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Review

Genetic modulation of borderline personality disorder: Systematic review and meta-analysis

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ABSTRACT

Borderline personality disorder (BPD) is a highly prevalent psychiatric disorder with high morbidity and mortality. Early theories ascribed an environmental etiology of BPD, but growing evidence supports a genetic vulnerability as well. The primary aim of this study was to systematically review genetic association studies focused on BPD. PubMed, ISI Web of Knowledge and PsycINFO databases were searched for studies published until December 2012. Meta-analyses were also performed when three or more studies reported genetic data on the same polymorphism. Data were analyzed with Cochrane Collaboration Review Manager Software (RevMan, version 5.0). Quality and publication bias were assessed.

The systematic review of association studies examining genetic polymorphisms and BPD produced conflicting results. Meta-analyses were performed for three serotonergic polymorphisms: two common polymorphisms of the serotonin transporter gene (SLC6A4), the promoter insertion/deletion (5-HTTLPR) and the intron 2 VNTR (STin2 VNTR), and the rs1800532 (A218C) polymorphism of the tryptophan hydroxylase 1 gene (TPH1), all showing no association.

No direct role of genetic polymorphisms was found in BPD. However, a few studies only are present in literature to draw definite conclusions. Further studies focusing on gene × gene and gene × environment interactions are needed to more deeply dissect the genetic role in the modulation of BPD.

1. Introduction

Borderline personality disorder (BPD) is a severe mental disorder, affecting about 1–2% of the general population, up to 10% of psychiatric outpatients and 20% of psychiatric inpatients (Torgersen et al., 2001). It is characterized by a heterogeneous symptomatology, with unstable and intense relationships, impulsive behaviors, and extreme dysregulation of mood and emotions. BPD patients experience significant functional impairment and show a high rate of substance abuse/dependence disorders. Moreover, nearly all patients have experienced suicidal ideation and about 10% committed suicide, a rate almost 50 times higher than in the general population (APA, 2000).

BPD etiology is complex and could be explained by several factors. Early theories recognized that environmental factors can induce dysfunctional behaviors, which might cause emotional dysregulation and impulsivity (Lieb et al., 2004). Among environmental factors involved in BPD etiology, sexual or physical abuse and parental divorce, loss or illness are identified as the most common ones (Links et al., 1988; Ogata et al., 1990; Shearer et al., 1990; Westen et al., 1990; Zanarini et al., 1989, 1997). Moreover, stressors early in development or for long periods of time are more likely to affect the development of particular personality traits than those later in life (Schmahl et al., 2002). However, not all individuals who have experienced serious life events (SLEs) develop BPD (Collishaw et al., 2007). Fossati et al. (1999), in their meta-analysis, reported a modest overall effect size only ($r = 0.28$) of childhood sexual abuse in BPD and Goodman and Yehuda (2002) estimated that 40–70% of BPD patients have a history of childhood trauma.

Growing evidence supports a genetic vulnerability as well (Kendler et al., 2008). In particular, a genetic predisposition to impulsivity and harm avoidance might contribute to an individual vulnerability to BPD (Siever et al., 2002). Focusing on genetic features, the BPD morbidity risk in first-degree relatives is 11.5% (Nigg and Goldsmith, 1994). In twins, BPD concordance rates are 35% in monozygotic and 7% in dizygotic twin pairs (Torgersen, 2000).

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Moreover, genetic and common environmental effects accounted for approximately 60% and 10% of the variance in liability, respectively (Torgersen et al., 2000).

BPD polymorphic symptomatology has been related to dysfunctions in neurotransmitter systems including serotonin, dopamine and norepinephrine (for reviews see: (Gurvits et al., 2000; Silk, 2000; Skodol et al., 2002)). Possible associations between genetic polymorphisms and BPD have been investigated with several genes of different neurotransmitter systems: serotonergic system: serotonin transporter (5-HTTLPR), tryptophan hydroxylase 1 (TPH1) and 2 (TPH2), serotonin receptors (HTR1A, HTR1B, HTR1D, HTR2A, HTR2C, HTR3A); dopaminergic system: dopamine transporter (DAT1), dopamine receptors (DRD2, DRD4), tyrosine hydroxylase (TH); and other candidate genes involved in different systems: monoamine oxidase A (MAO-A), catechol-O-methyltransferase (COMT), brain-derived neurotrophic factor (BDNF), arginine vasopressin receptor 1A (AVPR1A) and the sodium channel, voltage-gated, type IX, alpha subunit (SCN9A).

The primary aim of this study was to review all research evidence that has focused on the association between any genetic polymorphism and BPD. Moreover, we performed meta-analyses including the collected data on the association between genetic polymorphisms and BPD when at least three studies for each polymorphism were available for inclusion.

2. Methods

2.1. Search strategy

An electronic search of the literature was performed to identify association studies investigating the potential influence of any genetic polymorphism on BPD. PubMed, ISI Web of Knowledge and PsycINFO databases were used to search articles published until December 2012, using the term combinations “polymorphism” or “gene” and “borderline personality disorder” or “BPD”. We also examined reference lists from identified studies and reviews to find additional articles.

2.2. Study selection

Two reviewers (F.G. and R.C.) independently screened searches to identify potentially relevant studies. The full text was obtained and evaluated to detect pertinent studies.

Regarding the review, association studies were included if: 1) they analyzed the association between any genetic polymorphism and BPD or BPD traits; 2) they were published studies; 3) they were written in English. For each study, the following information was extracted: first author, publication year, diagnostic status, sample size, genes, polymorphisms, location/ethnicity, female rate, mean age, assessment scales, main results (Table 1). Studies were not taken into account if they did not exclude patients with: 1) psychotic disorder; 2) current active substance dependence disorder; 3) evidence of dementia or other irreversible organic brain syndromes.

We performed meta-analytic calculations when three or more studies reported genetic data of the same polymorphism. Studies were included in the meta-analysis if: 1) they were genetic association studies evaluating the association between genetic polymorphisms and BPD in adult patients; 2) BPD patients were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders IV edition criteria; 3) they showed genotypic or allelic frequencies; 4) they were published studies; 5) they were written in English. Studies were excluded if: 1) they were performed in non-clinical samples; 2) they focused on BPD traits but not on BPD diagnosis. For each selected study, genotype and/or allelic frequencies were extracted.

The quality of the included studies has been evaluated using two methods: we firstly evaluated studies’ adequacy in four key areas (methodological, clinical, genetic, and statistical); secondly, studies were screened with the use of a scale explicitly validated for the quality assessment of case-control studies, the Newcastle–Ottawa Scale (Wells et al., 2004).

2.3. Considered genes

2.3.1. Serotonergic system

2.3.1.1. Serotonin transporter. The serotonin transporter (5-HTT) is encoded by the SLC6A4 gene, positioned on chromosome 17q11.1-q12. A functional insertion/deletion polymorphism in the promoter region (5-HTTLPR) yields a long (L) or a short (S) allele with different transcriptional activity. In particular, the S allele reduces serotonergic expression, binding and reuptake (Collier et al., 1996). Interestingly, allele frequencies of this variant are different between Caucasians and Asians: the S allele is present in 42% of Caucasians and in 79% of Asians. Furthermore, an A/G single nucleotide polymorphism (SNP) (rs25531) in the L variant, dividing it into La and Lg (Nakamura et al., 2000), was found to modulate 5-HTTLPR expression, with Lg allele being equivalent to S allele in expression. Lg and S are thus reclassified as S′ and La as L′. These two polymorphisms form a multimarker genotype (triallelic) commonly used in research involving this locus.

In our meta-analysis, participants were grouped according to the presence or absence of the SS or S′S′ genotype (versus SL and LL or S′L′ and L′L′ genotypes). Secondary outcomes were the BPD biallelic and tri-allelic 5-HTTLPR frequencies separately considered.

Another common serotonin transporter polymorphism is a variable number tandem repeat in intron 2 (STin2 VNTR), which has several alleles: STin2.7, STin2.9, STin2.10, STin2.11 and STin2.12. Although its biological function is still unclear, it was found to be involved in the transcriptional regulatory pathways of the serotonin transporter (Lesch et al., 1994) with the 12 repeat allele acting as a stronger enhancer than the 10 repeat one (Fiskerstrand et al., 1999). Moreover, it seemed to be in linkage disequilibrium with 5-HTTLPR in different populations (Gelernter et al., 1999). In the meta-analysis, participants were grouped according to the presence or absence of the 12/12 genotype (versus 9/10, 9/12, 10/10, 10/12).

2.3.1.2. Tryptophan hydroxylase. Tryptophan Hydroxylase (TPH) gene variants are supposed to be related to pathogenesis events involving dysfunction of the serotonergic system, since TPH is the rate limiting enzyme in the biosynthesis of 5-HT. TPH has two isoforms coded by TPH1 and TPH2 genes.

TPH1 gene is located on chromosome 11p15.3-p14 (Craig et al., 1991). A biallelic SNP on position 218 (rs1800532, A218C) is located in intron 7 and is in strong linkage disequilibrium with TPH1 A779C (Nielsen et al., 1997). Lower levels of cerebrospinal fluid (CSF) concentrations of 5-Hydroxyindoleacetic acid (5-HIAA) have been found in healthy male volunteers with the TPH1 A allele (Jonsson et al., 1997), suggesting a role of this polymorphism in the regulation of serotonin turnover rate.

In the meta-analysis, participants were grouped according to the presence or absence of A allele (only allelic data were available in all the studies).

The TPH2 gene is located on chromosome 12q21.1 and codes for the rate-limiting enzyme in the biosynthesis of serotonin in the central nervous system (Haghighi et al., 2008).

2.3.1.3. Serotonin receptors. The serotonin 1A receptor (5-HT1A) gene (HTR1A) is located on chromosome 5q11.2-13. The rs6295 polymorphism (C1019G) in the promoter region has been found to be associated with an altered HTR1A expression and function