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CACNA1C (Ca_v1.2) in the pathophysiology of psychiatric disease

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Abstract

One of the most consistent genetic findings to have emerged from bipolar disorder genome wide association studies (GWAS) is with *CACNA1C*, a gene that codes for the α_{1C} subunit of the Ca_v1.2 voltage-dependent L-type calcium channel (LTCC). Genetic variation in *CACNA1C* have also been associated with depression, schizophrenia, autism spectrum disorders, as well as changes in brain function and structure in control subjects who have no diagnosable psychiatric illness. These data are consistent with a continuum of shared neurobiological vulnerability between diverse—Diagnostic and Statistical Manual (DSM) defined—neuropsychiatric diseases. While involved in numerous cellular functions, Ca_v1.2 is most frequently implicated in coupling of cell membrane depolarization to transient increase of the membrane permeability for calcium, leading to activation and, potentially, changes in intracellular signaling pathway activity, gene transcription, and synaptic plasticity. Ca_v1.2 is involved in the proper function of numerous neurological circuits including those involving the hippocampus, amygdala, and mesolimbic reward system, which are strongly implicated in psychiatric disease pathophysiology. A number of behavioral effects of LTCC inhibitors have been described including antidepressant-like behavioral actions in rodent models. Clinical studies suggest possible treatment effects in a subset of patients with mood disorders. We review the genetic structure and variation of *CACNA1C*, discussing relevant human genetic and clinical findings, as well as the biological actions of Ca_v1.2 that are most relevant to psychiatric illness.

Keywords

Calcium channel; *CACNA1C*; Genome wide association study; Bipolar disorder; Depression; Schizophrenia; Psychiatric genetics

1. CACNA1C in mental disorders

While a number of medications are used for the treatment of psychiatric disorders, the majority were developed based upon efficacy to reduce symptoms rather than to eliminate pathological processes. Current treatments are inadequate for many patients as recurrence is

common and the full clinical effects are often not obtained until after months of treatment. Despite these well-known inadequacies, improvements have been slow in coming largely due to a dearth of understanding regarding pathophysiology. This lack of knowledge has prevented the development of treatments specific for the underlying disease mechanisms of psychiatric illness.

Many neuropsychiatric disorders are highly heritable, indicating that genetics is certain to have a role in pathogenesis. For example, the individual heritability of bipolar disorder, major depression, and schizophrenia is estimated to be approximately 70–90%, 40–50%, and 80–85%, respectively (Cannon et al., 1998; Cardno and Gottesman, 2000; Kendler and Prescott, 1999; Kieseppä et al., 2004; McGuffin et al., 1996, 2003). There is also evidence for shared familial susceptibility between these three Diagnostic and Statistical Manual (DSM)-IV-defined disorders, and in particular between bipolar disorder and depression, and bipolar disorder and schizophrenia (Berrettini, 2003; Demjaha et al., 2011; Gottesman et al., 2010; Lichtenstein et al., 2009; McGuffin et al., 2003). These epidemiological data are supported by the more recent findings that specific genetic risk variants cross these diagnostic boundaries as well (Chubb et al., 2008; Maier, 2008; Williams et al., 2011). While there is a credible prediction that identifying susceptibility genes will eventually lead to targeted ‘cure therapeutics’ (Insel and Scolnick, 2006), there first remains a critical need to definitively identify such genes and to subsequently understand the functional consequences of the associated genetic variations (Fig. 1). However, identifying underlying susceptibility genes that are associated with psychiatric disorders in multiple populations has proven to be difficult due to a number of factors including less than adequate sample sizes, the polygenetic and multifactorial nature of the disorders, uncertainty or lack of precision in the diagnoses, and significant overlap both in terms of symptoms and likely pathophysiology as well.

However, encouraging results have emerged recently as the results of adequately powered genome-wide association studies (GWAS) have converged to implicate specific genetic polymorphisms. One gene in which such genetic polymorphisms have been identified is *CACNA1C*, which codes for the pore-forming α_{1C} subunit of the L-type voltage-gated calcium channel (LTCC), referred to as $Ca_v1.2$. $Ca_v1.2$ couples transient activation of inward calcium current to transcriptional regulation and plays an important role in dendritic development, neuronal survival, synaptic plasticity, memory formation, learning, and behavior (Barad, 2003; Dudkin et al., 1990; Kibrinsky et al., 2011; Moosmang et al., 2005; Shibasaki et al., 2010; West et al., 2001; Wheeler et al., 2008; White et al., 2008; Yoshii and Watabe, 1994).

The LTCC family consists of four distinct members referred to as $Ca_v1.1$ – $Ca_v1.4$ (Catterall, 2011). $Ca_v1.2$ is the primary LTCC expressed in the mammalian brain. In the mouse brain, quantitative polymerase chain reaction (qPCR) of RNA transcripts revealed that $Ca_v1.2$ accounts for approximately 85% of the LTCCs with $Ca_v1.3$ accounting for most of the remainder (Sinnegger-Brauns et al., 2009). A functional $Ca_v1.2$ channel consists of three subunits: transmembrane α_{1C} (*CACNA1C*) and $\alpha_2\delta$ (encoded by *CACNA2D-1*, *2* or *3*) as well as intracellular β (encoded by *CACNB1-4* genes) and calmodulin (CaM) (Dolphin, 2009). The major characteristics of the $Ca_v1.2$ channel such as voltage-sensing, ion selectivity, and pharmacological responses associated with binding of calcium channel blockers are encoded by *CACNA1C*. Auxiliary $\alpha_2\delta$, β and CaM are involved in regulation of expression and modulating select properties of $Ca_v1.2$.

There is evidence that functional mutations in the *CACNA1C* gene predispose to autism spectrum disorders. A rare human autosomal-dominant multisystem disorder, Timothy Syndrome, presenting with arrhythmias, webbed digits, congenital heart disease, and autism

spectrum symptoms is associated with a mutation in the exon 8A splice variant of *CACNA1C* that comprises about 23% of $\text{Ca}_v1.2$ in heart and brain (Splawski et al., 2004). It has been demonstrated that Timothy Syndrome is associated with the G406R mutation in the cytoplasmic end of the exon 8A-coded transmembrane segment IS6. This mutation greatly reduces voltage-dependent inactivation of the calcium channel with little effect on calcium-dependent inactivation (Barrett and Tsien, 2008), and thus may potentially cause a pathogenic calcium overload in cardiac and neuronal cells. An analogous mutation in alternative exon 8 (mutually exclusive with exon 8A), G402S, and a corresponding reduction in voltage-dependent inactivation were observed in $\text{Ca}_v1.2$ of an individual with a severe Timothy Syndrome variant (Splawski et al., 2005, 2004). Taken together, these results show pathogenic effect of naturally occurring gain-of-function mutations probably affecting $\text{Ca}_v1.2$ molecular determinant(s) of slow inactivation (Depil et al., 2011; Shi and Soldatov, 2002).

Interestingly, prior to GWA approaches *CACNA1C* was considered a potential candidate gene for bipolar disorder. As reported in 2002, *CACNA1C* was included in a family based association study (470 parent-proband trios) of 76 candidate genes and was one of two genes (the other being brain derived neurotrophic factor (*BDNF*)) where a single nucleotide polymorphism (SNP) in *CACNA1C* was found to be nominally associated with a bipolar disorder diagnosis (Sklar et al., 2002). However, the association with *CACNA1C* did not survive the confirmation analysis in a separate cohort, though the association with *BDNF* did (Sklar et al., 2002). In hindsight this lack of replication was likely related to the genotyped synonymous (silent) SNP (rs72552065) being located in exon 44, approximately 450 kb downstream from the SNPs subsequently implicated by GWA studies conducted later on.

In a manner not biased by the previous results, in 2008 Sklar et al. reported the results of a GWA study of 1461 bipolar disorder and 2008 control subjects combined with the results of the Wellcome Trust Case-Control Consortium GWA study (Burton et al., 2007), and reported that the strongest signal ($p = 1 \times 10^{-4}$) of association from these combined samples were from a SNP within the *CACNA1C* gene (rs1006737) (Sklar et al., 2008). The accepted standard for GWA significance is 5×10^{-8} (Pe'er et al., 2008). Subsequent studies with increasingly larger sample sizes have since confirmed this finding (Ferreira et al., 2008; Keers et al., 2009). See Table 1, which details the genetic evidence associating *CACNA1C* with psychiatric disorders, and includes p values for all GWA studies, as well as odds ratios. The strongest implicated SNP in these early GWA studies was rs1006737. Most recently, the results of the Psychiatric Genetics Consortium (PGC) Bipolar Working Group comparing 11,977 bipolar disorder subjects and 51,672 controls identified another SNP (rs4765913) in *CACNA1C* as the most significant finding in that study, at a significance level of $p = 1.52 \times 10^{-8}$ (Sklar et al., 2011).

Many of the studies described above utilized overlapping patient and control populations, which increased with subsequent studies. As the population size increased the strength of association increased in these studies and the first strong association with bipolar disorder was observed at rs1006737. However, subsequent GWA studies with larger population size have identified significant associations with other SNPs. Therefore, while overlapping populations in successive studies possibly contributed to identifying rs1006737 as a candidate susceptibility SNP associated with bipolar disorder, they have not always resulted in consistent replication of this particular SNP. While the inability to fully replicate specific GWAS-identified SNPs in all the studies is a concern, the consistency with which GWAS signals are identified within the same general region (intron 3) of *CACNA1C* indicates the likely importance of the gene in bipolar disorder psychopathology (Fig. 2).

The clinical genetic association of *CACNA1C* with mental disorders appears to be broader than for bipolar disorder only. Recent studies have established an association of *CACNA1C* genotype with schizophrenia (Bigos et al., 2010; Nyegaard et al., 2010) and major depression disorder (Casamassima et al., 2010b; Shi et al., 2011). Several studies have also implicated *CACNA1C* in combined analysis including distinct DSM-defined psychiatric disorders. For example, Green et al. (2010) conducted a GWAS with patients diagnosed with unipolar recurrent major depression ($N = 1196$), bipolar disorder ($N = 1868$) and schizophrenia ($N = 479$) compared to 15,316 nonpsychiatric control subjects. The authors found that the previously reported bipolar disorder risk SNP (rs1006737) conferred risk of schizophrenia and early recurrent major depression. The authors also noted that the association of rs1006737 with bipolar disorder was strengthened when they combined their data with that from the previous study by Ferreira et al. (2008). Recently, in a combined analysis of bipolar and schizophrenic ($n = 16,373$) patients compared to control ($n = 14,044$) subjects, rs4765905 located within *CACNA1C* was implicated as the top statistical hit (7.0×10^{-9}) (Ripke et al., 2011). Another recent combined analysis of bipolar disorder and schizophrenia data sets revealed significant association with *CACNA1C* SNP rs4765913 (Sklar et al., 2011). Most recently Hamshere et al. (2012), reported that rs4765905 achieved genome wide significance for an association with schizophrenia after combining additional subjects with the analysis by Ripke et al. (2011). rs4765905 is in complete linkage disequilibrium (LD), defined as the occurrence of genotypes at two loci that is significantly different than by chance alone, with rs1006737 ($D' = 1.0$, $r^2 = 1.0$; LD is denoted by D' , or a correlation coefficient r^2 , which both range from 0 to 1, with 1 indicating perfect LD) (Hill, 1974; Lewontin, 1964, 1988; Reich et al., 2001; Slatkin, 2008).

In terms of major depression, a meta analysis of two separate earlier GWA studies of bipolar and major depressive disorder patients, the *CACNA1C* SNPs rs1006737 and rs7297582 were found to reach a genome wide significance when both bipolar and unipolar mood disorders were combined (Liu et al., 2011). Further support for the involvement of *CACNA1C* in depression was provided by Dao et al. who reported that two SNPs in intron 3 (rs2370419 and rs2370411) showed significantly increased risk of illnesses in females, but not males, for bipolar and major depression disorder (Dao et al., 2010). This study used the GWAS data generated earlier from the National Institute of Mental Health-Genetics Initiative Bipolar Disorder (NIMH-GIBD) and Genetics of Recurrent Early-onset Major Depression (GenRED) consortium datasets, consisting of 2021 mood disorder cases and 1840 controls.

Thus, the results of a number of recently published studies in multiple populations have repeatedly linked polymorphisms in *CACNA1C* to multiple psychiatric disease diagnoses and indicate that associations between *CACNA1C* polymorphisms are not unique to one disorder (Table 1). The evidence implicates *CACNA1C* as currently the most statistically robust finding when combining multiple psychiatric disease categories. While the most statistically robust *CACNA1C* associations are in bipolar disorder, as compared to depression and schizophrenia, these data suggest that *CACNA1C* belongs to a class of shared susceptibility factors. These data support a conclusion that diagnostic categories are not appropriate for delineating the downstream effects of genes on behaviors.

Thus, *CACNA1C* is a common risk factor for which genetic evidence indicates that the identified intronic SNPs have significant correlation with pathological behaviors. The associated genetic changes in *CACNA1C* likely act through a common developmental and/or physiological process of central nervous system function in a manner that is common across current diagnostic categories, and at a level upstream from symptoms. Consistent with this hypothesis, as we discuss in more detail later, recent reports have associated the most consistently reported disease-associated SNP (rs1006737) with variations in brain

structure and function in psychiatrically healthy human subjects. However, the mechanisms underlying how genetic changes in *CACNA1C* modify risk for developing psychiatric disorders are unclear. Indeed, defining the implications of such *CACNA1C* genetic change in a context relevant to psychiatric disorder pathophysiology is essential.

2. *CACNA1C* genetic variation

CACNA1C is located on the short arm of chromosome 12p13.3, spanning an approximately 6.45 Mb genomic region (Gene ID 775). The gene consists of at least 55 exons (Soldatov, 1994), which span an approximately 740 kb region. A number of SNPs in *CACNA1C*, concentrated within the large 328.5-kb intron 3, have been linked to psychiatric illness (Table 1), with limited information currently available regarding functional consequences. The locations of these SNPs within the gene are detailed in Fig. 2. Given their location in a non-coding region of the gene, they are not expected to directly interfere with the structure-functional properties of Ca_v1.2 (e.g., as in the case of G402S in Timothy syndrome). However, a likely consequence of intronic variation is regulation of expression of the channel. Beginning to address these questions Bigos et al. reported an association between total expression of *CACNA1C* and a SNP in complete LD with rs1006737 in an earlier microarray based expression analysis of postmortem brains (Bigos et al., 2010). It is currently not known whether this effect is constant throughout development, and in what specific tissues or brain regions.

A few studies have assessed for an imbalance in the relative expression of the two *CACNA1C* alleles, referred to as allelic expression imbalance (AEI) (Yan et al., 2002). Estimating AEI involves measuring the relative expression of the alleles of a given gene within the same cell or the same tissue sample. This approach minimizes the non-allelic factors, such as environmental exposures, that can modify gene expression and maximizes the identification of effects caused by variation in individual alleles. While AEI for *CACNA1C* was not identified in cardiovascular tissues from transplant recipients (Johnson et al., 2008), lymphoblastoid cell lines from normal controls did show AEI at some SNPs (Quinn et al., 2010). Interestingly, these other SNPs are not in LD with SNPs identified in GWA studies (Quinn et al., 2010).

It is known that the *CACNA1C* transcript is subject to extensive alternative splicing that potentially could generate thousands of splice variants. However, complementary DNA (cDNA) cloning experiments have yielded a much more limited number of partially overlapping sequences that comprises of, at a minimum, 40 known splice variants (Tang et al., 2004; Tiwari et al., 2006) of which at least 23 are protein coding (National center for Biotechnology information database). The high degree of variation is due to several different mechanisms of alternative splicing, including splicing of exons at alternate junctions, the presence of mutually exclusive exons, exons that either splice as alternate exons or at alternate donor sites, and through utilization of alternate promoters (Abernethy and Soldatov, 2002; Dai et al., 2002; Pang et al., 2003; Perez-Reyes et al., 1990a,b).

CACNA1C is expressed in many tissues in the human body across various developmental stages (Pang et al., 2003). Its expression has been observed in embryonic, fetal, infant, and adult stages. The gene is widely expressed in the brain (especially hippocampus and thalamus), cerebral arteries, whole heart, cardiac muscle and fibroblasts (Narayanan et al., 2010; Perez-Reyes et al., 1990b; Powers et al., 1991; Schultz et al., 1993; Soldatov, 1992). Expression of the transcripts are species- and tissue-dependent, developmentally regulated and is affected by pathophysiological conditions (Barad, 2003; Brillantes et al., 1994; Feron et al., 1994; Hofmann et al., 1994; Liao et al., 2007; Obermair et al., 2004; Tang et al., 2009; Tiwari et al., 2006). The majority of known splice variation, which predominates on the 3'

end of the gene, is not in proximity to genetic changes associated with mood disorders and schizophrenia (Fig. 2). However, the diversity in phenotypes of *CACNA1C* splice variants is relevant in studying the functioning of the gene in psychiatric disorders and may have importance in understanding disease mechanisms (Wang et al., 2006). It also provides avenues to interrogate potential targets for drug development and selective modification of physiological functioning.

3. $\text{Ca}_v1.2$ calcium channel

The $\text{Ca}_v1.2$ α_{1C} subunit consists of four repeating domains (I–IV), each with six transmembrane α helical segments (S1–S6) that are connected by intra- and extra-cellular loops (Abernethy and Soldatov, 2002; Mikami et al., 1989; Tanabe et al., 1987) as well as a long C-terminus and shorter N-tail that both point to the cytoplasm. In neurons of the central nervous system, $\text{Ca}_v1.2$ channels are located primarily in the postsynaptic dendritic processes and somata, and are distributed throughout the dendritic tree (Leitch et al., 2009). This somatodendritic localization of $\text{Ca}_v1.2$ places it at a key position to couple neuronal excitation with $\text{Ca}_v1.2$ -mediated Ca^{2+} signaling that modulates gene transcription making $\text{Ca}_v1.2$ an effective regulator of signaling pathways. The widespread downstream effects of $\text{Ca}_v1.2$ and other LTCCs are achieved through CaM associated with CaM-binding sites situated in the α_{1C} C-terminal tail (Halling et al., 2005) and some other signaling molecules localized probably close to the channel pore. CaM is an essential component of the mechanism of calcium-dependent inactivation guarding against calcium overloading during long action potentials (Zuhlke et al., 1999). Other data suggest that calcium binding protein-1 (CaBP1) may also be involved in regulation of $\text{Ca}_v1.2$ activity (Oz et al., 2011; Zhou et al., 2004). A key downstream mechanism of calcium signaling is calcium-induced intracellular calcium release (CICR) through ryanodine receptors (RyR), which has been widely demonstrated in cardiac and skeletal muscle LTCCs. CICR mediated by ryanodine-sensitive stores in hippocampal and other central neurons is not affected by calcium channel blockers (Sandler and Barbara, 1999), although there is some data indicating that neuronal LTCCs may in fact mediate CICR (Kim et al., 2007; Kolarow et al., 2007).

While the full details of LTCC signaling to the nucleus are yet to be elucidated, studies have extensively linked LTCC-mediated calcium influx to the Ca^{2+} /CaM-dependent protein kinases (CaMK) cascade and the mitogen-activated protein kinase (MAPK) pathway. Immunoprecipitation studies have found that $\text{Ca}_v1.2$ is closely associated with CaMKII that is tethered to the channel by a binding site on the COOH terminus of the α_{1C} subunit in heart tissue (Hudmon et al., 2005) and to the $\text{Ca}_v\beta_1$ and β_2 subunits in forebrain tissue (Abiria and Colbran, 2010). Such molecular association may be spatially and temporally flexible because $\text{Ca}_v\beta$ subunits tend to form homo- and hetero-oligomers at the functional $\text{Ca}_v1.2$ calcium channels (Lao et al., 2010). This localization of CaMKII close to the channel has been shown to be important in integrating and coupling local calcium increases to cyclic adenosine monophosphate (cAMP) response element binding protein (CREB)-dependent gene transcription (Wheeler et al., 2008). There is also evidence that CaM bound to LTCCs is particularly effective in activating the MAPK cascade leading to sustained CREB phosphorylation (Dolmetsch et al., 2001). For example, recent work has shown that inhibition of extracellular signal-regulated kinases (Erk) 1 and 2 increases synaptic vesicle release by increasing the number of surface-bound LTCCs suggesting a mechanism by which LTCCs may be involved in modulation of synaptic transmission (Subramanian and Morozov, 2011).

One of the most robust effects of postsynaptic LTCC calcium influx is activation of CREB-dependent transcription (Bito et al., 1996; Deisseroth et al., 1998; Dolmetsch et al., 2001; Weick et al., 2003; West et al., 2001). The investigation of CREB-dependent transcriptional

regulation by the LTCC and cAMP established their role in activation of transient and stable signaling sub-microdomains of mixed and individual type (Kobrinisky et al., 2011). These discrete signaling microdomains might be differentially associated with such specialized processes as spontaneous contractions of muscle cells or the long-term changes underlying synaptic plasticity. While a number of genes are regulated by changes in free calcium generally, and CREB activity specifically, experiments show other levels of regulation. For example, BDNF is preferentially regulated by calcium influx through LTCCs when compared to calcium influx through N-methyl-D-aspartate (NMDA) receptors (Ghosh et al., 1994; Tabuchi et al., 2000). Specifically, calcium influx through LTCCs preferentially activates BDNF promoter I while BDNF promoter III is driven by LTCCs and NMDA receptors equally.

Little is known about the role of $Ca_v1.2$ during brain development, however, LTCCs in general are recognized to play a role in the development of ventral hippocampal parvalbumin containing interneurons (Jiang and Swann, 2005), as well as in calcium oscillations that occur in developing Purkinje neurons (Liljelund et al., 2000). It is worth noting that parvalbumin interneurons are reproducibly reported decreased in the brains of individual with schizophrenia (Lisman et al., 2008). Additionally, LTCCs are involved in gamma-aminobutyric acid (GABA) mediated calcium increases in embryonic hypothalamic neurons (Obrietan and van den Pol, 1995). LTCCs also mediate the increased amplitude of Ca^{2+} transients after activation of GABA-A receptors by muscimol in embryonic hypothalamic neurons after estradiol treatment (Perrot-Sinal et al., 2001), as well as the increased phosphorylation of cyclic AMP response element binding protein found in the hippocampus and hypothalamus of newborn male rats (Perrot-Sinal et al., 2003).

$Ca_v1.2$ has been associated with changes in calcium signaling and its effects in aging. For example, phosphorylation of $Ca_v1.2$ is increased in the hippocampus of aged rats, possibly accounting for the age-related increase in neuronal Ca^{2+} influx (Davare and Hell, 2003). Additionally, $Ca_v1.2$ channels have been shown in vitro to interact with amyloid precursor protein (APP), and APP deletion in mice leads to both increased $Ca_v1.2$ levels and GABAergic calcium currents in the striatum and hippocampus (Yang et al., 2009). Much work is needed to define how alterations in $Ca_v1.2$ levels and function in development and aging may progress into psychiatric dysfunctions.

4. Function of $Ca_v1.2$ in the brain circuits and behaviors of rodents

The importance of $Ca_v1.2$ channels in regulating the functions of brain circuits and behaviors has been shown through administration of LTCC agonists and antagonists, as well as using several genetic knockout approaches. A germline knockout of *Cacna1c* is embryonically lethal (Seisenberger et al., 2000), however conditional knockout and heterozygous mouse models have been successfully used. LTCCs have been found to play a role in behaviors mediated by the mesolimbic pathway. This pathway traditionally defines the ventral tegmental area (VTA) to nucleus accumbens (NAc) circuit, modulated by interactions with the hippocampus, medial prefrontal cortex, and amygdala (Pierce and Kumaresan, 2006), and is thought to be critical for reward and motivation that can be altered in mood disorders and schizophrenia (Juckel et al., 2003; Nestler and Carlezon, 2006). In rats, administration of the hydrophobic dihydropyridine LTCC antagonist isradipine dose-dependently attenuates intake of sweetened drinking water, a rewarding liquid (Calcagnetti and Schechter, 1992), as well as the reinforcing effects of amphetamine (Pucilowski et al., 1995), while nimodipine suppresses the effect of nicotine (Biala, 2003) in conditioned place preference. Additionally, there is evidence that the LTCC antagonist D-cis-diltiazem enhances the rewarding effects of cocaine in the conditioned place preference test when injected in the ventral NAc shell (Chartoff et al., 2006). In mice sensitized to

psychostimulants, increases in $\text{Ca}_v1.2$ protein levels in the frontal cortex and limbic forebrain were found (Ford et al., 2009; Shibasaki et al., 2010), as well as increased surface expression of $\text{Ca}_v1.2$ channels in pyramidal neurons of the medial prefrontal cortex (Ford et al., 2009).

$\text{Ca}_v1.2$ channels have also been shown to be important during sensitization to stimulants, a behavior mediated in part by VTA to NAc pathway. In rats sensitized to amphetamine, there is an up regulation of the $\text{Ca}_v1.2$ channel mRNA and protein in dopaminergic neurons in the VTA (Rajadhyaksha, 2004). Repeated micro-injections of LTCC dihydropyridine agonist BayK 8644 in the VTA of rats resulted in an increased behavioral response to cocaine (Licata et al., 2000), and BayK 8644-induced stimulation of LTCCs in the caudate putamen increases extracellular dopamine levels as measured by microdialysis (Okita et al., 2000). Additionally, it has been shown that peripheral administration of dihydropyridine antagonists attenuates sensitization to stimulants (Biala and Weglinska, 2004; Mills et al., 2007). Some data suggest that $\text{Ca}_v1.2$ channels are important for the behavioral expression of sensitization, but not the development of sensitization (Giordano et al., 2010; Schierberl et al., 2011).

Dysfunction of the hippocampus has been implicated in the pathogenesis of both mood disorders and schizophrenia, and may be relevant to emotional instability and hippocampal memory dysfunction observed in both disorders (Small et al., 2011). A region specific knockout of *Cacna1c* in the hippocampus and neocortex of mice leads to a loss of Shaffer collateral/CA1 late-phase long-term potentiation (LTP) (Moosmang et al., 2005). $\text{Ca}_v1.2$ channels regulate excitability, and have been linked to decreased activation of the MAPK pathway and reduced CREB-dependent transcription, in CA1 pyramidal neurons (Lacinova et al., 2008; Moosmang et al., 2005). Conditional deletion of *Cacna1c* in the hippocampus and cortex results in hippocampal-dependent behavioral changes, such as impaired spatial memory in the Morris water maze and in a labyrinth maze test (Moosmang et al., 2005; White et al., 2008).

The amygdala plays a central role in regulating fear circuits (Moosmang et al., 2005) and overall limbic system function that is implicated in neuropsychiatric illness (Krishnan and Nestler, 2010). LTCCs are known to modulate amygdala function, as well as behaviors mediated by the amygdala. For example, they have been shown to be important for long-term fear memory formation and LTP in the lateral amygdala (Bauer et al., 2002; Langwieser et al., 2010), as well as for induction of LTP in the basolateral amygdala to dentate gyrus pathway after stimulation (Niikura et al., 2004). Pharmacological inhibitors have demonstrated a role for LTCCs in presynaptic LTP at corticoamygdala synapses (Fourcaudot et al., 2009). In behavioral tests of fear memory, peripheral administration of LTCC blockers interfere with extinction, but not acquisition of fear memory (Cain et al., 2002; Suzuki et al., 2004). Administration of LTCC blockers into the ventricles or directly to the amygdala interferes with acquisition, but not extinction of fear learning (Bauer et al., 2002; Langwieser et al., 2010). Using a conditional knockout mouse model, as well as pharmacological methods, it has been shown that $\text{Ca}_v1.2$ but not $\text{Ca}_v1.3$ is the relevant LTCC genetic isoform in the thalamus-amygdala pathway (Langwieser et al., 2010). Genetically modified mice expressing dihydropyridine-insensitive $\text{Ca}_v1.2$ ($\text{Ca}_v1.2\text{DHP-/-}$) were resistant to the effects of the dihydropyridine antagonist nifedipine to impair fear extinction, suggesting a crucial role for $\text{Ca}_v1.2$ channels in fear conditioning (Busquet et al., 2008). Supporting this conclusion, the same group reported that $\text{Ca}_v1.3$ -deficient mice manifested extinction identical to the respective wild type mice (Busquet et al., 2008). Additionally, it has been found that amygdala levels of the $\text{Ca}_v1.2$ protein is increased in response to fear conditioning in rats (Shinnick-Gallagher et al., 2003). $\text{Ca}_v1.2$ channels also play a role in observational fear learning, as shown by impaired observational fear learning

in a mouse model with a selective deletion of $\text{Ca}_v1.2$ channels in the anterior cingulate cortex (Jeon et al., 2010).

Cacna1c heterozygous knockout mice, expressing decreased $\text{Ca}_v1.2$ protein levels as well as decreased LTCC current as adults, were protected against depression-like phenotypes (Dao et al., 2010). This finding, although reported in both sexes, was more robust in females. This is consistent with the finding that some SNPs in *CACNA1C* are associated with a mood disorder diagnosis only in females (Dao et al., 2010). Of potential relevance, the gonadal steroid estrogen has been reported to induce calcium influx via LTCCs in cultured hippocampal neurons in a non-genomic manner (not involving estrogen receptors) (Sarkar et al., 2008). A variety of $\text{Ca}_v1.2$ antagonists have been shown to reduce despair-like behavior similar to existing antidepressant medications (Cohen et al., 1997; Czyrak et al., 1989, 1990; Mogilnicka et al., 1987; Sinnegger-Brauns et al., 2004). Genetically modified dihydropyridine-insensitive $\text{Ca}_v1.2\text{DHP-/-}$ mice were resilient to the antidepressant-like effect of nifedipine in the forced swim test, suggesting that $\text{Ca}_v1.2$ mediates the antidepressant-like effects of LTCC antagonists (Sinnegger-Brauns et al., 2004).

Moosmang et al. (2005) reported that a conditional forebrain knockout of *Cacna1c* did not alter anxiety-like or exploratory behavior. However, while *Cacna1c* heterozygous knockout mice males showed normal performance in anxiety-related procedures, females showed increased anxiety or fewer risk taking behaviors (Dao et al., 2010). In a recent study Lee et al. (2012) showed that mice constitutively heterozygous for *Cacna1c* manifested anxiety-like behavior in the elevated plus maze test (adult females as well as adolescent males). The authors also generated forebrain specific conditional knockout mice and a prefrontal cortex specific *cacna1c* knockdown which both also resulted in increased anxiety like behavior (Lee et al., 2012). LTCC antagonists were reported to increase anxiety-like behavior in rats (Viveros et al., 1996), but the effect is apparently species-dependent, as anxiety-like behavior in mice was not affected (Biala and Kruk, 2007). Finally, it has recently been reported that mice expressing a constitutively active G406R mutation of $\text{Ca}_v1.2 \alpha_{1C}$ subunit, causative of Timothy syndrome in humans, manifested a number of behavioral changes reminiscent of autism including repetitive/perseverative behaviors, altered social interaction and ultrasonic vocalizations, and enhanced tone cued and contextual memory following fear conditioning (Bader et al., 2011).

5. Effects of *CACNA1C* on human brain function

Supporting the rodent data implicating $\text{Ca}_v1.2$ in basic brain function, a number of recent reports have associated a primary disease-associated SNP in *CACNA1C*, rs1006737, with variation in human brain function and structure in subjects who have no diagnosable psychiatric illness (Table 2). While polymorphisms in *CACNA1C* are significantly associated with bipolar disorder, depression, and schizophrenia, such genetic changes only increase probability of disease, and are not deterministic. Thus, a large percentage of the population who do not have disease also carry disease associated SNPs in *CACNA1C*, which allows for studies to dissect the effects of SNPs on brain function and structure. Specifically, multiple reports have associated rs1006737 genotype with differences in performance on a number of neuropsychological tasks in healthy control subjects. Krug et al. (2010) reported that the risk allele was associated with decreased performance on a test of semantic verbal fluency (Krug et al., 2010). The risk allele has also been associated with decreased attention-related performance in alerting and orienting as assessed with a scanner-adapted version of the Attention Network Test (Thimm et al., 2011), lower extraversion and higher harm avoidance, trait anxiety, and paranoid ideation scores as assessed via personality questionnaires, and increased startle reactivity (Roussos et al., 2011). Risk allele carriers were also reported to have manifested higher psychopathology scores for

depression, anxiety, obsessive-compulsive thoughts, interpersonal sensitivity, and neuroticism (Erk et al., 2010). Strohmaier et al. provided an interesting report of sex-specific effect of *CACNA1C* SNP rs1006737 in a large population based cohort (Strohmaier et al., 2012). In their investigation of personality traits relevant to affective disorders and schizophrenia the authors found that the risk allele of rs1006737 was significantly associated with higher sense of coherence in women. On the other hand, this allele in men was associated with lower sense of coherence, albeit statistically not significant. Overall, Strohmaier et al. observed opposite direction of effect of the genotype of rs1006737 in males and females for most of the personality traits studied in the cohort. Zhang et al. (2011) reported that the risk allele was associated with impaired working memory in schizophrenia patients and healthy controls, but not bipolar patients. Soeiro-de-Souza et al. (2012) have also recently reported that the risk allele was associated with impairment in facial emotion recognition in bipolar patients, but not in healthy controls.

Consistent with these findings, a large number of functional neuroimaging studies have revealed an association between rs1006737 genotype and brain activity in healthy controls while undertaking specific tasks. To date these findings include changes in brain activity while performing an attention network task (Thimm et al., 2011), amygdala activity during emotional processing (Jogia et al., 2011; Wessa et al., 2010), bilateral hippocampal activation during episodic memory recall and diminished functional coupling between left and right hippocampal regions (Erk et al., 2010), increased activation of the left inferior frontal gyrus as well as the left precuneus during a separate semantic verbal fluency task (Krug et al., 2010), mediotemporal emotional processing and prefronto-cortical working memory processing (Bigos et al., 2010), and reduced corticolimbic/frontotemporal functional connectivity during emotional face-processing (Wang et al., 2011). Radua et al. (2012) found that this same SNP was associated with significant modulation of effective connectivity from medial frontal gyrus to left putamen significantly reduced during perception of fearful faces, but that the effect was primarily in BPD subjects (vs. unaffected relatives and healthy controls).

Three published reports have now indicated that the rs1006737 risk allele is associated with increased brain gray matter, either total gray matter volume or in specific brain regions in healthy controls (Kempton et al., 2009; Perrier et al., 2011; Wang et al., 2011). Kempton et al. (2009) reported an increase in total gray matter volume. In a larger study with 585 individuals, Franke et al. (2010), specifically attempted to replicate these findings, but could not indicate discordance among reports. It is possible that differences in total gray matter may be reflective of changes in select brain regions, as reported by Perrier et al. (2011) where increases in right amygdala and right hypothalamus were noted. Wang et al. (2011) reported an increase in gray matter volume in select brain regions including bilateral ventral, rostral, and dorsolateral prefrontal cortex, and anterior cingulate and temporal cortices. Perrier et al. (2011) also reported that there was a significant interaction between genotype and a bipolar disorder diagnosis whereby the left putamen was smaller in bipolar patients carrying the risk allele. Additionally, it has been reported that the minor allele for three *CACNA1C* SNPs (rs2051992, rs2239050, rs7959938) that are all in high LD with each other but distant from rs1006737 are associated with increased brainstem volume in healthy controls (Franke et al., 2010). In this study there was also an association between rs7959938 and white matter volume in the brainstem, largely overlapping in areas of the midbrain and pons, and also in cerebellum. It is unclear if these effects of *CACNA1C* SNPs on structural and volumetric outcomes arose during early development, or are only present in adults. However, it is clear that such changes on their own are not pathological as they were identified mostly in psychiatrically normal subjects (Table 2).

6. L-type calcium channel antagonists in the treatment of psychiatric disease

LTCC antagonists are mainly used clinically for treating high blood pressure, angina, and abnormal heart rhythms. Chemically, they are represented by three different structural classes: dihydropyridines, benzothiazepines, and phenylalkylamines, which all act by binding to different sites on $\text{Ca}_v1.2$ and blocking the calcium current (Triggle, 1992). LTCC antagonists within the same structural class may vary in their affinity for the same calcium channel subtype, as well as for their penetration of the blood-brain barrier. For example, nimodipine and nicardipine, unlike some other dihydropyridines, are considered to have good CNS penetration (Kaplan, 1989). LTCC antagonists have been assessed for the treatment of bipolar disorder and also unipolar depression (see Casamassima et al., 2010a and Levy and Janicak, 2000 for comprehensive reviews). However, studies have yielded mixed results suggesting response in only a subset of patients (most notably rapid cycling where patients transition between mood episodes occurs at a rapid rate) or that these treatments have not yet been optimized (e.g. selectivity for $\text{Ca}_v1.2$ or blood brain barrier penetrance (Casamassima et al., 2010a; Levy and Janicak, 2000; Mallinger et al., 2008; Pazzaglia et al., 1998)). Many of the early studies were performed with the phenylalkamine verapamil, which has low blood-brain barrier permeability. More recent double-blind placebo studies with dihydropyridines including nimodipine and nicardipine that more efficiently cross blood-brain barrier have suggested that this class of calcium channel medication has efficacy as an adjunctive antidepressant treatment in combination with selective serotonin reuptake inhibitors (SSRIs) or electroconvulsive therapy (Dubovsky et al., 2001; Taragano et al., 2001, 2005). To the best of our knowledge, LTCC antagonists have not been assessed for efficacy in the treatment of schizophrenia. More extensive investigation with LTCC antagonists that readily cross the blood brain barrier are clearly necessary to define the specific profile of this class of medications in bipolar disorder, as well as depression and schizophrenia.

7. Conclusions

Underlying genetics are among the strongest risk factors for the development of mood disorders and schizophrenia, and there is shared genetic overlap between DSM-defined disorders including bipolar disorder, unipolar depression, and schizophrenia. This shared genetic overlap is coincident with shared environmental risk factors, as well as extensive overlap in neurobiology—as evidenced by biological markers and endophenotypes—and in efficacious treatments (Demjaha et al., 2011; Gottesman and Gould, 2003; Insel and Cuthbert, 2009). This has contributed to the view that future classification systems for psychiatric illness should be agnostic to current criteria (Cuthbert and Insel, 2010; Insel et al., 2010) and that new treatments that are based upon pathophysiology will eventually emerge through a thorough understanding of genetic susceptibility factors (Insel and Scolnick, 2006).

SNPs in *CACNA1C* are associated with risk of developing diverse DSM-defined disorders including bipolar disorder, depression, and schizophrenia. In addition to being a current statistical “top hit” resultant from bipolar disorder GWA studies, it is also the top finding when combining results of depression or schizophrenia with bipolar disorder sample sets, reinforcing the well established notion that diagnostic categories are not appropriate demarcation points for the effects of genes on behaviors (Gottesman and Gould, 2003; Meyer-Lindenberg and Weinberger, 2006). Available data suggest that *CACNA1C* belongs to a class of shared susceptibility factors, which cross DSM diagnostic boundaries to influence susceptibility (Table 1).

We have reviewed these human genetic and clinical findings, as well as the biological functions of $\text{Ca}_v1.2$ that are likely most relevant to psychiatric disease. While involved in numerous cellular functions, $\text{Ca}_v1.2$ is strongly implicated in the coupling of cell membrane depolarization to changes in calcium permeability and resultant intracellular signaling pathway activity and ultimately gene transcription and synaptic plasticity. Mouse genetic knockout experiments and studies with LTCC antagonist and agonists indicate that $\text{Ca}_v1.2$ is involved in proper functioning of many brain regions, including the mesolimbic reward system, hippocampus, and amygdala. Much of the work exploring the effects of LTCC antagonists on activation of signaling pathways and rodent behavior have not been able to distinguish the effects of inhibiting all LTCCs, most notably $\text{Ca}_v1.2$ and $\text{Ca}_v1.3$ in the brain, though genetically modified mice expressing dihydropyridine-insensitive $\text{Ca}_v1.2$ ($\text{Ca}_v1.2\text{DHP-/-}$) have been generated and used to begin to address this critical question (Busquet et al., 2008; Giordano et al., 2010; Sinnegger-Brauns et al., 2004). Existing preclinical and some clinical pharmacological data support inhibiting LTCCs as a possible mechanism of mood stabilization.

Prior to the recent genetic findings, there was *a priori* evidence suggesting that calcium signaling may play a role in bipolar disorder. Studies of bipolar patients have consistently reported elevated basal and stimulated intracellular calcium levels in peripheral blood cells (Casamassima et al., 2010a; Dubovsky et al., 1989; Emamghoreishi et al., 1997; Perova et al., 2008). However, the relevance of these reports to the current genetic association with *CACNA1C* is presently unclear. Additional investigation of the role of $\text{Ca}_v1.2$ in brain function in both humans and animal models will likely provide novel insights into the pathophysiology of psychiatric disorders and elucidate new approaches for their treatment.

It is evident from the increasing size of cases and controls that are being assessed and the odds ratios reported that the identified polymorphisms in *CACNA1C* impart only a small contribution to the overall heritability of psychiatric illness (Table 1). However, a number of reports now clearly indicate that genetic variant at SNP rs1006737 is associated with changes in brain structure and function in normal control subjects with a larger effect size (Table 2 and (Rose and Donohoe, 2012)). There is evidence indicating that genetic variation at rs1006737 may be involved in modulating gene expression, with the minor (risk) allele associated with increased expression levels of *CACNA1C* (Bigos et al., 2010). However, the mechanisms regarding how this gene is regulated by these SNPs or other SNPs in LD is not clear, and the resultant changes in $\text{Ca}_v1.2$ function and how it is related to disease have not been characterized. The mechanism by which genetic variation in *CACNA1C* influences risk is likely on the function of particular neuronal circuits, at a level far upstream from the development of disease or presentation of symptoms. Noting that *CACNA1C* is a susceptibility gene for diverse psychiatric diseases, these changes in circuit function likely converge in a manner that is common across diagnostic categories. It is, however, unclear if this effect of *CACNA1C* genetic variation is during development, in adults, or perhaps more likely both. A number of additional molecular genetic questions remain to be answered. These include the identification of *CACNA1C* splice variants associated with particular SNPs, and whether such an association is dependent on brain regions. It also remains critically important to fully address the consequences of changes in splice variation of *CACNA1C* on neurophysiology and whether these structural changes may lead to an identification of α_{1C} molecular determinant(s) to be used in high-throughput screening for research and development leading to new specific drugs to combat disease (Zuccotti et al., 2011). Defining the answers to these and other critical questions will likely provide important insight into neuropsychiatric disease susceptibility and potentially lead to novel therapeutic targets and approaches.

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Abbreviations

AEI	Allelic expression imbalance
ANK3	Ankyrin 3, node of Ranvier (ankyrin G)
APP	Amyloid precursor protein
BDNF	Brain derived neurotrophic factor
BPD	Bipolar disorder
CaBP1	Calcium binding protein-1
CACNA1C	Voltage dependent L type calcium channel, alpha 1C subunit
CaM	Calmodulin
cAMP	Cyclic adenosine monophosphate
CaMK	Ca ²⁺ /CaM-dependent protein kinases
Ca_v1.1 to 1.4	Calcium voltage-dependent channel, 1.1 to 1.4 representing the voltage of activation of the respective channel
cDNA	Complementary DNA
CICR	Calcium-induced intracellular calcium release
CREB	cAMP response element binding protein
DHP	Dihydropyridine
DSM IV	Diagnostic and Statistical Manual IV
Erk	Extracellular signal-regulated kinases
GABA	Gamma-aminobutyric acid
GenRED	Genetics of Recurrent Early-onset Major Depression consortium
GWAS	Genome-wide association study
LD	Linkage disequilibrium
LTCC	L-type calcium channel
LTP	long-term potentiation
MAOI	Monoamine oxidase inhibitor
MAPK	Mitogen-activated protein kinase
MDD	Major depressive disorder
MIR137	microRNA 137
NAc	Nucleus accumbens
NIMH-GIBD	National Institute of Mental Health-Genetics Initiative Bipolar Disorder consortium
NMDA	N-methyl-D-aspartate
ODZ4	odd Oz/ten-m homolog 4 (Drosophila)

OR	Odds ratio
PCR	Polymerase chain reaction
PGC	Psychiatric Genetics Consortium
RyR	Ryanodine receptors
SNP	Single nucleotide polymorphism
SSRI	Selective serotonin reuptake inhibitor
SZ	Schizophrenia
STAR*D study	Sequenced treatment alternatives to relieve depression study
TCA	Tricyclic antidepressant
VTA	Ventral tegmental area
WTCCC	Wellcome Trust Case–Control Consortium
ZNF804A	zinc finger protein 804A

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Fig. 1. Psychiatric disorders and their relationship with susceptibility genes, physiological factors, current classes of drugs, and possible novel treatments

Current treatments for psychiatric disorders were developed to treat symptoms, and in many instances likely have limited effects on underlying pathophysiology. It is hoped that treatments targeted toward pathophysiology will provide greater and sustained rates of remission. However, currently knowledge is lacking regarding the pathophysiology of most psychiatric diseases. Treatments that target the underlying pathophysiology of psychiatric disorders such as mood disorders will derive from understanding the neurobiology underlying the disease. As diseases with high heritability, genetic underpinnings are a link to pathophysiology. The top portion of the figure shows current treatments. The bottom portion of the figure indicates examples of current top genetic findings in psychiatric disorders, including *CACNA1C*. The middle portion of the figure suggests levels of analysis that will be critical to understand the role of genetic variation on disease pathophysiology and to direct the subsequent development of future treatments. MAOI, Monoamine oxidase inhibitor; SSRI, Selective serotonin reuptake inhibitor; TCA, Tricyclic antidepressant; *ANK3*, ankyrin 3, node of Ranvier (ankyrin G); *CACNA1C*, voltage-dependent L type calcium channel, $\alpha 1C$ subunit; *MIR137*, microRNA 137; *ODZ4*, odd Oz/ten-m homolog 4 (Drosophila); *ZNF804A*, zinc finger protein 804A.

Fig. 2. Mental disorder significant findings projected on the genomic map of CACNA1C
Genomic map of *CACNA1C* beginning with exon 1 (Soldatov, 1994); exons are indicated with vertical bars separated by introns. Identified mental disorder associated SNPs are shown by colored circles at approximate locations on the gene. GWAS significant associations are: rs1006737 and rs4765905 (which are in complete LD)—bipolar disorder, schizophrenia, and major depression. rs4765913—bipolar disorder and schizophrenia/ bipolar disorder combined analysis. rs7297582—bipolar disorder and major depression disorder combined analysis. rs2370411 and rs2370419: two SNPs showing sex specific association (females only). The red *star* (*) at exon 8/8a marks the Timothy syndrome loci. The image is of transcript variant 1, initially referred to as HFCC (Soldatov, 1992, GenBank accession #: NM_199460.2); not shown in the figure is alternative splicing of the gene.

Table 1
Genetic evidence associating CACNA1C with mental disorders

Bipolar Disorder (BPD), Schizophrenia (SZ), and Major Depressive Disorder (MDD). Odds Ratios (OR) are listed where available. Genome Wide Association Study (GWAS); Sequenced treatment alternatives to relieve depression (STAR*D) study.

SNP/Region (within intron 3 unless otherwise noted)	Association with/comments	Study participants	Statistics (uncorrected unless otherwise noted)	Reference
rs72552065 (WIAF-13171) Exon 44	BPD (Nominal)	136 parent-proband trios	$p = 0.011$	Sklar et al. (2002)
Exon 8 & 8a	Timothy syndrome, a multisystem syndrome including autistic features	19 affected children	Causative mutation	Splawski et al. (2005, 2004)
rs1006737	BPD; GWAS	1461 BPD, 2008 controls ^a	$p = 1 \times 10^{-4}$, OR = 1.21	Sklar et al. (2008)
rs1006737	BPD; GWAS	4387 BPD, 6209 controls ^a	$p = 7 \times 10^{-8}$, OR = 1.18	Ferreira et al. (2008)
<i>CACNA1C</i>	BPD; Gene-wide significance was assessed in genome-wide data rather than at SNP level	1868 BPD, 479 SZ, & 2938 controls ^a	Gene-wide $p_{\min} = 7 \times 10^{-4}$ (Min p value for a gene to be significant at genome-wide level)	Moskvina et al. (2009)
4 independent signals (including rs1006737)	BPD; BPD GWAS data analyzed with lower threshold for significance	1865 BPD, 14,297 controls ^a	Minimum p value was set at $p = 1.5 \times 10^{-4}$	Keers et al. (2009)
<i>CACNA1C</i>	MDD; GWAS; reported the p -value for the entire gene and not for a specific SNP	4387 MDD, 6209 controls ^a	$p = 0.03$	Sullivan et al. (2009)
rs2370419; rs2370411	SNPs in the genomic region of <i>CACNA1C</i> analyzed. Significant interaction with sex. Increased risk of mood disorder (BPD and MDD) in females only	2021 Mood disorder cases (1001 BPD & 1020 MDD), 1840 controls	rs2370419: $p = 1.4 \times 10^{-4}$, OR = 1.64; rs2370411: $p = 2.1 \times 10^{-4}$, OR = 1.32	Dao et al. (2010)
rs1006737	SZ	282 SZ, 440 controls	$p = 0.03$, OR = 1.77	Bigos et al. (2010)
rs1006737; rs10848635	Increased risk of treatment-emergent suicidality in non-psychotic MDD	1213 MDD (STAR*D study)	rs1006737: $p = 0.02$, OR = 1.34; rs10848635: $p = 0.04$, OR = 1.29	Casamassima et al. (2010b)
rs1006737	SZ	976 SZ, 1489 controls	$p = 0.015$, OR = 1.16	Nyegaard et al. (2010)
rs1006737	SZ and MDD	479 SZ, 1196 MDD, 15316 controls ^a	$p = 0.034$, OR = 1.15 (SZ), $p = 0.013$, OR = 1.15 (MDD)	Green et al. (2010)
rs1006737	Higher psychopathology scores for depression, anxiety, obsessive-compulsive thoughts, interpersonal sensitivity, and neuroticism on Beck Depression Inventory or State Trait Anxiety Inventory	110 healthy volunteers	$p < 0.05$	Erk et al. (2010)
rs1006737	Lower extraversion and higher harm avoidance, trait anxiety, and paranoid ideation scores as assessed via personality questionnaires	530 healthy volunteers	$p < 0.05$ (corrected)	Roussos et al. (2011)
rs1006737	Higher depressive and manic symptom scores among all groups	41 BPD, 25 unaffected first degree relatives, 50 controls	$p = 0.01$	Jogia et al. (2011)
rs7297582; rs1006737	Combined population of BPD and MDD in a meta analysis; GWAS	10596 BPD + MDD, 3456 controls ^a	rs7297582: $p = 3.4 \times 10^{-8}$, rs1006737: $p = 3.1 \times 10^{-8}$, OR for	Liu et al. (2011)

SNP/Region (within intron 3 unless otherwise noted)	Association with/comments	Study participants	Statistics (uncorrected unless otherwise noted)	Reference
rs4765913	BPD; GWAS; Combined analysis of BPD dataset and that of SZ dataset also showed significant association with both the disorders combined	11977 BPD, 51672 controls ^a	rs1006737 = 1.18 (BPD), 1.18 (MDD) $p = 1.52 \times 10^{-8}$, OR = 1.14	Sklar et al. (2011)
rs4765905	Combined analysis of SZ and BPD; GWAS	16374 BPD + SZ, 14044 controls ^a	$p = 7 \times 10^{-9}$	Ripke et al. (2011)
rs1006737	Psychotic subgroup of BPD	Family analysis; 158 psychotic BPD, 119 nonpsychotic BPD	$p = 0.017$	Lett et al. (2011)
rs4765905	SZ; GWAS	20476 SZ; 36737 controls ^a	$p = 1.23 \times 10^{-8}$, OR = 1.09	Hamshere et al. (2012)

^aThese studies contain some overlapping populations details of which are discussed in text.

Table 2
Genetic evidence associating CACNA1C with brain structure and function

Bipolar Disorder (BPD), Schizophrenia (SZ).

SNP	Details of Risk/Minor Allele Association	Population (psychiatrically normal volunteers unless otherwise noted)	Reference
rs1006737	Increased total brain gray matter volume	77 adults (British, Caucasian)	Kempton et al. (2009)
rs1006737	Increased amygdala activity in response to reward	64 adults (German descent)	Wessa et al. (2010)
rs2051992, rs2239050 and rs7959938 (single LD block distinct from rs1006737)	Increased brain stem volume	585 adults (European, Caucasian)	Franke et al. (2010)
rs1006737	Decreased performance on a test of semantic verbal fluency, and increased activation of the left inferior frontal gyrus as well as the left precuneus during a separate semantic verbal fluency task	63 adult males (German descent)	Krug et al. (2010)
rs1006737	Reduction of activity in the hippocampus, dorsal anterior cingulate cortex, ventral striatum, superior frontal, and temporal cortices as well as diminished functional coupling between left and right hippocampal regions during episodic memory recall; Risk allele carriers also manifested higher psychopathology scores for depression, anxiety, obsessive-compulsive thoughts, interpersonal sensitivity, and neuroticism	110 adults (German descent)	Erk et al. (2010)
rs1006737	Increased prefrontal activity (lower efficiency) during the N-back working memory task; Trend for an association with increased hippocampal activity during emotional memory processing and increased amygdala activity during an emotional face task; Risk allele associated with increased brain mRNA expression	N-back study: 316 adults Emotional memory processing: 116 adults Emotional faces task: 131 adults mRNA expression: 161 postmortem brains	Bigos et al. (2010)
rs1006737	Decreased attention-related performance in alerting and orienting as assessed with a scanner-adapted version of the Attention Network Test. Trend for an association with reduced neural activity in the right inferior parietal lobule during orienting and in the medial frontal gyrus during executive control of attention	80 adults (German descent)	Thimm et al. (2011)
rs1006737	Increased gray matter density in the right amygdala and right hypothalamus. Left putamen was smaller in BPD patients carrying the risk allele	40 healthy adults and 41 BPD (British descent)	Perrier et al. (2011)
rs1006737	Lower extraversion and higher harm avoidance, trait anxiety, and paranoid ideation scores as assessed via personality questionnaires, and increased startle reactivity	530 adult males (Greek, Caucasians)	Roussos et al. (2011)
rs1006737	Increased right amygdala activation during fear-face recognition relative to neutral faces; Reduced right ventrolateral prefrontal cortex activation during emotional processing only in BPD patients	50 healthy adults; 41 BPD and 25 first degree relatives (British descent)	Jogia et al. (2011)
rs1006737	Impaired working memory in schizophrenia patients and healthy controls, but not BPD subjects	401 healthy adults, 74 BPD, 318 SCZ (Chinese)	Zhang et al. (2011)
rs1006737	Increased grey matter volume and reduced corticolimbic/frontotemporal functional connectivity	55 adults (American, Caucasian)	Wang et al. (2011)
rs1006737	Facial emotion recognition impairment in BPD, but not healthy controls	40 healthy adults (Brazilian) BPD	Soeiro-de-Souza et al. (2012)
rs1006737	Effective connectivity from medial frontal gyrus to left putamen significantly reduced during perception of fearful faces, particularly in BPD subjects	20 healthy adults, 20 BPD (in remission), 20 unaffected first-degree relatives	Radua et al. (2012)
rs1006737	Lower emotional lability and stronger resilience (higher sense of coherence) in women	3793 adults (German) including 1989 women	Strohmaier et al. (2012)