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Genetic Associations between Voltage-Gated Calcium Channels and Psychiatric Disorders

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ABSTRACT

Psychiatric disorders are mental, behavioral or emotional disorders. These conditions are prevalent, one in four adults suffer from any type of psychiatric disorders world-wide. It has always been observed that psychiatric disorders have a genetic component, however new methods to sequence full genomes of large cohorts have identified with high precision genetic risk loci for these conditions. Psychiatric disorders include, but are not limited to, bipolar disorder, schizophrenia, autism spectrum disorder, anxiety disorders, major depressive disorder, and attention-deficit and hyperactivity disorder. Several risk loci for psychiatric disorders fall within genes that encode for voltage-gated calcium channels (Ca_Vs). Calcium entering through Ca_Vs is key for multiple neuronal processes. In this review, we will summarize recent findings that link Ca_Vs and their auxiliary subunits to psychiatric disorders. First, we will provide a general overview of Ca_Vs structure, classification, function, expression and pharmacology. Next, we will summarize tools and databases to study risk loci associated with psychiatric disorders. We will examine functional studies of risk variations in Ca_V genes when available. We will

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review pharmacological evidence of the use of Ca_V modulators to treat psychiatric disorders. Our review will be of interest for those studying pathophysiological aspects of Ca_Vs.

KEYWORDS

voltage-gated calcium channels; major depressive disorder; autism spectrum disorder; schizophrenia; bipolar disorder; attention-deficit and hyperactivity disorder; anxiety; calcium channel modulators; psychiatric disorders; auxiliary subunits; genetic risk variations

1. Introduction

Voltage-gated calcium channels (Ca_Vs) are transmembrane protein activated by depolarization of membrane potential. The calcium that enters through Ca_Vs is important for cellular processes including gene expression, hormone release, neurotransmitter release, cardiac muscle contraction, and pacemaker activity [1]. Some Ca_Vs are multi-protein complexes comprised by the $Ca_V\alpha_1$ pore-forming and the auxiliary subunits, $Ca_V\alpha_2\delta$ and $Ca_V\beta$. These auxiliary subunits have profound effects on the biophysical properties and membrane targeting of the $Ca_V\alpha_1$ subunit [2,3]. Targeted deletions or disruptive mutations of genes encoding for $Ca_V\alpha_1$, $Ca_V\alpha_2\delta$ and $Ca_V\beta$ result in deleterious effects, highlighting the importance of these genes [4–10]. Classically, dysfunction of Ca_Vs has been linked to neurological disorders including Parkinson's disease, epilepsy, migraine, ataxia and neuropathic pain [11–17]. More recently, due to the advancement in genetic techniques to sequence and analyze full human genomes, genes encoding Ca_Vs have been linked to psychiatric disorders [1,17,18]. All of this combined expands the relevance of Ca_Vs in health and disease.

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Ca_Vs are being considered as molecular targets to treat several neurological conditions including psychiatric disorders [17]. Furthermore, functional studies of Ca_V gene risk variations identified in patients with psychiatric disorders are providing mechanistic insights into these conditions. In this review, we will summarize literature on the structure and function of Ca_V genes, we will briefly overview some of the genetic tools that have allowed to establish genetic links between Ca_Vs and psychiatric disorders, then we will examine studies that have linked Ca_V genes to several psychiatric disorders including bipolar disorder (BD), schizophrenia (SCZ), autism spectrum disorders (ASD), anxiety disorders, major depressive disorder (MDD), and attention-deficit and hyperactivity disorder (ADHD). If available, we will provide a summary of functional studies of risk variations for Ca_Vs. Finally, we will synthesize the literature on therapeutic strategies that focus Ca_Vs as pharmacological targets.

2. Structure of voltage-gated calcium channels

$Ca_V\alpha_1$ subunits. Ten genes encode the $Ca_V\alpha_1$-pore-forming subunit of Ca_Vs (*CACNA1*). Depending on their pharmacology and sequence similarity, $Ca_V\alpha_1$ subunits are subdivided in three subfamilies (Ca_V1, Ca_V2 and Ca_V3) (Table 1) [2]. The Ca_V1 channel subfamily comprises $Ca_V1.1$ (*CACNA1S*), Cav1.2 (*CACNA11C*), $Ca_V1.3$ (*CACNA1D*) and $Ca_V1.4$ (*CACNA1F*) channels. Ca_V1 channels are sensitive to dihydropyridines (DHPs) and exhibit long-lasting activity relative to the members of Ca_V2 and Ca_V3, hence these channels are also known as L-type [19].

 doi:10.20944/preprints201906.0192.v1

The Ca_V2 channel subfamily is comprised of $Ca_V2.1$ (*CACNA1A*), $Ca_V2.2$ (*CACNA1B*), and $Ca_V2.3$ (*CACNA1E*). $Ca_V2.1$, $Ca_V2.2$, and $Ca_V2.3$ generate the P/Q-type, N-type and R-type currents respectively. These channels are generally localized in presynaptic terminals where they control calcium-dependent transmitter release in central and peripheral synapses, although $Ca_V2.3$ is also present in dendrites and extra postsynaptic sites [19]. Ca_V2 channels are selectively blocked with toxins. $Ca_V2.1$ is sensitive to ω-agatoxin IVA, $Ca_V2.2$ to ω-conotoxin GVIA, and $Ca_V2.3$ to SNX-482 [19].

The Ca_V3 subfamily comprises $Ca_V3.1$ (*CACNA1G*), $Ca_V3.2$ (*CACNA1H*), and $Ca_V3.3$ (*CACNA1I*), which generate T-type currents. Ca_V3 channels exhibit small single channel conductance, and relatively lower threshold of activation compared to all members of the Ca_V1 and Ca_V2 subfamilies (low voltage activation or LVA and high voltage activation or HVA, respectively) [20]. It is important to note that $Ca_V1.3$ channels exhibit a threshold of activation that is lower relative to the other members of the Ca_V1 subfamily and Ca_V2 channels, but slightly higher than all the Ca_V3 subfamily members [21]. All the *CACNA1* genes undergo extensive alternative splicing that originates various splice variants with differences in their tissue expression, pharmacology and biophysical properties [22]. In some cases, the pharmacological and biophysical properties of a given splice variant overlaps with those ones from members of a different subfamily [23].

The primary structure of the $Ca_V\alpha_1$ pore-forming subunit is organized into four homologous domains (DI-IV). Each domain contains six membrane-spanning segments (S1-S6), with a re-entrant loop between S5 and S6, which contains negatively charged residues

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(glutamates and/or aspartates) that are essential for the selectivity filter. S4 contains positively charged residues (arginines) that function as voltage-sensors. The amino and carboxyl termini, as well as linker sequences between the DI-II, DII-III, and DIII-IV are all cytosolic. These sites are important for the interaction of $Ca_V\alpha_1$ with intracellular proteins, as well as signaling cascades that regulate calcium entry through Ca_Vs (Figure 1) [24].

Members of the Ca_V1 and Ca_V2 subfamilies form membrane complexes with the auxiliary subunits $Ca_V\alpha_2\delta$ and $Ca_V\beta$, influencing several biophysical and pharmacological properties of the $Ca_V\alpha_1$ subunit [2,3,24].

$Ca_V\alpha_2\delta$ subunits. Four genes exist for the $Ca_V\alpha_2\delta$ subunits (*CACNA2D1-4*), which encode for $Ca_V\alpha_2\delta$1-4 proteins [24]. Each $Ca_V\alpha_2\delta$ subunit is translated from a single gene, which produces a protein that is cleaved into the α_2 and δ peptides. A disulphide bond links these peptides [25,26]. $Ca_V\alpha_2\delta$ is entirely extracellular but it is attached to the cell membrane by a glycosylphosphatidylinositol anchor (GPI) domain (Figure 1) [27]. Interestingly, the α_2 peptide contains structural domains such as the von Willebrand Factor A domain (vWA) and two Cache domains [28]. The vWA domain in $Ca_V\alpha_2\delta$ contains a metal-ion-adhesion site (MIDAS) that is important for membrane trafficking [29]. The functional role of the Cache domains is poorly understood [30,31]. $Ca_V\alpha_2\delta$-1 and $Ca_V\alpha_2\delta$-2 are targets for the gabapentinoid drugs gabapentin and pregabalin [32]. Similar to *CACNA1* genes, *CACNA2D* genes are also subject to extensive alternative splicing that impacts affinity for gabapentin and other functions of $Ca_V\alpha_2\delta$ subunits [33,34].

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$Ca_V\beta$ subunits. Four genes exist $Ca_V\beta$ subunits (*CACNB1-4*), which encode for $Ca_V\beta$s ($Ca_V\beta1$-$\beta4$). $Ca_V\beta$ subunits are located in the cytoplasm (Figure 1); however, some splice variants of $Ca_V\beta_2$ are attached to the membrane via a palmitoylation site [35,36], and both $Ca_V\beta_3$ and the splice variant $Ca_V\beta_{4c}$ can be mobilized to the nucleus [37–39]. $Ca_V\beta$ subunits contain three conserved domains: an inactive guanylate kinase domain (GK), an *src* homology domain 3 (SH3), and a HOOK region [40–43]. The $Ca_V\beta$-GK domain is important for the interaction with the AID domain in the I-II loop of the $Ca_V\alpha_1$ subunit [42]. The $Ca_V\beta$-SH3 and -HOOK domains mediate specific protein-protein interactions of $Ca_V\beta$ subunits, for example, with dynamin [44]. All *CACNB* genes undergo alternative splicing [35].

3. General function of voltage-gated calcium channels and auxiliary subunits

$Ca_V\alpha_1$ subunits. Ca_V channels are expressed in a wide variety of tissues where they serve specific functions. $Ca_V1.1$ is restricted to the skeletal muscle where the movement of the gating mechanisms induced by depolarization leads to opening of the ryanodine receptors (RYR), a class of calcium channels located in the sarcoplasmic membrane. The opening of RYR increases intracellular calcium, which results in activation of Ca^{2+}-dependent contractile proteins [45]. $Ca_V1.2$ and $Ca_V1.3$ are broadly co-expressed in various tissues including the brain, heart, smooth muscle, and neurosecretory systems [1]. These two channels are important for gene expression, calcium transients in dendrites, and the coupling of electrical signals to hormone secretion [46–50]. $Ca_V1.2$ controls contraction of heart muscle, and together with $Ca_V1.3$ controls the pacemaking activity of midbrain dopaminergic neurons and adrenal chromaffin cells [51–54].

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$Ca_V1.3$ is key for the pacemaking firing of the sinoatrial node and for transmitter release from hair cells of the inner ear [55–57]. $Ca_V1.4$ controls glutamate release from photoreceptors [58,59].

$Ca_V2.1$, $Ca_V2.2$, and $Ca_V2.3$ are involved in the release of neurotransmitters. $Ca_V2.1$ and $Ca_V2.2$ channels have a dominant role in the release of fast transmitters such as GABA, acetylcholine, and glutamate [60,61]. $Ca_V2.2$ channels are dominant in peripheral terminals that release glutamate and noradrenaline, as well as in central synapses that release dopamine, serotonin and noradrenaline [62–64]. $Ca_V2.2$ channels are also dominant in interneurons that express the cholecystokinin peptide [65,66]. $Ca_V2.3$ channels are present in the presynaptic terminals and dendrites of certain synapses of the central nervous system [67]. In the presynaptic terminals, $Ca_V2.3$ channels are localized in the active zones or in their periphery thereby controlling transmitter release [68]. In the dendrites, $Ca_V2.3$ channels control Ca^{2+}-dependent spikes [69]. G-protein coupled receptors for several neurotransmitters including GABA, endogenous opioids, and endocannabinoids heavily regulate Ca_V2 channels [70,71]. This is an important negative feedback mechanism to limit the release of neurotransmitter [72,73]. Ca_V2 channels interact with soluble N-ethylmaleimide sensitive fusion protein receptors (SNAREs), which promote the fusion of secretory vesicles to the membrane in a Ca^{2+}-dependent manner, this calcium generally enters through Ca_V2 channels [72].

$Ca_V3.1$, $Ca_V3.2$, and $Ca_V3.3$ channels control repetitive firing and pacemaking activity [20]. Ca_V3 channels open at relatively low voltages compared to members of the Ca_V1 and Ca_V2 subfamilies and have fast voltage-dependent inactivation. These unique biophysical properties

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underlie the role of Ca_V3 channels in rhythmic firing of action potentials [73,74]. Ca_V3 channels control the pacemaking activity of the sinoatrial node in the heart [75,76], and the rhythmic bursts of action potential in relay neurons in the thalamus [77]. Ca_V3 channels are not known to be associated with the auxiliary subunits $Ca_V\alpha_2\delta$ and $Ca_V\beta$, however, recent evidence suggests that Ca_V3 channels interact with CACHD1, a protein closely related to the $Ca_V\alpha_2\delta$ subunits (Table 1) [78–80].

$Ca_V\alpha_2\delta$ subunits. $Ca_V\alpha_2\delta$-1 is expressed in skeletal, cardiac and smooth muscle, secretory systems; central and peripheral neurons [32]. $Ca_V\alpha_2\delta$-2 is abundantly expressed in the cerebellum, and to a lesser extent in other areas of the brain [6]. $Ca_V\alpha_2\delta$-3 is expressed throughout the central and peripheral nervous systems [81,82]. Finally, $Ca_V\alpha_2\delta$-4 expression is limited to the retina and endocrine tissue [83]. Expression of $Ca_V\alpha_2\delta$ subunits increases membrane trafficking, stabilizes Ca_Vs complexes in the cell surface and produces shifts in voltage-dependence of activation as well as inactivation [2,30]. $Ca_V\alpha_2\delta$ subunits promote synaptogenesis by binding to thrombospondin [84], influence neurotransmission through interaction with α-neurexins [85,86], and affect synaptic plasticity by interacting with NMDA receptors [87].

$Ca_V\beta$ subunits. $Ca_V\beta$ subunits are broadly expressed in several tissues including brain, heart and skeletal muscle. These proteins promote trafficking of $Ca_V\alpha_1$ to the cell surface by occluding endoplasmic reticulum retention signals present in the linker between DI and DII of $Ca_V\alpha_1$ [88]. $Ca_V\beta$ subunits are key for modulation of Ca_V1 and Ca_V2 channels by G-protein

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coupled receptors and other signaling complexes including Ras-related GTPases [89]. $Ca_V\beta3$ and particularly $Ca_V\beta4$ are thought to induce gene expression [37,39].

4. Genetic analysis and tools to study psychiatric disorders

Few cases exist where the inheritance of a disorder involving Ca_V genes follow mendelian models. However, spinal cerebellar ataxia 6 (SCA6) and Timothy Syndrome (TS) are two cases that follow an autosomal dominant pattern. Alterations in the *CACNA1A* and *CACNA1C* genes underlie SCA6 and TS, respectively [90,91]. In SCA6, the *CACNA1A* gene contains between 20 and 33 CAG repeats that encode for glutamines in the C-terminus [92]. Although the molecular mechanism by which these repeats lead to the disease remains to be fully understood, current evidence suggests transcriptional dysregulation mediated by a $Ca_V2.1$ C-terminus fragment with the glutamine repeats [93]. In TS, mutations in *CACNA1C* (G402S and G406R) produce $Ca_V1.2$ channels with gain of function [94,95]. TS is a condition that affects the heart and the nervous system. Patients with Timothy syndrome present several characteristics seen in patients with ASD [91]. Recent evidence suggests that $Ca_V1.2$ mutations underlying TS produce defects in neuronal migration during cortical development [96]. In contrast to SCA6 and TS, most psychiatric disorders are genetically complex conditions that involve the interaction among several genes and their interactions with the environment [97,98].

Several genetic methods have been used to determine the genes or set of genes that are likely to underlie psychiatric disorders. Historically, linkage and linkage-disequilibrium studies provided the initial evidence of the genetic origins of psychiatric disorders [99,100]. However, it

 doi:10.20944/preprints201906.0192.v1

is now possible to perform genetic analysis using whole genomes from large populations through genome-wide association studies (GWAS) to discover new risk variations associated with psychiatric disorders [101] .

Linkage studies. Evidence for linkage is derived from observing the cosegregation of specific genomic regions with a given disorder. As such, this method is most effective for the study of disorders inherited in a Mendelian fashion. Pedigrees containing multiple generations of genetic data can be used to elucidate inheritance patterns and map potential genomic risk loci for a given disorder. The identification of large families with high prevalence of a given condition often facilitates linkage studies. In these studies, the inheritance of a genetic loci can be correlated with the presence or absence of the disorder [99].

Linkage-disequilibrium studies. In these studies, the aim is to map a nonrandom association of alleles at two or more loci to discover disease haplotypes. These haplotypes are thought to be inherited from one or a few founding members of isolated populations. [102].

Association Studies. Here the goal is to find risk loci for a specific condition by assessing correlations between disease status and genetic variation. Of the association studies, GWAS are becoming a popular method to screen markers or genetic variations of disease across whole genomes of large populations. GWAS have identified several genetic variations of Ca_V genes linked to BD, SCZ, ASD, ADHD, and MDD [17,18]. We will review several of these cases below. Thanks to GWAS data many new risk loci for psychiatric disorders have been found [103,104].

 doi:10.20944/preprints201906.0192.v1

All the genetic approaches mentioned above have helped to identify associations of several gene variations to psychiatric disorders. These variations include single nucleotide polymorphisms (SNPs), small indels, copy number variations (CNVs), *de novo* variations, and large chromosomal rearrangements [105].

Our understanding of psychiatric disorders is evolving towards a more comprehensive analysis that includes genetic, genomic, functional and behavioral studies. These are possible thanks to tools that allow to screen multiple patients (probands) and their corresponding unaffected relatives. Among these tools are next-generation sequencing, microarrays, endophenotype analysis, gene network analysis and computational modeling [105].

Next generation sequencing (NGS). These tools include whole exome and genome sequencing (WES and WGS, respectively), as well as RNA sequencing (RNA-seq). WES detects genetic variations through capture and sequencing of coding regions within the genomic DNA. Since most of the genome is noncoding, this approach greatly reduces the amount of sequencing to ~2% of the whole genome [106]. WGS offers an almost complete sequence coverage (~95%) that includes coding and non-coding regions and is more powerful to detect exome variations than WES. This increased coverage enables identification of non-coding regions that include splicing regulatory elements, promoters, enhancers, sites that regulate RNA transport and stability [107]. WES are more commonly used in genetic screenings for psychiatric disorders because of their lower cost compared to WGS [108]. Nevertheless, WES studies allow to focus on regions where variations can be identified and interpreted faster than in WGS studies [108].

 doi:10.20944/preprints201906.0192.v1

RNA-seq is a common tool used for genetic analysis of psychiatric disorders. This technology enables quantification of gene expression, detection and quantification of exon splicing, quantification of rare transcripts and non-coding RNAs, and detection of genome rearrangements. In summary, RNA-seq provides a whole transcriptome landscape with high signal to noise ratio and with small amount of RNA input [109].

Microarrays. Studies using microarrays are commonly used to identify genetic risk variations that involve structural changes > 1000 bp [105,110]. Large structural variations detected by microarrays are thought to increase the risk SCZ, ASD, and ADHD [111–117].

Gene network analysis. The discovery of risk variations associated with psychiatric disorders has been a stepping stone to elucidate the molecular mechanisms that underlie these conditions. Now the challenge is integrating this information to understand how genetic variation influence complex disorders and traits [118,119]. It is thought that complex interaction of genes in a network are more likely to explain phenotypes of psychiatry disorders, rather than the additive effect of those genes. Complex interaction of genes within networks include transcriptional regulatory, protein-protein interaction, metabolomic networks, and a hierarchical interaction with other gene networks [120–123]. Furthermore, complex interactions between gene networks with the environment are becoming increasingly important to fully explain phenotypes linked to psychiatric disorders [124–129].

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Endophenotypes. Despite recent advances linking genetic risk variations to psychiatric disorders, the phenotypic consequences of those variations are poorly understood. However, a combination of molecular genetics with endophenotypes might represent a promising approach to understand the behavioral links between risk variations and psychiatric disorders [130]. Endophenotypes are quantitative neurobehavioral traits that are associated with a disorder, are reasonably heritable, co-segregate with the disease and are independent of the clinical status of the disorder [131]. Endophenotypes provide clinical measures of disease diagnosis and progression. Examples of endophenotypes include deficits in pre-pulse inhibition and sensory gating, decline in working memory, and deficits in face emotion labeling [130,131]. Interestingly, the latter has been associated with *CACNA1C* in patients with bipolar disorder [132].

Computational psychiatry. Mathematical approaches are being used to integrate findings derived from genetic screenings, functional studies of gene risk variations, and behavioral phenotypes. Computational psychiatry is an emerging field that aims to model the compounded effects of individual genes, as well as their interaction with other genes (gene networks) and with the environment using mathematics [133–136]. Computational approaches have been successfully used to provide insightful mechanisms for disorders such as SCZ, ASD, and ADHD [137–139].

5. Overview of databases and resources to study the links between genetic risk variations and psychiatric disorders.

 doi:10.20944/preprints201906.0192.v1

To integrate genetic studies with phenotypes, an extensive collaboration between 15 research institutions to study functional genomics was performed, and the product of this collaboration is PsychEncode (http://www.psychencode.org/) [140]. PsychEncode is a public resource that contains multi-dimensional genomic relevant data from multiple consortia, single-cell studies and relevant data from functional characterization performed in model systems of regulatory elements and variations associated with disease [141,142]. The data captured within PsychENCODE includes a catalog of non-coding regulatory elements, epigenetic modification, and gene expression data from tissue- and cell-specific samples. In addition to human data, PsychENCODE includes data from mouse brain and reprogrammed induced pluripotent stem cells as model systems to provide integrative and functional analysis of disease [141,143].

PsychEncode merges data relevant to the brain from other databases including The Encyclopedia of DNA Elements (ENCODE), CommonMind Consortium (CMC), RoadMap Epigenomics Mapping Consortium (REMC), Genotype-Tissue Expression project (GTEx), and single-cell studies. The ENCODE project (http://www.encodeproject.org/) seeks to describe and annotate functional genetic and genomic elements from all tissue and cell-types from model organisms and humans [144,145]. CMC (http://www.synapse.org/CMC) contains information on large-scale genomic data from human subjects with psychiatric disorders [142]. REMC (http://www.roadmapepigenomics.org/) is a repository of healthy ex vivo tissue and cell sample data designed to provide a comprehensive epigenetic map for disease-focused research [146]. GTEx (http://gtexportal.org) project utilizes tissue samples from post-mortem donors taken from more than 40 different types of tissue from each donor to compile a tissue-specific map of gene

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expression, gene variance, and gene regulation within and between individuals. From GTEx, it is possible to analyze human expression Quantitative Trait Loci (eQTL) [119,147,148].

7. Genetic associations between Ca_V genes and psychiatric disorders

Gene network analyses have consistently implicated Ca_V genes in psychiatric disorders, which nicely correlates with the role calcium signaling in neuronal function [17,18]. In this section, we will review several large studies that have provided strong evidence linking Ca_V genes to psychiatric disorders and related endophenotypes. We will also briefly describe functional studies, when available, of risk variations for Ca_V genes.

a) *CACNA1C*

CACNA1C encodes $Ca_V1.2$, an ion channel that has been extensively studied in the heart. Here $Ca_V1.2$ channels tightly couple depolarization to muscle contraction through activation of RYR located in the ER of cardiomyocytes [149]. Additional studies have demonstrated that $Ca_V1.2$ is expressed in postsynaptic terminals in the brain, and together with $Ca_V1.3$, influences neuronal firing and couples excitation to gene expression [150]. The activity of neuronal $Ca_V1.2$ and $Ca_V1.3$ channels are implicated in several processes relevant to psychiatric disorders including learning, memory, and brain development [151,152]. Risk variations in *CACNA1C* have been found in several association studies of BD, and evidence suggest that some of *CACNA1C* variations are risk for SCZ, MDD, ADHD, and ASD.

 doi:10.20944/preprints201906.0192.v1

Several SNPs in *CACNA1C* have been linked to psychiatric disorders with most of them being located in a large intron (~330 kb) between exons 3 and 4 (intron 3). Significant association of the SNP rs1006737 to BD was originally found in a European cohort (> 4300 cases and >6000 controls) [153]. Associations of this SNP with BD have been replicated in several other studies, furthermore significant association of rs100637 with SCZ, ADHD and MDD has also been detected [154–156]. At the molecular level, rs100637 is correlated with changes in *CACNA1C* expression, including decreased expression in the cerebellum [157], but increased expression in the dorsolateral prefrontal cortex and induced human neurons [132,158]. The latter observation correlates with increased L-type currents seen in induced human neurons derived from individuals carrying rs1006737 [158]. Furthermore, the minor allele for rs1006737 (A) is associated with increased methylation of CpG islands located within intron 3 [159]. Imaging studies have shown associations of rs1006737 with changes in structure and activity of brain regions related to emotion processing, memory formation and cognition, including hippocampus, inferior occipital fusiform gyrus, prefrontal cortex and amygdala [132,160,161]. For example, carriers of rs1006737 show greater thickness of the medial orbitofrontal cortex than non-carriers, and the presence of this SNP correlates with age-related caudal anterior cingulate cortex thickening [161]. In addition, two independent studies have shown that rs1006737 is associated with increased amygdala volumes in adults and adolescents [162,163]. Behavioral studies in humans suggest that rs1006737 is linked to facial emotion recognition in both healthy individuals and patients with BD [164,165]. Some studies suggest that rs1006737 is also associated with borderline personality disorder in females, but not males [166,167]. rs1006737 has significant association with reduced baseline affective startle modulation in healthy males.

 doi:10.20944/preprints201906.0192.v1

Alterations in this endophenotype have been observed in severely depressed and anxious patients, as well as patients with BD in remission [168].

As mentioned above, rs1006737 has also shown strong associations with SCZ. Additive interaction of the SNP rs1006737 *CACNA1C* with rs1344706 in the zinc finger protein 804A gene (ZNF804A) has been linked to defects in white matter microstructure and psychosis [169], although the effect of rs1344706 is thought to be larger than rs1006737. In MDD, rs1006737 was associated with less baseline depressive severity [170]. Furthermore, rs1006737 showed biphasic association with antidepressant treatment in a European population. The A allele was associated with a better outcome of antidepressant treatment, but it shows the opposite association in a group of individuals with treatment-resistant depression [171].

The SNP rs2007044 has been associated with SCZ in several studies including Asian, East Asian, European and Ashkenazi Jew populations [172–176]. This SNP was associated with decreased functional connectivity between the right dorsolateral prefrontal cortex and right superior occipital gyrus/cuneus, as well as the anterior cingulate cortex; and at the behavioral level with poor working memory performance [177]. rs2007044 is also associated with increased concentrations of glutamate, glutamine and glutamate plus glutamine in subcortical regions. These observations have been reported in patients with SCZ, especially in subjects at risk of psychosis [178].

Sleep disturbance is consistently reported in patients with psychiatric disorders including SCZ, BD and MDD [179–181]. *CACNA1C* variations in intron 3 have been linked to sleep traits

 doi:10.20944/preprints201906.0192.v1

such as narcolepsy (rs10774044), sleep latency and sleep quality (rs7316184, rs7304986, rs7301906, rs16929275, rs16929276, rs16929278, rs2051990) [182–184]. The SCZ risk variations in *CACNA1C* (rs4765913, rs4765914, and rs2239063) are associated with sleep latency in infants [185]. rs4765914, together with rs7297582, was identified in two independent studies as genetic risks for BD, MDD, and SCZ [155,186].

Other SNPs in CACNA1C have been linked to several psychiatric conditions. The SNP rs73248708 (intron 3) and rs116625684 (intron 1) were not associated with SCZ or other psychiatric disorders, they affect the risk of developing depressive symptoms upon exposure to adult severe trauma in adulthood [187]. The SNP rs10848635 was identified in a Korean and in a Taiwanese population as risk factor for SCZ and BD, respectively [188,189]. Associations of rs10848635 with efficacy of the anti-depressant citalopram were also found [171]. The SNP rs4765913 was identified in two independent GWAS of European cohorts as genetic risk for BD [190,191]. rs10848653 and rs2239118 were identified using a family-based association test (parent/affected child trios) been linked to ASD, this study also identified SNPs in *CACNA1G* (see below) [190,191].

In addition to variations with mendelian inheritances (TS) and SNPs associated to psychiatric disorders, two *de novo* missense variations in *CACNA1C* were identified in a large whole-exome sequencing study using massively parallel short-read sequences of more than 2500 patients with SCZ and more than 2500 control subjects in a Swedish population [192]. One risk variant (G/T) is predicted to alter a canonical splice donor site for exon 21, which is part of a pair

 doi:10.20944/preprints201906.0192.v1

of mutually exclusive exons (together with exon 22), with exon 21 being dominant in the brain [22]. The second risk variant (C/T) introduces a premature stop codon [18].

b) *CACNA1D*

The *CACNA1D* gene encodes $Ca_V1.3$. This channel contributes to the rhythmic activity of the sinoatrial node and is thereby involved in the regulation of heart rate [54]. As stated above, $Ca_V1.3$ shares some functions with $Ca_V1.2$ in the brain. However, $Ca_V1.3$ is the main contributor to the pacemaking activity of dopaminergic neurons in the substantia nigra [54]. Risk variations in *CACNA1D* have been associated with BD, SCZ, ADHD, MDD, and ASD. The non-coding SNP rs893363, located in the 3' UTR of *CACNA1D* and the putative promoter region of the choline dehydrogenase gene (*CHDH*), was found in a genome-wide analysis of five major psychiatric disorders including BD, SCZ, ADHD, MDD, and ASD [155]. In a study with samples from a cohort of European-American individuals, 111 non-coding variations in regulatory elements that are predicted to modify binding of transcription factors to genomic regions of *CACNA1D* show significant association with BD [193]. Furthermore, two coding variations in *CACNA1D* (A1751P and R1771W) segregate with BD type I cases in a large pedigree [194]. Although a study in a Han Chinese population found no association between *CACNA1D* SNPs and SCZ [195], more recent studies that include larger populations of East Asian, Chinese, European and Ashkenazi Jewish individuals identified the SNP rs2358740 located in a putative promoter region for *CACNA1D* and the mRNA decapping enzyme 1A gene (*DCP1A*) as a risk variant for SCZ [173,196,197].

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Several studies point to links between *CACNA1D* and ASD. Through whole-exome sequencing three *de novo* missense variations in *CACNA1D* (A749G, G407R, and V401L) were identified as genetic risks for patients with sporadic autism and intellectual disability [198–200]. These genetic risk variations produce a gain of function of $Ca_V1.3$ channels [201–203]. Additional variations (A59V, S199L and R2021H) were also identified in using WES. The A59V maps to an N-terminal region of $Ca_V1.3$ that is key for calcium-dependent inactivation. S1977L and R2021H map to a proline-rich domain of the C-terminus that interacts with SH3 And Multiple Ankyrin Repeat Domain 3 protein (Shank3). Interestingly, *SHANK3* is another gene strongly linked to ASD [204]. The gene *CACNA1D* is subject to alternative splicing. Interestingly alterations in the relative abundance of several alternatively spliced exons in *CACNA1D* have been observed cortical samples of patients with ASD [205]. Finally, the variation Q567H is linked to moderate hearing impairment and intellectual disability, this variation results in a loss of function [206].

Although risk variations in *CACNA1S* and *CACNA1F* have been identified in GWAS and WES studies for BD and SCZ, we will not review them here because the expression of these two genes in the brain is extremely rare relative to the other Ca_V genes, therefore the links their corresponding risk variations to psychiatric disorders are hard to infer [18].

c) *CACNA1A*

CACNA1A is the most dominant presynaptic calcium channel in central synapses, particularly those ones from Purkinje cells in the cerebellum and excitatory synapses of cortex

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and hippocampus. Various mutations in *CACNA1A*, causing gain or loss of function, have been found in patients with hemiplegic migraine 1 (FHM-1), Episodic Ataxia 2 (EA-2), SCA-6, and epilepsy [14]. More recently, a clinical recharacterization of patients with EA-2 and SCA-6 showed that they also present delayed development, endophenotypes related to learning disabilities, ASD and ADHD [207]. In another study, some FHM-1 and EA-2 patients also presented SCZ, learning disabilities and ADHD [208]. Furthermore, analysis of the splice isoform landscape across several psychiatric disorders show that alternative splicing of *CACNA1A* is altered in ASD [209]. Finally, rs10409541 was among the top 15 most contributory SNPs for ASD diagnosis prediction in a Central European population [191].

d) *CACNA1B*

CACNA1B encodes $Ca_V2.2$ channels, which are dominant in presynaptic terminals of dorsal root ganglia and superior cervical ganglia, as well as some interneurons, and dopaminergic neurons of the midbrain. Several studies have linked *CACNA1B* to SCZ, but also some *CACNA1B* risk variations are associated with BD and ASD. Purcell, *et al.* identified a *de novo* variation (G/A) in patients with SCZ that introduces a premature stop codon in *CACNA1B* [192]. The intronic SNPs, rs7036881 and rs78178087, in *CACNA1B* have been found to be weakly associated with SCZ and the antipsychotic efficacy of paliperidone palmitate in a study with European patients [210]. In line with this, another study in a South African population found that the rs2229949 is linked to improved negative symptomatology during antipsychotic treatment [211]. Deletions in *CACNA1B* were detected in 16 patients and duplications of this same gene in 10 patients with SCZ [212].

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Several studies have reported that *CACNA1B* is linked to ASD, MDD, and BD. A monogenic duplication in *CACNA1B* has been linked to Asperger Syndrome, a condition that is part of ASD [213]. Pathway analysis of variations linked to ASD has shown that *CACNA1B*, together with *CACNA1C* and *CACNA1F*, converges on MAP kinase/cellular signaling and neuronal development/axon guidance [214]. *CACNA1B*, together with *CACNA1C* and *CACNA2D4*, has been also associated with suicide risk in patients with MDD [215]. Finally, WES of 200 individuals from 41 families identified 50 non-coding variations in *CACNA1B* that increase the risk for BD [193].

e) *CACNA1E*

CACNA1E encodes the $Ca_V2.3$ or R-type channels. $Ca_V2.3$ channels are broadly expressed throughout the nervous system and are located in presynaptic terminals, dendritic spines, and some extrasynaptic sites [67]. variations in the *CACNA1E* gene have been linked to ASD, MDD, SCZ, as well as some endophenotypes related to these conditions. In a study comprising 209 families with no previous history of ASD, parent-child with sporadic autism trios and unaffected siblings were sequenced and a *de novo* variant in *CACNA1E* (G1209S) was identified in one patient [198]. A second *de novo* synonymous variation in *CACNA1E* located near a splice site and is predicted to affect an exonic spicing regulator was identified in another patient with ASD [216]. In a genome-wide meta-analysis study of more than 135,000 cases with more than 340,000 controls, 44 significant risk loci for MDD were identified, including *CACNA1E* [217]. The SNP rs4652676 was linked to neuroticism and subjective well-being,

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which are endophenotypes associated with MDD [218]. The SNP rs704329 is implicated in the efficacy of serotonin reuptake inhibitors (SSRIs) in a Taiwanese population [219]. Similar to several other *CACNA1* genes, *CACNA1E* has been associated with SCZ as well as working memory related to cortex and cerebellum [155,220].

f) *CACNA1G*

CACNA1G encodes the $Ca_V3.1$, a T-type channel member of the Ca_V3 subfamily. Previous studies have identified risk variations of *CACNA1G* as genetic risk for ASD. A linkage study of sibling pairs with only male probands found a strong association of the chromosomic region 17q11-21, which contains among other genes, *CACNA1G* [216]. A later study confirmed *CACNA1G* as a novel candidate gene for ASD by identifying several SNPs within intron 9 with the strongest association relative to other genes present in the 17q11-21 region [221]. rs198538 and rs198545, together with some *CACNA1C* SNPs, were identified as risk variations for ASD [190]. Furthermore, a *de novo* synonymous variation in *CACNA1G* was identified in exome sequencing of 343 families with one proband and at least one unaffected sibling [199,222]. A *de novo* variation screening in childhood-onset cerebellar atrophy identified various disruptive variations in *CACNA1G*, some patients with this pathology exhibit autistic traits [223]. However new studies using transcriptome-wide association, which integrated GWAS with gene expression predictors from several databases from adult and fetal human brain, found no evidence of association between *CACNA1G* and ASD [224].

g) *CACNA1H*

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The *CACNA1H* gene encodes the $Ca_V3.2$ channel, also a T-type channel. This gene is normally associated with idiopathic epilepsy. However, multiple studies have found associations of *CACNA1H* with ASD and SCZ. Four missense variations (R212C, R902W, W962C and A1874V) were identified in a study of 461 probands with ASD and 480 ethnically matched individuals by targeted sequencing of the *CACNA1H* genomic region [225,226]. Functional analysis revealed that these variations produce loss of function of $Ca_V3.2$ by reducing channel conductance, and/or shifting voltage-dependence of activation in the depolarizing direction [225]. However, these variations have low penetrance, and some of them were also found in unaffected individuals [225]. In a more recent study using ultra deep sequencing of 78 ASD candidate genes in the cerebellum and cortical samples of several ASD cases and neurotypical controls, a synonymous *CACNA1H* variation was found in the frontal cortex but not in cerebellum [227]. In this same study, a missense variation (S1970C) was identified in a female diagnosed with ASD [227]. WES from more than 10,000 parents with only one child with ASD found *de novo* missense variations in *CACNA1H* [199,228]. Furthermore, a study of 262 patients with their unaffected parents from Japan identified a disruptive *de novo* missense variations in *CACNA1H* (R1189C) [229]. All of these studies support that *CACNA1H* is a susceptibility gene for ASD.

Two rare disruptive variations (7 bp and 2 bp deletions) for *CACNA1H* that are predicted to produce a frameshift were found in patients with SCZ [192]. Furthermore, a GWAS performed in a Swedish population, followed by a meta-analysis with previously identified genes associated with SCZ, found association of *CACNA1H* with this condition [230].

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h) *CACNA1I*

CACNA1I encodes $Ca_V3.3$ channels, the third T-type channel member of the Ca_V3 subfamily. Of the Ca_V3 members, $Ca_V3.3$ channels have the most depolarized threshold of activation, as well as the slowest opening and inactivation rate [20]. $Ca_V3.3$ channels regulate sleep spindles, which have been shown to be altered in patients with SCZ [181]. Not surprisingly, several studies have strongly linked *CACNA1I* to SCZ and related endophenotypes. Additional evidence also suggests risk variations of *CACNA1I* for ADHD and ASD.

Two rare, *de novo* missense variations of *CACNA1I* (R1346H and T797M) were identified by exome sequencing of trio samples that included 105 probands, parents, and unaffected siblings when available [231]. $Ca_V3.3$ was the only gene with more than one variation [231]. In particular, R1346H impairs N-glycosylation of $Ca_V3.3$ channels preventing membrane targeting and thereby reducing overall calcium currents [232]. The functional consequences of T797M are unknown, however this mutant produces similar calcium currents relative to WT [232]. A study by the SCZ working group of the PGC validated *CACNA1I* as a risk gene for SCZ [172]. This claim has been supported in other GWAS. The intergenic SNPs between *RPS19BP1* and *CACNA1I*, rs5757717 and rs9611198, were found in a GWA study of an Ashkenazi Jewish population and an Irish population respectively [173,233]. The intronic SNP rs3788567 was identified with very high significance in an Ashkenazi Jewish population [173]. In a study of an Uyghur Chinese population that comprised 985 patients and 1218 neurotypical controls, six SNPs within *CACNA1I* were significantly associated with SCZ (rs132575,

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rs136805, rs713860, rs738168, rs5757760, rs575087) [234]. Furthermore, rs4522708, rs3788568, rs5750862 were significantly associated with SCZ in a Han Chinese population [235,236]. Interestingly, rs4522708 was also found in a study of a European population [172]. *CACNA1I* has been also associated with endophenotypes related to SCZ, such as cognitive ability and sleep spindle activity. A genome wide meta-analysis study identified an association of *CACNA1I* with cognitive ability [237]. The genomic region Chr22: 39975017:40016914, which spans across *CACNA1I* was associated with higher amplitude, longer duration and higher intensity of slow spindles in healthy adolescents [238].

A recent GWAS linked the rs199694726 in *CACNA1I* to impulsive behavior under extreme negative emotions [239]. Impulsive traits are a common endophenotype related to psychiatric disorders including ADHD [240]. Furthermore, a study containing 1,013 probands of European descent at the Children's Hospital of Philadelphia (CHOP) found a *CACNA1I* CNV (large deletion) associated with ADHD [241]. *CACNA1I* was also identified as a risk gene for ASD in the family-based association test [242]. The SNP rs5750860 was significantly associated to ASD in an another GWAS [190].

8. Genetic associations between Cavα2δ and Cavβ auxiliary subunits and psychiatric disorders

In the previous section we summarized strong evidence linking several genes that encode $Ca_V\alpha_1$ pore-forming subunits to psychiatric disorders. Given that the auxiliary subunits, $Ca_V\alpha_2\delta$ and $Ca_V\beta$, heavily influence membrane targeting and overall activity of $Ca_V\alpha_1$, genes encoding

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these subunits are also strongly linked to psychiatric disorders. In this section, we will describe current studies associating the genes for $Ca_V\alpha_2\delta$ and $Ca_V\beta$ with multiple psychiatric disorders.

a) *CACNA2D1*

The *CACNA2D1* gene encodes the $Ca_V\alpha_2\delta$-1 subunit. This subunit is highly expressed in skeletal muscle, the brain and peripheral nervous system [79], and some studies suggest that it is enriched in glutamatergic neurons [243]. Various genetic studies have implicated the *CACNA2D1* gene in psychiatric disorders including MDD, BD and SCZ. The genome-wide association metanalysis of MDD that identified *CACNA1E*, also found *CACNA2D1* as potentially druggable target for this condition [217]. Furthermore, in a genome-wide association environment study, a suggestive association was found for rs17156280 in *CACNA2D1* with an interaction between depressive state and stressful events [244]. A strong association with depressive traits including subjective well-being and neuroticism was found for the SNPs in *CACNA2D1*, rs258668 and rs258677 [218].

A metanalysis of data collected by the Bipolar Disorder Genome Study Consortium identified rs2367911 as a risk SNP for BD with comorbid binge eating. Indeed, networks/interactomes for *CACNA2D1* and apolipoprotein B gene (*APOB*) were the top two hits for BD and binge eating in this study [245]. The same study that identified risk variations for *CACNA1C* and other Ca_V genes in a Swedish population, found a disruptive variation in *CACNA2D1* that produces a frameshift associated with SCZ [192]. A study in a Japanese population a found CNV for *CACNA2D1* (a large deletion) in one patient with SCZ [118].

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b) *CACNA2D2*

CACNA2D2 encodes $Ca_V\alpha_2\delta$–2. Although this protein is broadly expressed in the central nervous system, there is higher expression in the cerebellum relative to other areas of the brain, particularly in Purkinje cells [30]. In cortical tissue, some studies suggest that $Ca_V\alpha_2\delta$–2 is more abundant in interneurons than in glutamatergic neurons [243]. Purcell et al, found three *de novo* variations in *CACNA2D2* in patients with SCZ. Two of these three variations introduced premature stop codons, and a the third one is predicted to disrupt a splice donor site [194]. A *CACNA2D2* variation (A900T) scored as a putative second hit in a study of 558 patients with SCZ in a Spanish population [246].

c) *CACNA2D3*

CACNA2D3 encodes $Ca_V\alpha_2\delta$–3. This protein was initially characterized as a target to treat pain, however recent studies suggest that the *CACNA2D3* is strongly linked to ASD, and to a lesser extent, SCZ and BD. The same WES that identified variations in *CACNA1G*, found another variation in *CACNA2D3* that is predicted to disrupt a splice junction (A/G) [222]. An inherited variation with splicing disruption was identified in a study of 2,066 unique families with children diagnosed with ASD, the cohort consisted of 2,618 children with ASD (1,740 probands and 878 unaffected siblings) [247] . Furthermore, a *de novo* variation (E508Stop) predicting loss of function of $Ca_V\alpha_2\delta$–3 was found in two patients in an exome sequencing study that included 3871 ASD cases and 9937 ancestry controls. This study also identified several

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inherited variations in *CACNA2D3* which effect is unknown [248]. Analysis of CNVs in a study containing samples from 2,478 families with children affected with ASD identified through the Simons Simplex Collection found association to a deletion in *CACNA2D3* [249]. In a study where 208 candidate genes were sequenced in 11,730 cases and 2,867 controls, two *de novo* missense on *CACNA2D3* were identified (A773V and A275T) [250]. The SNP rs3773540 was among the top 15 SNPs contributing to ASD diagnosis as predicted by gene set enrichment analysis [191]. Analysis of data from the Hartwell Autism Research and Technology Initiative (iHART) has further confirmed that *CACNA2D3* is a risk gene for ASD [250].

Previous studies have shown that the 3p14 genetic region is associated with SCZ and with an endophenotype related to the function of the temporal lobe, the antisaccade reflex. Interestingly, this genomic region contains *CACNA2D3* [251]. Pathway analysis of SNPs with significant risk for SCZ suggest association of *CACNA2D3* with the response to lurasidone, an antipsychotic used to treat SCZ [252]. Also, the genomic region 3p21.1_1 is enriched in for both SCZ and BD, this region contains *CACNA1D* and *CACNA2D3* among six different genes [253]. The SNP rs9849795 located in *CACNA2D3* is associated with functional brain connectivity inferred by functional magnetic resonance, this trait thought to be compromised in BD and SCZ, this study also identified association with SNPs in *CACNA1C*, *CACNA2D4* and *CACNB2* [254].

d) *CACNA2D4*

CACNA2D4 encodes the $Ca_V\alpha_2\delta$-4 subunit. This protein is abundantly expressed in the retina, but it is also found in pituitary and adrenal glands [83,255]. Despite the relatively low

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expression of $Ca_V\alpha_2\delta$-4 in the brain compared with other auxiliary subunits, several studies have identified the *CACNA2D4* as a risk gene for some psychiatric disorders.

The SNP rs1024582 located between *CACNA2D4* and *CACNA1C* was found highly significant in a cross-disorder study that included ADHD, BD, ASD, SCZ and MDD [155]. In a later study by Purcell et al, a *de novo* variation that produces a frameshift in *CACNA2D4* was identified in patients with SCZ [192]. The SNP rs4765847 was found to associate with DMN, an endophenotype of SCZ [254]. Furthermore, partial deletions of 35.7 kb in *CACNA2D4* was found in two unrelated patients with late onset BD I and one in control individuals [256]. These three deletions eliminate exons 17-26 in *CACNA2D4*, which comprise most of the Cache domain [256]. In a linkage disequilibrium study to detect SNP-SNP interactions that are common in complex diseases a single interaction between SNPs located near *RYR2* and *CACNA2D4* was found in samples of the Wellcome Trust Case Control Consortium (WTCCC) [257].

Genetic associations of *CACNA2D4* with MDD and ASD have been also identified. In a WES study in brain samples of suicide victims suffering from MDD and control subjects with MDD who died from other causes, a variation in a splice donor (C/A) in *CACNA2D4* was identified [215]. For ASD, a rare homozygous deletion was detected in a male proband that is predicted to affect *CACNA1C* and *CACNA2D4* (12p13.33) [258].

e) *CACNB1*

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CACNB1 encodes for $Ca_V\beta_1$. A splice variant of this subunit was originally identified in skeletal muscle ($Ca_V\beta_{1a}$) as the only partner of $Ca_V1.1$, later it was demonstrated that splice variations of $Ca_V\beta_1$ are also expressed in the brain ($Ca_V\beta_{1b}$, $Ca_V\beta_{1c}$, and $Ca_V\beta_{1d}$), particularly in cerebral cortex, habenula, hippocampus and olfactory bulb [38]. Some studies suggest association of the *CACNB1* with ASD, BD and SCZ; however the evidence is scarce. A metanalysis of five genome-wide linkage scans in 634 affected sibling pairs found a suggestive association between the chromosome region 17p11.2-q12 and ASD, this region comprises *CACNB1*, however this finding requires further replication [259]. For BD, increased *CACNB1* expression was reported in IPSCs derived from patients with BD relative to IPSCs from their unaffected relatives [260]. In this study, *CACNA1G* and *CACNA1E* were downregulated [260]. Regarding SCZ, only one GWAS has linked *CACNB1*, together with other calcium channel genes, with SCZ and working memory across multiple ages in healthy individuals [220].

b) *CACNB2*

CACNB2 encodes the $Ca_V\beta_2$ subunit. $Ca_V\beta_2$ is widely expressed in the brain, heart, and other tissues such as lung, liver and pancreas. *CACNB2* has the largest number of splice variants among the *CACNB* genes, all these splice variants are abundant in the heart and brain [38]. *CACNB2*, together with *CACNA1C*, is one of most consistently found risk genes for psychiatric disorders, particularly SCZ and BD. Some evidence of association of *CACNB2* with MDD and ASD has also been reported.

 doi:10.20944/preprints201906.0192.v1

Several SNPs in *CACNB2* have been linked to SCZ with high significance including rs7893279, rs7099380, rs17691888, rs2799573, and rs10508558. rs7893279 was identified in a Psychiatric Genomics Consortium study for SCZ [172], rs7099380 in an Ashkenazi Jew population [173], rs17691888 in a Swedish population and was further confirmed using a regulatory trait concordance approach to prioritize SNPs and genes within SCZ loci [261–263]. rs2799573 has been identified across multiple disorders including SCZ, BD, ADHD and ASD [155,264]. rs10508558 was identified in genome-wide metanalysis for SCZ [265]. Other SNPs in *CACNB2* such as rs17661538 have been linked to antipsychotic responses of clozapine [266], and rs1277738 has been found across multiple disorders and also linked to DMN [254]. Other intronic SNPs in *CACNB2* are also associated with working memory and brain activity [220].

Similar to *CACNA1C*, SNPs in *CACNB2* have shown strong association with BD and other psychiatric disorders. In fact, the some of the SNPs in *CACNB2* that are associated with BD are also associated with SCZ. For example, an association of rs11013860 with BD and SCZ was identified in a Han Chinese and Taiwanese populations [189]. A study using a pleiotropy-informed conditional false discovery rate, which improved detection of common variations associated with BD, identified rs7083127 [266]. *CACNB2* has also been associated with binge eating and BD in a second study [245]. rs2489198, rs4747340, rs7083127, rs12247369, rs2799573 have been linked to the five major disorders ADHD, SCZ, ASD, BD, and MDD [155]. Furthermore, several SNPs in *CACNB2* are linked to the response to SSRIs [267].

In a WES study, three variations in *CACNB2* have been found in ASD probands but not in controls (G167S, S197F, and F240L), although with incomplete segregation. All three

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variations affect the kinetics of inactivation of calcium currents [268]. In a second study that included 85 family quartets (two parents and two affected siblings), the variations V2D was identified, but the functional effect of this variant is unknown [269].

c) *CACNB3*

CACNB3 encodes for the $Ca_V\beta3$ subunit and is mostly expressed in the brain and to some extent in heart, aorta, and kidney. Previous studies have shown associations of the *CACNB3* with BD and SCZ. The SNPs rs2070615 and rs11168751 were found to confer risk to BD in a European population [270,271]. QLTs in *CACNB3* have also been linked to both BD and ADHD [272]. Finally, pathway analysis has confirmed associations of *CACNB3* with SCZ [273].

d) *CACNB4*

CACNB4 encodes the $Ca_V\beta4$ subunit, and together with $Ca_V\beta3$, is one of the most abundant $Ca_V\beta$ subunits in the brain. $Ca_V\beta4$ subunit is the most commonly found $Ca_V\beta$ in complex with Ca_V2 channels suggesting an important role of this subunit in presynaptic transmitter release [274]. Several studies have linked *CACNB4* to MDD, anxiety disorders and SCZ [230,261,275].

9. Ca_V modulators for the treatment of psychiatric disorders

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Given the large amount of evidence from multiple studies implicating Ca_V genes in the pathophysiology of psychiatry disorders, it is worthwhile to consider targeting $Ca_V\alpha_1$, $Ca_V\alpha_2\delta$, and $Ca_V\beta$ subunits as a potential therapeutic strategy to treat these disorders. Although several drugs targeting $Ca_V\alpha_1$, $Ca_V\alpha_2\delta$, and $Ca_V\beta$ subunits already exist, they are typically prescribed to treat cardiovascular conditions, pain, and epilepsy [17]. However, drugs with anti-epileptic and analgesic effects such as gabapentin and pregabalin are now being explored as a novel approach to treat anxiety [276]. Similarly, topiramate, a drug that has several targets including $Ca_V2.2$ and $Ca_V2.3$ channels, has shown some promise to treat posttraumatic stress disorder (PTSD) comorbid with alcohol dependence [277]. $Ca_V2.2$ channel blockers such as Z160 and CNV2197944 are being considered to treat anxiety (Table 2) [17].

Currently several trials targeting Ca_Vs and auxiliary subunits have been completed or are being performed (www.clinicaltrials.gov). The L-type channel blockers, nimodipine and isradipine are being evaluated on cognitive performance in patients with SCZ. Ethosuximide, a drug that blocks Ca_V3 channels, is being tested for treatment-resistant depression. Gabapentin is also being tested for bipolar disorder. In recent years there has been over 35 clinical trials completed testing the efficacy of lamotrigine (a drug that targets $Ca_V2.3$ channels [278,279]) in bipolar disorder as well as clinical trials for major depression and schizophrenia. Drugs targeting Ca_Vs that are showing promise in animal models are the Ca_V3 channel enhancer, Sak3. This drug has been found to reduce depressive-like behaviors in mice by increasing serotonin and dopamine levels (Table 2) [280,281].

10. Conclusions

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Modern analysis of large cohorts has shed tremendous amount of light on the genetic risks associated with psychiatric disorders. Techniques such as next generation sequencing, microarrays, linkage studies, endophenotype analysis and computer modeling are increasing our chances to elucidate the cellular and molecular mechanisms underlying psychiatry disorders. Although most genetic studies strongly suggest that multiple genes are associated with psychiatric disorders, risk variations in Ca_V gene have been consistently found associated with the five major psychiatric disorders SCZ, MDD, ADHD, ASD, and BD. This nicely aligns with the neuronal functions of Ca_V genes.

The $Ca_V\alpha_1$, $Ca_V\alpha_2\delta$, and $Ca_V\beta$ subunits are relatively well-known pharmacological targets. Several studies have demonstrated their involvement in neuronal firing, axon guidance, neuronal development, synapse formation and activity-dependent function. However, a major challenge is to link risk variations of Ca_V genes to their pathophysiological functions in the context of psychiatric disorders. Studies on the SNP rs1006737 in *CACNA1C* are leading the way on this, several studies been performed at the molecular, cellular and behavioral level to elucidate how this risk variation is involved in BD. However, in addition to individual risk variations, it is important to weigh the compounded effect of individual variations as they interact with other genes, and with the environment. Machine learning is becoming a novel approach to integrate information arising from genetic studies to elucidate the various mechanisms that are likely to underlie psychiatric disorders, as shown with PsychEncode.

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For therapeutic purposes, tissue expression of Ca_V genes should be taken into account. For example, $Ca_V1.2$ channels are promising targets for BD and SCZ, however their robust expression in the heart and blood vessels poses a challenge for intervention. Further studies should aim at blocking or activating specific Ca_Vs present in the brain but not in the heart. Alternative splicing is a possible path for drug specificity, because $Ca_V1.2$ splice variants in the heart are substantially different from the ones in the brain [22]. Nonetheless, Ca_Vs offer an intriguing viable option to develop novel treatments for psychiatric disorders.

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FIGURE LEGENDS

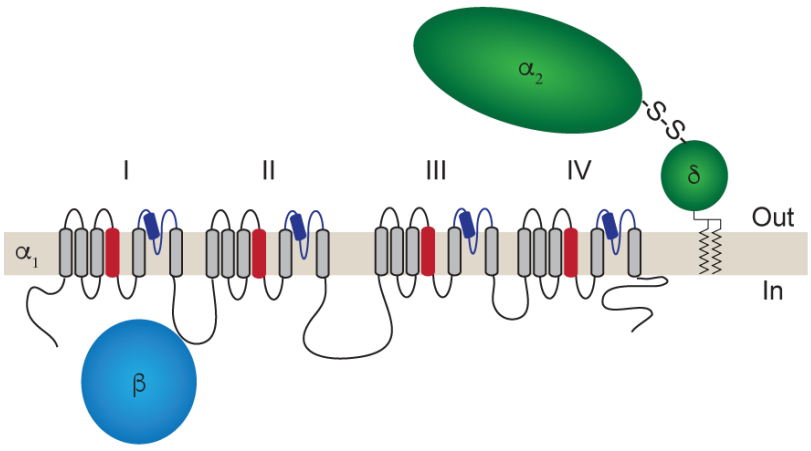

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Figure 1. Schematic representation of a Ca_V complex. The $Ca_V\alpha_1$, $Ca_V\alpha_2\delta$, and $Ca_V\beta$ subunits are depicted. The 24 transmembrane segments of the $Ca_V\alpha_1$ subunit are shown arranged in the four domains (D1-IV), the voltage sensors are indicated in red, and the reentrant loop between S5 and S6 (P-loop) in dark blue. The GPI-anchored $Ca_V\alpha_2\delta$ is shown in green, and the cytoplasmic $Ca_V\beta$ subunit in light blue.

Table 1. Nomenclature and classification of $Ca_V\alpha_1$ subunits based on sequence similarity and biophysical properties.

Gene name in human	Protein name (old)	Protein name (new)	Current type	Subfamily	Threshold of activation
CACNA1S	α_{1S}	$Ca_v1.1$	L	Ca_V1	HVA (associated with $Ca_V\alpha_2\delta$ and $Ca_V\beta$ subunits)
CACNA1C	α_{1C}	$Ca_v1.2$	L		
CACNA1D	α_{1D}	$Ca_v1.3$	L		
CACNA1F	α_{1F}	$Ca_v1.4$	L		
CACNA1A	α_{1A}	$Ca_v2.1$	P/Q	Ca_V2	
CACNA1B	α_{1B}	$Ca_v2.2$	N		
CACNA1E	α_{1E}	$Ca_v2.3$	R		
CACNA1G	α_{1G}	$Ca_v3.1$	T	Ca_V3	LVA (associated with CACHD1)
CACNA1H	α_{1H}	$Ca_v3.2$	T		
CACNA1I	α_{1I}	$Ca_v3.3$	T		

Table 2. Summary of genetic links between Ca_V genes and psychiatric disorders, classical modulators of Ca_Vs, and their potential use to treat psychiatric disorders

Gene name in human	Associated Disorder	Classical modulators	Potential therapeutic intervention for psychiatric disorders
CACNA1S	---	Dihydropyridines	• Nimodipine (SCZ) • Isradipine (BD, SCZ)
CACNA1C	ASD, SCZ, BD, MDD, ADHD		

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CACNA1D	ASD, SCZ, BD, MDD, ADHD		• Verapamil (BD) • Diltiazem (BD)
CACNA1F	---		
CACNA1A	SCZ, ADHD, MDD	ω-Agatoxin IVA	TBD
CACNA1B	SCZ, ASD, MDD	ω-Conotoxin GVIA	• CNV2197944 (anxiety) • Z160 (anxiety)
CACNA1E	ASD, MDD, SCZ	SNX 482	• Lamotrigine (BD, SCZ, treatment resistant depression, anxiety) • Topiramate (PTSD)
CACNA1G	ASD	TTA-A2, TTA-P2, ProTx-I, ProTx-II	• Sak3 (MDD)
CACNA1H	ASD, SCZ		
CACNA1I	SCZ, ADHD, ASD		
CACNA2D1	MDD, BD, SCZ	Gabapentin, pregabalin	• Pregabalin (anxiety, SCZ) • Gabapentin (anxiety, mood disorders)
CACNA2D2	SCZ		
CACNA2D3	ASD, SCZ, BD	TBD	TBD
CACNA2D4	ASD, SCZ, BD, MDD, ADHD		
CACNB1	ASD, BD, SCZ	TBD	TBD
CACNB2	ASD, SCZ, BD, MDD, ADHD		
CACNB3	ASD, BD, SCZ		
CACNB4	MDD, SCZ, anxiety disorders		

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