A molecule-based genetic association approach implicates a range of voltage-gated calcium channels associated with schizophrenia

Wen Li[1,2], Chun Chieh Fan[3,4], Tuomo Mäki-Marttunen[1,2], Wesley K. Thompson[5,6,7], Andrew J. Schork[8], Francesco Bettella[1,2], Schizophrenia Working Group of the Psychiatric Genomics Consortium[¶], Srdjan Djurovic[9,10], Anders M. Dale[3,4,5,11], Ole A. Andreassen[1,2], Yunpeng Wang[1,2,3,4,7*]

[1]NORMENT, KG Jebsen Centre for Psychosis Research, Institute of Clinical Medicine, University of Oslo 0424 Oslo, Norway
[2]Division of Mental Health and Addiction, Oslo University Hospital, 0407 Oslo, Norway
[3]Department of Neurosciences, University of California, San Diego, La Jolla, CA 92093, USA
[4]Multimodal Imaging Laboratory, University of California, San Diego, La Jolla, CA 92093, USA
[5]Department of Psychiatry, University of California, San Diego, La Jolla, CA 92093, USA
[6]Institute of Biological Psychiatry, Mental Health Centre Sct. Hans, Mental Health Services, Copenhagen, Denmark
[7]The Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, Copenhagen, Denmark
[8]Department of Cognitive Sciences, University of California, San Diego, La Jolla, CA92093, USA
[9]Department of Medical Genetics, Oslo University Hospital, 0407 Oslo, Norway.
[10]NORMENT, KG Jebsen Centre for Psychosis Research, Department of Clinical Science, University of Bergen, Bergen, Norway
[11]Department of Radiology, University of California, San Diego, La Jolla, CA 92093, USA

[¶] Memberships of the Schizophrenia Working Group of the Psychiatric Genomics Consortium are provided in Acknowledgments section.

Corresponding author information:
* Dr. Yunpeng Wang
NORMENT, KG Jebsen Centre
Building 49, Oslo University Hospital, Ullevål
Kirkeveien 166, PO Box 4956 Nydalen
0424 Oslo, Norway
Email: yunpeng.wang@medisin.uio.no
Phone +47 46 55 96 52
Fax: +47 23 02 73 33

Running title: Molecule-based genetic association test

Abstract

Traditional GWAS have successfully detected genetic variants associated with schizophrenia. However, only a small fraction of heritability can be explained. Gene-set/pathway based methods can overcome limitations arising from single SNP-based analysis, but most of them place constraints on size which may exclude highly specific and functional sets, like macromolecules. Voltage-gated calcium (Ca_v) channels, belonging to macromolecules, are composed of several subunits whose encoding genes are located far away or even on different chromosomes. We combined information about such molecules with GWAS data to investigate how functional channels associated with schizophrenia. We defined a biologically meaningful SNP-set based on channel structure and performed an association study by using a validated method: SNP-set (Sequence) Kernel Association Test. We identified 8 subtypes of Ca_v channels significantly associated with schizophrenia from a subsample of published data (N = 56,605), including the L-type channels ($Ca_v1.1$, $Ca_v1.2$, $Ca_v1.3$), P-/Q-type $Ca_v2.1$, N-type $Ca_v2.2$, R-type $Ca_v2.3$, T-type $Ca_v3.1$ and $Ca_v3.3$. Only genes from $Ca_v1.2$ and $Ca_v3.3$ have been implicated by the largest GWAS (N = 82,315). Each subtype of Ca_v channels showed relatively high chip heritability, proportional to the size of its constituent gene regions. The results suggest that abnormalities of Ca_v channels may play an important role in the pathophysiology of schizophrenia and these channels may represent appropriate drug targets for therapeutics. Analyzing subunit-encoding genes of a macromolecule in aggregate is a complementary way to identify more genetic variants of polygenic diseases. This study offers the potential of power for discovery the biological mechanisms of schizophrenia.

Keywords: schizophrenia, channels, molecule-based GWAS, SNP-sets, SKAT

Introduction

Schizophrenia is a highly heritable complex disease (Lichtenstein et al. 2009). The biological underpinnings of schizophrenia remain an enigma, making prevention difficult and delaying development of better treatment alternatives (Van Os and Kapur 2009). Recently, advances in technology and the establishment of an international consortium, the Psychiatric Genomics Consortium (PGC), have made it possible to perform genome-wide association studies (GWAS) involving more than a hundred thousand individuals. The latest study from PGC has reported 108 independent genomic regions associated with schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014). However, the variants identified can only explain a small fraction of the estimated heritability (Giusti-Rodríguez and Sullivan 2013; Goldstein 2009; Ripke et al. 2013; Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014), and the functional consequences of these variants remain largely uncharacterized. These problems may originate from inherent limitations of the GWAS methodology: The mass univariate testing approach requires an extremely stringent significance threshold to control false positives, thus reducing power; Genetic heterogeneity further complicate interpretation in large meta-analysis; Connecting SNP markers to the causal variants they represent is not straightforward; And, robust, efficient methods for detecting interactions among genetic variants remain elusive.

Gene-based, and gene-set/pathway based methods provide promising alternatives to overcome certain limitations of GWAS (Askland et al. 2012). Typically, genetic variants within or near to a gene are aggregated and tested for associations with a disease (Liu et al. 2010). Gene-set/pathway based analyses aggregate functionally related genes, providing a potentially powerful and biologically oriented bridge between genotypes and phenotypes (Ramanan et al.

2012; Wang et al. 2010). These methods, complementary to GWAS, have several advantages: They can reduce the number of tests performed; They may reduce the impact of genetic heterogeneity across cohorts; And they can facilitate the interpretation of findings. On the other hand, they also have limitations: Genes typically work in concert with one another (Liu et al. 2010), thus gene-based methods cannot take into account the joint effect among genes; The organization of pathways is typically derived from experiments of model organisms or predicted from mathematical models so uncertainties may be present (Bauer-Mehren et al. 2009); The mechanism of the pathways is rarely clear (Khatri et al. 2012); And most published gene-set/pathway analyses place constraints on size from ten to a few hundred genes (Ramanan et al. 2012). Restriction to pathways with more than ten genes may exclude highly specific and potentially informative functional SNP sets, like macromolecules.

A macromolecule is a very large molecule created by polymerization of multiple smaller subunits. Voltage-gated calcium (Ca_v) channels that belong to macromolecules, are pore-forming membrane proteins involved in diverse physiological processes including depolarization of neuronal action potentials, neurotransmitter release, neuronal excitability and intracellular signaling(Simms and Zamponi 2014). Before interesting GWAS findings emerged, they have already received considerable physiological investigations in psychiatric and neurological disorders due to their importance to brain function (Catterall 2000; Simms and Zamponi 2014). Ca_v channels are key mediators of calcium entry into neurons (Turner et al. 2011) and calcium signaling is involved in major molecular hypothesis of schizophrenia such as dopamine, glutamatergic and GABAergic hypothesis (Lidow 2003). In fact, calcium signaling dysfunction has been suggested as a unifying pathological mechanism in schizophrenia (Lidow 2003). Thus,

Ca_v channels gene variants are of large interest in relationship to schizophrenia and we chose to perform the macromolecular analysis of functional Ca_v channels.

Recent GWAS have identified several associated neuronal ion channel genes (e.g. *CACNA1C*, *CACNB2*, *CACNA1I*, *KCNB1*, *HCN1*, *CHRNA3*, *CHRNA5*, *CHRNB4*) (Cross-Disorder Group of the Psychiatric Genomics Consortium 2013; Ripke et al. 2013). In particular, associations at *CACNA1C*, *CACNB2* and *CACNA1I*, which encode Ca_v channel subunits, extend previous findings implicating members of Ca_v channels in schizophrenia (Hamshere et al. 2013; Ripke et al. 2013). Ca_v channels can either be monomers (one subunit), or heteromultimers (three or four subunits). Although these subunits physically bind together to form a channel, their encoding genes are located in different regions of a chromosome or even on different chromosomes. For example, in the $Ca_v1.1$ channel (Bannister and Beam 2013), the α_1 subunit gene *CACNA1S*, $\alpha_2\delta$ subunit gene *CACNA2D1*, β subunit gene *CACNB1* and γ subunit gene *CACNG1* are located at chromosomal bands 1q32, 7q21-q22, 17q21-q22 and 17q24, respectively (Fig. 1). Due to the limitations of gene-based and gene-set based analysis mentioned above, it is possible that taking the macromolecules (Ca_v channels) as a joint entity can explain more for the risk of schizophrenia than one single locus alone.

We defined a SNP set from single channel genes and investigated how this biologically functional unit is associated with schizophrenia, using the accessible PGC schizophrenia GWAS data (N = 56,605: 25,629 cases and 30,976 controls) divided into a discovery and a replication sample. We applied the SNP-set (Sequence) Kernel Association Test (SKAT) (Wu et al. 2010) and identified significant associations in eight subtypes of Ca_v channels ($Ca_v1.1$, $Ca_v1.2$, $Ca_v1.3$, $Ca_v2.1$, $Ca_v2.2$, $Ca_v2.3$, $Ca_v3.1$ and $Ca_v3.3$). In contrast, only genes (*CACNA1C*, *CACNB2* and *CACNA1I*) from two subtypes were implicated by the original GWAS despite its larger sample

(N = 82,315). These findings show the potential of the macromolecule approach to identify the possible etiology of diseases, and suggest that abnormalities of Ca_v channels may play an important role in the pathophysiology of schizophrenia.

Materials and Methods

Ca_v Genes

A total of 26 genes encoding subunits of Ca_v channels can be classified into 4 groups (Table 1) according to the types of subunits they encode (Catterall 2000; Simms and Zamponi 2014). Genes *CACNA1A*, *CACNA1B*, *CACNA1C*, *CACNA1D*, *CACNA1E*, *CACNA1F*, *CACNA1G*, *CACNA1H*, *CACNA1I*, *CACNA1S* encode the α_1 subunits, *CACNA2D1*, *CACNA2D2*, *CACNA2D3*, *CACNA2D4* encode the $\alpha_2\delta$ subunits, *CACNB1*, *CACNB2*, *CACNB3*, *CACNB4* encode the β subunits and *CACNG1*, *CACNG2*, *CACNG3*, *CACNG4*, *CACNG5*, *CACNG6*, *CACNG7*, *CACNG8* encode the γ subunits. We only analyzed genes located on the autosomes, so the gene *CACNA1F* on the X-chromosome was excluded.

Genotype data

Due to IRB restrictions from some sub-studies in PGC, we used the largest accessible PGC schizophrenia data which contains 36 case-control sub-studies (N = 56,605; 25,629 cases and 30,976 controls compared to 52 sub-studies and N=82,315 in the primary study) (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014). Quality control and imputation were performed by the PGC Statistical Analysis Group for each dataset separately. Briefly, SNP meets with following conditions were retained: SNP missingness < 0.05, SNP Hardy-Weinberg equilibrium $P > 1x10^{-6}$ in controls or $P > 1x10^{-10}$ in cases. Samples

with missing rate > 0.05 were removed. After quality control, the remaining genotypes were imputed using SHAPEIT2/IMPUTE2 (Delaneau et al. 2014; Howie et al. 2012) based on the full 1000 Genomes Project dataset (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014). To evaluate the replicability of our analysis, we selected out the data used in the first phase of PGC (PGC1) as a discovery sample (10,616 cases and 10,315 controls), and used the rest as replication sample (15,013 cases and 20,661 controls). In addition, we also used combined samples from both discovery and replication stages. We first merged the best-guessed genotype data (imputation information score > 0.8 and minor allele frequency > 0.05) across 36 sub-studies, and then, performed the second round of quality controls using parameters SNP-missingness < 0.05 and minor allele frequency > 0.05. To control the impact of population stratification on our analysis, we computed the first 20 principal components based on the merged and quality controlled genotype data by using the program EigenSoft (Price et al. 2006). Since some Ca_v genes are close together in genomic position (for example, *CACNG6*, *CACNG7* and *CACNG8*), it is possible that some SNPs may be assigned to more than one genes. In order to avoid such undesired bias, we annotated SNPs to the closest gene (GENCODEv1.9) based on genomic positions that were derived from the human genome assembly build hg19 (Supplementary Table S8). Then based on the SNPs list, the genotypes of the 25 Ca_v genes were extracted.

Ca_v channels can either be monomers (only the α_1 subunit), or heteromultimers (three subunits α_1, β, $\alpha_2\delta$; or four subunits α_1, β, $\alpha_2\delta$, γ). Great diversity of Ca_v channels allows them to fulfill highly specialized roles in specific neuronal subtypes (Simms and Zamponi 2014). Thus, for each α_1 subunit (principal subunit for classifying subtypes of Ca_v channels), co-assembly of a variety of ancillary subunits (β, $\alpha_2\delta$, γ) exists (Table 2). In some Ca_v channels, the

ancillary subunit types are not completely known. So for channel-level association analysis, we test all of the possible combinations based on the current literatures (Buraei and Yang 2010; Catterall 1996; Davies et al. 2010; Hofmann et al. 2014; Schlick et al. 2010). According to different subunit gene combinations (3 or 4 genes per set), genotypes of the genes consisting of a Ca_V channel were concatenated. Therefore, each SNP set is corresponding to one functional channel that exists in nature.

SNP-set (Sequence) Kernel Association Test (SKAT)

SKAT was used to test for association between a set of genetic variants and dichotomous or quantitative phenotypes. It uses the logistic kernel-machine regression modeling framework. SKAT aggregates individual score test statistics of SNPs in a SNP set and computes SNP-set level *P*-values. SKAT can be used for common or/and rare variants (Ionita-Laza et al. 2013; Wu et al. 2010; Wu et al. 2011). In the current study, we focus on the common variants in line with the PGC schizophrenia study and used SKAT version 1.07 (Wu et al. 2010). The linear kernel with *beta* (*p, 1.25*), where *p* is the minor allele frequency of a SNP, was used. In our analysis, we carefully selected the cohort indicators and the first six principal components as covariates after comparing results including different number of principal components (three, six and ten) (Supplementary Table S1). At the same time, to overcome the issue of the large number of degrees of freedom, SKAT employs a test that adaptively estimates the degrees of freedom by accounting for correlation (LD) among the SNPs (Wu et al. 2010). In this study, a SNP set can be a collection of SNPs from a gene or several genes consisting of a heteromeric channel. The Benjamini Hochberg (BH) procedure was used to correct for multiple comparisons both in the Table 1 and Table 2 (Hochberg and Benjamini 1990; Wu et al. 2011).

Estimate schizophrenia heritability contributed by Ca_v Channels SNPs

Channels significantly associated with schizophrenia (Table 2; Supplementary Table S6) were selected. For each subtype of Ca_v channel, all of the auxiliary subunit (β, $\alpha_2\delta$, γ) genes contributing to a significant association with schizophrenia were grouped with each α_1 gene. The following gene lists $Ca_v1.1$ (*CACNA1S*, *CACNA2D1*, *CACNB1*, *CACNG1*), $Ca_v1.2$ (*CACNA1C*, *CACNA2D1*, *CACNA2D2*, *CACNA2D3*, *CACNA2D4*, *CACNB1*, *CACNB2*, *CACNB3*, *CACNB4*, *CACNG1*, *CACNG2*, *CACNG3*, *CACNG4*, *CACNG5*, *CACNG6*, *CACNG7*, *CACNG8*), $Ca_v1.3$ (*CACNA1D*, *CACNA2D3*, *CACNB3*, *CACNB4*), $Ca_v2.1$ (*CACNA1A*, *CACNA2D1*, *CACNA2D3*, *CACNA2D4*, *CACNB1*, *CACNB4*), $Ca_v2.2$ (*CACNA1B*, *CACNA2D1*, *CACNA2D3*, *CACNB1*, *CACNB3*, *CACNB4*), $Ca_v2.3$ (*CACNA1E*, *CACNA2D1*, *CACNB1*, *CACNB2*, *CACNB3*, *CACNB4*), $Ca_v3.1$ (*CACNA1G*), $Ca_v3.3$ (*CACNA1I*) were used to extract genotype-phenotype data for estimating chip heritability by using the linear mixed method BOLT-REML (Loh et al. 2015). The level of enrichment for association with schizophrenia was represented by the ratio of proportion of chip heritability (from each subtype of channel) in total heritability (33%) (Ripke et al. 2013) to the proportion of their SNPs in all SNPs (9423850 variants, minor allele frequency > 0.05) from the 1000 Genomes Project.

Results

Association of Ca_v genes with schizophrenia (gene level)

Two genes, *CACNA1C* and *CACNA1I* significantly associate with schizophrenia in the discovery cohort (corrected $P < 0.05$) and in the replication cohort (corrected $P < 0.05$) both according to the SNP-set (Sequence) Kernel Association Test (SKAT) method (Table 1) and

univariate analysis (Supplementary Table S2). Within the combined sample (56,605 subjects) a further three genes were identified by the SKAT analysis: *CACNA1E*, *CACNA1G* and *CACNB2*. *CACNA1C*, *CACNA1I* and *CACNB2* were previously reported, while *CACNA1E* and *CACNA1G* have not been reported as schizophrenia candidates (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014).

Association of Ca_v channels with schizophrenia (macromolecule level)

Macromolecule-level testing in the discovery cohort identified heteromers $Ca_v1.2$ (all possible subunits combinations), $Ca_v2.3$ (α_{1E} β_2 $\alpha_2\delta_1$), and monomers $Ca_v3.1$ (α_{1G}) and $Ca_v3.3$ (α_{1I}) as associated (corrected $P < 0.05$). All of them except $Ca_v3.1$ (α_{1G}) were replicated in the separate samples by SKAT analysis (Table 2). In the combined sample, heteromers $Ca_v1.1$ (α_{1S} β_1 $\alpha_2\delta_1$ γ_1), $Ca_v1.2$ (all possible subunits combinations), $Ca_v1.3$ (α_{1D} β_3 $\alpha_2\delta_3$, α_{1D} β_4 $\alpha_2\delta_3$), $Ca_v2.1$ (α_{1A} β_1 $\alpha_2\delta_1$, α_{1A} β_4 $\alpha_2\delta_1$, α_{1A} β_4 $\alpha_2\delta_3$, α_{1A} β_4 $\alpha_2\delta_4$), $Ca_v2.2$ (α_{1B} β_1 $\alpha_2\delta_1$, α_{1B} β_1 $\alpha_2\delta_3$, α_{1B} β_3 $\alpha_2\delta_1$, α_{1B} β_3 $\alpha_2\delta_3$, α_{1B} β_4 $\alpha_2\delta_1$, α_{1B} β_4 $\alpha_2\delta_3$), and $Ca_v2.3$ (α_{1E} β_1 $\alpha_2\delta_1$, α_{1E} β_2 $\alpha_2\delta_1$, α_{1E} β_3 $\alpha_2\delta_1$, α_{1E} β_4 $\alpha_2\delta_1$), and monomers $Ca_v3.1$ (α_{1G}) and $Ca_v3.3$ (α_{1I}) associate with the risk of schizophrenia (corrected $P < 0.05$) (Table 2).

Chip heritability of Ca_v channels

We estimate that 0.0567% (s.e. 0.0391%), 0.5051% (s.e. 0.1172%), 0.2453% (s.e. 0.0946%), 0.1788% (s.e. 0.0708%), 0.2578% (s.e. 0.0929%), 0.176% (s.e. 0.0658%), 0.0272% (s.e. 0.0316%) and 0.0569% (s.e. 0.0464%) of the variance in schizophrenia can be explained by $Ca_v1.1$, $Ca_v1.2$, $Ca_v1.3$, $Ca_v2.1$, $Ca_v2.2$, $Ca_v2.3$, $Ca_v3.1$ and $Ca_v3.3$ SNPs respectively (Fig. 2a). The $Ca_v1.2$ account for the largest amount of chip heritability (0.5051%, s.e. 0.1172%) and the

$Ca_v3.1$ account for the least (0.0272%, s.e. 0.0316%). However, after accounting for the number of SNPs included in each Ca_v subtype, $Ca_v3.1$ and $Ca_v3.3$ show largest fold enrichment (39.83 and 36.51, respectively) (Fig. 2b). All tested subtypes of Ca_v channels show > 6-fold enrichment. The variance explained by each subtype of Ca_v channels is proportional to its number of SNPs (Supplementary Fig. S1). This is in line with the previous discovery that the larger the genomic region, the higher the proportion of chip heritability that can be accounted for (Yang et al. 2011).

Robustness of the channel-based association

Ca_v channels that are significantly associated with schizophrenia reported by SKAT were also identified by another program MAGMA (de Leeuw et al. 2015) (Supplementary Table S4 & Table S5). However, MAGMA identified fewer channels at the discovery stage compared with SKAT (Table 2; Supplementary Table S5). But for the largest European dataset (49 sub-studies), MAGMA reports similar results with SKAT.

Discussion

In the current study we applied a macromolecule approach to a subsample of published schizophrenia GWAS (N = 56,605) and identified eight subtypes of Ca_v channels associated with schizophrenia, including the L-type Ca_v channels ($Ca_v1.1$, $Ca_v1.2$, $Ca_v1.3$), P-/Q-type $Ca_v2.1$, N-type $Ca_v2.2$, R-type $Ca_v2.3$, T-type channels ($Ca_v3.1$, $Ca_v3.3$). Only genes (*CACNA1C*, *CACNB2* and *CACNA1I*) from $Ca_v1.2$ and $Ca_v3.3$ were implicated in the primary PGC analysis, which was based on a larger sample (N = 82,315) (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014). In addition, we used another published statistical tool MAGMA to

confirm our analysis. The results are highly consistent although the two programs are based on different assumptions and statistical models. It demonstrates that analyzing macromolecule subunit genes in aggregate is a complementary way to identify more genetic variants of schizophrenia compare to the traditional GWAS that treating each SNP separately.

The macromolecule subunits physically bind together to achieve their cellular functions, thus perturbations of any of their subunits may contribute to disease pathogenesis. In previous GWAS of schizophrenia, only a handful of channel subunits were implicated, perhaps due to the limited power of the massive univariate tests (Lichtenstein et al. 2009; Ripke et al. 2013; Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014). To the best of our knowledge, only Askland and coworkers (Askland et al. 2012) have performed an association analysis of ion channels with schizophrenia, but the gene-sets defined in their study is a mixture of subunit-encoding genes from many ionic species and does not therefore correspond to a macromolecule existing in nature. In addition, it was tested in a much smaller sample. In order to test whether each functional Ca_v channel is associated with schizophrenia or not, we composed specific gene-set based on molecular structures of Ca_v channels (Buraei and Yang 2010; Catterall 1996; Davies et al. 2010; Schlick et al. 2010; Simms and Zamponi 2014). For each channel (macromolecule-based analysis), although the containing genes locate far away or even on different chromosomes, the encoding subunits are physically binding together in one functional unit to deal with flow of calcium ions. This macromolecule-based approach is different from grouping genes based on their functional catalogs or pathways since their products (proteins) interact directly or indirectly and they could not form a unique functional macromolecule. Our approach combining biological priors with GWAS data identified eight subtypes of Ca_v channels associated with the risk of schizophrenia. It is possible that the

associations of whole channels with schizophrenia may be due to a highly associated component gene. This is likely the case for $Ca_v1.2$, where a few possible subunit combinations (for example, $Ca_v1.2$: α_{1C} β_1 $\alpha_2\delta_2$ that encoded by genes *CACNA1C*, *CACNB1* and *CACNA2D2*) show their significance thanks to the α_1 subunit gene *CACNA1C* (Table 1; Supplementary Table S7) although most of the others are not. The significant associations of the other heteromultimeric channels may be not due to a single significant gene. For example, during the discovery and replication stages, the $Ca_v2.3$ channel (subunits encoded by *CACNA1E*, *CACNB2* and *CACNA2D1*) was discovered and replicated by SKAT but none of their composing genes was identified at the gene-level test. The univariate analysis (min*P* SNP represents channel) could not identify this channel in small samples (discovery and replication stages), but the combined sample could confirm this finding when applying a macromolecule-based approach (Supplementary Table S3). None of the channels $Ca_v1.1$, $Ca_v1.3$, $Ca_v2.1$ and $Ca_v2.2$ subunit genes was identified in gene-level testing, but the channels show significant association with schizophrenia in the combined sample. These results indicate that subunit genes can collectively associate with disease susceptibility, even if individual genes do not exhibit significant association. It seems that analyzing channel SNPs as a set can capture the joint effect of multiple variants located on different chromosomes. Thus, genetic variants with weak or moderate effects could be identified when we combined them together based on biological knowledge of the macromolecule.

We also observed enrichment of heritability in significant Ca_v channels SNPs for schizophrenia and it may point to a major role of the inherited genetic variants in the risk of schizophrenia. These eight subtypes of Ca_v channels may provide more knowledge about the pathology of schizophrenia. Ca_v channels are the primary mediators of depolarization-induced

calcium entry into neurons (Simms and Zamponi 2014). Calcium-dependent processes such as neurotransmitter release, neuronal gene transcription, and activation of calcium-dependent enzymes are of critical importance to brain function (Clapham 2007; Simms and Zamponi 2014). L-type Ca_v channels ($Ca_v1.1$, $Ca_v1.2$, $Ca_v1.3$) are involved in learning, memory and synaptic plasticity (Moosmang et al. 2005; White et al. 2008; Woodside et al. 2004). Mutations in *CACNA1C*, the gene encoding the α_1 subunit of $Ca_v1.2$, are responsible for Timothy syndrome, a multisystem disorder including cognitive impairment and autism spectrum disorder (Splawski et al. 2005; Splawski et al. 2004). SNPs located in *CACNA1C* are linked to development of schizophrenia, bipolar disorder and depression (Dao et al. 2010; Green et al. 2010; He et al. 2014). Data from mice and humans suggest an involvement of $Ca_v1.3$ channels in neurophysiological functions, in particular in the dopaminergic system (Simms and Zamponi 2014), which is involved in the pathology of schizophrenia (Brisch et al. 2014). Although, in humans, mutations in $Ca_v1.1$ have been linked to hypokalemic periodic paralysis (Ptáček et al. 1994) and malignant hyperthermia (Monnier et al. 1997), a pathway analysis for a set of calcium channel genes implicated *CACNA1S* ($Ca_v1.1$ channel α_1 subunit gene) as one of the 20 gene regions associated in the five psychiatric disorder meta-analysis (Cross-Disorder Group of the Psychiatric Genomics Consortium 2013). P-/Q-type channel $Ca_v2.1$ and N-type channel $Ca_v2.2$ play a role in neurotransmitter release at the presynaptic terminal and in neuronal integration in many neuronal types (Williams et al. 1992). R-type channel $Ca_v2.3$ are strongly expressed in cortex, hippocampus, striatum, amygdala and interpeduncular nucleus (Parajuli et al. 2012). The T-type channels ($Ca_v3.1$, $Ca_v3.3$) appear to play important roles in regulating neuronal excitability (Simms and Zamponi 2014). Although there is no direct evidence associating $Ca_v2.1$, $Ca_v2.2$, $Ca_v2.3$ and $Ca_v3.1$ with schizophrenia, due to their strong expression and wide

distribution in the human brain, these four subtypes of Ca_v channels are likely involved in some aspects of schizophrenia pathology. A recent study of rare variants in schizophrenia demonstrated that a gene set containing 26 Ca_v genes yielded a large odds ratio of 8.4 (Purcell et al. 2014). Given the central role of Ca_v channels in regulating neurotransmitter release and neuronal gene transcription, the identified channels may represent convenient drug targets for novel therapeutics. Designing drugs for specific channels by targeting α_1 subunit, or designing more universal drugs for some channels by targeting shared ancillary subunits can improve efficiency of treatments. There are some Ca_v channels blockers in clinical use. A few L-type Ca_v channel antagonists such as verapamil and nifedipine which are used for hypertension, have been examined in clinical trials in schizophrenia (Lencz and Malhotra 2015). Revisiting the effect of existing agents on Ca_v channels or designing new drugs could be a high priority for new schizophrenia treatment development.

The genetic association test of macromolecules may also suggest candidates for non-additive interactions (epistasis) and improve polygenic predictions. In addition, while we only considered Ca_v channels, future work could consider other types of channels, such as potassium channels, sodium channels, and proton channels as interesting susceptibility candidates for schizophrenia and other psychiatric disorders.

The present findings illustrate the power of the macromolecule-based approach applied to schizophrenia, which identified eight subtypes of Ca_v channels associated with the disorder. The results highlight the combined role of different aspects of calcium signaling in schizophrenia pathophysiology, and suggest several new potential drug targets for development of novel therapeutics.

Acknowledgements

This work was supported by the EU funding (PsychDPC); Research Council of Norway [RCN #223273, #251134]; South East Norway Regional Health Authority; and KG Jebsen Foundation [SKGJ-MED-008].

The authors declare that they have no conflict of interest.

Schizophrenia Working Group of the Psychiatric Genomics Consortium

Stephan Ripke[1,2], Benjamin M. Neale[1,2,3,4], Aiden Corvin[5], James T. R. Walters[6], Kai-How Farh[1], Peter A. Holmans[6,7], Phil Lee[1,2,4], Brendan Bulik-Sullivan[1,2], David A. Collier[8,9], Hailiang Huang[1,3], Tune H. Pers[3,10,11], Ingrid Agartz[12,13,14], Esben Agerbo[15,16,17], Margot Albus[18], Madeline Alexander[19], Farooq Amin[20,21], Silviu A. Bacanu[22], Martin Begemann[23], Richard A Belliveau Jr[2], Judit Bene[24,25], Sarah E. Bergen [2,26], Elizabeth Bevilacqua[2], Tim B Bigdeli [22], Donald W. Black[27], Richard Bruggeman[28], Nancy G. Buccola[29], Randy L. Buckner[30,31,32], William Byerley[33], Wiepke Cahn[34], Guiqing Cai[35,36], Murray J. Cairns[39,120,170], Dominique Campion[37], Rita M. Cantor[38], Vaughan J. Carr[39,40], Noa Carrera[6], Stanley V. Catts[39,41], Kimberly D. Chambert[2], Raymond C. K. Chan[42], Ronald Y. L. Chen[43], Eric Y. H. Chen[43,44], Wei Cheng[45], Eric F. C. Cheung[46], Siow Ann Chong[47], C. Robert Cloninger[48], David Cohen[49], Nadine Cohen[50], Paul Cormican[5], Nick Craddock[6,7], Benedicto Crespo-Facorro[210], James J. Crowley[51], David Curtis[52,53], Michael Davidson[54], Kenneth L. Davis[36], Franziska Degenhardt[55,56], Jurgen Del Favero[57], Lynn E. DeLisi[128,129] , Ditte Demontis[17,58,59], Dimitris Dikeos[60], Timothy Dinan[61], Srdjan Djurovic[14,62], Gary Donohoe[5,63], Elodie Drapeau[36], Jubao Duan[64,65], Frank Dudbridge[66], Naser Durmishi[67], Peter Eichhammer[68], Johan Eriksson[69,70,71], Valentina Escott-Price[6], Laurent Essioux[72], Ayman H. Fanous[73,74,75,76], Martilias S. Farrell[51], Josef Frank[77], Lude Franke[78], Robert Freedman[79], Nelson B. Freimer[80], Marion Friedl[81], Joseph I. Friedman[36], Menachem Fromer[1,2,4,82], Giulio Genovese[2], Lyudmila Georgieva[6], Elliot S. Gershon[209], Ina Giegling[81,83], Paola Giusti-Rodríguez[51], Stephanie Godard[84], Jacqueline I. Goldstein[1,3], Vera Golimbet[85], Srihari Gopal[86], Jacob Gratten[87], Lieuwe de Haan[88], Christian Hammer[23], Marian L. Hamshere[6], Mark Hansen[89], Thomas Hansen[17,90], Vahram Haroutunian[36,91,92], Annette M. Hartmann[81], Frans A. Henskens[39,93,94], Stefan Herms[55,56,95], Joel N. Hirschhorn[3,11,96], Per Hoffmann[55,56,95], Andrea Hofman[55,56], Mads V. Hollegaard[97], David M. Hougaard[97], Masashi Ikeda[98], Inge Joa[99], Antonio Julià[100], René S. Kahn[34], Luba Kalaydjieva[101,102], Sena Karachanak-Yankova[103], Juha Karjalainen[78], David Kavanagh[6], Matthew C. Keller[104], Brian J. Kelly[120], James L. Kennedy[105,106,107], Andrey Khrunin[108], Yunjung Kim[51], Janis Klovins[109], James A. Knowles[110], Bettina Konte[81], Vaidutis Kucinskas[111], Zita Ausrele Kucinskiene[111], Hana Kuzelova-Ptackova[112], Anna K. Kähler[26], Claudine Laurent[19,113], Jimmy Lee Chee Keong[47,114], S. Hong Lee[87], Sophie E. Legge[6], Bernard Lerer[115], Miaoxin Li[43,44,116] Tao Li[117], Kung-Yee Liang[118], Jeffrey Lieberman[119], Svetlana Limborska[108], Carmel M.

Loughland[39,120], Jan Lubinski[121], Jouko Lönnqvist[122], Milan Macek Jr[112], Patrik K. E. Magnusson[26], Brion S. Maher[123], Wolfgang Maier[124], Jacques Mallet[125], Sara Marsal[100], Manuel Mattheisen[17,58,59,126], Morten Mattingsdal[14,127], Robert W. McCarley[128,129], Colm McDonald[130], Andrew M. McIntosh[131,132], Sandra Meier[77], Carin J. Meijer[88], Bela Melegh[24,25], Ingrid Melle[14,133], Raquelle I. Mesholam-Gately[128,134], Andres Metspalu[135], Patricia T. Michie[39,136], Lili Milani[135], Vihra Milanova[137], Younes Mokrab[8], Derek W. Morris[5,63], Ole Mors[17,58,138], Kieran C. Murphy[139], Robin M. Murray[140], Inez Myin-Germeys[141], Bertram Müller-Myhsok[142,143,144], Mari Nelis[135], Igor Nenadic[145], Deborah A. Nertney[146], Gerald Nestadt[147], Kristin K. Nicodemus[148], Liene Nikitina-Zake[109], Laura Nisenbaum[149], Annelie Nordin[150], Eadbhard O'Callaghan[151], Colm O'Dushlaine[2], F. Anthony O'Neill[152], Sang-Yun Oh[153], Ann Olincy[79], Line Olsen[17,90], Jim Van Os[141,154], Psychosis Endophenotypes International Consortium[155], Christos Pantelis[39,156], George N. Papadimitriou[60], Sergi Papiol[23], Elena Parkhomenko[36], Michele T. Pato[110], Tiina Paunio[157,158], Milica Pejovic-Milovancevic[159], Diana O. Perkins[160], Olli Pietiläinen[158,161], Jonathan Pimm[53], Andrew J. Pocklington[6], John Powell[140], Alkes Price[3],[162], Ann E. Pulver[147], Shaun M. Purcell[82], Digby Quested[163], Henrik B. Rasmussen[17,90], Abraham Reichenberg[36], Mark A. Reimers[164], Alexander L. Richards[6], Joshua L. Roffman[30,32], Panos Roussos[82,165], Douglas M. Ruderfer[6,82], Veikko Salomaa[71], Alan R. Sanders[64,65], Ulrich Schall[39,120], Christian R. Schubert[166], Thomas G. Schulze[77,167], Sibylle G. Schwab[168], Edward M. Scolnick[2], Rodney J. Scott[39,169,170], Larry J. Seidman[128,134], Jianxin Shi[171], Engilbert Sigurdsson[172], Teimuraz Silagadze[173], Jeremy M. Silverman[36,174], Kang Sim[47], Petr Slominsky[108], Jordan W. Smoller[2,4], Hon-Cheong So[43], Chris C. A. Spencer[175], Eli A. Stahl[3,82], Hreinn Stefansson[176], Stacy Steinberg[176], Elisabeth Stogmann[177], Richard E. Straub[178], Eric Strengman[179,34], Jana Strohmaier[77], T. Scott Stroup[119], Mythily Subramaniam[47], Jaana Suvisaari[122], Dragan M. Svrakic[48], Jin P. Szatkiewicz[51], Erik Söderman[12], Srinivas Thirumalai[180], Draga Toncheva[103], Paul A. Tooney[39,120,170] , Sarah Tosato[181], Juha Veijola[182,183], John Waddington[184], Dermot Walsh[185], Dai Wang[86], Qiang Wang[117], Bradley T. Webb[22], Mark Weiser[54], Dieter B. Wildenauer[186], Nigel M. Williams[6], Stephanie Williams[51], Stephanie H. Witt[77], Aaron R. Wolen[164], Emily H. M. Wong[43], Brandon K. Wormley[22], Jing Qin Wu[39,170], Hualin Simon Xi[187], Clement C. Zai[105,106], Xuebin Zheng[188], Fritz Zimprich[177], Naomi R. Wray[87], Kari Stefansson[176], Peter M. Visscher[87], Wellcome Trust Case-Control Consortium 2[189], Rolf Adolfsson[150], Ole A. Andreassen[14,133], Douglas H. R. Blackwood[132], Elvira Bramon[190], Joseph D. Buxbaum[35,36,91,191], Anders D. Børglum[17,58,59,138], Sven Cichon[55,56,95,192], Ariel Darvasi[193], Enrico Domenici[194], Hannelore Ehrenreich[23], Tõnu Esko[3,11,96,135], Pablo V. Gejman[64,65], Michael Gill[5], Hugh Gurling[53], Christina M. Hultman[26], Nakao Iwata[98], Assen V. Jablensky[39,102,186,195], Erik G. Jönsson[12,14], Kenneth S. Kendler[196], George Kirov[6], Jo Knight[105,106,107], Todd Lencz[197,198,199], Douglas F. Levinson[19], Qingqin S. Li[86], Jianjun Liu[188,200], Anil K. Malhotra[197,198,199], Steven A. McCarroll[2,96], Andrew McQuillin[53], Jennifer L. Moran[2], Preben B. Mortensen[15,16,17], Bryan J. Mowry[87,201], Markus M. Nöthen[55,56], Roel A. Ophoff[38,80,34], Michael J. Owen[6,7], Aarno Palotie[2,4,161], Carlos N. Pato[110], Tracey L. Petryshen[2,128,202], Danielle Posthuma[203,204,205], Marcella Rietschel[77], Brien P. Riley[196], Dan Rujescu[81,83], Pak C. Sham[43,44,116] Pamela Sklar[82,91,165], David St Clair[206], Daniel R. Weinberger[178,207], Jens R. Wendland[166], Thomas Werge[17,90,208], Mark J. Daly[1,2,3], Patrick F. Sullivan[26,51,160] & Michael C. O'Donovan[6,7]

[1]Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, Massachusetts 02114, USA.

[2]Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, Massachusetts 02142, USA.

[3]Medical and Population Genetics Program, Broad Institute of MIT and Harvard, Cambridge, Massachusetts 02142, USA.

[4]Psychiatric and Neurodevelopmental Genetics Unit, Massachusetts General Hospital, Boston, Massachusetts 02114, USA.

[5]Neuropsychiatric Genetics Research Group, Department of Psychiatry, Trinity College Dublin, Dublin 8, Ireland.

[6]MRC Centre for Neuropsychiatric Genetics and Genomics, Institute of Psychological Medicine and Clinical Neurosciences, School of Medicine, Cardiff University, Cardiff, CF24 4HQ, UK.

[7]National Centre for Mental Health, Cardiff University, Cardiff, CF24 4HQ, UK.

[8]Eli Lilly and Company Limited, Erl Wood Manor, Sunninghill Road, Windlesham, Surrey, GU20 6PH, UK. [9]Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London, SE5 8AF, UK.

[10]Center for Biological Sequence Analysis, Department of Systems Biology, Technical University of Denmark, DK-2800, Denmark.

[11]Division of Endocrinology and Center for Basic and Translational Obesity Research, Boston Children's Hospital, Boston, Massachusetts, 02115USA.

[12]Department of Clinical Neuroscience, Psychiatry Section, Karolinska Institutet, SE-17176 Stockholm, Sweden.

[13]Department of Psychiatry, Diakonhjemmet Hospital, 0319 Oslo, Norway.

[14]NORMENT, KG Jebsen Centre for Psychosis Research, Institute of Clinical Medicine, University of Oslo, 0424 Oslo, Norway.

[15]Centre for Integrative Register-based Research, CIRRAU, Aarhus University, DK-8210 Aarhus, Denmark.

[16]National Centre for Register-based Research, Aarhus University, DK-8210 Aarhus, Denmark.

[17]The Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, Denmark.

[18]State Mental Hospital, 85540 Haar, Germany.

[19]Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, California 94305, USA.

[20]Department of Psychiatry and Behavioral Sciences, Atlanta Veterans Affairs Medical Center, Atlanta, Georgia 30033, USA.

[21]Department of Psychiatry and Behavioral Sciences, Emory University, Atlanta Georgia 30322, USA.

[22]Virginia Institute for Psychiatric and Behavioral Genetics, Department of Psychiatry, Virginia Commonwealth University, Richmond, Virginia 23298, USA.

[23]Clinical Neuroscience, Max Planck Institute of Experimental Medicine, Göttingen 37075, Germany.

[24]Department of Medical Genetics, University of Pécs, Pécs H-7624, Hungary.

[25]Szentagothai Research Center, University of Pécs, Pécs H-7624, Hungary.

[26]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm SE-17177, Sweden.

[27]Department of Psychiatry, University of Iowa Carver College of Medicine, Iowa City, Iowa 52242, USA.

[28]University Medical Center Groningen, Department of Psychiatry, University of Groningen NL-9700 RB, The Netherlands.

[29]School of Nursing, Louisiana State University Health Sciences Center, New Orleans, Louisiana 70112, USA.

[30]Athinoula A. Martinos Center, Massachusetts General Hospital, Boston, Massachusetts 02129, USA.

[31]Center for Brain Science, Harvard University, Cambridge, Massachusetts, 02138 USA.

[32]Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts, 02114 USA.

[33]Department of Psychiatry, University of California at San Francisco, San Francisco, California, 94143 USA.

[34]University Medical Center Utrecht, Department of Psychiatry, Rudolf Magnus Institute of Neuroscience, 3584 Utrecht, The Netherlands.

[35]Department of Human Genetics, Icahn School of Medicine at Mount Sinai, New York, New York 10029 USA.

[36]Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York 10029 USA.

[37]Centre Hospitalier du Rouvray and INSERM U1079 Faculty of Medicine, 76301 Rouen, France.

[38]Department of Human Genetics, David Geffen School of Medicine, University of California, Los Angeles, California 90095, USA.

[39]Schizophrenia Research Institute, Sydney NSW 2010, Australia.

[40]School of Psychiatry, University of New South Wales, Sydney NSW 2031, Australia.

[41]Royal Brisbane and Women's Hospital, University of Queensland, Brisbane, St Lucia QLD 4072, Australia.

[42]Institute of Psychology, Chinese Academy of Science, Beijing 100101, China.

[43]Department of Psychiatry, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China.

[44]State Key Laboratory for Brain and Cognitive Sciences, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China.

[45]Department of Computer Science, University of North Carolina, Chapel Hill, North Carolina 27514, USA.

[46]Castle Peak Hospital, Hong Kong, China.

[47]Institute of Mental Health, Singapore 539747, Singapore.

[48]Department of Psychiatry, Washington University, St. Louis, Missouri 63110, USA.

[49]Department of Child and Adolescent Psychiatry, Assistance Publique Hopitaux de Paris, Pierre and Marie Curie Faculty of Medicine and Institute for Intelligent Systems and Robotics, Paris, 75013, France.

[50] Blue Note Biosciences, Princeton, New Jersey 08540, USA

[51]Department of Genetics, University of North Carolina, Chapel Hill, North Carolina 27599-7264, USA.

[52]Department of Psychological Medicine, Queen Mary University of London, London E1 1BB, UK.

[53]Molecular Psychiatry Laboratory, Division of Psychiatry, University College London, London WC1E 6JJ, UK.

[54]Sheba Medical Center, Tel Hashomer 52621, Israel.

[55]Department of Genomics, Life and Brain Center, D-53127 Bonn, Germany.

[56]Institute of Human Genetics, University of Bonn, D-53127 Bonn, Germany.

[57]Applied Molecular Genomics Unit, VIB Department of Molecular Genetics, University of Antwerp, B-2610 Antwerp, Belgium.

[58]Centre for Integrative Sequencing, iSEQ, Aarhus University, DK-8000 Aarhus C, Denmark.

[59]Department of Biomedicine, Aarhus University, DK-8000 Aarhus C, Denmark.

[60]First Department of Psychiatry, University of Athens Medical School, Athens 11528, Greece.

[61]Department of Psychiatry, University College Cork, Co. Cork, Ireland.

[62]Department of Medical Genetics, Oslo University Hospital, 0424 Oslo, Norway.

[63]Cognitive Genetics and Therapy Group, School of Psychology and Discipline of Biochemistry, National University of Ireland Galway, Co. Galway, Ireland.

[64]Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, Illinois 60637, USA.

[65]Department of Psychiatry and Behavioral Sciences, NorthShore University HealthSystem, Evanston, Illinois 60201, USA.

[66]Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK.

[67]Department of Child and Adolescent Psychiatry, University Clinic of Psychiatry, Skopje 1000, Republic of Macedonia.

[68]Department of Psychiatry, University of Regensburg, 93053 Regensburg, Germany.

[69]Department of General Practice, Helsinki University Central Hospital, University of Helsinki P.O. Box 20, Tukholmankatu 8 B, FI-00014, Helsinki, Finland

[70]Folkhälsan Research Center, Helsinki, Finland, Biomedicum Helsinki 1, Haartmaninkatu 8, FI-00290, Helsinki, Finland.

[71]National Institute for Health and Welfare, P.O. BOX 30, FI-00271 Helsinki, Finland.

[72]Translational Technologies and Bioinformatics, Pharma Research and Early Development, F. Hoffman-La Roche, CH-4070 Basel, Switzerland.

[73]Department of Psychiatry, Georgetown University School of Medicine, Washington DC 20057, USA.

[74]Department of Psychiatry, Keck School of Medicine of the University of Southern California, Los Angeles, California 90033, USA.

[75]Department of Psychiatry, Virginia Commonwealth University School of Medicine, Richmond, Virginia 23298, USA.

[76]Mental Health Service Line, Washington VA Medical Center, Washington DC 20422, USA.

[77]Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Heidelberg , D-68159 Mannheim, Germany.

[78]Department of Genetics, University of Groningen, University Medical Centre Groningen, 9700 RB Groningen, The Netherlands.

[79]Department of Psychiatry, University of Colorado Denver, Aurora, Colorado 80045, USA.

[80]Center for Neurobehavioral Genetics, Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, California 90095, USA.

[81]Department of Psychiatry, University of Halle, 06112 Halle, Germany.

[82]Division of Psychiatric Genomics, Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA.

[83]Department of Psychiatry, University of Munich, 80336, Munich, Germany.

[84]Departments of Psychiatry and Human and Molecular Genetics, INSERM, Institut de Myologie, Hôpital de la Pitiè-Salpêtrière, Paris, 75013, France.

[85]Mental Health Research Centre, Russian Academy of Medical Sciences, 115522 Moscow, Russia.

[86]Neuroscience Therapeutic Area, Janssen Research and Development, Raritan, New Jersey 08869, USA.

[87]Queensland Brain Institute, The University of Queensland, Brisbane, Queensland, QLD 4072, Australia.

[88]Academic Medical Centre University of Amsterdam, Department of Psychiatry, 1105 AZ Amsterdam, The Netherlands.

[89]Illumina, La Jolla, California, California 92122, USA.

[90]Institute of Biological Psychiatry, Mental Health Centre Sct. Hans, Mental Health Services Copenhagen, DK-4000, Denmark.

[91]Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA.

[92]J. J. Peters VA Medical Center, Bronx, New York, New York 10468, USA.

[93]Priority Research Centre for Health Behaviour, University of Newcastle, Newcastle NSW 2308, Australia.

[94]School of Electrical Engineering and Computer Science, University of Newcastle, Newcastle NSW 2308, Australia.

[95]Division of Medical Genetics, Department of Biomedicine, University of Basel, Basel, CH-4058, Switzerland.

[96]Department of Genetics, Harvard Medical School, Boston, Massachusetts 02115, USA.

[97]Section of Neonatal Screening and Hormones, Department of Clinical Biochemistry, Immunology and Genetics, Statens Serum Institut, Copenhagen, DK-2300, Denmark.

[98]Department of Psychiatry, Fujita Health University School of Medicine, Toyoake, Aichi, 470-1192, Japan.

[99]Regional Centre for Clinical Research in Psychosis, Department of Psychiatry, Stavanger University Hospital, 4011 Stavanger, Norway.

[100]Rheumatology Research Group, Vall d'Hebron Research Institute, Barcelona, 08035, Spain.

[101]Centre for Medical Research, The University of Western Australia, Perth, WA 6009, Australia.

[102]The Perkins Institute for Medical Research, The University of Western Australia, Perth, WA 6009, Australia.

[103]Department of Medical Genetics, Medical University, Sofia1431, Bulgaria.

[104]Department of Psychology, University of Colorado Boulder, Boulder, Colorado 80309, USA.

[105]Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, Ontario, M5T 1R8, Canada.

[106]Department of Psychiatry, University of Toronto, Toronto, Ontario, M5T 1R8, Canada.

[107]Institute of Medical Science, University of Toronto, Toronto, Ontario, M5S 1A8, Canada.

[108]Institute of Molecular Genetics, Russian Academy of Sciences, Moscow123182, Russia.

[109]Latvian Biomedical Research and Study Centre, Riga, LV-1067, Latvia.

[110]Department of Psychiatry and Zilkha Neurogenetics Institute, Keck School of Medicine at University of Southern California, Los Angeles, California 90089, USA.

[111]Faculty of Medicine, Vilnius University, LT-01513 Vilnius, Lithuania.

[112] Department of Biology and Medical Genetics, 2nd Faculty of Medicine and University Hospital Motol, 150 06 Prague, Czech Republic.

[113] Department of Child and Adolescent Psychiatry, Pierre and Marie Curie Faculty of Medicine, Paris 75013, France.

[114]Duke-NUS Graduate Medical School, Singapore 169857, Singapore.

[115]Department of Psychiatry, Hadassah-Hebrew University Medical Center, Jerusalem 91120, Israel.

[116]Centre for Genomic Sciences, The University of Hong Kong, Hong Kong, China.

[117]Mental Health Centre and Psychiatric Laboratory, West China Hospital, Sichuan University, Chengdu, 610041, Sichuan, China.

[118]Department of Biostatistics, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland 21205, USA.

[119]Department of Psychiatry, Columbia University, New York, New York 10032, USA.

[120]Priority Centre for Translational Neuroscience and Mental Health, University of Newcastle, Newcastle NSW 2300, Australia.

[121]Department of Genetics and Pathology, International Hereditary Cancer Center, Pomeranian Medical University in Szczecin, 70-453 Szczecin, Poland.

[122]Department of Mental Health and Substance Abuse Services; National Institute for Health and Welfare, P.O. BOX 30, FI-00271 Helsinki, Finland

[123]Department of Mental Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland 21205, USA.

[124]Department of Psychiatry, University of Bonn, D-53127 Bonn, Germany.

[125]Centre National de la Recherche Scientifique, Laboratoire de Génétique Moléculaire de la Neurotransmission et des Processus Neurodégénératifs, Hôpital de la Pitié Salpêtrière, 75013, Paris, France.

[126]Department of Genomics Mathematics, University of Bonn, D-53127 Bonn, Germany.

[127]Research Unit, Sørlandet Hospital, 4604 Kristiansand, Norway.

[128]Department of Psychiatry, Harvard Medical School, Boston, Massachusetts 02115, USA.

[129]VA Boston Health Care System, Brockton, Massachusetts 02301, USA.

[130]Department of Psychiatry, National University of Ireland Galway, Co. Galway, Ireland.

[131]Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh EH16 4SB, UK.

[132]Division of Psychiatry, University of Edinburgh, Edinburgh EH16 4SB, UK.

[133]Division of Mental Health and Addiction, Oslo University Hospital, 0424 Oslo, Norway.

[134]Massachusetts Mental Health Center Public Psychiatry Division of the Beth Israel Deaconess Medical Center, Boston, Massachusetts 02114, USA.

[135]Estonian Genome Center, University of Tartu, Tartu 50090, Estonia.

[136]School of Psychology, University of Newcastle, Newcastle NSW 2308, Australia.

[137]First Psychiatric Clinic, Medical University, Sofia 1431, Bulgaria.

[138]Department P, Aarhus University Hospital, DK-8240 Risskov, Denmark.

[139]Department of Psychiatry, Royal College of Surgeons in Ireland, Dublin 2, Ireland.

[140]King's College London, London SE5 8AF, UK.

[141]Maastricht University Medical Centre, South Limburg Mental Health Research and Teaching Network, EURON, 6229 HX Maastricht, The Netherlands.

[142]Institute of Translational Medicine, University of Liverpool, Liverpool L69 3BX, UK.

[143]Max Planck Institute of Psychiatry, 80336 Munich, Germany.

[144]Munich Cluster for Systems Neurology (SyNergy), 80336 Munich, Germany.

[145]Department of Psychiatry and Psychotherapy, Jena University Hospital, 07743 Jena, Germany.

[146]Department of Psychiatry, Queensland Brain Institute and Queensland Centre for Mental Health Research, University of Queensland, Brisbane, Queensland, St Lucia QLD 4072, Australia.

[147]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA.

[148]Department of Psychiatry, Trinity College Dublin, Dublin 2, Ireland.

[149]Eli Lilly and Company, Lilly Corporate Center, Indianapolis, 46285 Indiana, USA.

[150]Department of Clinical Sciences, Psychiatry, Umeå University, SE-901 87 Umeå, Sweden.

[151]DETECT Early Intervention Service for Psychosis, Blackrock, Co. Dublin, Ireland.

[152]Centre for Public Health, Institute of Clinical Sciences, Queen's University Belfast, Belfast BT12 6AB, UK.

[153]Lawrence Berkeley National Laboratory, University of California at Berkeley, Berkeley, California 94720, USA.

[154]Institute of Psychiatry, King's College London, London SE5 8AF, UK.

[155]A list of authors and affiliations appear in the Supplementary Information.

[156]Melbourne Neuropsychiatry Centre, University of Melbourne & Melbourne Health, Melbourne, Vic 3053, Australia.

[157]Department of Psychiatry, University of Helsinki, P.O. Box 590, FI-00029 HUS, Helsinki, Finland.

[158]Public Health Genomics Unit, National Institute for Health and Welfare, P.O. BOX 30, FI-00271 Helsinki, Finland

[159]Medical Faculty, University of Belgrade, 11000 Belgrade, Serbia.

[160]Department of Psychiatry, University of North Carolina, Chapel Hill, North Carolina 27599-7160, USA.

[161]Institute for Molecular Medicine Finland, FIMM, University of Helsinki, P.O. Box 20

FI-00014, Helsinki, Finland

[162]Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts 02115, USA.

[163]Department of Psychiatry, University of Oxford, Oxford, OX3 7JX, UK.

[164]Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, Virginia 23298, USA.

[165]Institute for Multiscale Biology, Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA.

[166]PharmaTherapeutics Clinical Research, Pfizer Worldwide Research and Development, Cambridge, Massachusetts 02139, USA.

[167]Department of Psychiatry and Psychotherapy, University of Gottingen, 37073 Göttingen, Germany.

[168]Psychiatry and Psychotherapy Clinic, University of Erlangen, 91054 Erlangen, Germany.

[169]Hunter New England Health Service, Newcastle NSW 2308, Australia.

[170]School of Biomedical Sciences and Pharmacy, University of Newcastle, Callaghan NSW 2308, Australia.

[171]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland 20892, USA.

[172]University of Iceland, Landspitali, National University Hospital, 101 Reykjavik, Iceland.

[173]Department of Psychiatry and Drug Addiction, Tbilisi State Medical University (TSMU), N33, 0177 Tbilisi, Georgia.

[174]Research and Development, Bronx Veterans Affairs Medical Center, New York, New York 10468, USA.

[175]Wellcome Trust Centre for Human Genetics, Oxford, OX3 7BN, UK.

[176]deCODE Genetics, 101 Reykjavik, Iceland.

[177]Department of Clinical Neurology, Medical University of Vienna, 1090 Wien, Austria.

[178]Lieber Institute for Brain Development, Baltimore, Maryland 21205, USA.

[179]Department of Medical Genetics, University Medical Centre Utrecht, Universiteitsweg 100, 3584 CG, Utrecht, The Netherlands.

[180]Berkshire Healthcare NHS Foundation Trust, Bracknell RG12 1BQ, UK.

[181]Section of Psychiatry, University of Verona, 37134 Verona, Italy.

[182]Department of Psychiatry, University of Oulu, P.O. BOX 5000, 90014, Finland

[183]University Hospital of Oulu, P.O.BOX 20, 90029 OYS, Finland.

[184]Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin 2, Ireland.

[185]Health Research Board, Dublin 2, Ireland.

[186]School of Psychiatry and Clinical Neurosciences, The University of Western Australia, Perth WA6009, Australia.

[187]Computational Sciences CoE, Pfizer Worldwide Research and Development, Cambridge, Massachusetts 02139, USA.

[188]Human Genetics, Genome Institute of Singapore, A*STAR, Singapore 138672, Singapore.

[189]A list of authors and affiliations appear in the Supplementary Information.

[190]University College London, London WC1E 6BT, UK.

[191]Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA.

[192]Institute of Neuroscience and Medicine (INM-1), Research Center Juelich, 52428 Juelich, Germany.

[193]Department of Genetics, The Hebrew University of Jerusalem, 91905 Jerusalem, Israel.

[194]Neuroscience Discovery and Translational Area, Pharma Research and Early Development, F. Hoffman-La Roche, CH-4070 Basel, Switzerland.

[195]Centre for Clinical Research in Neuropsychiatry, School of Psychiatry and Clinical Neurosciences, The University of Western Australia, Medical Research Foundation Building, Perth WA 6000, Australia.

[196]Virginia Institute for Psychiatric and Behavioral Genetics, Departments of Psychiatry and Human and Molecular Genetics, Virginia Commonwealth University, Richmond, Virginia 23298, USA.

[197]The Feinstein Institute for Medical Research, Manhasset, New York, 11030 USA.

[198]The Hofstra NS-LIJ School of Medicine, Hempstead, New York, 11549 USA.

[199]The Zucker Hillside Hospital, Glen Oaks, New York,11004 USA.

[200]Saw Swee Hock School of Public Health, National University of Singapore, Singapore 117597, Singapore.

[201]Queensland Centre for Mental Health Research, University of Queensland, Brisbane 4076, Queensland, Australia.

[202]Center for Human Genetic Research and Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts 02114, USA.

[203]Department of Child and Adolescent Psychiatry, Erasmus University Medical Centre, Rotterdam 3000, The Netherlands.

[204]Department of Complex Trait Genetics, Neuroscience Campus Amsterdam, VU University Medical Center Amsterdam, Amsterdam 1081, The Netherlands.

[205]Department of Functional Genomics, Center for Neurogenomics and Cognitive Research, Neuroscience Campus Amsterdam, VU University, Amsterdam 1081, The Netherlands.

[206]University of Aberdeen, Institute of Medical Sciences, Aberdeen, AB25 2ZD, UK.

[207]Departments of Psychiatry, Neurology, Neuroscience and Institute of Genetic Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland 21205, USA.

[208]Department of Clinical Medicine, University of Copenhagen, Copenhagen 2200, Denmark.

[209]Departments of Psychiatry and Human Genetics, University of Chicago, Chicago, Illinois 60637, USA.

[210]University Hospital Marqués de Valdecilla, Instituto de Formación e Investigación Marqués de Valdecilla, University of Cantabria, E-39008 Santander, Spain

Compliance with ethical standards

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Data availability

Schizophrenia genotype data from the Psychiatric Genomics Consortium can be accessed by following the consortium's data policies: https://www.med.unc.edu/pgc/shared-methods.

References

Askland K, Read C, O'Connell C, Moore JH (2012) Ion channels and schizophrenia: a gene set-based analytic approach to GWAS data for biological hypothesis testing. Human Genet 131: 373-391.

Bannister RA, Beam KG (2013) Ca V 1.1: the atypical prototypical voltage-gated Ca 2+ channel. Biochim Biophys Acta 1828: 1587-1597.

Bauer-Mehren A, Furlong LI, Sanz F (2009) Pathway databases and tools for their exploitation: benefits, current limitations and challenges. Mol Syst Biol 5: 290.

Brisch R, Saniotis A, Wolf R, Bielau H, Bernstein H-G, Steiner J, Bogerts B, Braun AK, Jankowski Z, Kumaritlake J (2014) The role of dopamine in schizophrenia from a neurobiological and evolutionary perspective: old fashioned, but still in vogue. Front psychiatry 5.

Buraei Z, Yang J (2010) The β subunit of voltage-gated Ca2+ channels. Physiol Rev 90: 1461-1506.

Catterall WA (1996) Molecular properties of sodium and calcium channels. J Bioenerg Biomembr 28: 219-230.

Catterall WA (2000) Structure and regulation of voltage-gated Ca2+ channels. Annu Rev Cell Dev Biol 16: 521-555.

Clapham DE (2007) Calcium signaling. Cell 131: 1047-1058.

Cross-Disorder Group of the Psychiatric Genomics Consortium (2013) Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. Lancet 381: 1371-1379.

Dao DT, Mahon PB, Cai X, Kovacsics CE, Blackwell RA, Arad M, Shi J, Zandi PP, O'Donnell P, Knowles JA (2010) Mood disorder susceptibility gene CACNA1C modifies mood-related behaviors in mice and interacts with sex to influence behavior in mice and diagnosis in humans. Biol Psychiatry 68: 801-810.

Davies A, Kadurin I, Alvarez-Laviada A, Douglas L, Nieto-Rostro M, Bauer CS, Pratt WS, Dolphin AC (2010) The α2δ subunits of voltage-gated calcium channels form GPI-anchored proteins, a posttranslational modification essential for function. Proc Natl Acad Sci U S A 107: 1654-1659.

de Leeuw CA, Mooij JM, Heskes T, Posthuma D (2015) MAGMA: generalized gene-set analysis of GWAS data. PLoS Comput Biol 11: e1004219.

Delaneau O, Marchini J, Consortium GP (2014) Integrating sequence and array data to create an improved 1000 Genomes Project haplotype reference panel. Nat Commun 5: 3934.

Giusti-Rodríguez P, Sullivan PF (2013) The genomics of schizophrenia: update and implications. J Clin Investi 123: 4557.

Goldstein DB (2009) Common genetic variation and human traits. N Engl J Med 360: 1696.

Green EK, Grozeva D, Jones I, Jones L, Kirov G, Caesar S, Gordon-Smith K, Fraser C, Forty L, Russell E (2010) The bipolar disorder risk allele at CACNA1C also confers risk of recurrent major depression and of schizophrenia. Mol Psychiatry 15: 1016-1022.

Hamshere ML, Walters JTR, Smith R, Richards A, Green E, Grozeva D, Jones I, Forty L, Jones L, Gordon-Smith K (2013) Genome-wide significant associations in schizophrenia to ITIH3/4, CACNA1C and SDCCAG8, and extensive replication of associations reported by the Schizophrenia PGC. Mol Psychiatry 18: 708-712.

He K, An Z, Wang Q, Li T, Li Z, Chen J, Li W, Wang T, Ji J, Feng G (2014) CACNA1C, schizophrenia and major depressive disorder in the Han Chinese population. Br J Psychiatry 204: 36-39.

Hochberg Y, Benjamini Y (1990) More powerful procedures for multiple significance testing. Stat Med 9: 811-818.

Hofmann F, Flockerzi V, Kahl S, Wegener JW (2014) L-type CaV1. 2 calcium channels: from in vitro findings to in vivo function. Physiol Rev 94: 303-326.

Howie B, Fuchsberger C, Stephens M, Marchini J, Abecasis GR (2012) Fast and accurate genotype imputation in genome-wide association studies through pre-phasing. Nat Genet 44: 955-959.

Ionita-Laza I, Lee S, Makarov V, Buxbaum JD, Lin X (2013) Sequence kernel association tests for the combined effect of rare and common variants. Am J Hum Genet 92: 841-853.

Khatri P, Sirota M, Butte AJ (2012) Ten years of pathway analysis: current approaches and outstanding challenges. PLoS Comput Biol 8: e1002375.

Lencz T, Malhotra A (2015) Targeting the schizophrenia genome: a fast track strategy from GWAS to clinic. Mol Psychiatry 20: 820-826.

Lichtenstein P, Yip BH, Björk C, Pawitan Y, Cannon TD, Sullivan PF, Hultman CM (2009) Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. Lancet 373: 234-239.

Lidow MS (2003) Calcium signaling dysfunction in schizophrenia: a unifying approach. Brain Res Rev 43: 70-84.

Liu JZ, Mcrae AF, Nyholt DR, Medland SE, Wray NR, Brown KM, Hayward NK, Montgomery GW, Visscher PM, Martin NG (2010) A versatile gene-based test for genome-wide association studies. Am J Hum Genet 87: 139-145.

Loh P-R, Bhatia G, Gusev A, Finucane HK, Bulik-Sullivan BK, Pollack SJ, de Candia TR, Lee SH, Wray NR, Kendler KS (2015) Contrasting genetic architectures of schizophrenia and other complex diseases using fast variance-components analysis. Nat Genet 47:1385-1392.

Monnier N, Procaccio V, Stieglitz P, Lunardi J (1997) Malignant-hyperthermia susceptibility is associated with a mutation of the a1-subunit of the human dihydropyridine-sensitive L-type voltage-dependent calcium-channel receptor in skeletal muscle. Am J Hum Genet 60: 1316-1325.

Moosmang S, Haider N, Klugbauer N, Adelsberger H, Langwieser N, Müller J, Stiess M, Marais E, Schulla V, Lacinova L (2005) Role of hippocampal Cav1. 2 Ca2+ channels in NMDA receptor-independent synaptic plasticity and spatial memory. J Neurosci 25: 9883-9892.

Parajuli LK, Nakajima C, Kulik A, Matsui K, Schneider T, Shigemoto R, Fukazawa Y (2012) Quantitative regional and ultrastructural localization of the CaV2. 3 subunit of R-type calcium channel in mouse brain. J Neurosci 32: 13555-13567.

Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D (2006) Principal components analysis corrects for stratification in genome-wide association studies. Nat Genet 38: 904-909.

Ptáček LJ, Tawil R, Griggs RC, Engel AG, Layzer RB, Kwieciński H, McManis PG, Santiago L, Moore M, Fouad G (1994) Dihydropyridine receptor mutations cause hypokalemic periodic paralysis. Cell 77: 863-868.

Purcell SM, Moran JL, Fromer M, Ruderfer D, Solovieff N, Roussos P, O'Dushlaine C, Chambert K, Bergen SE, Kähler A (2014) A polygenic burden of rare disruptive mutations in schizophrenia. Nature 506: 185-190.

Ramanan VK, Shen L, Moore JH, Saykin AJ (2012) Pathway analysis of genomic data: concepts, methods, and prospects for future development. Trends Genet 28: 323-332.

Ripke S, O'Dushlaine C, Chambert K, Moran JL, Kähler AK, Akterin S, Bergen SE, Collins AL, Crowley JJ, Fromer M (2013) Genome-wide association analysis identifies 13 new risk loci for schizophrenia. Nat Genet 45: 1150-1159.

Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014) Biological insights from 108 schizophrenia-associated genetic loci. Nature 511: 421-427.

Schlick B, Flucher B, Obermair G (2010) Voltage-activated calcium channel expression profiles in mouse brain and cultured hippocampal neurons. Neuroscience 167: 786-798.

Simms BA, Zamponi GW (2014) Neuronal voltage-gated calcium channels: structure, function, and dysfunction. Neuron 82: 24-45.

Splawski I, Timothy KW, Decher N, Kumar P, Sachse FB, Beggs AH, Sanguinetti MC, Keating MT (2005) Severe arrhythmia disorder caused by cardiac L-type calcium channel mutations. Proc Natl Acad Sci U S A 102: 8089-8096.

Splawski I, Timothy KW, Sharpe LM, Decher N, Kumar P, Bloise R, Napolitano C, Schwartz PJ, Joseph RM, Condouris K (2004) Ca v 1.2 calcium channel dysfunction causes a multisystem disorder including arrhythmia and autism. Cell 119: 19-31.

Turner RW, Anderson D, Zamponi GW (2011) Signaling complexes of voltage-gated calcium channels. Channels 5: 440-448.

Van Os J, Kapur S (2009) Schizophrenia. Lancet 374: 635-645.

Wang K, Li M, Hakonarson H (2010) Analysing biological pathways in genome-wide association studies. Nat Rev Genet 11: 843-854.

White JA, McKinney BC, John MC, Powers PA, Kamp TJ, Murphy GG (2008) Conditional forebrain deletion of the L-type calcium channel CaV1. 2 disrupts remote spatial memories in mice. Learn Mem 15: 1-5.

Williams ME, Brust PF, Feldman DH, Patthi S, Simerson S, Maroufi A, McCue AF, Velicelebi G, Ellis SB, Harpold MM (1992) Structure and functional expression of an omega-conotoxin-sensitive human N-type calcium channel. Science 257: 389-395.

Woodside B, Borroni A, Hammonds M, Teyler T (2004) NMDA receptors and voltage-dependent calcium channels mediate different aspects of acquisition and retention of a spatial memory task. Neurobiol Learn and Mem 81: 105-114.

Wu MC, Kraft P, Epstein MP, Taylor DM, Chanock SJ, Hunter DJ, Lin X (2010) Powerful SNP-set analysis for case-control genome-wide association studies. Am J Hum Genet 86: 929-942.

Wu MC, Lee S, Cai T, Li Y, Boehnke M, Lin X (2011) Rare-variant association testing for sequencing data with the sequence kernel association test. Am J Hum Genet 89: 82-93.

Yang J, Manolio TA, Pasquale LR, Boerwinkle E, Caporaso N, Cunningham JM, De Andrade M, Feenstra B, Feingold E, Hayes MG (2011) Genome partitioning of genetic variation for complex traits using common SNPs. Nat Genet 43: 519-525.

Figure Legends

Fig. 1 Molecular organization of voltage-gated calcium channels and chromosome locations of their subunit-coding genes.

Most Ca_v channels are multi-subunit structure (containing 3 or 4 subunits, α_1, β, $\alpha_2\delta$, with or without γ subunits), but T-type Ca_v channels only have the α_1 subunit. In one specific channel, the subunits are physically bound together, but their encoding genes are localized far apart or even on different chromosomes. Nine autosomal genes (*CACNA1A*, *CACNA1B*, *CACNA1C*, *CACNA1D*, *CACNA1E*, *CACNA1G*, *CACNA1H*, *CACNA1I*, *CACNA1S*) encode α_1 subunit (connected by red lines), four genes (*CACNB1*, *CACNB2*, *CACNB3*, *CACNB4*) encode β subunits (connected by blue lines), four genes (*CACNA2D1*, *CACNA2D2*, *CACNA2D3*, *CACNA2D4*) encode $\alpha_2\delta$ subunit (connected by green lines) and eight genes (*CACNG1*, *CACNG2*, *CACNG3*, *CACNG4*, *CACNG5*, *CACNG6*, *CACNG7*, *CACNG8*) encode γ subunit (connected by grey lines). The numbers 1, 2, 3, 7, 9, 10, 12, 16, 17, 19 & 22 represent chromosome numbers.

Fig. 2 Estimates of the schizophrenia variance explained by SNPs from each subtype of Ca_v channels. (a) Chip heritability of each significant subtype of Ca_v channel, (b) Fold enrichment of each significant subtype of Ca_v channel in schizophrenia. The fold enrichment is the ratio of the proportion of chip heritability (from each significant subtype of channel) in total heritability (33%) to the proportion of their SNPs in all SNPs (9,423,850 variants, minor allele frequency > 0.05) from 1000 Genomes Projects.