Neuroscience and Biobehavioral Reviews xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

CACNA1C rs1006737 genotype and bipolar disorder: Focus on intermediate phenotypes and cardiovascular comorbidity

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ARTICLE INFO

Article history:
Received 27 August 2014
Received in revised form 28 April 2015
Accepted 30 April 2015
Available online xxx

Keywords:
CACNA1C
Bipolar disorder
Magnetic resonance imaging
Cognition
Calcium channel blockers

ABSTRACT

Recently, multiple genome-wide association studies have identified a genetic polymorphism (*CACNA1C* rs1006737) that appears to confer susceptibility for BD. This article aims to summarize the existing literature regarding the impact of rs1006737 on functional and structural neuroimaging intermediate phenotypes. Twenty eight articles, representing 2486 healthy participants, 369 patients with BD and 104 healthy first-degree relatives of patients with BD, are incorporated. Multiple studies have demonstrated structural differences, functional differences associated with emotion-related and frontal-executive tasks, and/or differences in behavioral task performance in risk allele carriers (AA or AG). Results comparing participants with BD to health controls are generally less pronounced than within-group genetic comparisons. The review concludes with an integration of how cardiovascular comorbidity may be a relevant mediator of the observed findings, and proposes future directions toward optimized therapeutic use of calcium channel blockers in BD.

Contents

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http://dx.doi.org/10.1016/j.neubiorev.2015.04.022
0149-7634/

Table of Acronyms:

Acronym	Term
BD	Bipolar disorder
CVD	Cardiovascular disease
SNP	Single nucleotide polymorphism
SCZ	Schizophrenia
(f)MRI	(Functional) Magnetic resonance imaging
ACC	Anterior cingulate cortex
PFC	Prefrontal cortex
ACC	Anterior cingulate cortex
CBF	Cerebral blood flow
CCB	Calcium channel blocker

1. Introduction

Bipolar disorder (BD) is an impairing mood disorder, characterized by episodes of depression and mania, which affects 2–5% of adolescents and adults (Kessler et al., 2012; Merikangas et al., 2011). In addition to the direct burden of mood symptoms, BD is associated with multiple other comorbidities including high rates of substance abuse, anxiety, and cardiovascular disease (CVD) (Goldstein et al., 2009; Krishnan, 2005). Moreover, cognitive impairment across multiple domains (e.g., working memory, attention, processing speed) is evident within mood episodes and during euthymia (Goldberg and Chengappa, 2009). There is no known cause of BD, however there is substantial evidence that BD is associated with structural and functional neuroanatomic features, as well as peripheral markers of inflammation, oxidative stress, and neurotrophic factors (Berk et al., 2011; Frey et al., 2013). Despite the fact that the high degree of heritability of BD has been recognized for decades(Berk et al., 2011), only recently have molecular genetic studies provided compelling replicated evidence that specific genotypes confer risk for BD (Birmaher et al., 2009, 2013).

In 2008, two genome-wide association studies found significant associations between BD and a single nucleotide polymorphism (SNP) on the calcium channel, voltage dependent, L type, alpha 1C subunit gene (*CACNA1C*), rs1006737 (Ferreira et al., 2008; Sklar et al., 2008). Since then, studies have replicated the association between *CACNA1C* rs1006737 (henceforth, rs1006737) and BD (Fiorentino et al., 2014; Gonzalez et al., 2013; Green et al., 2013; Zhang et al., 2013). Collectively, these studies provide the strongest evidence to date for a specific polymorphism associated with BD. Nonetheless, given the modest magnitude (odds ratio approximately 1.2) of the association between rs1006737 and BD, and given similar findings in recurrent Major Depressive Disorder and schizophrenia (SCZ) (Athanasiu et al., 2010; Casamassima et al., 2010b; Gonzalez et al., 2013; Green et al., 2010, 2012; Nyegaard et al., 2010; Williams et al., 2011), rs1006737 is likely associated with symptom clusters and/or intermediate phenotypes that are salient to BD rather than with BD as a monolithic construct. rs1006737 has been positively associated both with high depression scores among BD patients as well as with psychotic BD specifically (Lett et al., 2011). Therefore, it appears that the mechanism of rs100637 acts in a complex fashion manifested through multiple symptom domains.

The question arises as to which mediating biological factors may subserve these associations. *CACNA1C* is the gene that encodes the $Ca_v1.2$ L-type voltage gated calcium channel, responsible for mediating calcium influx and subsequent depolarization of cells (Lacerda et al., 1991). Previous authors have posited that rs1006737 may mark another SNP within a large block of linkage disequilibrium (Jogia et al., 2011; Kempton et al., 2009; Perrier et al., 2011). Alternatively, because rs1006737 is intronic with no apparent impact on gene function, it may confer risk of BD through changes in gene expression or interference with normal cellular signaling (Balog et al., 2010; Gershon et al., 2013; Guella et al., 2013; Quinn et al., 2010). At this point, however, causative mediators remain uncertain.

Nonetheless, findings within these genome-wide association studies have been received with excitement by a field that is hungry for progress in the understanding of pathophysiology in BD. The primary purpose of this review is to summarize the existent literature as it relates to putative intermediate phenotypes underlying the association between rs1006737 and BD. In addition, we set out to highlight implications for intervention, and to consider the potential relevance of rs1006737 to the link between BD and vascular dysfunction.

2. Methods

Relevant published articles in English were identified using PubMed and MEDLINE (1950–July 2014). Search terms included: *CACNA1C*; and bipolar disorder or mania or manic; and imaging or functional magnetic resonance imaging (MRI) or structural MRI or brain or cognition or neurocognition. The search was supplemented by manually reviewing reference lists generated from the articles identified. Articles were selected based on their relevance to rs1006737 and BD. In addition, we selectively reviewed the literature regarding calcium channels blockers and vascular function in relation to rs1006737 and cognition. The final review incorporates 28 articles, which reflect MRI results of 2486 healthy participants, 369 patients with BD, and 104 healthy first-degree relatives of patients with BD. Furthermore, this review also reports neurocognitive task performance results from separate samples of 1290 healthy participants, 273 patients with BD and their 34 healthy first-degree relatives.

3. Results

Most psychiatric disorders, including BD, are heterogeneous and even in the best of circumstances the measurement of diagnoses and symptoms is of suboptimal reliability (Clarke et al., 2013). One approach that has recently generated progress regarding our understanding of the pathophysiology of psychiatric disorders is that of intermediate phenotypes (also described as endophenotypes) (Erk et al., 2013; Insel and Cuthbert, 2009; Yeo et al., 2014). Advances in functional and structural brain MRI have provided alternative methods for studying core phenotypes that may be more proximal to genetic contributions and that may underlie psychiatric illness (Hariri et al., 2006). Several studies have applied combined imaging-genetics approaches to better understanding the role of rs1006737 in BD, in some instances by examining patients with BD and in other instances by examining relevant intermediate MRI phenotypes in healthy adults.

3.1. Structural neuroimaging

Studies that have reported the effects of rs1006737 on brain morphology are summarized in Table 1. Several studies have found associations between rs1006737 and brain structure in healthy adults, while others have not (Erk et al., 2010). Wang et al. ($N = 55$) reported greater total gray matter volume among risk allele carrier (AA/AG) vs. GG homozygotes in the cortico-limbic frontal–temporal (Wang et al., 2011).

In another study in 77 healthy adults of British descent, Kempton et al. found increases in total gray matter without significant increase in regional gray matter among healthy risk allele carriers,

Please cite this article in press as: Ou, X., et al., *CACNA1C* rs1006737 genotype and bipolar disorder: Focus on intermediate phenotypes and cardiovascular comorbidity. Neurosci. Biobehav. Rev. (2015), http://dx.doi.org/10.1016/j.neubiorev.2015.04.022