced and variants rs62427038, rs34610829, rs17082709, rs214976, and rs17082701 were identified in exons 18, 22, 23, 26, and 27 respectively. Polyphen and SIFT predictions of how well non-synonymous variants would be tolerated by the protein can be seen in Table1. We found the synonymous variants, rs149670417 and rs138705766, using HRM gene scanning of *SYNE1* exon 19 and 31 respectively, which cause a rise in GC content from 46.23 % to 46.09 % and 57.74 % to 58.26 % respectively (Genscript). Both variants lead to a minor decrease in the likelihood of the gene being expressed with a 0.01 reduction in the codon adaptation index from 0.66, where 1 represents 100 % expression (Genscript).

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It should be noted that two individuals were compound heterozygotes for rs62427038 and either rs149670417 or rs214976. Similarly, three individuals were compound heterozygotes for rs138705766 and rs17082701, whereas another individual carried mutant alleles for rs138705766, rs17082701 and rs4343926. Three individuals carried the variant alleles of rs4343926 as well as that of one of the following SNPs: rs17082709, rs17082701 or rs138705766. Therefore, nine patients are compound heterozygotes for rare variants in *SYNE1/CPG2* suggesting that there may be an additive effect of these base pair changes.

Genotyping of rare non-synonymous variants—HRM identified three rare non-synonymous variants in the *CPG2* region of *SYNE1*, which we genotyped in our case control sample (Table 2). In *SYNE1* exon 20, one BPD sample harboured the missense mutation, rs374866393, where the methionine residue would be larger and more hydrophobic than the wildtype threonine, which could result in a loss of hydrogen bonds and may disrupt correct protein folding (Project Hope). In *SYNE1* exon 25, HRM screening identified one BPD subject carried the G>A non-synonymous variant, rs148346599, leading to a change from glutamic acid to lysine. The glutamate residue is negatively charged while lysine is a larger residue with a positive charge, which might lead to repulsion with other residues as well as to the repulsion of ligands (Project Hope). We identified a third non-synonymous variant in *SYNE1* exon 29, rs200629713, which leads to an alanine to valine amino acid change and predicted to increase the size of the residue (Project Hope). Burden analysis does not show a significant difference between the number of rare variants in BPD cases and controls (Fisher's Exact Test, P = 1.00, df = 1, n = 5963).

Imputed tests of association in *SYNE1* in bipolar affective disorder—Imputation analysis using IMPUTE2 and SNPTEST predicted eight intronic or promoter regulatory region SNPs, located in both the *SYNE1* and *CPG2* transcripts, are significantly associated in the UCL BPD samples (supplementary eTable 2). None of the imputed intronic or regulatory region variants were predicted to be in regions showing enrichment for the H3K27Ac histone mark, which is the acetylation of lysine 27 of the H3 histone protein, often found near active regulatory elements (ENCODE) (ENCODE Project Consortium, 2011).

Discussion

We have screened exons 14 to 33 and the intronic regions 14 and 33 of *SYNE1*, overlapping the *CPG2* transcript, using HRM in 937 BPD cases. Six synonymous and six non-synonymous variants were identified. We genotyped three rare non-synonymous variants in the UCL case control sample of 2,155 individuals, which were predicted to increase the size of the protein residue and may affect bending of the peptide chain. Unfortunately, we did not find a significant association between these three non-synonymous variants in *SYNE1* or *CPG2* and BPD using burden analysis.

Nine samples carried more than one of the variants detected from scanning the *SYNE1* gene. Thus, multiple variants may have a compound effect on protein function, similar to Parkin compound heterozygous mutations associated with Parkinson's disease (Malek et al., 2016). To date there is no replicated evidence that compound heterozygosity contributes to BPD

(Kember et al., 2015; Knight et al., 2009) or schizophrenia (Rees et al., 2015; Ruderfer et al., 2015). However, additive and interactive combinations of rare coding variants in the *ABCA13* gene have been suggested to contribute to the complex phenotypes of both BPD and schizophrenia (Knight et al., 2009). The compound heterozygous variants in *SYNE1/CPG2* identified here reinforce the possibility of interactive effects of rare coding variants contributing significantly to the aetiology of BPD.

Genetic variants in the *SYNE1/CPG2* genes may impair CPG2 function or disrupt protein interaction in BPD patient carriers. Expression of the brain specific *SYNE1* splice variant, *CPG2*, was first discovered to be upregulated by kainite-induced seizures in the rat dentate gyrus (Nedivi et al., 1993). The CPG2 protein contains several spectrin repeats and coils. Proteins with similar motifs often play a role in the organisation of protein complexes (Burkhard et al., 2001). The CPG2 protein localises to the post-synaptic component of dendritic spines and shafts in human hippocampal neurons and regulates the rapid cycling of synaptic glutamate receptors via clathrin-mediated endocytosis (CME) (Loebrich et al., 2016). Interestingly, CPG2-knockdown reduces glutamate receptor internalisation and membrane insertion, increases the number of post-synaptic clathrin-coated vesicles and decreases dendritic spine size (Cottrell et al., 2004). Synaptic glutamate receptor internalization in dendritic spines is dependent on F-actin physically binding to CPG2. Thus, CPG2 bound to F-actin functionally mediates post-synaptic endocytosis in the spine cytoskeleton necessary for vesicle un-coating (Loebrich et al., 2013). Furthermore, CPG2 appears to play a role in processes underlying long-term depression of neuronal synapses (Cottrell et al., 2004). Altered glutamate levels in plasma, serum, brain tissue and cerebrospinal fluid; disrupted glutamate receptor function (Cherlyn et al., 2010); and decreased NMDA receptor expression and cellular plasticity cascades (McCullumsmith et al., 2007) have been associated with BPD. It would be interesting to characterise the functional effects of the variants reported here on CPG2-mediated glutamatergic NMDA receptor signalling (Cottrell et al., 2004) and AMPAR surface expression (Gong and De Camilli, 2008).

In this study, we identified 12 genetic variants in *SYNE1* and/or *CPG2,* which did not appear to have a significant role in susceptibility to BPD. However, imputation analysis of our whole genome sequencing data identified eight SNPs that were significantly associated with BPD. The association between BPD and common variants in the *SYNE1* gene warrants further investigation in a much larger sample. Further work is also necessary to characterise the functional effects of compound heterozygous rare variants on CPG2 and nesprin-1 proteins.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Variants detected by high resolution melt curve analysis.

Variant ID[1]	Position Chr 6[2]	Base pair Change	Amino Acid Change[3]	Minor Allele Frequency	Genotype Counts[4]	Predicted functional effects[5]
rs4343926	152793575	A>G	N/A	0.0059	GG 0, GA 11, AA 926	N/A
rs4331993	152793572	T>A	N/A	0.0016	AA 0, AT 3, TT 934	N/A
rs62427038	152786447	T>C	N/A	0.0032	CC 0, CT 6, TT 931	N/A
rs149670417	152784602	C>T	N/A	0.0037	TT 0, TC 7, CC 930	N/A
rs374866393	152783949	C>T	T725M	0.0005	TT 0, CT 1, CC 936	Tolerated/Benign to both SYNE1 and CPG2 (SIFT and Polyphen)
rs34610829	152779933	C>T	R843C	0.0053	TT 0, TC 10, CC 927	Tolerated to SYNE1 (SIFT); Possibly damaging to SYNE1 (PolyPhen); Damaging/deleterious to CPG2 (PolyPhen, SIFT)
rs17082709	152777095	A>C	L885V	0.0037	CC 0, CA 7, AA 930	Benign to both SYNE1 and CPG2 (SIFT/PolyPhen)
rs148346599	152774753	C>T	E999K	0.0005	TT 0, CT 1, CC 936	Tolerated to SYNE1 (SIFT); Probably damaging to SYNE1 (Polyphen); Probably damaging/deleterious to CPG2 (PolyPhen, SIFT)
rs214976	152772264	T>C	V1035A	0.0048	CC 0, CT 9, TT 928	Tolerated/Benign by SYNE1 (SIFT/PolyPhen); Tolerated/ Benign by CPG2 (PolyPhen); Deleterious to CPG2 (SIFT)
rs17082701	152771849	G>A	N/A	0.0069	AA 0, AG 13, GG 924	N/A
rs200629713	152768615	C>T	A1216V	0.0005	TT 0, TC 1, CC 936	Tolerated/Benign by SYNE1 (SIFT); Possibly damaging to both SYNE1 (PolyPhen) and CPG2 (PolyPhen, SIFT)
rs138705766	152763258	A>G	N/A	0.0043	GG 0, GA 8, AA 929	N/A

[1] Single nucleotide polymorphism reference identifier number.

[2] NCBI37/hg19 human genome version.

[3] Nesprin-1, isoform 1 protein NCBI Reference Sequence, NP_892006.3.

[4] Genotype counts from screening 937 Bipolar disorder, BPD, cases.

[5] SIFT (Kumar et al., 2009) and PolyPhen-2 (Adzhubei et al., 2010) predict the possible impact of amino acid substitutions on the structure and function of spectrin repeat containing nuclear envelope protein 1 (nesprin-1) and candidate plasticity gene 2 (CPG2).

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Table 2

Tests of association with *SYNE1/CPG2* rare variants in UCL bipolar disorder samples relative to controls

Variant ID[1]	Position Chr6[2]	Base pair Change[3]	Amino Acid Change	BPD *vs*. Controls[4]	N[5]	Minor Allele Frequency	Genotype Counts	*P* Value[6]
rs374866393	152783949	C>T	T725M	Case	1069	0.0005	TT 0, CT 1, CC 1,068	1.00[7]
				Control	926	0	TT 0, CT 0, CC 926	
rs148346599	152774753	C>T	E999K	Case	1073	0.0014	TT 0, CT 3, CC 1,070	0.71[8]
				Control	908	0.0022	TT 0, CT 4, CC 904	
rs200629713	152768615	C>T	A1216V	Case	1069	0.0005	TT 0, CT 1, CC 1,068	1.00[9]
				Control	918	0.0005	TT 0, CT 1, CC 917	

[1] Single nucleotide polymorphism reference identifier number.

[2] NCBI37/hg19 human genome version.

[3] Nesprin-1, isoform 1 protein NCBI Reference Sequence, NP_892006.3.

[4] BPD, Bipolar disorder.

[5] N, number.

[6] P Value, Probability value determined with Fisher's Exact Test analysis.

[7] rs374866393 Fisher's Exact test: (df = 1, N = 1,995)

[8] chr6:15277475 Fisher's Exact test: (df = 1, N = 1,981)

[9] rs200629713 Fisher's Exact test: (df = 1, N = 1,987)