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Clinical report

A preliminary candidate gene study in body dysmorphic disorder

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ABSTRACT

This is the first study to examine the genetic basis of body dysmorphic disorder (BDD), a common and impairing disorder. Evidence suggests that BDD may be related to obsessive–compulsive disorder (OCD); thus, polymorphisms in nine genes in the serotonin, dopamine, and gamma-aminobutyric acid (GABA) systems were examined, all of which have been implicated previously in OCD. Fifty subjects with DSM-IV BDD were individually matched for ethnicity and gender to 50 healthy controls. Preliminary association was demonstrated for the *GABA$_A$-γ2* gene ($p=0.012$), the A allele occurring more frequently in BDD subjects than in controls; however, it did not survive correction for multiple testing. A trend association was also suggested for serotonin transporter *5-HTTLPR* ($p=0.064$) when considering all three genotypes, with the *s/s* genotype occurring more frequently in BDD subjects than in controls. This result became more significant when testing for association with the long allele ($p=0.041$) but did not survive correction for multiple testing. No association was demonstrated for the other examined genes. Genetic analysis of antidepressant response was negative. These results should be considered preliminary, because of the small sample size and limited power. Nonetheless, they provide preliminary support for the role of serotonin and GABA-ergic systems in BDD.

1. Introduction

Body dysmorphic disorder (BDD) is characterized by a distressing and/or impairing preoccupation with nonexistent or slight defects in one's physical appearance as well as excessive repetitive behaviors that are done in response to the appearance preoccupations (for example, repetitive mirror checking) (APA, 2013). Recently, BDD was moved to the new diagnostic category of obsessive–compulsive and related disorders (OCRDs) in DSM-5, given the overlapping features of BDD and obsessive–compulsive disorder (OCD) (APA, 2013). Recurrent and unwanted thoughts often focus on the face or head, but any body area can be the source of concern (Bjornsson, Didie, & Phillips, 2010; Phillips, 2004a). Research on BDD has recently increased, spurred by the recognition that BDD is common (Bienvenu et al., 2000; Bohne, Keuthen, Wilhelm, Deckersbach & Jenike, 2002; Buhlmann et al., 2010; Koran, Abujaoude, Large, & Serpe, 2008) and is associated with notably poor psychosocial functioning and quality of life (Phillips, 2000; Phillips, Menard, Fay, & Pagano, 2005a; Phillips, Quinn, & Stout, 2008), as well as a high rate of suicidal ideation and suicide attempts (Veale et al., 1996; Phillips et al., 2005b; Phillips, 2007).

Available data, while limited, suggest that BDD is familial. A study of 200 probands with DSM-IV BDD, which used the family history method, found that 20.0% of probands had at least one first-degree relative with BDD and that 5.8% of all first-degree relatives had BDD (Phillips, Menard, & Fay, 2005c). This rate is higher than the community prevalence of 1.7–2.4% reported in the most methodologically rigorous studies to date (e.g., Buhlmann et al., 2010; Koran et al., 2008). No adoption or twin studies have been done, but it is likely that, like other psychiatric disorders, BDD has a genetic basis. A recent twin study of 3544 females from the St. Thomas UK Twin Registry examined the heritability of "dysmorphic concern" (Monzani et al., 2012a), a construct that considerably overlaps with DSM-IV BDD. Monzani et al. (2012a) reported that genetic factors accounted for approximately 44% of the variance in body dysmorphic concern. However, to our

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knowledge, the genetic basis of BDD has not been directly investigated.

BDD is widely conceptualized as an OCRD (Cohen, Stein, & Simeon, 1997; Phillips et al., 2010). Like OCD, BDD is characterized by obsessions and repetitive behaviors (e.g., mirror checking, and excessive grooming) (Phillips et al., 1993, Phillips et al., 2010). In addition, BDD and OCD are often comorbid (Conceição Costa et al., 2012; Gunstad & Phillips, 2003). Several BDD–OCD comparison studies ($n=139$ and $n=295$) found more similarities than differences between these disorders; they did not significantly differ in terms of sex ratio; most other demographic, course, and impairment variables; illness severity; or lifetime frequency of most associated disorders in probands or first-degree relatives (Phillips, Gunderson, Mallya, McElroy, & Carter, 1998; Phillips et al., 2007). In addition, several large controlled and blinded family studies found that BDD was significantly more common in first-degree relatives of OCD probands than in control probands (Bienvenu et al., 2000; Bienvenu et al., 2012). Moreover, the above-noted twin study observed that there is a 64% genetic overlap between "dysmorphic concern" and obsessive–compulsive behaviors (Monzani et al., 2012b) in a non-clinical sample. Furthermore, available treatment data indicate that BDD responds to serotonin-reuptake inhibitors (SRIs), probably preferentially (Hollander et al., 1999; Phillips & Hollander, 2008).

This study is to our knowledge the first to directly examine the genetic basis of BDD. Because of BDD's similarities to OCD, we tested a total of 10 polymorphisms in nine genes in the serotonin, dopamine, glutamatergic, and gamma-aminobutyric acid (GABA) systems (Table 1), all of which have been implicated previously in OCD (Pauls, 2010; Pauls, Abramovitch, Rauch, & Geller, 2014; Taylor, 2013). The concept of OCD as a genetic disorder is now broadly accepted (Nicolini, Arnold, Nestadt, Lanzagorta, & Kennedy, 2009; Pauls et al., 2014). Given that SRIs are the first-line treatment of OCD and also appear preferentially efficacious for BDD, serotonergic system genes were investigated. We were also interested in dopamine system genes because BDD patients often present with psychotic symptoms; the appearance beliefs of more than one-third of this population are currently delusional, and one third experience delusions of reference related to their supposed disfigurement (Phillips, 2004b; Phillips, Hart, Simpson, & Stein, 2014). In addition, glutamatergic system genes have been robustly implicated in OCD (Arnold et al., 2004; Mattheisen et al., 2014; Stewart et al., 2013a, 2013b) and, therefore, we also included the glutamate (N-methyl-D-aspartate NMDA) subunit receptor gene (*GRIN2B*). We also explored the association between these genes and response to treatment with an SRI.

2. Methods

Fifty individuals with DSM-IV BDD participated in the study. Subjects were excluded if they had a metabolic or neurologic disease by history, schizophrenia, or schizoaffective disorder. All subjects met DSM-IV criteria for lifetime BDD based on the Structured Clinical Interview for DSM-IV (SCID-IV; First, Spitzer, Gibbon, & Williams, 2002). Thirty-eight subjects with primary BDD (i.e., BDD was the primary reason for seeking consultation or treatment) were obtained from the BDD specialty clinical and research program at Butler Hospital (Brown University). An additional 19 subjects were recruited from an ongoing study of the genetics of OCD at the Centre for Addiction and Mental Health (CAMH). The BDD sample from Butler Hospital consisted of 57.9% females and was 94.7% Caucasian [$N=36$], 2.6% Asian [$N=1$], and 2.6% African American [$N=1$], with a mean age of 35.7 ± 12.0 years; 35.5% had comorbid lifetime OCD. Due to poor DNA quality, seven subjects from Butler Hospital were excluded; 31 were therefore included in analyses. The BDD sample from CAMH comprised 66.7% females and 84.2% Caucasian [$N=16$], 10.5% East Indian [$N=2$], and 5% Chinese [$N=1$], with a mean age of 30.5 ± 7.6 years. All of the CAMH subjects had DSM-IV OCD in addition to BDD. The 50 BDD subjects (31 from Butler Hospital and 19 from CAMH) were individually matched for ethnicity and gender to 50 healthy controls. Controls were collected by advertisement in the Toronto area; they were screened for lack of major psychiatric disorders with the SCID, a semi-structured interview for determining the major DSM-IV Axis I diagnoses. The study was

Table 1
Genotype and allele frequencies in selected candidate genes in body dysmorphic disorder.

Marker	Location	Genotyping reference	Chi Square (1)	*p* Value
GABA				
GABRG2 (*GABA$_A$-γ2*) (*NciI*)	5q31.1-q33.2	Sander et al., 1999	Allelle=5.258	Allele=0.022
rs211013		Richter et al., 2009	Genotype=8.895	Genotype=0.012
Serotonin				
SLC6A4 (*5HTT*)-*LPR*	17q11.1-q12	Heils et al., 1996	Allelle=3.402	Allelle=0.065
Microsatellite			Genotype=5.485	Genotype=0.064
SLC6A4 (*5HTT*)-VNTR	17q11.1-q12	Cook et al., 1997	Allelle=1.649	Allelle=0.438
Microsatellite			Genotype=1.645	Genotype=0.889
HTR1B (*5HT1D-ß*) (*HincII*)	6q13	Lappalainen et al., 1995	Allelle=1.270	Allelle=0.260
rs6296		Mundo et al., 2002	Genotype=2.198	Genotype=0.333
HTR1A-(CA)n	5q11.2-q13	Bolos & Goldman, 1993	Allelle=0.003	Allelle=0.6183
Microsatellite			Genotype=0.003	Genotype=0.61
TPH (*BfaI*)	11p15.3-p14	Bellivier et al., 1998	Allelle= 0.017	Allelle=0.895
rs1800532			Genotype=0.299	Genotype=0.861
Dopamine				
DRD4-(exon 3)-VNTR	11p15.5	Lichter et al., 1993	Allelle=4.537	Allelle=0.338
Microsatellite			Genotype=0.102	Genotype=0.334
DRD5 (*AlwNI*)	4p16.1-p15.3	Hawi et al., 2003	Allelle=0	Allelle=0.997
rs1967551			Genotype=0.435	Genotype=0.805
DAT1-VNTR	5p15.3	Vandenbergh et al., 1992	Allelle=1.534	Allelle=0.216
Microsatellite			Genotype=2.317	Genotype=0.314
Glutamate				
GRIN2B (*BstYI*)	12p12	Arnold et al., 2004	Allelle=0.348	Allelle=0.555
rs890			Genotype=0.869	Genotype=0.648

(1) df: allele=1, genotype=2, except for *5-HTT*-VNTR (allele=2, genotype=3) and *DRD4* (allele=4, genotype=8).