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The role of immune genes in the association between depression and inflammation: A review of recent clinical studies

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ABSTRACT

The role for dysregulation of the immune system in the pathogenesis of depressive disorder is well established, and emerging research suggests the role of an underlying genetic vulnerability. The purpose of this review is to summarize the existing literature on the genetic variants involved in neurobiological pathways associated with both immune activation and depression.

Using PubMed, Scopus, The Cochrane Library, Embase, Ovid of Medline, PsycINFO and ISI web of Knowledge, we selected 52 papers which are relevant for this literature review.

Findings across the literature suggest that functional allelic variants of genes for interleukin-1beta (IL)-1β, tumor necrosis factor-alpha (TNF-α) and C-reactive protein (CRP), as well as genetic variations affecting T-cell function, may increase the risk for depression. Moreover, single nucleotide polymorphisms (SNPs) in the IL-1β, IL-6 and IL-11 genes, and in those regulating T-cell function may be associated with reduced responsiveness to antidepressant therapy. There is also some evidence indicative of a role of genetic variants of the enzymes, Cyclo-oxygenase2 (COX-2) and Phospholipase2 (PLA2), in the aetiology of depression. Finally, SNPs in genes related to the serotonin pathway may play a fundamental role in the shared genetic liability to both immune activation and depressive symptoms.

Our review confirms that genetic variants influence the biological mechanisms by which the innate immune system contributes to the development of depression. However, future studies are necessary to identify the molecular mechanisms underlying these associations.

1. Introduction

Depressive disorder is a multi-factorial and complex disease, the aetiology of which is not well understood. However, the role for dysregulation of the immune system in the pathogenesis of the disease is well established (Miller et al., 2009; Pollak and Yirmiya, 2002; Zunszain et al., 2011a). Emerging research suggests that the biological mechanisms involved in the relationship between immune activation and depression could be influenced by underlying genetic vulnerability.

A variety of studies have reported increased levels of inflammatory cytokines and their soluble receptors in peripheral blood and cerebrospinal fluid (CFS) of patients with major depression. In addition, patients with major depression have been found to exhibit elevations in peripheral blood concentrations of acute phase proteins, chemokines, adhesion molecules, and inflammatory mediators such as prostaglandins (Raison et al., 2006). Furthermore, recently it has been suggested that elevations of cytokines are actually reflected in the brain itself. Microarray mRNA expression analysis conducted on post-mortem brain tissue samples, from Brodmann area 10 (BA-10) in the prefrontal cortex of depressed patients, has shown up-regulation of a variety of pro- and anti-inflammatory cytokines, including interleukins (IL)-1α, IL-2, IL-3, IL-5, IL-8, IL-9, IL-10, IL-12A, IL-13, IL-15, IL-18, interferon-gamma (IFN-γ), and lymphotoxin-alpha (Shelton et al., 2011). Similarly, a study of teenage suicide victims has shown that the mRNA and protein expression levels of IL-1β, IL-6, and tumor necrosis factor-alpha (TNF-α) were significantly increased in BA-10 of suicide victims compared with normal control subjects (Pandey et al., 2011).

Twin studies have shown that both phenotypes (depression and increased immune activation) are heritable, and that the link between immune activation and depression, at least in part, is due to shared genes regulating immune function and inflammatory response. For example, in a sample of predominantly healthy twins, Su et al., (2009a) found a robust correlation between the severity of depressive symptoms and increased plasma levels of IL-6 and of C-reactive protein (CRP). Furthermore, genetic modelling established

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a significant genetic correlation between IL-6 and depressive symptoms, indicating that about 66% of the covariance could be explained by shared genetic factors (Su et al., 2009a). In a sample of twins with a history of Major Depressive Disorder (MDD), Vaccarino and colleagues (2008) found higher levels of myeloperoxidase (MPO) (Vaccarino et al., 2008), an enzyme produced by activated leukocytes, during the innate immune response (Nauseef, 2001). They also found that, among dizygotic MDD-discordant twin pairs, twins with MDD had 77% higher MPO than their brothers without MDD.

In the last 10 years it has been observed that functional polymorphisms in the promoter region of regulatory genes predict phenotypes of interest in interaction with predisposing behavioural or biological factors (Caspi et al., 2003; Manuck et al., 2004). Since it has been established that polymorphisms in inflammation-related genes are associated with increased secretion or expression of inflammatory biomarkers, there is a growing body of evidence investigating a relationship between single nucleotide polymorphisms (SNPs) in cytokine genes and the risk of depressive disorder. At present, the most promising findings for candidate genes or SNPs related to depression have come from GWASs. One candidate gene for TNF-α and two other candidate genes for dendritic nuclear protein-1 (DCNP-1) and neuropeptide Y (NPY) have been confirmed (Bosker et al., 2011). These genes have important immunological functions and recently, it has been suggested that such risk alleles for depression may in fact serve an adaptive purpose as they also encode for a host of immunological and behavioural responses (Raison and Miller, 2012).

This review synthesizes the current literature on the genetic variants involved in neurobiological pathways associated with both immune activation and depression. We focus on the relationship between genetic polymorphisms of immune activation-related genes and the risk for the most prevalent depressive disorders, including Major Depressive Disorder (MDD), Major Recurrent Depression, Dysthymia, Childhood Onset Major Depression and Geriatric Depression. In addition, we have included studies examining the prevalence of depression in subjects with medical illnesses such as cardiac diseases, cancer, and those receiving cytokine therapy such as interferon-alpha (IFN-α). Showing a common genetic substrate for depression and immune activation would be of substantial scientific and clinical interest, as it might help illuminate the mechanisms by which the innate immune system contributes to the development of depression. This is the first attempt, to the best of our knowledge, to summarize the existing literature on the genetic variants within key elements of the relationship between immune activation and depression.

2. Methods

This review encompasses the literature published between 2000 and 2012. We limited our review to these years in order to best characterize current thinking about the genetic relationship between immune activation and depression, and to include studies using methods which are considered standard today.

The literature reviewed was identified through the following sources: PubMed, The Cochrane Library, Scopus Embase, Ovid of Medline, PsycINFO and ISI web of Knowledge. We considered case-control, prospective, twin/family-based association and genome-wide association studies. In addition we included pharmacogenetic studies to better understand the mechanisms involved in the relationship between immune activation and depression in relation to antidepressant response. Keywords included the following: "gene" or "genes" or "single nucleotide polymorphisms" or "SNPs"; "depression" or "depressive disorder"; and "inflammation" or "inflammatory cytokine" or "interleukin" or "interferon-α treatment" or "CRP". Papers concerning animal models were excluded. The search was also limited to English-language studies. We selected a total of 48 papers and checked the references from all of these to add 4 further articles, obtaining a total of 52 papers.

3. Results

This review covers 52 papers in which 27 are case-control studies. Numerous studies have tested more than one genetic variant.

We will begin with an examination of the existing evidence on the contribution that polymorphisms in pro- and anti-inflammatory cytokine genes, T-cell-function genes, and C-reactive protein (CRP) gene, make to susceptibility to depressive disorder and antidepressant response. We then describe the evidence for a relationship between genetic variations in enzymes involved in immune activation and oxidative stress, and depressive disorder. Finally, we conclude with a description of the evidence for genetic influences within key elements of the serotonin pathway. The latter were included because of the direct pathophysiological links between immune activation and serotonergic function.

3.1. Pro- and anti-inflammatory cytokines genes

We identified 34 studies which examined polymorphisms in pro- and anti-inflammatory cytokine genes, these are summarized in Table 1.

3.1.1. Interleukin-1 beta (IL-1β)

A large number of studies have examined the C-511T polymorphism. The first genetic study of C-511T polymorphism was conducted by Yu et al., (2003a), in a sample of 157 patients with MDD and 112 controls. No significant difference in either genotype or allelic distribution was found between the two groups. However, a subgroup of MDD patients who were homozygous for the "low producer", −511C allele, were found to have higher depressive symptom severity and a less favourable response to fluoxetine treatment when compared with −511T carriers (Yu et al., 2003a). In line with this report, Tadic et al. (2008) demonstrated that the IL-1β −511(C/C) genotype showed a slower and less pronounced response to paroxetine than patients with the IL-1β −511(C/T) or −511(T/T) genotype. In contrast, no association was found between the IL-1β C-511T gene variant and mirtazapine treatment response (Tadic et al., 2008). In a Chinese population, neither an association between geriatric depression and IL-1β −511(C/T) polymorphism, nor a genetic effect of this −511(C/T) polymorphism on depression severity, was found (Hwang et al., 2009). However and again confirming a somehow worse outcome in these subjects, depressed patients carrying the C/C genotype showed a significantly earlier age of onset of depression (7 years) compared with depressed subjects who were C/T heterozygous or homozygous for the T allele. Furthermore, the authors did not find any effect of the IL-1β −511(C/T) polymorphism on cognitive function in geriatric depressive subjects (Hwang et al., 2009). Similar findings were also reported in dysthymic patients, who had a higher prevalence of the −511C allele compared with controls (Fertuzinhos et al., 2004). On the other hand, an association was found between the IL-1β −511T variant and depressive symptoms in subjects with Alzheimer's disease (McCulley et al., 2004) and schizophrenia (Rosa et al., 2004).

Recently, in addition to −511(C/T), a polymorphism in the promoter region of the IL-1β gene, at position −31(T/C) (rs1143627), has been investigated in patients with major recurrent depression. Correspondence analysis revealed that a combination of genotype T/T for polymorphic site −31 and genotype C/C at position −511 was associated with the major recurrent depression group, while

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