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Association of genetic polymorphisms in the type II deiodinase gene with bipolar disorder in a subset of Chinese population

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ABSTRACT

Objective: Genetic factors play a critical role in the etiology of bipolar disorder (BPAD). Previous studies suggested an association between thyroid dysfunction and BPAD. We hypothesize that genetic variations in the type II deiodinase (DIO2) gene that possibly alter the bioactivity of thyroid hormones are associated with BPAD. *Method:* A case–control association study was conducted in a subset of Chinese Han population. Two single nucleotide polymorphisms (SNP), open reading frame a (ORFa)-Gly3Asp (rs12885300) and Thr92Ala (rs225014) with potential functions on the activity of DIO2, were selected. The frequencies of allele, genotype and haplotype of the two SNPs were compared between the BPAD patients and the control group. *Results:* Statistical significance between the BPAD patients and the control group was observed for the allele ($\chi^2 = 7.746$, $P = 0.005$, $df = 1$) and genotype frequencies ($\chi^2 = 8.158$, $P = 0.017$, $df = 2$) at the locus of ORFa-Gly3Asp, and for the allele ($\chi^2 = 15.838$, $P = 7.00e{-}005$, $df = 1$) and genotype frequencies ($\chi^2 = 17.236$, $P = 0.0002$, $df = 2$) at Thr92Ala. Distribution of allele 3Gly and 92Ala were significantly higher in the BPAD patients, with odds ratios of 1.489 [95% confidence interval (CI) = 1.124–1.973] and 1.616 [95% CI = 1.275–2.048], respectively. Individuals with two copies of the variant 3Gly or 92Ala were at greater risk of BPAD than individuals with one copy (dose–response manner). Haplotypes ORFa-3Asp-92Ala and ORFa-3Gly-92Ala indicated higher susceptibility for BPAD with odds ratios of 3.759 (95% CI = 2.013–7.020) and 1.292 (95% CI = 1.017–1.642), respectively, while ORFa-3Asp-92Thr probably played a protective role with an odds ratio of 0.395 (95% CI = 0.284–0.549). *Conclusion:* Data generated from this study supported our hypothesis that genetic variations of the DIO2 gene were associated with BPAD and suggested further consideration on the possible involvement of these functionally active variants in the pathophysiology of BPAD.

1. Introduction

Bipolar disorder (BPAD) is a major affective disorder marked by severe mood swings (manic or major depressive episodes) with the tendency to remit and recur, affecting around 2.6% of the U.S. population aged 18 and older in a given year (Kessler et al., 2005). The epidemiology of BPAD in Chinese population is still under study. The etiology of BPAD may include genetic, developmental, social, cultural and environmental factors, among which genetic factors have been shown to play an important role through multiple family, twin and adoption studies (Bertelsen et al., 1977; Kendler et al., 1993; Mendlewicz and Rainer, 1977). Although inconsistent results existed, linkage studies have mentioned several loci on chromosome 4 (Adams et al., 1998; Badenhop et al., 2003; Blackwood et al., 1996; Liu et al., 2003), 13q (Detera-Wadleigh et al., 1999; Potash et al., 2003; Stine et al., 1997), chromosome X (Ekholm et al., 2002; Pekkarinen et al., 1995; Zandi et al., 2003), etc. Molecular genetic studies have also identified genes that may be associated with BPAD, such as the catechol-O-methyltransferase (COMT) gene (Lachman et al., 1996; Rotondo et al., 2002), the dopamine transporter (DAT) gene (Greenwood et al., 2001), the 5-hydroxytryptamine transporter (5-HTT) gene (Collier et al., 1996; Rotondo et al., 2002), the monoamine oxidase A (MAOA) gene (Preisig et al., 2000), the brain-derived neurotrophic factor (BDNF) gene (Sklar et al., 2002).

Association studies between thyroid function and affective disorders as well as mood instability have a long history, revealing

Abbreviations: 5-HTT, 5-hydroxytryptamine transporter; BDNF, brain-derived neurotrophic factor; BPAD, bipolar disorder; CI, confidence interval; COMT, catechol-O-methyltransferase; DAT, dopamine transporter; DIO2, Type II deiodinase; DNA, deoxyribonucleic acid; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders 4th edition; LD, linkage disequilibrium; MAOA, monoamine oxidase A; ORFa, open reading frame a; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; SD, standard deviation; SNP, single nucleotide polymorphism; T3, triiodothyronine; T4, thyroxine.

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that abnormalities of thyroid system are involved in the pathogenesis of various psychiatric disorders. Thyroid hormones play an important role in fetal and early postnatal brain development, and thus babies lacking thyroid hormones often suffer from abnormal brain development. The association between myxedema and psychosis was first reported by Gull in the 19th century (Pearce, 2006). In 1888, a London committee also reported that 36% of the patients with myxedema also had insanity symptoms (Bahls and de Carvalho, 2004). Specifically, the association between thyroid dysfunction and depression or schizophrenia was also found. Kirkegaard and Faber (1998) reviewed that the triiodothyronine (T3) level in depression patients was reduced while the thyroxine (T4) level was elevated. Patients with schizophrenia showed accumulation of metabolically active T3 in the peripheral blood, due to enhanced T4 degradation in the peripheral tissues (Turianitsa et al., 1991).

It has been suggested that BPAD, depression and schizophrenia share similar phenotypes, as well as common genetic factors and environmental causes. In recent studies on BPAD, there were also proofs on its association with thyroid dysfunction. The association between decreased T3 level and mood instability was observed in the BPAD patients (Hatterer et al., 1988). In a study of lithium prevention for BPAD, T4 level was found to be associated with mood instability: a low free T4 level was associated with depression and more episodes, while a high free T4 level was associated with mania (Frye et al., 1999). BPAD, and particularly the clinical picture of 'rapid cycling', was also linked to both thyroid hypofunction and to autoimmune thyroiditis (Oomen et al., 1996; Valle et al., 1999). In a prospective cohort study, patients hospitalized with hypothyroidism showed a greater risk of readmission with BPAD (Thomsen et al., 2005).

The amount of the two main hormones in human thyroid system, T3 and T4, is regulated by deiodinase, a key enzyme for the conversion of T4 to T3. There are three types of deiodinase, among which type II deiodinase (DIO2) is a tissue-specific regulator of intracellular T3 concentrations in the brown fat and pituitary and is particularly important for the conversion of T4 to T3 in the brain. DIO2 is essential for providing the brain with appropriate levels of T3 during the critical period of development (Croteau et al., 1996). It produced more than 75% of the nuclear T3 in the rat cerebral cortex (Crantz et al., 1982). Extensive studies have been conducted on DIO2 and its encoding gene, the DIO2 gene, as well as its potential effects on affective disorders. DIO2 could be induced by psychotropic agents such as lithium and carbamazepine (Baumgartner et al., 1997). Positive association of the DIO2 gene with mental retardation was also found, confirmed by two associated single nucleotide polymorphisms (SNPs), indicating its involvement in mental development (Guo et al., 2004).

No study has been conducted to investigate the relationship between the DIO2 gene and BPAD until now. We hypothesize that genetic variations in the DIO2 gene that possibly alter the bioactivity of thyroid hormones are associated with BPAD. This is a new viewpoint that has not been paid sufficient attention to previously. Two SNPs, open reading frame a (ORFa)-Gly3Asp (rs12885300) and Thr92Ala (rs225014) in linkage disequilibrium (LD) (Meulenbelt et al., 2008) with extensive functional results were selected and a case–control association study in a subset of Chinese Han population was conducted. The frequencies of allele, genotype and haplotype of the two SNPs were compared between the BPAD patients and the control group in order to investigate the potentially existing association of the two genetic polymorphisms with BPAD.

2. Methods

2.1. Subjects

A total of 279 patients with BPAD [157 males and 122 females with a mean age of 33.8 years, standard deviation (SD) = 11.5] and 284 psychiatrically healthy control subjects (138 males and 146 females with a mean age of 18.3 years, SD = 3.1) were recruited in this case–control study. All subjects were biologically unrelated native Chinese Han people. 186 and 93 patients were recruited from Bio-X Center of Shanghai Jiao Tong University and Beijing Anding Hospital, respectively, with BPAD diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV). All diagnostic evaluations were completed without previous knowledge on the genotyping data. The control subjects were recruited from Peking University Health Science Center without presence or past history of psychiatric illness or known genetic diseases. All subjects participated in this study voluntarily. Written informed consents were obtained from all subjects following a complete description of the study. The institutional ethics committees approved the study.

2.2. Genotyping

Polymerase chain reaction (PCR) followed by restriction fragment length polymorphism (RFLP) analysis was used to obtain the genotypes of the two groups. Genomic deoxyribonucleic acid (DNA) was extracted from peripheral blood with a standard phenol/chloroform extraction method, and diluted to a final concentration of 20 ng/μl with 1×TE buffer (pH7.6). Twenty nanograms of genomic DNA were amplified in a 20 μl reaction containing 1 μM forward primer and 1 μM reverse primer (listed in Table 1), 1×PCR buffer (10 mM Tris hydrochloride pH 8.5, 50 mM potassium chloride), 0.2 mM deoxynucleotide triphosphates, 1.5 mM magnesium chloride, and 1 U of Taq DNA polymerase (Invitrogen). PCR was performed at 95 °C for 2 min, followed by 30 cycles each at 95 °C for 45 s, 51 °C (for ORFa-Gly3Asp) or 53.8 °C (for Thr92Ala) for 30 s, 72 °C for 30 s, and a final extension step of 72 °C for 10 min. After purification with PCR product purification kit (Qiagen), PCR products were digested with respective restriction endonucleases at 37 °C for 4 h in enzyme buffers (NEB). 7% native polyacrylamide gel electrophoresis followed by ethidium bromide staining visualized the digestion products and determined the genotype of each subject. The RFLP genotyping methods were verified by a 100% concordance rate after sequencing eight PCR products of each genotype. The SNP genotyping method including primer sequences, PCR products length, restriction endonucleases and genotype determination on the gel is summarized in Table 1.

2.3. Data analysis

Hardy–Weinberg equilibrium test, allele and genotype frequencies analysis, LD calculation, as well as haplotype estimation and comparison were performed with SHEsis program (Shi and He,

Table 1
Primers and restriction endonucleases for SNP genotyping.

SNP	Primer sequences	PCR products (bp)	Restriction endonucleases	Genotype determination on the gel
ORFa-Gly3Asp (C/T)	Forward: 5′-AAAGCTGGCGTACTCGTC-3′ Reverse: 5′-AAAGAGCATAGAGACAATGAAAG-3′	145	CviKI-1 (NEB)	CC: 117 bp/24 bp/4 bp CT: 145 bp/117 bp/24 bp/4 bp TT: 145 bp
Thr92Ala (T/C)	Forward: 5′-AATGTAGACCAGCAGGAAGT-3′ Reverse: 5′-AGGTGAAATTGGGTGAGGAT-3′	263	RsaI (NEB)	TT: 180 bp/53 bp/30 bp TC: 180 bp/83 bp/53 bp/30 bp CC: 180 bp/83 bp

Table 2
Allele and genotype analysis in the BPAD patients and the control group.

	ORFa-Gly3Asp (C/T)					Thr92Ala (T/C)				
	Allele		Genotype			Allele		Genotype		
	C	T	CC	CT	TT	T	C	TT	TC	CC
BPAD (frequency)	448 (0.806)	108 (0.194)	178 (0.640)	92 (0.331)	8 (0.029)	260 (0.474)	288 (0.526)	65 (0.237)	130 (0.474)	79 (0.288)
Control (frequency)	415 (0.736)	149 (0.264)	150 (0.532)	115 (0.408)	17 (0.060)	337 (0.593)	231 (0.407)	96 (0.338)	145 (0.511)	43 (0.151)
χ^2	7.746		8.158			15.838		17.236		
P	0.005		0.017			7.00e−005		0.0002		
Odds ratio [95% CI]	1.489 [1.124–1.973]		1.483 [1.046–2.105][a]			1.616 [1.275–2.048]		2.049 [1.319–3.183][b]		

[a] Calculation of ORFa-3Gly–3Gly/ORFa-3Gly–3Asp (CC/CT) genotypes.
[b] Calculation of 92Ala–92Ala/92Thr–92Ala (CC/TC) genotypes.

2005). Statistical significance was defined at $p<0.05$. Power calculations were performed using the G*Power 3 program (Faul et al., 2007).

3. Results

3.1. Analysis of allele and genotype frequencies

Of the two SNPs genotyped, deviation from Hardy–Weinberg equilibrium was observed in neither the BPAD patients nor the control group. The allele and genotype frequencies of the two SNPs, as well as their comparison between the two groups were presented in Table 2. Statistical significance between the BPAD patients and the control group was observed for the allele ($\chi^2=7.746$, $P=0.005$, $df=1$) and genotype frequencies ($\chi^2=8.158$, $P=0.017$, $df=2$) at the locus of ORFa-Gly3Asp, and for the allele ($\chi^2=15.838$, $P=7.00e-005$, $df=1$) and genotype frequencies ($\chi^2=17.236$, $P=0.0002$, $df=2$) at Thr92Ala. Distribution of allele 3Gly and 92Ala was significantly higher in the BPAD patients, with odds ratios of 1.489 [95% confidence interval (CI) = 1.124–1.973] and 1.616 [95% CI = 1.275–2.048], respectively.

3.2. Haplotype analysis

When data from both the BPAD patients and the control group were taken into account, the two SNPs were in medium to low LD ($D'=0.543$, $r^2=0.077$). In a separate analysis, an acceptable LD ($D'=0.781$, $r^2=0.150$) was observed in the control group when compared with a quite low LD ($D'=0.192$, $r^2=0.010$) in the BPAD patients. The haplotype analysis results are shown in Table 3. We found three haplotypes with significant differences between cases and controls: ORFa-3Asp-92Ala and ORFa-3Gly-92Ala indicated higher susceptibility for BPAD with odds ratios of 3.759 (95% CI = 2.013–7.020) and 1.292 (95% CI = 1.017–1.642), respectively, while ORFa-3Asp-92Thr probably played a protective role with an odds ratio of 0.395 (95% CI = 0.284–0.549).

4. Discussion

4.1. Key findings from the allele, genotype and haplotype analysis

The main aim of the present study was to identify genetic factors associated with BPAD, by focusing on the DIO2 gene. It is the first report on the association between DIO2 genetic polymorphisms and BPAD, to our knowledge. The results of this study supported an association between the two SNPs (ORFa-Gly3Asp, Thr92Ala) of the DIO2 gene and BPAD: the 3Gly and 92Ala alleles were associated with higher BPAD risk (detection power: 0.795 and 0.978), indicating the probable existence of risky alleles; for both SNPs an association between the genotype and BPAD was observed. Besides, the 3Gly–3Gly and 92Ala–92Ala genotypes increased the BPAD risk when compared with the single allele carriers, which meant that individuals with two copies of the variant were at greater risk of BPAD than those with only one copy, and thus a dose–response relationship of the association was considered. It should be noted that the subtype information on the BPAD patients was not obtained, thus stratification within the BPAD patients may exist and have some effects on the association results.

The LD analysis showed that the two SNPs were in medium to low LD in the whole sample size and the BPAD patients, which was inconsistent with the high LD value obtained from the control group alone, from a previous report (Meulenbelt et al., 2008) and in the Hapmap release 22 ($D'=1.0$, Logarithm of odds = 8.97, $r^2=0.168$ in Chinese Han and Japanese in Tokyo population). Two possibilities may cause this deviation: 1) different recombination rates in the DIO2 gene existed between the BPAD patients and the control group; 2) a recent mutation occurred in certain populations. The haplotype analyses of the two SNPs confirmed the LD result and lead to the detection of all four possible haplotypes, in which ORFa-3Asp–92Ala and ORFa-3Gly–92Ala represented high susceptibility for BPAD and ORFa-3Asp–92Thr was a protective factor.

4.2. Functional description of ORFa-Gly3Asp and Thr92Ala

Previous studied showed that ORFa-Gly3Asp and Thr92Ala are two functional SNPs, and 3Gly and 92Ala alleles may have inverse effects on DIO2 activity. ORFa functioned as a possible inhibitory element for DIO2 expression, whose effect could be weakened by the naturally occurring variant ORFa-Gly3Asp (Coppotelli et al., 2006; Gereben et al., 2002; Peeters et al., 2005). Association was also found between ORFa-Gly3Asp and circulating iodothyronine levels (Peeters et al., 2005). On the other hand, residue 92 was the first amino acid of an 18-amino acid loop that conferred metabolic instability as the key determinant of DIO2 turnover rate (Dentice et al., 2005). Torlontano et al. (2008) reported that hyroidectomized patients with 92Ala/92Ala needed a

Table 3
Haplotype analysis in the BPAD patients and the control group.

Haplotype	ORFa-3Gly–92Thr (C–T)	ORFa-3Gly–92Ala (C–C)	ORFa-3Asp–92Thr (T–T)	ORFa-3Asp–92Ala (T–C)
BPAD (frequency)	197.19 (0.361)	242.81 (0.445)	60.81 (0.111)	45.19 (0.083)
Control (frequency)	199.22 (0.353)	215.78 (0.383)	135.78 (0.241)	13.22 (0.023)
χ^2	0.076	4.415	31.861	19.585
P	0.783	0.036	1.75e−008	9.83e−006
Odds ratio [95% CI]	1.035 [0.810–1.323]	1.292 [1.017–1.642]	0.395 [0.284–0.549]	3.759 [2.013–7.020]

higher T4 dose to achieve target thyrotropin level. DIO2 velocity was significantly lower in thyroid and skeletal muscle samples from 92Ala/92Ala subjects (Canani et al., 2005). Since no differences in mRNA level or biochemical properties of the protein were observed, suggesting that a direct effect of the 92Ala allele occurred on protein translation or stability.

In our study, the alleles 3Gly and 92Ala, the genotypes 3Gly–3Gly and 92Ala–92Ala, as well as the haplotype ORFa-3Gly–92Ala, which were more frequently found in the BPAD patients, potentially decreased the enzyme activity of DIO2, led to an alteration of the absolute and relative T3 and T4 levels, affected multiple functions in the brain, and contributed to the pathogenesis of BPAD. The similar reasoning process can be used to explain the possible protective role of the alleles 3Asp and 92Thr, the genotypes 3Asp–3Asp and 92Thr–92Thr, as well as the haplotype ORFa-3Asp–92Thr. Another assumption was that the SNPs we studied were in LD with other functional variants in a gene nearby, which was associated with BPAD.

4.3. Perspectives

In association studies of human complex diseases such as BPAD, due to genetic heterogeneity, further studies need to replicate the association in different families and across different ethnic populations. BPAD probably involves environmental factors as well as many genes, with each gene contributing a small to moderate effect to its pathogenesis. Therefore, future association studies may attempt to look at possible gene–gene or gene–environment interactions. Many hormonal systems were suggested to be involved in the pathogenesis of BPAD, not only the thyroid system, but also the adrenal–glucocorticoid system (Schatzberg and Lindley, 2008; Willour et al., 2008). The immune system could also be involved (Cunha et al., 2008; Czerski et al., 2008; Ortiz-Dominguez et al., 2007; Shao and Vawter, 2008). Multiple interactions may act as confounding factors, making it relatively difficult to interpret the effect of only one factor. BPAD has been shown to share common genetic factors with other affective disorders, such as depression and schizophrenia, and thus DIO2 could also be regarded as a suggestive genetic factor involved in those diseases and worthy of further investigation.

5. Conclusion

This is the first report on the association between the DIO2 genetic polymorphisms and BPAD. Data generated from this study supported our hypothesis that genetic variations of the DIO2 gene were associated with BPAD and suggested further consideration of the possible involvement of these functionally active variants in the pathophysiology of BPAD, although it should be kept in mind that the etiology of BPAD is multifactorial. Repetitive studies in different ethnic populations and combined meta-analysis across different studies are recommended to extend the results of this study in the future.

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