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Rapid Communication

The HLA-G low expressor genotype is associated with protection against bipolar disorder

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ABSTRACT

Implication of immune processes in bipolar disorder (BD) has recently gained increasing attention. Tolerogenic molecules, among which HLA-G plays a prominent role, mediate the modulation of such processes. The HLA-G locus is characterized by a high number of polymorphisms including a functionally relevant 14 base pair (bp) insertion/deletion (Ins/Del) allele affecting the HLA-G expression. Here, we analyzed the distribution of this polymorphism in 561 BD patients and 161 healthy and found that the HLA-G 14bp Ins/Ins genotype was significantly more prevalent in healthy controls than in patients (corrected p; $pc = 0.032$) and that the prevalence of such protective genotype is lower among patients born during the winter season as compared to those born in other periods ($pc = 0.006$). Possible mechanisms between low HLA G expression and resistance to infections as well as potential relationships between infections in early life and susceptibility to BD are discussed.

1. Introduction

Bipolar disorder (BD) is a common severe mental illness ranked as the 4th leading cause of disability, affecting 1–4% of the population worldwide [1]. Although the pathogenic mechanism remains elusive, BD is recognized as a multifactorial disorder involving interactions between multiple genetic and environmental factors [2,3]. The reported heritability ranges from 60% to 85% indicating that genetic factors are important in the etiopathology of the disorder [4] while the significance of environmental factors is highlighted by a concordance rate of only 40–70% among monozygotic twins [5]. Moreover, patients with bipolar disorder show excess of winter births (5.8%) possibly associated with early-life environmental infective insult [6]. Further accumulating evidence pinpoints towards an immunological substratum encompassing both the innate and adaptive immunity in the etiopathology of BD [7,8]. Indeed, the existence of a chronic low-grade inflammation in BD patients both during acute episodes and euthymia is evidenced by the elevated plasma levels of various proinflammatory factors [7]. Although no specific gene influencing immune dysregulation in BD has been identified, genetic association between a TNF alpha promoter variant and mood disorders

Abbreviations: Bp, base pair; BD, bipolar disorder; CTLA4, cytotoxic T lymphocyte antigen 4; CI, confidence interval; EBV, Epstein-Barr virus; CMV, cytomegalovirus; HSV, Herpes simplex virus; HERV-W, human endogenous retrovirus-W; HTLV-1, human T cell leukemia/lymphoma virus type 1; GWAS, genome-wide association studies; miRNAs, microRNAs; OR, odds ratio; PCR, polymerase chain reaction; Treg, regulatory T cells; sHLA-G, Soluble HLA-G.

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including BD that range from clinical conditions close to symptoms of depression (“vital exhaustion” syndrome) to late life depression and BD has been reported [9–11]. Such immune dysfunction is further strengthened by the preferential association of BD with organ-specific auto-immunity, in particular thyroiditis [12–14]. Potential contribution of infections in the pathogenesis of BD is exemplified by the association between Borna and Herpes simplex virus (HSV) infections and the incidence rate of BD incidence rate [15,16], although recently contested concerning Borna virus [17]. In addition, genome-wide association studies (GWAS) demonstrated a significant genetic association of the major histocompatibility complex (MHC) regions with BD [18,19]. Altogether these findings raise the possibility that impaired immune regulation could be central to the pathogenesis of BD, at least in a subset of BD patients and common genetic variations in the immune regulatory genes of the MHC region may be associated with the genetic susceptibility to and/or resistance against BD.

Among the pivotal modulators of immune function, the human leukocyte antigen-G (HLA-G) molecules are of particular interest because of their various immunosuppressive/immune tolerogenic properties [20–22]. Belonging to the non-classical HLA-class Ib family and encoded by a locus mapped telomeric to HLA-A gene, the HLA-G molecules are structurally similar to their HLA classical counterparts, yet are distinct by their limited tissue distribution in physiological conditions, diversity of their protein isoforms [membrane-bound and soluble isoforms (sHLA-G)] and a unique pattern of polymorphisms in the non-coding regions especially within the promoter and the 3′-untranslated regions (3′UTR) [23,24]. As identified to date, HLA-G gene presents a limited number of exonic polymorphisms with 46 alleles accounting for 15 protein variants (IMGT/HLA sequence database). Each of these alleles bears either a 14-base pair (bp) insertion (Ins) or deletion (Del) polymorphism in the 3′UTR that influences the HLA-G expression. Indeed, the 14bp Ins allele was demonstrated to be associated with low levels of both HLA-G mRNA and circulating sHLA-G isoforms [25,26] and hence we denominated it as “low expressor” allele [27]. Reduced expression of HLA-G has been predicted to compromise the efficacy of the process of immune tolerance.

Disease association studies implicating the HLA-G locus included a variety of clinical entities viz gestational complications, auto-immunity, infections, cancers and post-transplantation complications [24,27]. But, to our knowledge, its potential implication in psychiatric disorders has not been explored so far. Given the immune dysfunctional phenotypes of BD, we investigated, in a case/control study, if the functionally relevant 14bp dimorphism of the HLA-G gene is associated with BD.

2. Subjects and methods

2.1. Sample composition

Five hundred and sixty-one BD patients meeting DSM-IV criteria [28] for BD (type I or II), consecutively admitted to three French university-affiliated psychiatry departments (Paris-Créteil, Bordeaux and Nancy), were interviewed by trained psychiatrists, using the French version of the Diagnostic Interview for Genetic Studies (DIGS version 3.0) [29]. All patients were euthymic at inclusion (i.e. having a Montgomery–Asberg depression rating scale [30] score and a mania rating scale [31] score no more than five. The mean age of the patient cohort is 22 years (range: 16–67). A set of demographic and/or clinical variables (Table 1) was taken into account and recorded while diagnosing the patients. One hundred and sixty-one ethnically matched healthy controls, with a mean age of 43 years (range: 19–64), were recruited from blood donors at the Pitié-Salpêtrière and Henri Mondor Hospitals (France) and interviewed with the DIGS for personal history of psychiatric disorders and about family history using the National Institute for Mental Health Family Interview for Genetic Studies [32]. Only those, with neither personal nor family history (first degree) of psychiatric disorders, affective disorders or suicidal behavior were included. All patients and controls were of French descent, with at least three grandparents from mainland France. Written informed consent was obtained from all participating subjects and the institutional ethical committee approved the research protocol. The present study stems from a larger National French program called “Genes and Bipolar Disorders” which started in February 2006 and is still ongoing. All patients and controls included in the present study were consecutively recruited between February 2006 and January 2010.

Table 1
Demographic and clinical characteristics of study subjects.

Mean age (years, y)	22y (range: 16–67)	43y (range: 19–64)
Sex		
Male	42% (211)	62% (99)
Female	58% (292)	38% (62)
Season of birth*	*n* = 503	*n* = 161
Winter	23% (115)	23% (36)
Spring	27% (134)	25% (40)
Summer	22% (113)	26% (42)
Autumn	28% (141)	26% (43)
Thyroiditis*	*n* = 494	*n* = 161
Yes	15% (73)	
No	85% (421)	100%
Positive family history for BD*	*n* = 490	
Yes	73% (359)	
No	27% (131)	100%
Suicidal behavior*	*n* = 499	
Yes	32% (158)	
No	68% (341)	100%
Violent suicide*	*n* = 496	
Yes	11% (53)	
No	89% (443)	100%
Polarity of the first episode*	*n* = 490	Not concerned
Manic	24% (115)	
Depressive	62% (305)	
Hypomanic	10% (49)	
Mixte episode	3.5% (18)	
Others	0.5% (03)	

* Phenotype data were not available for the whole cohort.

2.2. HLA-G genotyping

Genomic DNA was extracted from EDTA-treated peripheral blood samples using a standard salting out procedure. The 14-bp Ins/Del polymorphism (rs66554220) in the exon 8 encoding the HLA-G 3′ UTR was genotyped as previously described [33]. Briefly, after polymerase chain reaction (PCR), amplified products were size-discriminated by agarose gel electrophoresis with appropriate controls of known HLA-G genotypes that had previously been characterized by nucleotide sequencing. Alleles having the 14bp sequence in exon 8 were termed HLA-G 14pb Ins whereas those without, HLA-G 14pb Del.

2.3. Statistical analysis

Comparisons of genotype and allele frequencies between patients and controls were performed using the Chi-square testing with Yate’s correction or Fisher exact test whenever appropriate. *p* values (two tailed) were corrected (*pc*) using the Bonferroni method and findings considered statistically significant for *pc*