The serotonin-1Dβ receptor gene and severity of obsessive-compulsive disorder in women with bulimia nervosa

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Abstract

Background: There is significant evidence that eating disorders have an important biological overlap with obsessive-compulsive disorder (OCD), though the specific mediators of this relationship remain unclear. Recent evidence suggests that the G861C polymorphism of the 5HT-1Dβ receptor gene and the G allele in particular may play a role in OCD. We thus hypothesized that, among a heterogeneous group of probands with bulimia nervosa (BN), this same G allele might predict the presence and/or severity of OCD pathology. Methods: 165 consecutive female probands with BN were genotyped for the G861C polymorphism of the 5HT-1Dβ receptor gene. Rates of full syndrome OCD, partial syndrome OCD and no OCD were compared across the three genotypic groups defined by this polymorphism. Results: 45 out of 165 BN probands (27.3%) had either full or partial syndrome OCD. In the full sample, there was a significant difference in the distribution of the three diagnostic groups by genotype ($\chi^2 = 10.07$, df = 4, $p = .039$). The G861C polymorphism did not strongly predict which probands had any vs. no OCD pathology. However, among the 45 probands with OCD symptoms, the G861C polymorphism did strongly differentiate full syndrome vs. partial syndrome OCD.

KEYWORDS
Bulimia nervosa; Obsessive-compulsive disorder; Serotonin-1Dβ receptor gene; Co-morbidity; Genetic association studies

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1. Introduction

There is significant converging evidence that both bulimia nervosa (BN) and anorexia nervosa (AN) are biologically related to obsessive-compulsive disorder. Numerous studies have found high rates of full or partial syndrome OCD in eating disorder patients (Thiel et al., 1995; Lennkh et al., 1998; Matsunaga et al., 1999; von Ranson et al., 1999; Albert et al., 2001; Anderluh et al., 2003), while others have found evidence for eating disorder pathology in patients with OCD (Rubenstein et al., 1992; Grabe et al., 2000a). Yet other studies have found strong similarities on various measures of pathology relevant to both disorders (Bulik et al., 1992; Jarry and Vaccarino, 1996). Based on this evidence, prior authors have postulated that eating disorders are part of a broader obsessive-compulsive spectrum of illness (Hollander et al., 1996; Bienvenu et al., 2000). Family studies further support a shared genetic liability for the eating disorders and OCD. Bellodi et al. (2001) found a significantly higher morbidity risk for OCD spectrum disorders among 436 relatives of probands with a primary eating disorder than in 358 relatives of control subjects. There is preliminary evidence that a major gene might play a role in this shared risk (Cavallini et al., 2000).

Notwithstanding an extensive body of research pointing to a shared vulnerability factor for the eating disorders and OCD, no studies to date have demonstrated a particular genetic factor that might contribute to this overlap. Serotonin genes are of particular interest in this regard, in that serotonin dysfunction is strongly implicated both in BN (Brewerton et al., 1992; Levitan et al., 1997; Kaye et al., 1998) and in OCD (Murphy et al., 1989; Pigott et al., 1993). Highly similar abnormal responses to the serotonin receptor agonist m-CPP have been reported in the two disorders (Zohar et al., 1987; Brewerton et al., 1992; Pigott et al., 1993; Goodman et al., 1995; Levitan et al., 1997), and both disorders show a specific responsivity to high dose SSRIs (FBNC study group, 1992; Jenike et al., 1997; Greist and Jefferson, 1998; Pigott and Seay, 1999). Regarding particular serotonin system genes, Mundo et al. (2002) have found a significant association between the G861C polymorphism of the 5HT-1D receptor gene and OCD in a large Canadian family-based control sample. In this study, the G allele was associated with the overall diagnosis of OCD and predicted severity of obsessional symptoms at a trend level of significance. A subsequent study extended the latter finding by demonstrating a statistically significant association between the G allele and severity of obsessions (Camarena et al., 2004). Other studies have failed to find an association between the 5HT-1D receptor gene and OCD (Di Bella et al., 2002; Hemmings et al., 2003) or have found an association in males only (Lochner et al., 2004). Taken as a whole, these and other studies (Moret and Briley, 2000) suggest that, at least in some cases, the 5HT-1D receptor gene may contribute to the pathophysiology of OCD, with a possible primary effect on symptom development and/or a modulatory effect on symptom severity.

To date, there has been just a single genetic association study of the serotonin-1D gene in an eating disorder population. Based on preclinical research showing that the serotonin-1D receptor has important modulatory effects on feeding behavior and thus body weight (Lee and Simansky, 1997), our group examined whether the G861C polymorphism of the 5HT-1D gene (also called the serotonin-1B receptor gene or HTR1B) was associated with minimum and maximum lifetime body mass indices (BMIs) in a sample of women with BN (Levitan et al., 2001). A highly significant difference in minimum lifetime BMI across the three genotypic groups was found, with both the G/C and C/C genotypes being associated with significantly lower minimum lifetime BMIs than was the G/G genotype (Levitan et al., 2001). We speculated that the G/G genotype might serve an adaptive function by robustly preserving a minimum body weight in the face of semi-starvation, perhaps by an effect on satiety mechanisms. If the G allele is in fact related to obsessive-compulsive behaviour, an alternative hypothesis is that it might be associated with compulsive eating and/or an adaptive obsession with food when food supplies are restricted. This could be a mechanism to preserve body weight and/or reflect the typical threat-focused of obsessions. In these ways, the association of the 5HT-1D gene with body weight regulation could be mediated by OCD symptoms.

To summarize, there is a clear shared morbidity risk for OCD and the eating disorders, a possible role for the 5HT-1D receptor gene in OCD and a relationship between this gene and minimum lifetime BMI in BN. The G allele of the G861C polymorphism in particular has been associated with the diagnosis of OCD, OCD syndrome severity and preservation of body mass at minimum weight. The goal of the current study was to explore three hypotheses related to the G861C polymorphism (particularly the G allele) and OCD pathology in female probands with BN. The first hypothesis
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