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Evaluation of Paraoxonase 1 Polymorphisms in Patients with Bipolar Disorder

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Abstract. *Aim: Bipolar disorder (BD) has a complex genetic etiology, with multiple unidentified genes and environmental factors playing important roles in its pathogenesis. A growing body of evidence suggests that reactive oxygen species (ROS) may be crucially involved in the pathogenesis of psychiatric diseases, including BD. The association between paraoxonase 1 (PON1), an important antioxidant enzyme, and development of BD has been scarcely investigated. We thus attempted to examine genetic variants in the PON1 gene, a putative BD susceptibility gene, in patients with bipolar disease and their first-degree relatives. Materials and Methods: The study population consisted of 292 healthy individuals, 199 patients with BD, and 280 unaffected first-degree relatives of the patients. Genotyping of PON1 L55M and Q192R polymorphisms was performed by polymerase chain reaction and restriction enzyme digestion. Results: Patients mostly shared the same PON1 genotypes with their first-degree relatives. The frequency of MM genotype of PON1 L55M polymorphism was lower and that of LM genotype was higher in patients and relatives than healthy controls. PON1 enzyme activities did not differ between patient, relative and healthy control groups but were influenced by PON1 genotype. Conclusion: Our findings indicate an association between the genetic variants of PON1 and BD. The PON1 L55M MM genotype seems to be protective against the development of BD.*

Bipolar disorder (BD) is a chronic, severe, and highly disabling psychiatric disorder which is estimated to affect 1% of the world population (1-3). BD has a complex genetic etiology, with multiple unidentified genes and environmental factors playing important roles in its pathogenesis (4-6) .

A growing body of evidence has suggested that reactive oxygen species (ROS) may be involved in the pathogenesis of psychiatric diseases, including BD (7-9). Glutamate and dopamine are highly redox-reactive molecules producing ROS during normal neurotransmission. Increased dopamine levels, which are associated with symptoms of mania, have been related to oxidative stress (10, 11).

Under physiological conditions, cells produce antioxidants to overcome the damage brought by oxidative stress (12, 13). However, in situations of imbalance between ROS production and antioxidant activity, oxidative damage occurs, generating deleterious effects on signal transduction, structural plasticity and cellular resilience, mostly by inducing lipid peroxidation in membranes, and oxidation of proteins and genes (14, 15).

Polymorphisms in antioxidant genes have been suggested as predisposing factors and susceptibility candidates for psychiatric disorders (16, 17). Paraoxonase 1 (PON1) is an important antioxidant enzyme playing a role in protection against oxidative modification of low-density lipoprotein (LDL), and is responsible for de-activation of organophosphates in the central nervous system (18-20). The main PON1 encoding gene is located on 7q21.3 and has two common polymorphisms in its coding region, leading to a glutamine to arginine substitution at position 192 and leucine to methionine substitution at position 55 (21-23).

First-degree relatives of persons with BD carry an elevated risk for development of BD compared to the normal healthy population (24). Although BD is a highlyheritable psychiatric disorder, its etiology remains largely unknown despite extensive efforts to identify susceptibility genes. In order to investigate the association of the PON1 antioxidant enzyme with BD, we attempted to examine genetic variants in the PON1 gene, a putative BD susceptibility gene, in patients with BD and their first-degree relatives. In addition, we sought to explore the relationship between the clinical characteristics of BD and PON1-related genetic variants.

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Materials and Methods

Study population. Individuals with BD were recruited at the Psychiatric Department of Istanbul Erenkoy Psychiatric and Neurological Disorders Hospital with an inpatient ward for patients with acute psychiatric disorders. Assessment for diagnosis of BD using Diagnostic and Statistical Manual of Mental Disorders (DSM IV) (25) criteria were performed by two psychiatrists based on consensus, utilization of cross-sectional interviews and case records. All patients had active symptoms at the time of the study. The study population consisted of 292 healthy individuals [mean (±SD) age=45.45±14.46 years; age of 170 females/122 males=44.28±14.63/ 47.07±14.11 years] 199 patients with BD [mean (±SD) age=40.55±12.23 years; age of 128 females/71 males=43.48±14.33/ 44.81±14.04 years], and 280 unaffected first-degree relatives of patients [mean (±SD) age=45.07±14.87 years; age of 146 females/134 males=45.48±15.07/44.56±14.67 years]. Healthy and unrelated volunteers without psychiatric disorders were selected as the control group. Relatives were selected from parents, sisters or brothers of patients with BD. To minimize the effect of ethnic differences in gene frequencies, the study participants were recruited from the Turkish population living in the western region of Turkey. The study was approved by the Medical Ethics Committee of Istanbul Medical Faculty (approval number: 2012-158), and all participants (*i.e.* controls, patients or unaffected family members (on behalf of some patients) gave written informed consents.

Inclusion and exclusion criteria. Patients with BD were screened for respective diagnostic criteria as derived from Structured Clinical Interview the Patient Version of the DSM-IV. Patients were excluded if their primary diagnosis was not BD. For controls, relatives and patients, the following exclusion criteria were applied: (a) neurological disorder that would affect neuropsychological function (*i.e.* seizures, head trauma, stroke, brain tumor, meningitis); (b) alcohol and substance abuse or dependence; (c) type II diabetes mellitus (NIDDM); (d) lipid disorders; (e) cardiovascular disease; and (f) hypertension or family history of the same. These factors are known to affect oxidative stress. Individuals using any medication for other medical problems were also excluded.

Measurements, protocol and procedure. All individuals were examined according to a standardized interview. Assessment was done on a semi-structured sociodemographic pro forma which required information regarding demographic and personal details of the patients and complaints of the patients, history of present illness, details of medical or surgical interventions, past history, family history, personal history, premorbid personality, details of physical examination, mental status examination and diagnostic formulation. The potential cases were interviewed by two psychiatrists, and their medical records were reviewed whenever relevant. Secondly, a consultant psychiatrist audited the first-phase results and confirmed or rejected the diagnosis. Finally, two psychiatrists set the diagnosis, blind to each other's classification, using written information collected about the patients. Only patients who received a diagnosis of BD from both investigators were included. The diagnosis was made using Structured Clinical Interview for DSM-IV (SCID-I) (26, 27). The patients were then screened on various rating scales such as the Brief Psychiatric Rating Scale (28, 29) for patients with BD, and the Rating Scale for Mania (30, 31) for BD. Controls and relatives were screened by the Structured Clinical Interview for DSM-IV (SCID-I) interviews. We investigated their demographic data, medical and psychiatric history.

Genetic and biochemical determinations. Blood samples were taken after a minimum of 8 h of fasting. Genomic DNA was extracted from peripheral whole blood containing EDTA according to the salting-out technique (32). Genotyping was performed by polymerase chain reaction and restriction enzyme digestion. The primers described by Humbert *et al*. (23) were used for determining *PON1* polymorphisms. The following polymerase chain reaction conditions were used: 95˚C for 9 min, 35 cycles consisting of 95˚C for 1 min, 60˚C (*PON1* L55M) or 58˚C (*PON1* Q192R) for 1 min and 72˚C for 1 min; followed by a final extension step of 72˚C for 10 min. The PON1 L55M product was digested with 10 U *Hsp92*II and the *PON1* Q192R product was digested with 8U BspI at 37˚C for 16 h. The digested products were analyzed on 3% agarose gel stained with ethidium bromide and examined under transillumination. Two individuals read *PON1* genotypes independently, and in cases of conflict, genotyping was repeated. PON1 activities of sera were measured by using the method of Furlong *et al*. (33).

Statistical analysis. Statistical analyses were performed using the SPSS software package, revision 15.0(SPSS Inc., Chicago, IL). Distributions of genotypes and alleles were compared by x2 test. Lewontin's D' coefficient was used to assess the strength of linkage disequilibrium between the PON1 L55M and Q192R polymorphisms. D' and r2 values were obtained through the Haploview program (http://www.broad.mit.edu/mpg/haploview/documentation.php). PON1 activity was expressed as the mean±standard deviation (SD). Kruskal–Wallis and Mann–Whitney *U*-tests were used to compare genotypes with PON1 activity. Non-parametrical analysis was used since PON1 activity levels covered a very broad range. Power analysis was performed using PS version 3 package program (http://biostat.mc.vanderbilt.edu/wiki/bin/view/Main/PowerSampleSize). A p-value of less than 0.05 was considered to be significant.

Results

Table I summarizes the clinical characteristics of the study groups. There were significant differences in age between patients and relatives ($p<0.001$) and between patients and controls ($p<0.001$) but not between relatives and controls as assessed by Student's t-test. The number of women was higher than men in all study groups but there were no statistically significant differences among groups by the Fisher's exact test.

The genotypic frequencies of *PON1* are presented in Table II. Genotypic frequencies for *PON1* Q192R were in agreement with the Hardy–Weinberg equilibrium in all groups. However, *PON1* L55M deviated from Hardy–Weinberg equilibrium in relatives and controls but not patients. The frequency of MM genotype of *PON1* L55M was significantly decreased in both patients ($p<0.01$) and their first-degree relatives ($p<0.01$) compared to controls, while LM genotype of *PON1* L55M was more frequent in patients ($p<0.01$) and relatives ($p<0.001$) than in controls.

Table I. *Clinical characteristics of patients with bipolar disorder, relatives, and controls.*

Parameter	Patients with bipolar disorder	First-degree relatives	Controls
Mean age ±SD, years	40.55±12.23*	45.07±14.87	45.45±14.46
Gender (female/male)	128/71	146/134	170/122
Family history of patients, n (%)			
Depression	24 (12)		
Psychosis	27 (13.6)		
Bipolar affective disorder	30 (15.1)		
Other	1 (0.5)		
Absent	117 (58.8)		
Mean age±SD at onset of disease, years	24.92±9.31		
Mean duration of disease±SD, years	15.7±10.79		
Type of treatment, n (%)			
Typical neuroleptic	70 (35.2)		
Atypical neuroleptic	17 (8.5)		
Typical+atypical neuroleptic	42 (21.1)		
Atypical mood stabilizers	20 (10.1)		
Typical mood stabilizers	50 (25.1)		

*$p<0.001$, *versus* relative and control groups.

On the other hand, LL frequency was moderately diminished in relatives as compared with controls ($p<0.05$). Although the frequency of QQ genotype of *PON1* Q192R was lower in patients and their relatives as compared to controls, these values did not reach significance. There was no significant difference in RR genotype among the three groups. There were also no significant differences between the frequencies of Q-R and L-M alleles among study groups.

Patients with BD with QQ genotype had significantly lower PON1 activity than relatives and controls with the same genotype by both Kruskal–Wallis and Mann–Whitney *U*-tests. There were no significant differences in serum PON1 activity levels of those with other genotypes among the study groups. Overall, PON1 activity showed a trend towards displaying higher levels in patients, relatives and healthy controls with the RR and LL genotypes (Table III). Weak linkage disequilibrium was observed between Q192R and L55M (D'=0.37, r^2=0.077). Neither the L55M nor Q192R coding polymorphisms were associated with the family history of patients, age at disease onset, duration of disease, or response to drugs. Power analysis performed by a power sample size program yielded a very high power for our study (PS version 3 package program; http://biostat.mc.vanderbilt.edu/wiki/bin/view/Main/PowerSample Size). A *p*-value of less than 0.05 was considered to be significant).

Discussion

There is a strong genetic component to the risk of developing BD, however, this is a complex genetic trait and no consensus candidate susceptibility genes have yet emerged from the studies (6, 24). In the present study, as far as we are aware of, for the first time, we observed significant evidence of an association between genetic variants of the PON1 gene and BD in this Turkish population. Moreover, we also showed that patients share similar *PON1* genotypes with their first-degree relatives. The frequency of MM genotype of *PON1* L55M was lower and that of the LM genotype was higher in patients and relatives than in controls. Thus, the MM genotype seems to be protective against development of BD, while the LM genotype is associated with an increased frequency of BD.

To our knowledge, there are only two previously published studies on the association of *PON1* and BD, and both studies have assessed Tunisian populations. In one study, patients with BD were found to have significantly lower PON1 enzyme activity than healthy controls (34), whereas in the other study, a significant association was recorded between BD, L55M and Q192R polymorphisms (35), suggesting that patients carrying homozygous or heterozygous mutated alleles of *PON1* might display susceptibility to BD. However, in contrast with our study, the LL genotypic frequency was significantly diminished in patients and that for the MM genotype was slightly higher in patients than healthy controls. Our study also failed to confirm a significant link between BD and Q192R polymorphisms. Our results are in agreement with another study, which did not find a significant association between *PON1* Q192R polymorphism and depression in an English population (36). These results suggest that the association between *PON1* polymorphisms and BD widely differs based on ethnic and geographical features.

The mechanism by which MM genotype of *PON1* L55M confers protection against BD is unclear. It has been shown

Table II. *Frequency of L55M and Q192R Paraoxonase 1 (PON1) genotypes in study groups.*

PON1 Genotype/allele	Patients with bipolar disease n=199	First-degree relatives n=280	Controls n=292
Q192R genotype, n (%)			
QQ	75 (37.7)	110 (39.2)	120 (41.1)
QR	92 (46.2)	141 (50.4)	130 (44.5)
RR	32 (16.1)	29 (10.4)	42 (14.4)
Q192R allele, n (%)			
Q	242 (60.80)	361 (64.46)	370 (63.35)
R	156 (39.19)	199 (35.53)	214 (36.64)
L55M genotype, n (%)			
LL	70 (35.2)	85 (30.4)*	112 (38.3)
LM	102 (51.3)**	153 (54.6)***	110 (37.7)
MM	27 (13.6)**	42 (15.0)**	70 (23.9)
L55M allele, n (%)			
L	242 (60.80)	323 (57.67)	334 (57.19)
M	156 (39.19)	237 (42.32)	250 (42.80)

*$p<0.05$; **$p<0.01$; ***$p<0.001$, compared to controls.

Table III. *Paraoxonase 1 (PON1) activity (U/ml) in all study groups according to L55M and Q192R Paraoxonase 1 (PON1) genotype.*

PON1 Genotype	Patients with bipolar disorder	First-degree relatives	Controls	All study groups
Q192R				
QQ	101.90±73.21*#	125.22±84.51	115.14±49.16	120.92±76.97
QR	122.99±64.02	131.32±75.22	127.45±63.55	128.93±69.52
RR	158.78±109.41	147.81±123.69	131.57±63.67	139.29±97.48
L55M				
LL	116.31±89.27	134.21±76.54	131.38±68.10	130.39±79.29
LM	124.73±65.87	130.68±84.41	120.39±50.83	126.49±73.65
MM	119.83±90.32	122.83±107.53	127.97±62.23	123.27±83.74

*$p<0.05$, compared to controls using the Mann–Whitney *U*-test; #$p<0.05$, comparison among three groups was evaluated with Kruskal–Wallis test.

that the MM genotype of PON1 is more protective against oxidative stress than the LL genotype (6), suggesting that patients with BD without the MM genotype might not efficiently cope with neuronal oxidative stress. On the other hand, healthy relatives of patients with BD carry similar *PON1* genotypes as patients with BD, suggesting that a *PON1* polymorphism alone is not sufficient to cause BD and additional, possibly environmental, triggers are also required. Moreover, *PON1* L55M and Q192R are not the only polymorphisms associated with the antioxidant activity of *PON1*. For instance, there is linkage disequilibrium with T108C polymorphism in the promoter region of *PON1* (37). There are also many other genes, such as *DISC1* (*Disrupted in schizophrenia 1*), *CACNA1C* (*calcium channel, voltage-dependent, L type, alpha 1C subunit*), *ANK3* (*Ankyrin 3*), *DTNBP1* (*dystrobrevin binding protein 1*) and GPR50 (G protein-coupled receptor 50), that have been associated with development of BD (6, 37). BD might therefore emerge as a result of the complex interactions between numerous BD-associated genes rather than defective functioning of a single gene. It is also notable that PON1 activity was not altered in patients with L55M polymorphism of *PON1*, suggesting that this polymorphism might influence disease development through mechanisms that are not related to PON1 activity.

If genetic variants of *PON1* do indeed increase neuronal oxidative stress, the exact mechanisms of this interaction needs to be clarified.

Glutamate and dopamine, implicated in BD pathogenesis, are highly redox-reactive molecules and produce ROS during normal neurotransmission (9). An Increased dopamine level is an important source of oxidative metabolism of dopamine. Dopamine is enzymatically metabolized by monoamine

oxidase, subsequently producing hydrogen peroxide and dihydroxyphenylacetic acid (38); or is non-enzymatically hydroxylated in the presence of ferrous ion and hydrogen peroxide, leading to formation of 6-hydroxydopamine (39, 40), which is toxic to the nervous system. Frey *et al*. showed increased oxidative stress levels in a dopaminergic animal model of mania induced by amphetamine (41). They also reported that there was an increase in thiobarbituric acid-reactive substances and superoxide anion production in submitochondrial particles from prefrontal cortex and hippocampus. Increased neuronal oxidative stress levels generate deleterious effects on signal transduction, structural plasticity and cellular resilience, mostly by inducing lipid peroxidation of membranes, proteins and genes (42, 43). Increased oxidative stress affects serotonin and noradrenalin transmitter-related major depression (44, 45). These findings support the notion that oxidative stress is associated with the pathophysiology of BD.

A limitation of our study was the lack of measurement of oxidative stress markers and glutamine or dopamine levels, which should be addressed in future studies.

Conclusion

Our results represent the first assessment of the association between PON1 enzyme activity and genetic variants of *PON1* in patients with BD. We have also confirmed the association between genetic variants of *PON1* and BD. Therefore, *PON1* may be a plausible candidate gene associated with development of BD.

Conflicts of Interest

The Authors have no conflicts of interest to disclose.

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