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Association between polymorphisms in the metallophosphoesterase (*MPPE1*) gene and bipolar disorder

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Abstract

Genetic linkage studies in bipolar disorder (BPD) suggest that a susceptibility locus exists on chromosome 18p11. The metallophosphoesterase (*MPPE1*) gene maps to this region. Dysregulation of protein phosphorylation and subsequent abnormal cellular signaling has been postulated to be involved in neuropsychiatric disorders thus making *MPPE1* a plausible biological candidate gene for BPD. In this study, we hypothesized that genetic variation in the *MPPE1* gene contributes to BPD. We tested this hypothesis by genotyping 4 SNPs (rs871044; rs3974590; rs593713; rs602201) in BPD patients (n=570) and healthy controls (n=725). Genotypes and allele frequencies were compared between groups using Chi square contingency analysis. Linkage disequilibrium (LD) between markers was calculated and estimated haplotype frequencies were compared between groups. Single marker analysis revealed an association of rs3974590 with BPD (p=0.009; permutation corrected p=0.046). Haplotype analysis did not show any significant association with disease after permutation correction. Our results provide evidence of an association between a polymorphism in the *MPPE1* gene and BPD. Additional studies are necessary to confirm and elucidate the role of *MPPE1* as a susceptibility gene for BPD on chromosome 18p.

Keywords

linkage; chromosome 18; association; polymorphism; MPPE1; metallophosphoesterase 1

Bipolar disorder (BPD) is a chronic psychiatric disease, which affects approximately 1% of the general population and is characterized by episodes of mania and depression. Family, adoption and twin studies show that BPD has a strong genetic component (Craddock and Jones 1999). Linkage studies in BPD suggest that a susceptibility locus exists on chromosome 18p11 (Bennett and others 2002; Berrettini and others 1994; Bowen and others 1999; Detera-Wadleigh and others 1999; McInnes and others 1996; Mukherjee and others 2006; Nothen and others 1999; Stine and others 1995). Several genes in that region have been investigated previously but results are inconclusive and no functional variations of major effect have been identified so far (Berrettini and others 1998; Chavarria-Siles and others 2007; Corradi and others 2005; Esterling and others 1997; Evans and others 2008; Ishiguro and others 2001; Lohoff and Berrettini 2005; Lohoff and others 2008a; Lohoff and others 2008b; Mulle and others 2007; Ohnishi and others 2007; Reyes and others 2002; Rojas and others 2000; Tsiouris and others 1996; Washizuka and others 2004; Washizuka and others 2003; Weller and others 2006; Yoshikawa and others 2000; Yoshikawa and

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others 1997). In addition, recent whole genome association analyses failed to show a significant association between BPDs and the chromosome 18p region (Baum and others 2008; Ferreira and others 2008; Sklar and others 2008; TheWellcomeTrustCaseControlConsortium 2007).

Difficulties in elucidating BPD susceptibility factors in the 18p region might be due to the complex mode of inheritance, clinical and locus heterogeneity and use of underpowered samples. Another hypothesis is that several genes with small effects might contribute to the linkage peak, complicating the detection of risk alleles by the classic single candidate gene approach. In an attempt to further investigate the 18p region in BPD, we identified and investigated the metallophosphoesterase (*MPPE1*) gene as another candidate gene (Vuoristo and Ala-Kokko 2001).

MPPE1 encodes a metallophosphoesterase protein that is widely brain expressed (Vuoristo and Ala-Kokko 2001) and is a member of the calcineurin-like phosphoesterase superfamily. Phosphoesterases are involved in a variety of diverse biochemical reactions, including protein phosphorylation-dephosphorylation processes that modulate functional properties of proteins. Despite the large number of metallophosphoesterases that have been biochemically characterized, the function of *MPPE1* remains unknown and no natural substrate has been identified so far (Miller and others 2007; Vogel and others 2002). Nevertheless, variation in the *MPPE1* gene might lead to an altered enzyme with downstream effects on protein phosphorylation involved in cellular signaling. In fact, emergent data suggest that alterations in protein phosphorylation play a critical role in dopaminergic neurotransmission implicated in BPD and schizophrenia, as shown for the phosphoprotein DARPP-32 (Greengard and others 1999; Liu and others 2005). Dysregulation of protein phosphorylation and subsequent abnormal cellular signaling might contribute to the etiology of neuropsychiatric disorders thus making *MPPE1* a plausible biological candidate gene for BPD. Based on the chromosomal location and the biological function of the *MPPE1* gene we hypothesize that genetic variants might increase susceptibility to neuropsychiatric syndromes. To test this hypothesis, we designed a case-control association study using BPD patients and healthy controls of European descent and genotyped four genetic markers distributed across the *MPPE1* gene.

DNA samples from five hundred and seventy unrelated BPD type I patients were collected at centers involved in the National Institute of Mental Health (NIMH) Genetics Initiative on BPD (<http://zork.wustl.edu/nimh/bp.html>). The diagnosis of BPD type I was in accordance with the DSM-IV criteria. Background, inclusion and exclusion criteria as well as detailed methodology for the NIMH Genetics Initiative are described elsewhere (Dick and others 2003). All subjects were assessed with the Diagnostic Instrument for Genetic Studies (DIGS) (Nurnberger and others 1994). Family history information was obtained through the Family Interview for Genetic Studies (FIGS), and medical records were requested. Final best estimate diagnosis was made using all available information including medical records, information from relatives, and the DIGS interview, by two independent senior diagnosticians adhering to DSM-IV criteria. The patient group consisted of 38% males and 62% females. The average age at recruitment was 41.6 years. Psychotic symptoms were present in 66% of the probands at some point during their illness. Psychosis was defined as presence of auditory/visual hallucinations and/or paranoid or bizarre delusions. Seven hundred and twenty-five DNA samples from unrelated controls were collected by the NIMH Genetic Initiative (<http://www.nimhgenetics.org>). Control participants were screen online using a self-report-based survey on the Composite International Diagnostic Interview Short-Form (CIDI-SF) (Kessler and others 1998). Accepted controls had no history of psychiatric or chronic neurological disease and consisted of 50% males and 50% females with an average age of 51.8 years at recruitment. All cases and controls were of European descent.

Informed consent was obtained from all individuals in accordance with Institutional Review Board (IRB) procedures. DNA was extracted from peripheral leukocytes using standard protocol.

The *MPPE1* gene is located on chromosome 18p11.21 and is flanked by the G protein Golf alpha (*GNAL*) gene and the myo-inositol monophosphatase gene (*IMPA2*). Interestingly, *MPPE1* and *GNAL* are oriented tail-to-tail with partially overlapping 3'UTRs (Vuoristo and Ala-Kokko 2001). *MPPE1* contains 12 exons and spans 25,090 bp (Ensembl Human Exon View accession OTTHUMG00000131661). SNPs for genotyping were selected using the tagging SNP algorithm based on available HapMap data with a minor allele frequency > 0.25 in the Caucasian European population and a pairwise linkage disequilibrium (LD) r^2 cutoff of > 0.8 (SNP1: rs871044; SNP2: rs3974590; SNP3: rs593713; SNP4: rs602201). SNP genotyping was performed using Applied Biosystems Inc. (ABI) (Foster City, CA, USA) 'Assays-on-demand' as per manufacturer protocol. Quality control was maintained by genotyping 10% duplicates for cases and controls.

Genotype and allele frequencies were compared between groups using χ^2 contingency analysis. A two-tailed type I error rate of 5% was chosen for the analysis. Linkage disequilibrium (LD) and haplotype frequencies were estimated using the Haploview software (version 4.1). Haplotype blocks were identified using the solid spine of LD method in Haploview (Barrett and others 2005). Correction for multiple testing was performed using permutation correction by the Haploview program (Barrett and others 2005). This approach corrects for multiple testing but takes into account the correlation between markers. Permutation correction is thus less conservative than the Bonferroni correction but is appropriate for independent tests with multiple markers (Camargo and others 2008). For the single-marker analysis, 10,000 permutations were carried out to estimate the significance of the best results, correcting for the four loci tested. Haplotype analysis was performed using the Haploview software and *P*-values were corrected by permutation analysis as described above. Hardy-Weinberg equilibrium (HWE) was calculated separately for cases and controls. Our sample size had reasonable power to detect a disease association at a *P* value less than or equal to 0.05, assuming an odds ratio of 1.5 and a minor allele frequency (MAF) of 25% (99% for a log additive mode of inheritance, 92% for a dominant and 43% for a recessive mode of inheritance). Power analysis was performed using the *Quanto* program (Gauderman, 2002).

None of the genotype distributions deviated significantly from those expected by HWE for cases or controls. LD measures and haplotype blocks across the *MPPE1* gene are shown in Fig. 1. We observed weak LD across the gene with the exception of SNP2 and SNP3 that are in strong LD. Single marker analysis (Table 1) revealed a statistically significant association of rs3974590 with BPD (SNP2: allelic $p=0.009$; permutation corrected $p=0.046$) and a trend towards association for SNP3 ($p=0.051$). Haplotype analysis of all four SNP configurations did not reveal an association with BPD (Table 2). However, two-marker haplotype analysis, involving the two markers in strong LD (SNP2 and SNP3), revealed an association between the GA haplotype and BPD (Table 3). Genotyping success rates were between 97.1% and 98.2%. The concordance rate for all the markers was 100% with respect to the 10% of samples that were genotyped twice for quality control. Allelic frequencies were consistent with those reported in the HapMap database for Utah residents with Northern and Western Europe ancestry from the CEPH collection.

In the present study, we show a statistically significant association between polymorphisms in the *MPPE1* gene on chromosome 18p and BPD. Interestingly, both associated markers (SNP2 and SNP3) are in strong LD ($D':0.88$; $r^2: 0.77$); however, only SNP2 remains statistically significant after correction for multiple testing. Our results indicate a protective

effect of the major allele for SNP2 and SNP3. Haplotype analysis of these 2 markers further confirms a protective effect, with the frequency of the major allele diplotype (G-A) in the control group being significantly increased when compared to cases (70% versus 66%; corrected p-value: 0.04).

Although there are no data available in the literature that would suggest that either of the associated SNPs has functional effects, the *MPPE1* protein contains metal binding and active sites similar to serine/threonine phosphoprotein phosphatase catalytic subunits. These phosphatases are involved in a variety of cellular processes, including gene expression, cell growth and cell differentiation. Dysregulation of protein phosphorylation and subsequent abnormal cellular signaling might play a significant role in the pathophysiology of neuropsychiatric disorders (Greengard and others 1999; Liu and others 2005), thus making *MPPE1* a plausible biological candidate gene for BPD as well as other phenotypes such as schizophrenia. Even though our study provides evidence for a possible association between variation in the *MPPE1* gene and BPD, it could be possible that other variations which are in LD with these SNPs might contribute to the observed association or that a haplotype confers risk rather than a single polymorphism. In fact, several studies investigating the adjacent genes *GNAL* and *IMPA2* documented some positive and negative associations of genetic polymorphisms with BPD (Corradi and others 2005; Ohnishi and others 2007; Sjoholt and others 2004; Sjoholt and others 2000; Tsiouris and others 1996; Vuoristo and others 2000; Yoshikawa and others 1997). Together, these studies suggest genetic heterogeneity or that multiple genes of small effect on chromosome 18p confer risk or protective properties to BPD. Additional genetic (including sequencing), computational and biological studies are necessary to further evaluate the role of the *MPPE1*, *GNAL* and *IMPA2* in this BPD linkage region.

There are several limitations to our study that should be mentioned. First, it is possible that our finding might be a false positive result due to population stratification. All cases and controls in this study were of European descent; however, undetected differences in population structure might contribute to false positive results in association studies (Freedman and others 2004; Pritchard and Donnelly 2001). Furthermore, cases and controls were not matched for age, gender or regional European ancestry which might also contribute to population stratification effects. Possible strategies to control for these stratification issues are the use of genomic controls (Bacanu and others 2000; Devlin and Roeder 1999) and/or the use of a family-based association design, a method that matches the genotype of an affected offspring with parental alleles not inherited by the offspring (Spielman and Ewens 1996). In addition to population stratification issues, spurious positive association findings remain a valid concern as shown recently in a statistical simulation study of the *COMT* gene by Sullivan (2007). Thus, our results should be interpreted with caution and ultimately require careful replication and confirmation in an independent population of patients and controls.

Our candidate gene was selected based on prior linkage evidence for BPD on chromosome 18p and suggestive evidence of phosphorylation and signal transduction dysregulation in affective disorders (Newberg and others 2008). This candidate gene approach has the advantage of taking prior research into account and provides adequate power for genes of small to moderate effect sizes. While recent technological advances have made it possible to conduct genome-wide association studies (GWAS) in complex diseases like BPD (Baum and others 2008; TheWellcomeTrustCaseControlConsortium 2007), the initial results have been limited with a lack of breakthrough findings and little or no replication between several datasets. Although the concept of a “hypothesis-free” design in GWAS is appealing as an approach to discover new genes and pathways involved in neuropsychiatric disease, it ignores previous advances in neuroscience research and disregards *a priori* biological

relevance. It is furthermore likely that much larger sample sizes are needed for GWAS, in the ten-thousands, in order to achieve adequate power in the face of multiple testing (Frayling 2007). Candidate gene approaches, including cluster analyses of genes involved in neurobiological pathways, are thus still a reasonable strategy to investigate genetic factors of complex disorders (Serretti and Mandelli 2008). Although our SNP selection was based on available HapMap data and four tagging SNPs were selected in order to cover the majority of the gene region, it is possible that we missed additional markers that might have been associated with disease. As indicated by the relatively weak observed LD, additional genotyping of markers might improve gene coverage; however, ultimately future studies will also have to include deep sequencing of this genomic region in order to detect rare variants that might confer risk to disease.

In conclusion, we show a positive association between polymorphisms in the *MPPE1* gene and BPD. While the study requires replication in an independent sample, it provides additional information on the 18p genomic region and serves to further characterize this region that has been implicated in BPD. Additional experiments, including subphenotype and endophenotypic analyses, are necessary to elucidate the genetic factors contributing to the linkage peak on 18p11.

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Figure 1.

Linkage disequilibrium measures (D') across the *MPPE1* gene. From left to right, the SNPs are aligned from 5' to 3'. Black boxes represent exons. LD patterns and haplotype blocks were defined by the “solid spine of LD” using the Haploview software. A standard color scheme is used to display LD pattern, with dark red for very strong LD, white for no LD, and shades of red for intermediate LD. Increasing intensity of red indicates increasing degrees of LD.

Table 1

Genotype and Allele frequencies of variations in the *MPPE1* gene

SNP	Sample	n	Genotype frequency		P*	Allele frequency	P**
rs871044	Bipolar	554	G/G	G/A	A/A	f(G)	
	Controls	722	0.354	0.478	0.168	0.593	0.704
rs3974590	Bipolar	567	0.348	0.506	0.147	0.600	
	Controls	724	G/G	G/A	A/A	f(G)	
rs593713	Bipolar	567	0.467	0.441	0.092	0.688	0.009 ^d
	Controls	724	0.544	0.381	0.075	0.735	
rs602201	Bipolar	563	A/A	A/G	G/G	f(A)	
	Controls	719	0.472	0.435	0.092	0.690	0.051
	Bipolar	565	0.530	0.391	0.079	0.725	
	Controls	712	T/T	T/A	A/A	f(T)	
	Bipolar	565	0.405	0.469	0.126	0.946	0.739
	Controls	712	0.397	0.472	0.131	0.633	

* P values for comparison of genotype frequencies between bipolar individuals and controls

** P values for comparison of allele frequencies between bipolar individuals and controls.

^dPermutation correction p-value: 0.046

Table 2

Analysis of four-marker haplotypes in the *MPPE1* gene

Haplotype block	Case frequencies	Control frequencies	Chi square	P Value	Permutation P value
Block 1					
GGAT	0.278	0.294	0.790	0.374	0.962
AGAT	0.192	0.206	0.761	0.383	0.966
GGAA	0.146	0.157	0.533	0.465	0.991
GAGA	0.095	0.091	0.131	0.717	1.000
AAGT	0.095	0.077	2.495	0.114	0.503
AAGA	0.053	0.047	0.415	0.520	0.997
AGAA	0.044	0.051	0.680	0.410	0.977
GAGT	0.034	0.033	0.651	0.420	0.981
GAAT	0.017	0.009	2.786	0.095	0.431

Table 3

Analysis of two-marker haplotypes in the *MPPEI* gene

Haplotype block	Case frequencies	Control frequencies	Chi square	P Value	Permutation P value
Block 1					
GA	0.661	0.708	6.589	0.010	0.0495
AG	0.282	0.249	3.607	0.058	0.259
GG	0.027	0.026	0.054	0.816	1.000
AA	0.030	0.017	4.475	0.034	0.170