Manuscript Details

Manuscript number	NEUBIOREV_2015_365
Title	A Review of Molecular Genetic Studies of Neurocognitive Deficits in Schizophrenia
Article type	Review Article

Abstract

Schizophrenia is a complex and debilitating illness with strong genetic loading. In line with its heterogeneous symptomatology, evidence suggests genetic etiologies for the phenotypes in schizophrenia. A search across endophenotypes has pointed towards consistent findings in its neurocognitive deficits. Extensive literature has demonstrated impaired cognition including executive function, attention, and memory in schizophrenia patients when compared to healthy subjects. This review 1) provides an overview of recent studies and 2) develops an up-to-date conceptualization of genetic variations influencing neurocognitive functions in schizophrenia patients. Several neurotransmitter system genes have been examined given knowledge of their role in brain functions and their reported genetic associations with schizophrenia and cognition. Several genetic variations have emerged as having preliminary effects on neurocognitive deficits in schizophrenia. These include genes in the neurotrophic, serotonin, cell adhesion, and sodium channel systems. Limited evidence also suggests the dopaminergic system genes, with the most studied catechol-o-methyltransferase (COMT) gene showing inconsistent findings. Further investigations with larger samples and replications are required to elucidate genetic risk for cognitive deficits in schizophrenia.

Keywords	Genetics; schizophrenia; neurocognition; cognitive deficits; candidate gene studies; genome-wide association studies (GWASs)
Corresponding Author	Gwyneth Zai
Order of Authors	Gwyneth Zai, Barbara Sahakian, Trevor Robbins, James Kennedy
Suggested reviewers	Vish Nimgaonkar, Katherine Burdick, Dan Rujescu, William Byerley

Submission Files Included in this PDF

File Name [File Type]

Zai G - SCZ Cognition Genetics Review_Cover Letter_Aug29_2016.doc [Cover Letter]
Zai G - SCZ Cognition Genetics Review_Response to Reviewer_Aug29_2016.doc [Response to reviewers]
Genetic of Neurocognition in Schizophrenia - Review_Aug29_2016.doc [Manuscript]
Zai G - SCZ Cognition Genetics Review_Figure1_Aug29_2016.docx [Figure]
Genetic of Neurocognition in Schizophrenia - Review_Tables1-2_Aug29_2016.doc [Table]
Zai G - SCZ Cognition Genetics Review_Supplementary Table1_Aug29_2016.doc [Table]
Zai G - SCZ Cognition Genetics Review_Highlights_Dec1_2015.docx [Highlights]

To view all the submission files, including those not included in the PDF, click on the manuscript title on your EVISE Homepage, then click 'Download zip file'.

A Review of Molecular Genetic Studies of Neurocognitive Deficits in Schizophrenia

Gwyneth Zai ^{1,2,3,4*}, Trevor W. Robbins ^{3,5}, Barbara J. Sahakian ^{3,4}, James L. Kennedy ^{1,2}

¹ *Neurogenetics Section, Centre for Addiction and Mental Health, Toronto, Canada*

² *Department of Psychiatry and Institute of Medical Science, University of Toronto, Toronto, Canada*

³ *MRC/Wellcome Trust Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge, UK*

⁴ *Department of Psychiatry, University of Cambridge, Cambridge, UK*

⁵ *Department of Psychology, University of Cambridge, Cambridge, UK*

* Corresponding authors:

Dr. Gwyneth Zai, Centre for Addiction and Mental Health, 250 College Street, Toronto, ON M5T 1R8, Canada (Phone: 1-416-535-8501 ext. 30145; Fax: 1-416-979-4666; E-mail: gwyneth.zai@camh.ca)

Submitted to: *Biological Psychiatry*

Short Title: Genetics of Neurocognition in Schizophrenia

Keywords: Genetics; schizophrenia; neurocognition; cognitive deficits; candidate gene studies;

genome-wide association studies (GWASs)

Word Count: 202 for abstract and 4000 for article body

Number of Tables: 2

Number of Figures: 1

Supplementary Information: 1 supplementary table

HIGHLIGHTS:

- Schizophrenia patients present with impaired cognitive functions.
- Evidence suggests strong genetic etiology for cognitive deficits in schizophrenia.
- Neurotransmitter system genes showed effect on cognitive deficits in schizophrenia.
- Limited evidence suggests the dopaminergic system genes with inconsistent findings.
- Larger samples are required to examine genetic risk of cognition in schizophrenia.

ABSTRACT (Word count = 170):

Schizophrenia is a complex and debilitating illness with strong genetic loading. In line with its heterogeneous symptomatology, evidence suggests genetic etiologies for the phenotypes in schizophrenia. A search across endophenotypes has pointed towards consistent findings in its neurocognitive deficits. Extensive literature has demonstrated impaired cognition including executive function, attention, and memory in schizophrenia patients when compared to healthy subjects. This review 1) provides an overview of recent studies and 2) develops an up-to-date conceptualization of genetic variations influencing neurocognitive functions in schizophrenia patients. Several neurotransmitter system genes have been examined given knowledge of their role in brain functions and their reported genetic associations with schizophrenia and cognition. Several genetic variations have emerged as having preliminary effects on neurocognitive deficits in schizophrenia. These include genes in the neurotrophic, serotonin, cell adhesion, and sodium channel systems. Limited evidence also suggests the dopaminergic system genes, with the most studied catechol-o-methyltransferase (*COMT*) gene showing inconsistent findings. Further investigations with larger samples and replications are required to elucidate genetic risk for cognitive deficits in schizophrenia.

INTRODUCTION

Schizophrenia is a chronic and severe neuropsychiatric disorder with a lifetime prevalence of 0.4-1% in the general population (1, 2). The core features of this disorder are characterized by three symptom domains including positive symptoms, negative symptoms, and cognitive deficits (1). The identification of neurocognitive deficits in schizophrenia patients is important because cognitive impairment is associated with poor functional outcome (3). Up to 98% of schizophrenia patients have a degree of neurocognitive impairment (4, 5). Although antipsychotic medications reduce positive symptoms significantly, they have limited efficacy for remediating neurocognitive deficits and negative symptoms of schizophrenia (6, 7).

Cognitive dysfunction has repeatedly been identified as one of the hallmark features of schizophrenia starting as early as 1950 by Bleuler (8) and recently in the past decade (3, 4, 9, 10). A systematic review reported global cognitive impairment and specifically worse verbal memory, executive function, and general IQ, in first-episode psychotic patients when compared to healthy controls (11). Recent meta-analyses also detected significant deficits in working memory, attention/vigilance, verbal/visual learning and memory, executive functions (reasoning and problem solving), processing speed, social cognition, and psychomotor control (7, 12).

Evidence has shown that schizophrenia and cognitive impairment have heritability ranging between 70-90% and 24-55% respectively (13, 14). Schizophrenia is a complex and heterogeneous neuropsychiatric disorder with a polygenic architecture (15) and even following recent genome-wide association studies (GWAS) (16, 17), multiple small gene effects with only several replicable findings have been found to contribute to risk. Therefore, the identification of endophenotypes, with an attempt to ascertain a more homogeneous phenotype for genetic studies, is important for elucidating the etiology of schizophrenia. The search for

endophenotypes is guided by their strong association with the illness, high heritability, and observable similar deficits in unaffected relatives (18). Cognitive deficits are heritable and are core features of schizophrenia, thus they may be valuable endophenotypes for schizophrenia. Twin studies (19-21) and two recent molecular genetic studies (22, 23) have reported significant genetic overlap between neurocognition and schizophrenia. Additionally, neuropsychological studies have observed that unaffected relatives of schizophrenia patients performed significantly worse in estimated intelligence, immediate and delayed logical memory, immediate visual reproduction, and sustained attention, therefore implicating genetic loading within families (24-26). Although research on the genetics of neurocognitive domains in schizophrenia has grown rapidly over the last decade in parallel with attempts to determine the genetic etiology of schizophrenia, the last review to have covered some genetic studies of cognitive endophenotypes in schizophrenia was published in 2008 (27). Therefore, we now provide an up-to-date review of this important topic.

Methods:

We reviewed all molecular genetic studies of cognition in schizophrenia that were published in PubMed and/or MEDLINE until January 1, 2015. Specific search terms used included: genetics, molecular genetics, schizophrenia, cognition, neurocognition, cognitive or neurocognitive or neuropsychological deficits or impairments or endophenotypes or traits. ~~Eighty-two~~Seventy-three original studies were included in this review article. A summary can be found on Table 1 (Table S1 in Supplement 1 for full details).

Results:

Many genes have been reported to be associated with cognitive impairment in schizophrenia as shown in Table S1 in Supplement 1. The next sections of this review will provide a comprehensive summary of these genetic findings organized according to important bio-molecular systems (Figure 1).

Dopaminergic System Genes:

The dopaminergic system genes that have been investigated in neurocognitive deficits of schizophrenia include catechol-O-methyltransferase (*COMT*) (10, 28-47), dopamine transporter (*DAT*) (10, 28, 41, 47, 48), dopamine D1 receptor (*DRD1*) (10), dopamine D2 receptor (*DRD2*) (10, 43, 45), dopamine D3 receptor (*DRD3*) (10, 46, 48), dopamine D4 receptor (*DRD4*) (30), dopamine D5 receptor (*DRD5*) (49), dopamine beta-hydroxylase (*DBH*) (12, 46), vesicular monoamine transporter 2 (*SLC18A2*) (10, 46), ankyrin repeat and kinase domain containing 1 (*ANKKI*) (10), and protein phosphatase 1, regulatory (inhibitor) subunit 1B (*PPP1R1B*) (10).

The most extensively examined candidate gene in neurocognition of schizophrenia is *COMT*. A reduction in dopaminergic neurotransmission in specific brain regions such as the anterior cingulate and the dorso-lateral prefrontal cortex has been postulated to alter cognition, specifically executive function and working memory, in schizophrenia (50). A functional polymorphism within *COMT*, Val158Met, accounts for a four-fold variation in its enzymatic activity and dopamine catabolism in the prefrontal cortex, with Met as the low functioning allele (34). Twenty three studies were found as defined by our search criteria (31). Barnett et al. (31) performed a meta-analysis including 12 studies of the impact of *COMT* Val158Met on executive function and detected significant association between Val/Val and worse cognitive performance than Met/Met only in healthy controls but not in schizophrenia patients. A recent study (43)

similarly reported no association between this locus and theory of mind dysfunction in schizophrenia but detected worse performance in Met-carrier females in the combined schizophrenia and control sample. However, a 94-multi-gene family study examining *COMT*, found associations with verbal learning, ‘false’ memory, and prepulse inhibition in schizophrenia patients (44). Twamley et al. (51) also reported better learning, memory, and abstraction with the Met allele than Val, and when Green et al. (52) investigated cognitive function in schizophrenia patients with childhood trauma history, they detected significant links of the Val homozygotes with worse cognitive performance in the absence of childhood adversity, and better executive function with positive abuse history, suggesting a gene-environment interaction. Overall, given the pleiotropic effects of most genes, it appears unlikely that changes in cognition in relation to *COMT* are specific to schizophrenia.

Other dopamine-related genes, *DAT*, *DRD1*, *DRD2*, *DRD3*, *DRD4*, *DRD5*, *DBH*, *SLC18A2*, *ANKK1*, and *PPP1R1B*, have also been investigated in cognitive deficits of schizophrenia. These genes were examined because of their prior association with schizophrenia, antipsychotic actions, and/or their involvement in dopamine neurotransmission. Four studies involved *DAT*, one with rs6350 and three with the functional 3’ VNTR, but none reported association with cognitive measures in schizophrenia (28, 41, 47, 48). Three studies investigated *DRD2* markers in executive functioning (45) and theory of mind impairment (43) in schizophrenia (10) and all were negative. Two significant and one negative studies of *DRD3* have been published. Firstly, Szekeres et al. (48) reported a significant association between the *DRD3* Ser9Gly low functioning (53) Ser/Ser genotype and fewer categories completed and more perseverative errors on the Wisconsin Card Sort Test (WCST) than Ser/Gly. Secondly, a 94-multi-gene study reported a significant association between *DRD3* and emotional recognition

(44). However, Bombin et al. (45) only detected significant associations of *DRD3* in the combined first-episode psychosis and healthy adolescents suggesting a lack of power. One *DRD5* study (49) reported a significant association between the presence of two copies of the 7 (148-bp) allele in the (CT/GT/GA)_n microsatellite and lower word generation (visual voluntary attention) than one copy of the 7 allele in schizophrenia ($P=0.018$) and their relatives. Kukshal et al. (46) reported no association between *COMT*, *DRD3*, *DBH*, and *SLC18A2* with performance in the Trail Making Test. For the *DBH* 19-bp deletion, Hui et al. (12) detected significantly poorer immediate memory with the carriers in schizophrenia patients but not in controls. Several markers across *DAT*, *DRD1*, *DRD3*, and *SLC18A2* were also found to be significantly associated with poorer cognitive functions in schizophrenia patients in a multi-gene study (10).

Thus, dopamine-related genes may be implicated to a limited extent in the neurocognitive deficits in schizophrenia patients, especially in memory, attention and executive function. However, except for *COMT*, few studies have examined other dopamine-related genes and recent GWAS of cognitive performance in schizophrenia (22, 23, 54, 55) failed to implicate any dopamine-related genes, suggesting the existence of additional possible mechanisms and interactions in the genetic etiology of neurocognitive deficits in schizophrenia and the need for more systematic studies.

Neurodevelopmental and Neuroplasticity Genes:

Genes related to neurodevelopment and neuroplasticity are obvious candidates for cognitive deficits in schizophrenia.

The dystrobrevin binding protein 1 (*DTNBPI*) gene encodes dysbindin, a key subunit of the biogenesis of lysosome-related organelles complex-1, which regulates protein trafficking and

cell-surface expression of neurotransmitter receptors (56). It has been shown to modulate prefrontal cortical activity via glutamatergic neurotransmission (57, 58). Significant reduction of *DTNBP1* in glutamatergic neuronal terminal fields in the hippocampus has been reported and Talbot et al. (57) postulated that glutamatergic dysconnectivity may contribute to cognitive impairment in schizophrenia. ~~Three-Four~~ studies examined the effect of this gene in cognitive deficits of schizophrenia. Burdick et al. (59) first demonstrated an association between a schizophrenia risk haplotype of *DTNBP1* (rs909706-rs1018381-rs2619522-rs760761-rs2619528-rs1011313), CTCTAC, and greater decline in IQ in 183 schizophrenia/schizoaffective disorder patients. Baek et al. (60) later reported a significant association between *DTNBP1* rs760761 and rs1018381 and the attention/vigilance domain when comparing schizophrenia patients to controls. Another study (61) reported that the *DTNBP1* rs2619539-rs3213207-rs2619538 C-A-T haplotype was associated with impaired spatial working memory performance. However, one study (62) did not report any association between single tagging sequence variants and their relevant haplotypes across *DTNBP1* and neurocognitive endophenotypes in schizophrenia after separating individuals into cognitive deficit and cognitive sparing groups.

The disrupted in schizophrenia 1 (*DISC1*) gene is considered to be a central hub of cellular development and regulation given its importance in neurogenesis and neuroplasticity (63). It has been previously shown to be associated with schizophrenia, initially from a large multiplex family although not specific to schizophrenia (64) and a recent European meta-analysis (65). Furthermore, the down-stream cascade of *DISC1* and its interaction with phosphodiesterase-4B have been implicated in learning, memory, and mood (66). Thus, *DISC1* has become a candidate for the genetic study of neurocognitive dysfunctions in schizophrenia (67). ~~Only three~~Five studies have been reported. The first (68) reported an association between

the *DISC1*/translin-associated factor X (*TRAX*) haplotype and impairments in short- and long-term memory and reduced gray matter density in the prefrontal cortex. The second (69) reported an association between the *DISC1-HEP3* (rs751229-rs3738401) haplotype and poorer performance on short-term visual memory and attention. The third demonstrated a significant finding between *DISC1* rs821616 Ser/Ser genotype and reduced performance on WMS Logical Memory II subsection in schizophrenia patients in addition to a lower WCST category scores in the entire sample (schizophrenia, unaffected siblings, parents, and healthy controls) (70). Burdick et al. (71) observed positive association between *DISC1* rs2255340 genotype and rapid visual search and verbal working memory. The last is a recently published multi-gene study (28) who reported a trend association between *DISC1* rs12133766 and deficient verbal fluency in schizophrenia males ($P=0.049$).

Neurotrophic factors have been postulated to affect cognition given their roles in neuroplasticity and their interactive and modulatory effects on various neurotransmitter systems. The brain-derived neurotrophic factor (*BDNF*) gene has been examined due to its role in cell differentiation, survival, long-term potentiation, synaptic plasticity, learning, and memory (72-75). Its functional polymorphism, rs6265 (Val66Met), has been extensively investigated with prior significant associations in memory impairment (76) and schizophrenia (77). Three-Eight studies in addition to a multi-gene study and a meta-analysis including twoseven studies from our search were detected. The first study Egan et al. (78) detected a significant association between individuals with one or two Met allele(s) regardless of their disease status (schizophrenia patients, their healthy siblings, and healthy controls) and lower abilities to perform tasks of learning and memory. Another study (79) reported that schizophrenia patients with the high-functioning Val/Val genotype of *BDNF* Val66Met had superior scores for both

voluntary and involuntary attention tasks, in contrast to the serotonin 2A receptor gene (*HTR2A* T102C)T-Met combination, linked to inferior performance for voluntary attention but superior performance for involuntary attention. Ho et al. (80) ~~reported-observed~~ a significant association between the *BDNF* Met allele with poorer verbal memory performance in both schizophrenia patients and healthy volunteers, and visuospatial impairment in schizophrenia only. Val carriers were found to be associated with better visuospatial and constructional performance in both schizophrenia and healthy subjects whereas only schizophrenic Met carriers had significantly greater attention impairment (81). In another study, schizophrenic Met carriers showed higher percentage of WCST perseverative errors especially in males (82). Although Rybakowski et al. (83), Ho et al. (84), and Chung et al. (85) reported no association between *BDNF* Val66Met and cognitive performance-on WCST-but, Rybakowski et al. (80) demonstrated that Val/Val was significantly associated with higher correct responses on the N-back test. A recent meta-analysis, which included 12 studies including Egan et al. (78), Ho et al. (80), Rybakowski et al. (83), Ho et al. (84), Chung et al. (85), Lu et al. (82), and Zhang et al. (81) compared neurocognitive domain scores between Met carriers and Val homozygotes in 1890 schizophrenic patients and did not report any significant difference (86) and a recent multi-gene study also did not support a role of *BDNF* in schizophrenia patients with cognitive deficits (Nicodemus et al., 2013).

Although ~~threewe~~ of the ~~three-four~~ studies above showed modest significant association between *DTNBPI* variants and poor cognitive performance in schizophrenia patients, and ~~three~~ five studies suggested some associations of *DISC1* genetic variants in neurocognitive deficits in schizophrenia, the recent GWAS (23) support neither of these genes as being strongly related to schizophrenia. Furthermore, a recent meta-analysis did not support the involvement of *BDNF*

Val66Met in psychotic patients with neurocognitive deficits. Thus, the overall status of these genes in neurocognitive function in schizophrenia remains unresolved.

Glutamatergic System Genes:

The glutamatergic neurotransmitter system has received much attention given its neuronal excitatory properties in network functions throughout the brain, especially in the cerebral cortex, its influence in psychotic and cognitive symptoms, as well as being a source of potential drug targets (87, 88). In animal studies, the mGluR3 knockout mouse showed hyperactivity and impaired working memory (89, 90), and these cognitive deficits are consistent with those of schizophrenia patients (7, 11). Reduction in glutamate levels has also been found in schizophrenia patients with impaired cognitive control functioning but not in healthy controls (87).

Effects of glutamatergic modulatory drugs such as mGluR2/3 agonists (i.e. metabotropic glutamate receptor group II agonists), have been investigated in animal models of schizophrenia (91, 92). Other drugs that regulate activation or inhibition of the N-methyl-D-aspartate (NMDA) receptor including the glycine transporter-1 inhibitors (93) and NMDA receptor antagonist (94) have also been investigated for their potential role in the treatment of cognitive impairment in schizophrenia. These medications have had mixed results in early clinical trials in schizophrenia but more recently, a mGluR2/3 agonist has shown promising results in the treatment of early psychosis (95), possibly with relatively good efficacy for cognition, in particular, working memory (96).

Of the glutamatergic system genes, only three have been studied: the glutamate receptor, ionotropic, N-methyl-D-aspartate, subunit 2B (*GRIN2B*) (28, 97), *GRIN2A* (97), and glutamate

receptor, metabotropic 3 (*GRM3*) (97). Jablensky et al. (97) reported a significant association between the *GRIN2B* rs220599 T allele with poorer immediate and delayed recall on the Rey Auditory Verbal Learning Test; however, Nicodemus et al. (28) did not detect any positive findings with this gene in cognitive deficits of schizophrenia. Jablensky et al. (97) also observed enhanced cognitive performance with the *GRM3* rs2189814 C allele but not with *GRIN2A*.

Very few studies of glutamate system genes have examined neurocognitive impairments in schizophrenia, although new medications targeting the glutamatergic system have shown possibly promising results in the treatment of cognitive deficits in schizophrenia and in reducing psychosis. The use of genetic tools to subdivide groups of patients in trials of new glutamatergic drugs may help to identify patients, whose cognition will show greater improvement, thus pointing to more personalized treatment options.

Serotonergic System Genes:

The serotonergic system interacts with many neurotransmitter systems and serotonin plays an important role in the regulation of morphogenesis in CNS development, neuronal proliferation, migration, differentiation, and cognition (98-100). In terms of gene expression, the frontal cortex and anterior cingulate cortex have approximately 10-fold higher mRNA expression of the serotonin 2A receptor (*HTR2A*) than hippocampus or caudate and putamen according to the Genetic Tissue Expression database (GTEx: <http://www.gtexportal.org>).

Five studies have examined the *HTR2A* T102C polymorphism (28, 79, 101-103) with three significant associations. As mentioned above, Alfimova et al. (104) reported a significant association between the T allele and more time for performing the test in addition to the T- (*BDNF* Val66Met)Met combination and lower scores for voluntary attention and higher scores

for involuntary attention. Uçok et al. (103) reported significant associations between the high expression (105) T allele with a lower hit rate in Continuous Performance Task (CPT) and the T/C genotype with more commission errors on CPT and fewer correct responses on WCST. Alfimova et al. (101) reported a significant association between the T/T homozygotes and lower verbal fluency in male schizophrenia patients only and not the entire sample, including controls. Although Chen et al. (102) did not detect a significant association between the *HTR2A* T102C polymorphism and cognitive deficits in schizophrenia patients. The authors observed a trend between T/C genotype and better verbal fluency and less motor co-ordination soft neurological signs. Nicodemus et al. (28) however did not demonstrate any role of this genetic variation in cognitive deficits in schizophrenia.

Besides *HTR2A*, one study of the serotonin 1A receptor (*HTR1A*) (106) and three studies of the serotonin transporter (*5HTT*, also known as *SLC6A4*) (107) have been conducted. Bosia et al. (106) reported schizophrenia patients with the low-expression (108) CC genotype of *HTR1A* - 1019C/G polymorphism performed better on Theory of Mind tasks. Bosia et al. (107) reported a significant association between the *HTTLPR* polymorphism and executive function and sustained attention, specifically the high activity long allele with better executive performance and with poorer attention, but two additional studies were negative (45, 47).

Genome-Wide Association Studies (GWAS):

To date, five GWAS have been published recently (see Table S1 in Supplement 1 for full details). The first GWAS was published in 2012 and written in Chinese (109). Xiang et al. (109) identified five risk genes, which were associated with memory deficits. The second GWAS examining genetic influence of neurocognitive traits in schizophrenia found the strongest

genetic enrichments for performance in a colour-interference Stroop test and sets associated with the rate of learning (23). The third GWAS (22) reported significant genetic overlap between general cognitive ability and risk for schizophrenia, implicating similar pathophysiological processes between the two. Although schizophrenia patients had lower general cognitive ability than healthy controls, the authors did not detect genome-wide significance. In the meta-analysis (22), they observed significant association between MAD1 mitotic arrest deficient-like 1 (*MAD1L1*) and cyclin M2 (*CNNM2*) and lower general cognitive ability. Additionally, the LSM1 homologue, U6 small nuclear RNA associated (*LSM1*) and the neurogranin (protein kinase C substrate, RC3) (*NRGN*) schizophrenia risk alleles were associated with higher cognitive ability in schizophrenia patients (22). Through the recent PGC schizophrenia GWAS, Hargreaves et al. (54) detected an increased polygenic risk score for the cell adhesion molecule pathway with poorer performance on memory and attentional tasks. The strongest signal was detected within the human leukocyte antigen system, *HLA-DQA1* rs9272105 marker, which was associated with attentional control only. The latest GWAS (55) showed genome-wide significant associations between cognitive ability in schizophrenia and polymorphisms in the sodium channel, voltage-gated, type II, alpha subunit (*SCN2A*) gene.

Genetics of Normal Cognition, Alzheimer's Disease, and Other Cognitive Disorders:

General intelligence may in fact play a role in cognitive deficits of schizophrenia patients. Therefore, we included a brief summary of the genetics of general intelligence in healthy individuals and patients with cognitive disorders in order to determine whether there are distinct genetic risks that differentiate between healthy individuals, patients with cognitive disorders, and schizophrenia patients with cognitive deficits.

A GWAS of general intelligence has not yielded genome-wide significance in 3,511 healthy adults (110); however, using a gene-based approach, Davies et al. (110) detected a genome-wide significant association with the forming-binding protein 1-like (*FBNPIL*) gene but it was not replicated in an independent sample from the same study. The apolipoprotein E (*APOE*) gene was found to be associated with cognition in older individuals, suggesting a genetic overlap with Alzheimer's disease (111). A recent review article on GWAS in Alzheimer's disease identified several major pathways, including amyloid, immune system, inflammation, lipid transport and metabolism, synaptic functioning, and endocytosis (112). Similarly in a recent review of the genetics of recessive cognitive disorders, significant associations have been found in genes that are involved in synaptic function, basic cellular processes including DNA transcription, translation, and degradation, mRNA splicing, energy metabolism, and fatty-acid synthesis and turnover (113, 114).

There are genetic overlaps between general intelligence in healthy individuals, cognitive disorders, and cognitive deficits in schizophrenia (Table 2). Interestingly, energy metabolism appears to be a common genetic pathway that affects cognition regardless of disease status. Nonetheless, many genes have been detected in specific disorders but replication studies are required to further expand on these reports and to differentiate disease-specific genetic markers.

Treatment Implications:

Pharmacotherapy of schizophrenia has only shed light in the treatment of positive, but not cognitive or negative symptoms. No known treatment has provided significant improvement in these latter symptoms to date. Since cognitive and negative symptoms are associated with poor functional outcome, the development of new pharmacological strategies is crucial for reducing

disease-related disability. Recent studies of cognitive enhancers and immunomodulatory drugs have reported promising effects on cognition in schizophrenia (115, 116); however, replications are warranted to provide support for clinical application. Thus, the search for genetic vulnerability in cognition and eventual discovery of a biomarker will enable researchers to identify new drug targets, which will hopefully lead to the improvement of cognitive deficits in schizophrenia patients.

Discussion:

This is the first comprehensive attempt to review all molecular genetic studies of cognitive impairments in schizophrenia to date. Neurocognitive deficits are one of the key symptom dimensions of schizophrenia. The study of cognition in schizophrenia is a strong and important unmet need for new drug targets since cognitive deficits are often the most difficult to treat.

Although ~~73~~82 publications were qualified according to our search criteria, a considerable expansion of current work will be required to further identify risk loci for cognitive dysfunction in schizophrenia. Multiple genetic variants have been examined in different cognitive domains in schizophrenia but there have been few replication studies to date. The most examined candidate genes include *COMT*, *DISC1*, *HTR2A*, and *BDNF*, which all provided inconsistent findings, often associated with different aspects of cognitive dysfunction in schizophrenia.

Evidence has suggested overlapping genetic etiology between neurocognition and schizophrenia (21). Although the number of molecular genetic studies is growing, these studies use traditional clinical and convenient neuropsychological test measures, which are often

insensitive, non-specific, and neurally ill-defined. The hope is for a more homogeneous phenotype; however, current studies often use the label of cognitive impairment loosely in schizophrenia. Many of these studies focused on genes that were previously implicated in schizophrenia and very few of them have investigated interactions between genetic variations across different genes. Calcium and sodium channels have emerged in recent schizophrenia genetic association studies as well as the most recent GWAS examining cognitive impairment in schizophrenia. These will hopefully lead researchers to search for an underlying common mechanism that may partly explain the etiology of schizophrenia and its related cognitive deficits. Advances in bioinformatics are allowing researchers to analyze large datasets despite the relatively low prevalence of schizophrenia and multiple common loci explaining only small fractions of the genetic variance. Linking functional implication to identified genetic markers (e.g., expression via GTEx) and testing these functional hypotheses may prove to advance our understanding of the etiology of neurocognitive dysfunction in schizophrenia.

The complexities of both schizophrenia and cognition provide additional challenges including the potential role of illness epiphenomena and illness-specific mechanisms of cognitive impairment. Furthermore, one of the two twin studies that have examined the genetic influences in schizophrenia and cognition detected limited genetic overlap between the two (117). Suggestive of the lack of overlap can be observed in two schizophrenia risk alleles counter-intuitively being associated with better cognitive performance (22). Common genetic markers affecting cognitive performance in schizophrenia may not have been detected at present given the complex interactions of genetic, environmental, and random influences that affect individuals across their developmental stages and lifespan. Investigating interactions between other endophenotypes of schizophrenia that may be related to cognitive functions, such as

neuroimaging findings, are potentially crucial for linking genetics to brain structure and function. Larger sample sizes with definition of homogeneous subgroups may aid in the identification of specific and shared genetic markers that influence schizophrenia and cognition. Moreover, there are numerous different facets of neurocognition and many different methods for testing these cognitive domains; thus, development of a broad battery of systematic and well-standardized cognitive tasks that are reliable, easy to interpret, and comparable based on modern cognitive neuroscience approaches will be required in order to derive more definitive conclusions. Significant associations with performance on a single test of a particular function such as working memory or attention will ideally be supported by more than one test measure. The behavioural specificity of such effects will also need to be carefully assessed. One major, though controversial, hypothesis relating to intellectual deficits in schizophrenia is that it may be driven by the general factor, *g*, from conventional IQ tests (118, 119). The relationship of specific, or general, aspects of cognition to identified neural system dysfunction is also required so that neurocognitive phenotypes and endophenotypes can be accurately delineated.

Further research is warranted to target known hypotheses and mechanisms of cognitive deficits in schizophrenia, which may in turn contribute to the development of preventative measures and new drug targets. Cognitive deficits in schizophrenia are associated with poor functional outcome and therefore, the identification of biomarkers to predict different outcomes may influence treatment options including the intensity, duration, choice of medication, and type of therapy such as brain stimulation. Genetic markers related to electrophysiology and/or neuroplasticity such as *BDNF* may attract interest and attention in treatment utilizing brain stimulation techniques. New advances in differentiating cognitive deficits, impairment in social cognition, and negative symptoms of schizophrenia, including motivational and emotional

measures, may further delineate different subgroups within the current schizophrenia population. Genetic biomarkers may aid in the identification of these subgroups, which may in turn translate into clinical utility via personalized medicine.

Word Count: ~~4000~~4296 including track changes (excluding title page, abstract, acknowledgements, references, tables, and figures).

ACKNOWLEDGEMENTS

Dr. Gwyneth Zai is currently in the Clinician Investigator Program at the University of Toronto. Dr. Zai is supported by the Canadian Institutes of Health Research (CIHR) Postdoctoral Fellowship and the W. Garfield Weston Doctoral Fellowship.

FINANCIAL DISCLOSURE

Professor Barbara Sahakian and Professor Trevor Robbins both consult for Cambridge Cognition and have share options in the company. Professor Sahakian also consults for Peak (Brainbow), Servier, Otsuka, and Lundbeck, holds a grant from Janssen/Johnson & Johnson. Dr. James Kennedy is a Scientific Advisory Board member of AssureRx who only pays for expenses. Dr. Kennedy has also received speaker honoraria and expenses from Eli Lilly and Novartis, and consultant honoraria and expenses from Roche. Dr. Gwyneth Zai has no conflict of interest.

REFERENCES

1. (APA) APA. Diagnostic and Statistical Manual of Mental Disorders (DSM-V). 5th ed. Washington, DC: American Psychiatric Press; 2013.
2. McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. *Epidemiologic reviews*. 2008;30:67-76.
3. Lepage M, Bodnar M, Bowie CR. Neurocognition: clinical and functional outcomes in schizophrenia. *Canadian journal of psychiatry Revue canadienne de psychiatrie*. 2014;59(1):5-12.
4. Heinrichs RW, Zakzanis KK. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology*. 1998;12(3):426-45.
5. Keefe RS, Eesley CE, Poe MP. Defining a cognitive function decrement in schizophrenia. *Biological psychiatry*. 2005;57(6):688-91.
6. Carpenter WT, Koenig JI. The evolution of drug development in schizophrenia: past issues and future opportunities. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2008;33(9):2061-79.
7. Keefe RS, Harvey PD. Cognitive impairment in schizophrenia. *Handbook of experimental pharmacology*. 2012(213):11-37.
8. Bleuler E. *Dementia Praecox or the Group of Schizophrenias*. New York, NY: International Universities Press; 1950.
9. Green MF, Kern RS, Braff DL, Mintz J. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? *Schizophrenia bulletin*. 2000;26(1):119-36.
10. Barnett JH, Robbins TW, Leeson VC, Sahakian BJ, Joyce EM, Blackwell AD. Assessing cognitive function in clinical trials of schizophrenia. *Neuroscience and biobehavioral reviews*. 2010;34(8):1161-77.
11. Aas M, Dazzan P, Mondelli V, Melle I, Murray RM, Pariante CM. A Systematic Review of Cognitive Function in First-Episode Psychosis, Including a Discussion on Childhood Trauma, Stress, and Inflammation. *Frontiers in psychiatry*. 2014;4:182.
12. Green MF, Nuechterlein KH, Gold JM, Barch DM, Cohen J, Essock S, et al. Approaching a consensus cognitive battery for clinical trials in schizophrenia: the NIMH-MATRICES conference to select cognitive domains and test criteria. *Biological psychiatry*. 2004;56(5):301-7.
13. Greenwood TA, Braff DL, Light GA, Cadenhead KS, Calkins ME, Dobie DJ, et al. Initial heritability analyses of endophenotypic measures for schizophrenia: the consortium on the genetics of schizophrenia. *Archives of general psychiatry*. 2007;64(11):1242-50.
14. Sabb FW, Bearden CE, Glahn DC, Parker DS, Freimer N, Bilder RM. A collaborative knowledge base for cognitive phenomics. *Molecular psychiatry*. 2008;13(4):350-60.
15. Sullivan PF, Daly MJ, O'Donovan M. Genetic architectures of psychiatric disorders: the emerging picture and its implications. *Nature reviews Genetics*. 2012;13(8):537-51.
16. Ripke S, O'Dushlaine C, Chambert K, Moran JL, Kahler AK, Akterin S, et al. Genome-wide association analysis identifies 13 new risk loci for schizophrenia. *Nature genetics*. 2013;45(10):1150-9.
17. Biological insights from 108 schizophrenia-associated genetic loci. *Nature*. 2014;511(7510):421-7.
18. Gur RE, Calkins ME, Gur RC, Horan WP, Nuechterlein KH, Seidman LJ, et al. The Consortium on the Genetics of Schizophrenia: neurocognitive endophenotypes. *Schizophrenia bulletin*. 2007;33(1):49-68.

19. Cannon TD, Huttunen MO, Lonnqvist J, Tuulio-Henriksson A, Pirkola T, Glahn D, et al. The inheritance of neuropsychological dysfunction in twins discordant for schizophrenia. *American journal of human genetics*. 2000;67(2):369-82.
20. Pardo PJ, Knesevich MA, Vogler GP, Pardo JV, Towne B, Cloninger CR, et al. Genetic and state variables of neurocognitive dysfunction in schizophrenia: a twin study. *Schizophrenia bulletin*. 2000;26(2):459-77.
21. Touloupoulou T, Picchioni M, Rijdsdijk F, Hua-Hall M, Ettinger U, Sham P, et al. Substantial genetic overlap between neurocognition and schizophrenia: genetic modeling in twin samples. *Archives of general psychiatry*. 2007;64(12):1348-55.
22. Lencz T, Knowles E, Davies G, Guha S, Liewald DC, Starr JM, et al. Molecular genetic evidence for overlap between general cognitive ability and risk for schizophrenia: a report from the Cognitive Genomics consortium (COGENT). *Molecular psychiatry*. 2014;19(2):168-74.
23. Fernandes CP, Christoforou A, Giddaluru S, Ersland KM, Djurovic S, Mattheisen M, et al. A genetic deconstruction of neurocognitive traits in schizophrenia and bipolar disorder. *PloS one*. 2013;8(12):e81052.
24. Faraone SV, Seidman LJ, Kremen WS, Toomey R, Pepple JR, Tsuang MT. Neuropsychologic functioning among the nonpsychotic relatives of schizophrenic patients: the effect of genetic loading. *Biological psychiatry*. 2000;48(2):120-6.
25. Agnew-Blais J, Seidman LJ. Neurocognition in youth and young adults under age 30 at familial risk for schizophrenia: a quantitative and qualitative review. *Cognitive neuropsychiatry*. 2013;18(1-2):44-82.
26. Hilti CC, Hilti LM, Heinemann D, Robbins T, Seifritz E, Cattapan-Ludewig K. Impaired performance on the Rapid Visual Information Processing task (RVIP) could be an endophenotype of schizophrenia. *Psychiatry research*. 2010;177(1-2):60-4.
27. Golimbet VE. [Molecular genetics of cognitive deficit in schizophrenia]. *Molekuliarnaia biologii*. 2008;42(5):830-9.
28. Nicodemus KK, Elvegag B, Foltz PW, Rosenstein M, Diaz-Asper C, Weinberger DR. Category fluency, latent semantic analysis and schizophrenia: a candidate gene approach. *Cortex; a journal devoted to the study of the nervous system and behavior*. 2013.
29. Cruz BF, de Resende CB, Abreu MN, Rocha FL, Teixeira AL, Keefe RS, et al. How specific are negative symptoms and cognitive impairment in schizophrenia? An analysis of PANSS and SCoRS. *Cognitive neuropsychiatry*. 2013;18(3):243-51.
30. Alfimova MV, Golimbet VE, Gritsenko IK, Lezheiko TV, Abramova LI, Strel'tsova MA, et al. [Dopamine system genes interaction and neurocognitive traits in patients with schizophrenia, their relatives and healthy controls from general population]. *Zhurnal neurologii i psikiatrii imeni SS Korsakova / Ministerstvo zdravookhraneniia i meditsinskoi promyshlennosti Rossiiskoi Federatsii, Vserossiiskoe obshchestvo nevrologov [i] Vserossiiskoe obshchestvo psikiat*. 2006;106(7):57-63.
31. Barnett JH, Jones PB, Robbins TW, Muller U. Effects of the catechol-O-methyltransferase Val158Met polymorphism on executive function: a meta-analysis of the Wisconsin Card Sort Test in schizophrenia and healthy controls. *Molecular psychiatry*. 2007;12(5):502-9.
32. Bilder RM, Volavka J, Czobor P, Malhotra AK, Kennedy JL, Ni X, et al. Neurocognitive correlates of the COMT Val(158)Met polymorphism in chronic schizophrenia. *Biological psychiatry*. 2002;52(7):701-7.

33. Bosia M, Bechi M, Marino E, Anselmetti S, Poletti S, Cocchi F, et al. Influence of catechol-O-methyltransferase Val158Met polymorphism on neuropsychological and functional outcomes of classical rehabilitation and cognitive remediation in schizophrenia. *Neuroscience letters*. 2007;417(3):271-4.
34. Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE, et al. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America*. 2001;98(12):6917-22.
35. Galderisi S, Maj M, Kirkpatrick B, Piccardi P, Mucci A, Invernizzi G, et al. COMT Val(158)Met and BDNF C(270)T polymorphisms in schizophrenia: a case-control study. *Schizophrenia research*. 2005;73(1):27-30.
36. Goldberg TE, Egan MF, Gscheidle T, Coppola R, Weickert T, Kolachana BS, et al. Executive subprocesses in working memory: relationship to catechol-O-methyltransferase Val158Met genotype and schizophrenia. *Archives of general psychiatry*. 2003;60(9):889-96.
37. Golimbet V, Gritsenko I, Alfimova M, Lebedeva I, Lezheiko T, Abramova L, et al. Association study of COMT gene Val158Met polymorphism with auditory P300 and performance on neurocognitive tests in patients with schizophrenia and their relatives. *The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry*. 2006;7(4):238-45.
38. Joob R, Gauthier J, Lal S, Bloom D, Lalonde P, Rouleau G, et al. Catechol-O-methyltransferase Val-108/158-Met gene variants associated with performance on the Wisconsin Card Sorting Test. *Archives of general psychiatry*. 2002;59(7):662-3.
39. Nolan KA, Bilder RM, Lachman HM, Volavka J. Catechol O-methyltransferase Val158Met polymorphism in schizophrenia: differential effects of Val and Met alleles on cognitive stability and flexibility. *The American journal of psychiatry*. 2004;161(2):359-61.
40. Rosa A, Peralta V, Cuesta MJ, Zarzuela A, Serrano F, Martinez-Larrea A, et al. New evidence of association between COMT gene and prefrontal neurocognitive function in healthy individuals from sibling pairs discordant for psychosis. *The American journal of psychiatry*. 2004;161(6):1110-2.
41. Rybakowski JK, Borkowska A, Czerski PM, Dmitrak-Weglarz M, Skibinska M, Kapelski P, et al. Performance on the Wisconsin Card Sorting Test in schizophrenia and genes of dopaminergic inactivation (COMT, DAT, NET). *Psychiatry research*. 2006;143(1):13-9.
42. Szoke A, Schurhoff F, Meary A, Mathieu F, Chevalier F, Trandafir A, et al. Lack of influence of COMT and NET genes variants on executive functions in schizophrenic and bipolar patients, their first-degree relatives and controls. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 2006;141B(5):504-12.
43. Alfimova MV, Golimbet VE, Korovaitseva GI, Aksenova EV, Lezheiko TV, Abramova LI, et al. [The association of COMT and DRD2 gene polymorphisms with a cognitive ability to understand others in schizophrenic patients]. *Zhurnal nevrologii i psikiatrii imeni SS Korsakova / Ministerstvo zdravookhraneniia i meditsinskoi promyshlennosti Rossiiskoi Federatsii, Vserossiiskoe obshchestvo nevrologov [i] Vserossiiskoe obshchestvo psikiat*. 2013;113(8):50-6.
44. Greenwood TA, Lazzaroni LC, Murray SS, Cadenhead KS, Calkins ME, Dobie DJ, et al. Analysis of 94 candidate genes and 12 endophenotypes for schizophrenia from the Consortium on the Genetics of Schizophrenia. *The American journal of psychiatry*. 2011;168(9):930-46.

45. Cassidy C, Buchy L, Bodnar M, Dell'elce J, Choudhry Z, Fathalli F, et al. Association of a risk allele of ANK3 with cognitive performance and cortical thickness in patients with first-episode psychosis. *Journal of psychiatry & neuroscience : JPN*. 2014;39(1):31-9.
46. Swaminathan S, Shen L, Kim S, Inlow M, West JD, Faber KM, et al. Analysis of copy number variation in Alzheimer's disease: the NIALOAD/ NCRAD Family Study. *Current Alzheimer research*. 2012;9(7):801-14.
47. Ayoub MA, Angelicheva D, Vile D, Chandler D, Morar B, Cavanaugh JA, et al. Deleterious GRM1 mutations in schizophrenia. *PloS one*. 2012;7(3):e32849.
48. Szekeres G, Keri S, Juhasz A, Rimanoczy A, Szendi I, Czimmer C, et al. Role of dopamine D3 receptor (DRD3) and dopamine transporter (DAT) polymorphism in cognitive dysfunctions and therapeutic response to atypical antipsychotics in patients with schizophrenia. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 2004;124B(1):1-5.
49. Golimbet VE, Alfimova MV, Gritsenko IK, Lezheiko TV, Ebstein R. Association of dopamine receptor D5 gene polymorphism with peculiarities of voluntary attention in schizophrenic patients and their relatives. *Bulletin of experimental biology and medicine*. 2008;145(1):65-7.
50. Malhotra AK, Kestler LJ, Mazzanti C, Bates JA, Goldberg T, Goldman D. A functional polymorphism in the COMT gene and performance on a test of prefrontal cognition. *The American journal of psychiatry*. 2002;159(4):652-4.
51. Twamley EW, Hua JP, Burton CZ, Vella L, Chinh K, Bilder RM, et al. Effects of COMT genotype on cognitive ability and functional capacity in individuals with schizophrenia. *Schizophrenia research*. 2014.
52. Green MJ, Chia TY, Cairns MJ, Wu J, Tooney PA, Scott RJ, et al. Catechol-O-methyltransferase (COMT) genotype moderates the effects of childhood trauma on cognition and symptoms in schizophrenia. *Journal of psychiatric research*. 2014;49:43-50.
53. Jeanneteau F, Funalot B, Jankovic J, Deng H, Lagarde JP, Lucotte G, et al. A functional variant of the dopamine D3 receptor is associated with risk and age-at-onset of essential tremor. *Proceedings of the National Academy of Sciences of the United States of America*. 2006;103(28):10753-8.
54. Hargreaves A, Anney R, O'Dushlaine C, Nicodemus KK, Gill M, Corvin A, et al. The one and the many: effects of the cell adhesion molecule pathway on neuropsychological function in psychosis. *Psychological medicine*. 2013:1-11.
55. Dickinson D, Straub RE, Trampush JW, Gao Y, Feng N, Xie B, et al. Differential Effects of Common Variants in SCN2A on General Cognitive Ability, Brain Physiology, and messenger RNA Expression in Schizophrenia Cases and Control Individuals. *JAMA psychiatry*. 2014.
56. Tang TT, Yang F, Chen BS, Lu Y, Ji Y, Roche KW, et al. Dysbindin regulates hippocampal LTP by controlling NMDA receptor surface expression. *Proceedings of the National Academy of Sciences of the United States of America*. 2009;106(50):21395-400.
57. Talbot K, Eidem WL, Tinsley CL, Benson MA, Thompson EW, Smith RJ, et al. Dysbindin-1 is reduced in intrinsic, glutamatergic terminals of the hippocampal formation in schizophrenia. *The Journal of clinical investigation*. 2004;113(9):1353-63.
58. Numakawa T, Yagasaki Y, Ishimoto T, Okada T, Suzuki T, Iwata N, et al. Evidence of novel neuronal functions of dysbindin, a susceptibility gene for schizophrenia. *Human molecular genetics*. 2004;13(21):2699-708.

59. Burdick KE, Goldberg TE, Funke B, Bates JA, Lencz T, Kucherlapati R, et al. DTNBP1 genotype influences cognitive decline in schizophrenia. *Schizophrenia research*. 2007;89(1-3):169-72.
60. Baek JH, Kim JS, Ryu S, Oh S, Noh J, Lee WK, et al. Association of genetic variations in DTNBP1 with cognitive function in schizophrenia patients and healthy subjects. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 2012;159B(7):841-9.
61. Donohoe G, Morris DW, Clarke S, McGhee KA, Schwaiger S, Nangle JM, et al. Variance in neurocognitive performance is associated with dysbindin-1 in schizophrenia: a preliminary study. *Neuropsychologia*. 2007;45(2):454-8.
62. Peters K, Wiltshire S, Henders AK, Dragovic M, Badcock JC, Chandler D, et al. Comprehensive analysis of tagging sequence variants in DTNBP1 shows no association with schizophrenia or with its composite neurocognitive endophenotypes. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 2008;147B(7):1159-66.
63. Millar JK, Wilson-Annan JC, Anderson S, Christie S, Taylor MS, Semple CA, et al. Disruption of two novel genes by a translocation co-segregating with schizophrenia. *Human molecular genetics*. 2000;9(9):1415-23.
64. Blackwood DH, Fordyce A, Walker MT, St Clair DM, Porteous DJ, Muir WJ. Schizophrenia and affective disorders--cosegregation with a translocation at chromosome 1q42 that directly disrupts brain-expressed genes: clinical and P300 findings in a family. *American journal of human genetics*. 2001;69(2):428-33.
65. Schumacher J, Laje G, Abou Jamra R, Becker T, Muhleisen TW, Vasilescu C, et al. The DISC locus and schizophrenia: evidence from an association study in a central European sample and from a meta-analysis across different European populations. *Human molecular genetics*. 2009;18(14):2719-27.
66. Millar JK, Pickard BS, Mackie S, James R, Christie S, Buchanan SR, et al. DISC1 and PDE4B are interacting genetic factors in schizophrenia that regulate cAMP signaling. *Science*. 2005;310(5751):1187-91.
67. Ishizuka K, Paek M, Kamiya A, Sawa A. A review of Disrupted-In-Schizophrenia-1 (DISC1): neurodevelopment, cognition, and mental conditions. *Biological psychiatry*. 2006;59(12):1189-97.
68. Cannon TD, Hennah W, van Erp TG, Thompson PM, Lonnqvist J, Huttunen M, et al. Association of DISC1/TRAX haplotypes with schizophrenia, reduced prefrontal gray matter, and impaired short- and long-term memory. *Archives of general psychiatry*. 2005;62(11):1205-13.
69. Hennah W, Tuulio-Henriksson A, Paunio T, Ekelund J, Varilo T, Partonen T, et al. A haplotype within the DISC1 gene is associated with visual memory functions in families with a high density of schizophrenia. *Molecular psychiatry*. 2005;10(12):1097-103.
70. Callicott JH, Straub RE, Pezawas L, Egan MF, Mattay VS, Hariri AR, et al. Variation in DISC1 affects hippocampal structure and function and increases risk for schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America*. 2005;102(24):8627-32.
71. Burdick KE, Hodgkinson CA, Szeszko PR, Lencz T, Ekholm JM, Kane JM, et al. DISC1 and neurocognitive function in schizophrenia. *Neuroreport*. 2005;16(12):1399-402.
72. Numakawa T, Suzuki S, Kumamaru E, Adachi N, Richards M, Kunugi H. BDNF function and intracellular signaling in neurons. *Histology and histopathology*. 2010;25(2):237-58.

73. Guillin O, Diaz J, Carroll P, Griffon N, Schwartz JC, Sokoloff P. BDNF controls dopamine D3 receptor expression and triggers behavioural sensitization. *Nature*. 2001;411(6833):86-9.
74. Cowansage KK, LeDoux JE, Monfils MH. Brain-derived neurotrophic factor: a dynamic gatekeeper of neural plasticity. *Current molecular pharmacology*. 2010;3(1):12-29.
75. Lee JL, Everitt BJ, Thomas KL. Independent cellular processes for hippocampal memory consolidation and reconsolidation. *Science*. 2004;304(5672):839-43.
76. Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, et al. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell*. 2003;112(2):257-69.
77. Gratacos M, Gonzalez JR, Mercader JM, de Cid R, Urretavizcaya M, Estivill X. Brain-derived neurotrophic factor Val66Met and psychiatric disorders: meta-analysis of case-control studies confirm association to substance-related disorders, eating disorders, and schizophrenia. *Biological psychiatry*. 2007;61(7):911-22.
78. Egan MF, Weinberger DR, Lu B. Schizophrenia, III: brain-derived neurotrophic factor and genetic risk. *The American journal of psychiatry*. 2003;160(7):1242.
79. Alfimova MV, Lezheiko TV, Golimbet VE, Korovaitseva GI, Lavrushkina OM, Kolesina N, et al. [Investigation of association of the brain-derived neurotrophic factor (BDNF) and a serotonin receptor 2A (5-HT_{2A}) genes with voluntary and involuntary attention in schizophrenia]. *Zhurnal nevrologii i psikiatrii imeni SS Korsakova / Ministerstvo zdravookhraneniia i meditsinskoi promyshlennosti Rossiiskoi Federatsii, Vserossiiskoe obshchestvo nevrologov [i] Vserossiiskoe obshchestvo psikiat*. 2008;108(4):62-9.
80. Ho BC, Milev P, O'Leary DS, Librant A, Andreasen NC, Wassink TH. Cognitive and magnetic resonance imaging brain morphometric correlates of brain-derived neurotrophic factor Val66Met gene polymorphism in patients with schizophrenia and healthy volunteers. *Archives of general psychiatry*. 2006;63(7):731-40.
81. Zhang XY, Chen DC, Xiu MH, Haile CN, Luo X, Xu K, et al. Cognitive and serum BDNF correlates of BDNF Val66Met gene polymorphism in patients with schizophrenia and normal controls. *Human genetics*. 2012;131(7):1187-95.
82. Lu W, Zhang C, Yi Z, Li Z, Wu Z, Fang Y. Association between BDNF Val66Met polymorphism and cognitive performance in antipsychotic-naïve patients with schizophrenia. *Journal of molecular neuroscience : MN*. 2012;47(3):505-10.
83. Rybakowski JK, Borkowska A, Skibinska M, Szczepankiewicz A, Kapelski P, Leszczynska-Rodziewicz A, et al. Prefrontal cognition in schizophrenia and bipolar illness in relation to Val66Met polymorphism of the brain-derived neurotrophic factor gene. *Psychiatry and clinical neurosciences*. 2006;60(1):70-6.
84. Ho BC, Andreasen NC, Dawson JD, Wassink TH. Association between brain-derived neurotrophic factor Val66Met gene polymorphism and progressive brain volume changes in schizophrenia. *The American journal of psychiatry*. 2007;164(12):1890-9.
85. Chung S, Chung HY, Jung J, Chang JK, Hong JP. Association among aggressiveness, neurocognitive function, and the Val66Met polymorphism of brain-derived neurotrophic factor gene in male schizophrenic patients. *Comprehensive psychiatry*. 2010;51(4):367-72.
86. Ahmed AO, Mantini AM, Fridberg DJ, Buckley PF. Brain-derived neurotrophic factor (BDNF) and neurocognitive deficits in people with schizophrenia: a meta-analysis. *Psychiatry research*. 2015;226(1):1-13.

87. Falkenberg LE, Westerhausen R, Craven AR, Johnsen E, Kroken RA, EM LB, et al. Impact of glutamate levels on neuronal response and cognitive abilities in schizophrenia. *NeuroImage Clinical*. 2014;4:576-84.
88. Egerton A, Stone JM. The glutamate hypothesis of schizophrenia: neuroimaging and drug development. *Current pharmaceutical biotechnology*. 2012;13(8):1500-12.
89. Amann LC, Gandal MJ, Halene TB, Ehrlichman RS, White SL, McCarren HS, et al. Mouse behavioral endophenotypes for schizophrenia. *Brain research bulletin*. 2010;83(3-4):147-61.
90. Fujioka R, Nii T, Iwaki A, Shibata A, Ito I, Kitaichi K, et al. Comprehensive behavioral study of mGluR3 knockout mice: implication in schizophrenia related endophenotypes. *Molecular brain*. 2014;7(1):31.
91. Schlumberger C, Schafer D, Barberi C, More L, Nagel J, Pietraszek M, et al. Effects of a metabotropic glutamate receptor group II agonist LY354740 in animal models of positive schizophrenia symptoms and cognition. *Behavioural pharmacology*. 2009;20(1):56-66.
92. Woolley ML, Pemberton DJ, Bate S, Corti C, Jones DN. The mGlu2 but not the mGlu3 receptor mediates the actions of the mGluR2/3 agonist, LY379268, in mouse models predictive of antipsychotic activity. *Psychopharmacology*. 2008;196(3):431-40.
93. Hashimoto K, Malchow B, Falkai P, Schmitt A. Glutamate modulators as potential therapeutic drugs in schizophrenia and affective disorders. *European archives of psychiatry and clinical neuroscience*. 2013;263(5):367-77.
94. Meltzer HY, Rajagopal L, Huang M, Oyamada Y, Kwon S, Horiguchi M. Translating the N-methyl-D-aspartate receptor antagonist model of schizophrenia to treatments for cognitive impairment in schizophrenia. *The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum*. 2013;16(10):2181-94.
95. Kinon BJ, Gomez JC. Clinical development of pomaglumetad methionil: a non-dopaminergic treatment for schizophrenia. *Neuropharmacology*. 2013;66:82-6.
96. Coyle JT, Tsai G. The NMDA receptor glycine modulatory site: a therapeutic target for improving cognition and reducing negative symptoms in schizophrenia. *Psychopharmacology*. 2004;174(1):32-8.
97. Jablensky A, Morar B, Wiltshire S, Carter K, Dragovic M, Badcock JC, et al. Polymorphisms associated with normal memory variation also affect memory impairment in schizophrenia. *Genes, brain, and behavior*. 2011;10(4):410-7.
98. Vitalis T, Parnavelas JG. The role of serotonin in early cortical development. *Developmental neuroscience*. 2003;25(2-4):245-56.
99. Schmitt JA, Wingen M, Ramaekers JG, Evers EA, Riedel WJ. Serotonin and human cognitive performance. *Current pharmaceutical design*. 2006;12(20):2473-86.
100. Arnsten AF. Adrenergic targets for the treatment of cognitive deficits in schizophrenia. *Psychopharmacology*. 2004;174(1):25-31.
101. Alfimova MV, Golimbet VE, Mitiushina NG. [Polymorphism of the serotonin receptor (5-HT_{2A}) gene and verbal fluency in normalcy and schizophrenia]. *Molekuliarnaia biologiya*. 2003;37(1):68-73.
102. Chen RY, Sham P, Chen EY, Li T, Cheung EF, Hui TC, et al. No association between T102C polymorphism of serotonin-2A receptor gene and clinical phenotypes of Chinese schizophrenic patients. *Psychiatry research*. 2001;105(3):175-85.

103. Uçok A, Alpsan H, Cakir S, Saruhan-Direskeneli G. Association of a serotonin receptor 2A gene polymorphism with cognitive functions in patients with schizophrenia. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 2007;144B(5):704-7.
104. Alfimova MV, Golimbet VE, Korovaitseva GI, Lezheiko TV, Abramova LI, Kaleda VG, et al. The modulatory influence of polymorphism of the serotonin transporter gene on characteristics of mental maladaptation in relatives of patients with endogenous psychoses. *Neuroscience and behavioral physiology*. 2008;38(3):253-8.
105. Polesskaya OO, Sokolov BP. Differential expression of the "C" and "T" alleles of the 5-HT2A receptor gene in the temporal cortex of normal individuals and schizophrenics. *Journal of neuroscience research*. 2002;67(6):812-22.
106. Bosia M, Anselmetti S, Bechi M, Lorenzi C, Pirovano A, Cocchi F, et al. Effect of 5-HT1A-receptor functional polymorphism on Theory of Mind performances in schizophrenia. *Psychiatry research*. 2011;188(2):187-90.
107. Bosia M, Anselmetti S, Pirovano A, Ermoli E, Marino E, Bramanti P, et al. HTTLPR functional polymorphism in schizophrenia: executive functions vs. sustained attention dissociation. *Progress in neuro-psychopharmacology & biological psychiatry*. 2010;34(1):81-5.
108. Lemonde S, Turecki G, Bakish D, Du L, Hrdina PD, Bown CD, et al. Impaired repression at a 5-hydroxytryptamine 1A receptor gene polymorphism associated with major depression and suicide. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2003;23(25):8788-99.
109. Xiang B, Wu JY, Ma XH, Wang YC, Deng W, Chen ZF, et al. [Genome-wide association study with memory measures as a quantitative trait locus for schizophrenia]. *Zhonghua yi xue yi chuan xue za zhi = Zhonghua yixue yichuanxue zazhi = Chinese journal of medical genetics*. 2012;29(3):255-9.
110. Davies G, Tenesa A, Payton A, Yang J, Harris SE, Liewald D, et al. Genome-wide association studies establish that human intelligence is highly heritable and polygenic. *Molecular psychiatry*. 2011;16(10):996-1005.
111. Shi J, Han P, Kuniyoshi SM. Cognitive impairment in neurological diseases: lessons from apolipoprotein E. *Journal of Alzheimer's disease : JAD*. 2014;38(1):1-9.
112. Tosto G, Reitz C. Genome-wide association studies in Alzheimer's disease: a review. *Current neurology and neuroscience reports*. 2013;13(10):381.
113. Najmabadi H, Hu H, Garshasbi M, Zemojtel T, Abedini SS, Chen W, et al. Deep sequencing reveals 50 novel genes for recessive cognitive disorders. *Nature*. 2011;478(7367):57-63.
114. Musante L, Ropers HH. Genetics of recessive cognitive disorders. *Trends in genetics : TIG*. 2014;30(1):32-9.
115. Koola MM, Buchanan RW, Pillai A, Aitchison KJ, Weinberger DR, Aaronson ST, et al. Potential role of the combination of galantamine and memantine to improve cognition in schizophrenia. *Schizophrenia research*. 2014;157(1-3):84-9.
116. Kroken RA, Loberg EM, Dronen T, Gruner R, Hugdahl K, Kompus K, et al. A critical review of pro-cognitive drug targets in psychosis: convergence on myelination and inflammation. *Frontiers in psychiatry*. 2014;5:11.
117. Fowler T, Zammit S, Owen MJ, Rasmussen F. A population-based study of shared genetic variation between premorbid IQ and psychosis among male twin pairs and sibling pairs from Sweden. *Archives of general psychiatry*. 2012;69(5):460-6.

118. Barnett JH, Salmond CH, Jones PB, Sahakian BJ. Cognitive reserve in neuropsychiatry. *Psychological medicine*. 2006;36(8):1053-64.
119. Leeson VC, Sharma P, Harrison M, Ron MA, Barnes TR, Joyce EM. IQ trajectory, cognitive reserve, and clinical outcome following a first episode of psychosis: a 3-year longitudinal study. *Schizophrenia bulletin*. 2011;37(4):768-77.

Figure 1. Candidate gene studies according to their biomolecular systems. Dopaminergic system genes have been examined the most in genetic studies of cognition in schizophrenia given the important role of dopamine in the etiology of schizophrenia and cognition. Neurodevelopmental genes are amongst the second most commonly studied candidate, followed by serotonergic and glutamatergic system genes. Although the glutamate hypothesis in schizophrenia has sparked new insight into the mechanism of schizophrenia, only 4% of studies have examined genes related to glutamatergic system.

Table 1. Molecular genetic studies of cognitive deficits in schizophrenia (for full details, please refer to Table S1 in Supplement 1).*

System	Gene	N	Candidate Gene Studies		Significant		Cognitive Domains	Reference
			Positive	Negative	Multi-gene	GWAS		
Dopamine	<i>COMT</i>	23	12	11	2	-	Executive function, theory of mind, reaction time, processing speed, attention, IQ, spatial working memory, attentional flexibility and planning	(1-25)
	<i>DAT/SLC6A3</i>	4	0	4	1	-	- Speed of information processing, attention/vigilance, verbal learning and memory, working memory, reasoning and problem solving, set shifting, and verbal comprehension	(1, 7, 21, 23, 26)
	<i>DRD1</i>	-	-	-	1	-	- Speed of information processing, attention/vigilance, verbal learning and memory, working memory, reasoning and problem solving, set shifting, and verbal comprehension	(23)
	<i>DRD2</i>	2	0	2	1	-	-	(2, 22, 23)
	<i>DRD3</i>	3	1	2	1	-	Perseveration - Speed of information processing, attention/vigilance, verbal learning and memory, working memory, reasoning and problem solving, set shifting, and verbal comprehension	(20, 22, 23, 26)
	<i>DRD4</i>	1	1	0	-	-	Working memory, verbal fluency	(5)
	<i>DRD5</i>	1	1	0	-	-	Visual voluntary attention	(27)
	<i>DBH</i>	2	1	1	-	-	Immediate memory	(20, 28)
	<i>SLC18A2</i>	1	0	1	-	-	- Speed of information processing, attention/vigilance, verbal learning and memory, working memory, reasoning and problem solving, set shifting, and verbal comprehension	(20)
	<i>ANKK1</i>	-	-	-	1	-	-	(23)
Neuro	<i>PPP1R1B</i>	-	-	-	1	-	-	(23)
	<i>DISC1</i>	5	5	0	2	-	Verbal fluency, verbal working memory, short- and long-term memory, short-term visual memory, visual search, attention	(1, 17, 23, 29-32)
	<i>DTNBP1</i>	4	3	1	1	-	Attention/vigilance domain, spatial working memory, IQ	(23, 33-36)
	<i>BDNF</i>	8	5	4 (one of which is a meta-analysis)	1	-	Voluntary and involuntary attention, verbal memory, visuospatial skills, working memory - Speed of information processing, attention/vigilance, verbal learning and memory, working memory, reasoning and problem solving, set shifting, and verbal comprehension	(1, 23, 37-45)
	<i>NRG1</i>	2	2	0	2	-	Processing speed, visuomotor speed, attention, long-term episodic memory, short-term memory	(17, 23, 46, 47)
	<i>NRG3</i>	2	2	0	-	-	Visuomotor speed, processing speed, mental flexibility, executive function, sustained attention	(48, 49)
	<i>NRN1</i>	1	1	0	-	-	General intellectual ability	(50)
	<i>SNAP-25</i>	1	1	0	-	-	Verbal memory, attention, executive function	(51)
	<i>PRODH</i>	1	0	1	1	-	-	(23, 52)
	<i>P2RX7</i>	-	-	-	1	-	-	(23)
Serotonin	<i>NPY</i>	-	-	-	1	-	-	(23)
	<i>NQO1</i>	-	-	-	1	-	-	(23)
	<i>GST-1</i>	-	-	-	1	-	-	(23)
	<i>GST-2</i>	-	-	-	1	-	-	(23)
	<i>5HTT</i>	2	1	1	1	-	Executive function, attention	(17, 21, 53)
	<i>HTR1A</i>	1	1	0	1	-	Theory of mind	(17, 23, 54)
	<i>HTR2A</i>	5	3	2	2	-	Voluntary and involuntary attention, executive function, verbal fluency	(1, 17, 23, 37, 55-57)
	<i>NET</i>	2	0	2	-	-	-	(6, 7)

System	Gene	N	Candidate Gene Studies		Significant		Cognitive Domains	Reference
			Positive	Negative	Multi-gene	GWAS		
Oligodendrocyte	<i>QKI</i>	1	0	1	-	-	-	(46)
	<i>MAG</i>	1	1	0	-	-	Processing speed, visuomotor speed, attention	(46)
	<i>CNP</i>	1	0	1	-	-	-	(46)
	<i>OLIG2</i>	1	0	1	-	-	-	(46)
	<i>ERBB4</i>	1	0	1	1	-	Verbal learning, abstraction, visuospatial memory	(17, 46)
Glutamate	<i>GRIN2A</i>	1	0	1	-	-	-	(58)
	<i>GRIN2B</i>	2	1	1	1	-	Immediate and delayed recall (verbal memory)	(1, 17, 58)
	<i>GRM1</i>	-	-	-	1	-	Attention, verbal learning, abstraction, visuospatial memory, spatial processing	(17)
	<i>GRM3</i>	1	1	0	1	-	Enhanced performance	(23, 58)
	<i>SLC1A2</i>	-	-	-	1	-	Attention, abstraction, spatial memory	(17)
	<i>DAOA</i>	1	1	0	1	1	Verbal memory	(23, 59, 60)
	<i>GAD1</i>	-	-	-	1	-	-	(23)
	<i>CACNA1C</i>	2	1	1	-	-	Logical memory	(1, 61)
Ion channel	<i>SCN2A</i>	-	-	-	-	1	Cognitive ability	(62)
Energy metabolism	<i>LYRM4</i>	1	1	0	-	-	Verbal memory	(63)
	<i>FARS1</i>	1	1	0	-	-	Verbal memory	(63)
	<i>ATP2C2</i>	1	0	1	-	-	-	(1)
	<i>ANK3</i>	2	2	0	-	-	Working memory, verbal memory, attention	(22, 64)
Others	<i>TCF4</i>	1	1	0	-	-	Reasoning, problem-solving, attention-related tasks	(65, 66)
	<i>CNNM2</i>	1	0	1	-	-	Social cognition	(67)
	<i>CSMD1</i>	1	1	0	-	1	General cognitive ability, memory cognition	(68, 69)
	<i>STH</i>	2	2	0	-	-	Executive function	(25, 70)
	<i>ACT</i>	1	0	1	-	-	-	(71)
	<i>DCDC2</i>	1	0	1	-	-	-	(1)
	<i>DYX1C1</i>	1	0	1	-	-	-	(1)
	<i>KIAA0319</i>	1	1	0	-	-	Verbal learning and recall	(1)
	<i>NAGPA</i>	1	0	1	-	-	-	(1)
	<i>ZNF804A</i>	4	3	1	-	-	Verbal learning and recall, verbal and spatial working memory, verbal episodic memory, visual memory	(1, 72-74)
	<i>CLSTN2</i>	1	0	1	-	-	-	(1)
	<i>WWC1</i>	2	0	2	-	-	-	(1, 75)
	<i>ATRNL1</i>	1	0	1	-	-	-	(1)
	<i>C20orf196</i>	1	0	1	-	-	-	(1)
	<i>CRTC3</i>	1	0	1	-	-	-	(1)
	<i>DIP2C</i>	1	0	1	-	-	-	(1)
	<i>NFKBIL1</i>	1	0	1	-	-	-	(1)

System	Gene	N	Candidate Gene Studies		Significant		Cognitive Domains	Reference
			Positive	Negative	Multi-gene	GWAS		
	<i>PDE1C</i>	1	0	1	-	-	-	(1)
	<i>PKNOX1</i>	1	0	1	-	-	-	(1)
	<i>SPATA7</i>	1	0	1	-	-	-	(1)
	<i>ADCY8</i>	2	0	2	-	-	-	(1, 58)
	<i>CAMK2G</i>	2	0	2	-	-	-	(1, 58)
	<i>PRKACG</i>	1	0	1	-	-	-	(58)
	<i>PRKCA</i>	1	1	0	-	-	Verbal memory	(58)
	<i>HEY1</i>	-	-	-	-	1	Working memory	(76)
	<i>MAD1L1</i>	-	-	-	-	1	Cognitive ability	(77)
	<i>LSM1</i>	-	-	-	-	1	Cognitive ability	(77)
	<i>CAM</i>	-	-	-	-	1	Memory, attention	(78)
	<i>HLA-DQA1</i>	-	-	-	-	1	Attention	(78)
	<i>RASGRF2</i>	-	-	-	-	1	Memory cognition	(69)
	<i>PLCG2</i>	-	-	-	-	1	Memory cognition	(69)
	<i>LMO1</i>	-	-	-	-	1	Memory cognition	(69)
	<i>PRKG1</i>	-	-	-	-	1	Memory cognition	(69)
	<i>EPO</i>	1	1	0	-	-	Processing speed, short-term memory, and tasks requiring distinct fine motor component	(79)
	<i>EPOR</i>	1	1	0	-	-	Processing speed, short-term memory, and tasks requiring distinct fine motor component	(79, 80)
	<i>RGS4</i>	1	1	-	1	-	Face and verbal memory speed	(23)
	<i>PIP5K2A</i>	-	-	-	1	-	-	(23)
	<i>AKT1</i>	-	-	-	1	-	-	(23)
	<i>LRRTM1</i>	-	-	-	1	-	-	(23)
	<i>FGF2</i>	-	-	-	1	-	- Speed of information processing, attention/vigilance, verbal learning and memory, working memory, reasoning and problem solving, set shifting, and verbal comprehension	(23)
	<i>FGFR1</i>	-	-	-	1	-	-	(23)
	<i>GPM6A</i>	-	-	-	1	-	-	(23)
	<i>GABRA6</i>	-	-	-	1	-	-	(23)
	<i>NOS1</i>	1	1	-	1	-	General cognitive ability, verbal and spatial working memory	(23, 81)
	<i>RGS2</i>	-	-	-	1	-	-	(23)
	<i>ROBO1</i>	-	-	-	1	-	-	(23)
	<i>CHRM3</i>	-	-	-	1	-	-	(23)
	<i>TBX1</i>	-	-	-	1	-	-	(23)
	<i>ADRA2C</i>	-	-	-	1	-	-	(23)
	<i>FKBP5</i>	-	-	-	1	-	- Speed of information processing, attention/vigilance, verbal learning and memory, working memory, reasoning and problem solving, set shifting, and verbal comprehension	(23)
	<i>DNMT3B</i>	-	-	-	1	-	- Speed of information processing, attention/vigilance, verbal learning and memory, working memory, reasoning and problem solving, set shifting, and verbal comprehension	(23)
	<i>CNR1</i>	-	-	-	1	-	-	(23)

System	Gene	N	Candidate Gene Studies		Significant		Cognitive Domains	Reference
			Positive	Negative	Multi-gene	GWAS		
	<i>MTHFR</i>	1	1	-	1	-	IQ, spatial working memory, attentional flexibility and planning	(23, 24)
	<i>MTR</i>	-	-	-	1	-	-	(23)
	<i>MTRR</i>	-	-	-	1	-	-	(23)
	<i>EHMT1</i>	-	-	-	1	-	-	(23)
	<i>EHMT2</i>	-	-	-	1	-	-	(23)
	<i>PRDM2</i>	-	-	-	1	-	-	(23)

* This table did not include the genome-wide association study by Fernandes et al., 2013 (82) because no specific genes were identified.

Abbreviations for genes: serotonin transporter (*5HTT*), alpha-1-antichymotrypsin (*ACT*, also known as serine proteinase inhibitor 3 [*SERPINA3*]), adenylate cyclase (*ADCY8*), adrenoceptor alpha 2C (*ADRA2C*), v-akt murine thymoma viral oncogene homolog 1 (*AKT1*), ankyrin 3 (*ANK3*), ankyrin repeat and kinase domain containing 1 (*ANKK1*), ATPase, Ca++ transporting, type 2C, member 2 (*ATP2C2*), attractin-like 1 (*ATRNL1*), brain-derived neurotrophic factor (*BDNF*), chromosome 20 open reading frame 196 (*C20orf196*), calcium channel, voltage-dependent, L type, alpha 1C (*CACNA1C*), cell adhesion molecules (CAM), calcium/calmodulin-dependent protein kinase II gamma (*CAMK2G*), cholinergic receptor, muscarinic 3 (*CHRM3*), calypten 2 (*CLSTN2*), cyclin M2 (*CNNM2*), 2',3'-cyclic nucleotide 3'-phosphodiesterase (*CNP*), cannabinoid receptor 1 (brain) (*CNR1*), catechol-O-methyltransferase (*COMT*), CREB regulated transcription coactivator 3 (*CRTC3*), CUB and Sushi multiple domains 1 (*CSMD1*), D-amino acid oxidase activator (*DAOA*), dopamine transporter (*DAT*, also known as *SLC6A3*), dopamine beta-hydroxylase (*DBH*), doublecortin domain containing 2 (*DCDC2*), DIP2 disco-interacting protein 2 homolog C (Drosophila) (*DIP2C*), disrupted in schizophrenia 1 (*DISC1*), DNA (cytosine-5)-methyltransferase 3 beta (*DNMT3B*), dopamine D1 receptor (*DRD1*), dopamine D2 receptor (*DRD2*), dopamine D3 receptor (*DRD3*), dopamine D4 receptor (*DRD4*), dopamine D5 receptor (*DRD5*), dystrobrevin binding protein 1 (*DTNBP1*), dyslexia susceptibility 1 candidate 1 (*DYX1C1*), euchromatic histone-lysine N-methyltransferase 1 (*EHMT1*), euchromatic histone-lysine N-methyltransferase 2 (*EHMT2*), erythropoietin (*EPO*), erythropoietin receptor (*EPOR*), v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 4 (*ERBB4*), phenylalanyl-tRNA synthetase 2, mitochondrial (*FARS2*), fibroblast growth factor 2 (basic) (*FGF2*), fibroblast growth factor receptor 1 (*FGFR1*), FK506 binding protein 5 (*FKBP5*), gamma-aminobutyric acid (GABA) A receptor, alpha 6 (*GABRA6*), glutamate decarboxylase 1 (brain, 67kDa) (*GAD1*), glycoprotein M6A (*GPM6A*), glutamate receptor, ionotropic, N-methyl-D-aspartate, subunit 2A (*GRIN2A*), glutamate receptor, ionotropic, N-methyl-D-aspartate, subunit 2B (*GRIN2B*), glutamate receptor, metabotropic, 3 (*GRM3*), glutathione S-transferase-1 (*GST-1*), glutathione S-transferase (*GST-2*), hairy/enhancer-of-split related with YRPW motif 1 (*HEY1*), human leukocyte antigen (*HLA*), serotonin 1A receptor (*HTR1A*), serotonin 2A receptor (*HTR2A*), LIM domain only 1 (*LMO1*), leucine rich repeat transmembrane neuronal 1 (*LRRTM1*), LSM1 homolog, U6 small nuclear RNA associated (*LSM1*), MAD1 mitotic arrest deficient-like 1 (*MAD1L1*), myelin-associated glycoprotein (*MAG*), MicroRNA 137 (*MIRN137*), mitochondrial pyruvate carrier 2 (*MPC2*), methylenetetrahydrofolate reductase (NAD(P)H) (*MTHFR*), 5-methyltetrahydrofolate-homocysteine methyltransferase (*MTR*), 5-methyltetrahydrofolate-homocysteine methyltransferase reductase (*MTRR*), N-acetylglucosamine-1-phosphodiester alpha-N-acetylglucosaminidase (*NAGPA*), norepinephrine transporter (*NET*, also known as *SLC6A2*), nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor-like 1 (*NFKBIL1*), nitric oxide synthase 1 (neuronal) (*NOS1*), neuropeptide Y (*NPY*), NAD(P)H dehydrogenase, quinone 1 (*NQO1*), neuregulin 1 (*NRG1*), neuregulin 3 (*NRG3*), neurogranin (protein kinase C substrate, RC3) (*NRGN*), neuritin 1 (*NRN1*), 5'-nucleotidase, cytosolic II (*NT5C2*), oligodendrocyte lineage transcription factor 2 (*OLIG2*), purinergic receptor P2X, ligand-gated ion channel, 7 (*P2RX7*), prostate-specific transcript (non-protein coding) (*PCGEM1*), phosphatidylinositol-5-phosphate 4-kinase, type II, alpha (*PIP4K2A*), PBX/knotted 1 homeobox 1 (*PKNOX1*), phospholipase C, gamma 2 (*PLCG2*), protein phosphatase 1, regulator (inhibitor) subunit 1B (*PPP1R1B*), PR domain containing 2, with ZNF domain (*PRDM2*), protein kinase, cAMP-dependent, catalytic, gamma (*PRKACG*), protein kinase C, alpha (*PRKCA*), protein kinase, cGMP-dependent, type 1 (*PRKG1*), proline dehydrogenase (oxidase) 1 (*PRODH*), quaking (*QKI*), Ras-specific guanine nucleotide-releasing factor 2 (*RASGRF2*), regulator of G-protein signalling 2, 24kDa (*RGS2*), regulator of G-protein signalling 4 (*RGS4*), roundabout, axon guidance receptor, homolog 1 (Drosophila) (*ROBO1*), sodium channel, voltage-gated, type II, alpha subunit (*SCN2A*), serologically defined colon cancer antigen 8 (*SDCCAG8*), vesicular monoamine transporter 2 (*SLC18A2*), zinc finger, spermatogenesis associated 7 (*SPATA7*), saitohein (*STH*), synaptosomal-associated protein 25 (*SNAP-25*), T-box 1 (*TBX1*), transcription factor 4 (*TCF4*), translin-associated factor X (*TRAX*), SWIM-type containing 6 (*ZSWIM6*).

1. Nicodemus KK, Elvevag B, Foltz PW, Rosenstein M, Diaz-Asper C, Weinberger DR. Category fluency, latent semantic analysis and schizophrenia: a candidate gene approach. *Cortex*; a journal devoted to the study of the nervous system and behavior. 2013.
2. Alfimova MV, Golimbet VE, Korovaitseva GI, Aksenova EV, Lezheiko TV, Abramova LI, et al. [The association of COMT and DRD2 gene polymorphisms with a cognitive ability to understand others in schizophrenic patients]. *Zhurnal nevrologii i psikiatrii imeni SS Korsakova / Ministerstvo zdravookhraneniia i meditsinskoi promyshlennosti Rossiiskoi Federatsii, Vserossiiskoe obshchestvo nevrologov [i] Vserossiiskoe obshchestvo psikiat.* 2013;113(8):50-6.
3. Barnett JH, Jones PB, Robbins TW, Muller U. Effects of the catechol-O-methyltransferase Val158Met polymorphism on executive function: a meta-analysis of the Wisconsin Card Sort Test in schizophrenia and healthy controls. *Molecular psychiatry.* 2007;12(5):502-9.

4. Bosia M, Bechi M, Marino E, Anselmetti S, Poletti S, Cocchi F, et al. Influence of catechol-O-methyltransferase Val158Met polymorphism on neuropsychological and functional outcomes of classical rehabilitation and cognitive remediation in schizophrenia. *Neuroscience letters*. 2007;417(3):271-4.
5. Alfimova MV, Golimbet VE, Gritsenko IK, Lezheiko TV, Abramova LI, Strel'tsova MA, et al. [Dopamine system genes interaction and neurocognitive traits in patients with schizophrenia, their relatives and healthy controls from general population]. *Zhurnal nevrologii i psikiatrii imeni SS Korsakova / Ministerstvo zdravookhraneniia i meditsinskoi promyshlennosti Rossiiskoi Federatsii, Vserossiiskoe obshchestvo nevrologov* [i] *Vserossiiskoe obshchestvo psikiat*. 2006;106(7):57-63.
6. Szoke A, Schurhoff F, Meary A, Mathieu F, Chevalier F, Trandafir A, et al. Lack of influence of COMT and NET genes variants on executive functions in schizophrenic and bipolar patients, their first-degree relatives and controls. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 2006;141B(5):504-12.
7. Rybakowski JK, Borkowska A, Czerski PM, Dmitrzak-Weglarz M, Skibinska M, Kapelski P, et al. Performance on the Wisconsin Card Sorting Test in schizophrenia and genes of dopaminergic inactivation (COMT, DAT, NET). *Psychiatry research*. 2006;143(1):13-9.
8. Ho BC, Wassink TH, O'Leary DS, Sheffield VC, Andreasen NC. Catechol-O-methyl transferase Val158Met gene polymorphism in schizophrenia: working memory, frontal lobe MRI morphology and frontal cerebral blood flow. *Molecular psychiatry*. 2005;10(3):229, 87-98.
9. Galderisi S, Maj M, Kirkpatrick B, Piccardi P, Mucci A, Invernizzi G, et al. Catechol-O-methyltransferase Val158Met polymorphism in schizophrenia: associations with cognitive and motor impairment. *Neuropsychobiology*. 2005;52(2):83-9.
10. Nolan KA, Bilder RM, Lachman HM, Volavka J. Catechol O-methyltransferase Val158Met polymorphism in schizophrenia: differential effects of Val and Met alleles on cognitive stability and flexibility. *The American journal of psychiatry*. 2004;161(2):359-61.
11. Rosa A, Peralta V, Cuesta MJ, Zarzuela A, Serrano F, Martinez-Larrea A, et al. New evidence of association between COMT gene and prefrontal neurocognitive function in healthy individuals from sibling pairs discordant for psychosis. *The American journal of psychiatry*. 2004;161(6):1110-2.
12. Goldberg TE, Egan MF, Gscheidle T, Coppola R, Weickert T, Kolachana BS, et al. Executive subprocesses in working memory: relationship to catechol-O-methyltransferase Val158Met genotype and schizophrenia. *Archives of general psychiatry*. 2003;60(9):889-96.
13. Joober R, Gauthier J, Lal S, Bloom D, Lalonde P, Rouleau G, et al. Catechol-O-methyltransferase Val-108/158-Met gene variants associated with performance on the Wisconsin Card Sorting Test. *Archives of general psychiatry*. 2002;59(7):662-3.
14. Bilder RM, Volavka J, Czobor P, Malhotra AK, Kennedy JL, Ni X, et al. Neurocognitive correlates of the COMT Val(158)Met polymorphism in chronic schizophrenia. *Biological psychiatry*. 2002;52(7):701-7.
15. Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE, et al. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America*. 2001;98(12):6917-22.
16. Green MJ, Chia TY, Cairns MJ, Wu J, Tooney PA, Scott RJ, et al. Catechol-O-methyltransferase (COMT) genotype moderates the effects of childhood trauma on cognition and symptoms in schizophrenia. *Journal of psychiatric research*. 2014;49:43-50.
17. Greenwood TA, Lazzeroni LC, Murray SS, Cadenhead KS, Calkins ME, Dobie DJ, et al. Analysis of 94 candidate genes and 12 endophenotypes for schizophrenia from the Consortium on the Genetics of Schizophrenia. *The American journal of psychiatry*. 2011;168(9):930-46.
18. Twamley EW, Hua JP, Burton CZ, Vella L, Chinh K, Bilder RM, et al. Effects of COMT genotype on cognitive ability and functional capacity in individuals with schizophrenia. *Schizophrenia research*. 2014.

19. Lopez-Garcia P, Young Espinoza L, Molero Santos P, Marin J, Ortuno Sanchez-Pedreno F. Impact of COMT genotype on cognition in schizophrenia spectrum patients and their relatives. *Psychiatry research*. 2013;208(2):118-24.
20. Kukshal P, Kodavali VC, Srivastava V, Wood J, McClain L, Bhatia T, et al. Dopaminergic gene polymorphisms and cognitive function in a north Indian schizophrenia cohort. *Journal of psychiatric research*. 2013;47(11):1615-22.
21. Zilles D, Meyer J, Schneider-Axmann T, Ekawardhani S, Gruber E, Falkai P, et al. Genetic polymorphisms of 5-HTT and DAT but not COMT differentially affect verbal and visuospatial working memory functioning. *European archives of psychiatry and clinical neuroscience*. 2012;262(8):667-76.
22. Bombin I, Arango C, Mayoral M, Castro-Fornieles J, Gonzalez-Pinto A, Gonzalez-Gomez C, et al. DRD3, but not COMT or DRD2, genotype affects executive functions in healthy and first-episode psychosis adolescents. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 2008;147B(6):873-9.
23. Simons CJ, van Winkel R. Intermediate phenotype analysis of patients, unaffected siblings, and healthy controls identifies VMAT2 as a candidate gene for psychotic disorder and neurocognition. *Schizophrenia bulletin*. 2013;39(4):848-56.
24. Kontis D, Theochari E, Fryssira H, Kleisas S, Sofocleous C, Andreopoulou A, et al. COMT and MTHFR polymorphisms interaction on cognition in schizophrenia: an exploratory study. *Neuroscience letters*. 2013;537:17-22.
25. Bosia M, Pigioli A, Pirovano A, Lorenzi C, Spangaro M, Buonocore M, et al. COMT and STH polymorphisms interaction on cognition in schizophrenia. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*. 2014.
26. Szekeres G, Keri S, Juhasz A, Rimanoczy A, Szendi I, Czimmer C, et al. Role of dopamine D3 receptor (DRD3) and dopamine transporter (DAT) polymorphism in cognitive dysfunctions and therapeutic response to atypical antipsychotics in patients with schizophrenia. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 2004;124B(1):1-5.
27. Golimbet VE, Alfimova MV, Gritsenko IK, Lezheiko TV, Ebstein R. Association of dopamine receptor D5 gene polymorphism with peculiarities of voluntary attention in schizophrenic patients and their relatives. *Bulletin of experimental biology and medicine*. 2008;145(1):65-7.
28. Hui L, Zhang X, Yu YQ, Han M, Huang XF, Chen da C, et al. Association between DBH 19 bp insertion/deletion polymorphism and cognition in first-episode schizophrenic patients. *Schizophrenia research*. 2013;147(2-3):236-40.
29. Cannon TD, Hennah W, van Erp TG, Thompson PM, Lonnqvist J, Huttunen M, et al. Association of DISC1/TRAX haplotypes with schizophrenia, reduced prefrontal gray matter, and impaired short- and long-term memory. *Archives of general psychiatry*. 2005;62(11):1205-13.
30. Hennah W, Tuulio-Henriksson A, Paunio T, Ekelund J, Varilo T, Partonen T, et al. A haplotype within the DISC1 gene is associated with visual memory functions in families with a high density of schizophrenia. *Molecular psychiatry*. 2005;10(12):1097-103.
31. Burdick KE, Hodgkinson CA, Szeszko PR, Lencz T, Ekholm JM, Kane JM, et al. DISC1 and neurocognitive function in schizophrenia. *Neuroreport*. 2005;16(12):1399-402.
32. Callicott JH, Straub RE, Pezawas L, Egan MF, Mattay VS, Hariri AR, et al. Variation in DISC1 affects hippocampal structure and function and increases risk for schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America*. 2005;102(24):8627-32.
33. Baek JH, Kim JS, Ryu S, Oh S, Noh J, Lee WK, et al. Association of genetic variations in DTNBP1 with cognitive function in schizophrenia patients and healthy subjects. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 2012;159B(7):841-9.

34. Peters K, Wiltshire S, Henders AK, Dragovic M, Badcock JC, Chandler D, et al. Comprehensive analysis of tagging sequence variants in DTNBP1 shows no association with schizophrenia or with its composite neurocognitive endophenotypes. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 2008;147B(7):1159-66.
35. Donohoe G, Morris DW, Clarke S, McGhee KA, Schwaiger S, Nangle JM, et al. Variance in neurocognitive performance is associated with dysbindin-1 in schizophrenia: a preliminary study. *Neuropsychologia*. 2007;45(2):454-8.
36. Burdick KE, Goldberg TE, Funke B, Bates JA, Lencz T, Kucherlapati R, et al. DTNBP1 genotype influences cognitive decline in schizophrenia. *Schizophrenia research*. 2007;89(1-3):169-72.
37. Alfimova MV, Lezheiko TV, Golimbet VE, Korovaitseva GI, Lavrushkina OM, Kolesina N, et al. [Investigation of association of the brain-derived neurotrophic factor (BDNF) and a serotonin receptor 2A (5-HTR2A) genes with voluntary and involuntary attention in schizophrenia]. *Zhurnal nevrologii i psikiatrii imeni SS Korsakova / Ministerstvo zdravookhraneniia i meditsinskoj promyshlennosti Rossiiskoi Federatsii, Vserossiiskoe obshchestvo nevrologov [i] Vserossiiskoe obshchestvo psikiat*. 2008;108(4):62-9.
38. Ho BC, Milev P, O'Leary DS, Librant A, Andreasen NC, Wassink TH. Cognitive and magnetic resonance imaging brain morphometric correlates of brain-derived neurotrophic factor Val66Met gene polymorphism in patients with schizophrenia and healthy volunteers. *Archives of general psychiatry*. 2006;63(7):731-40.
39. Rybakowski JK, Borkowska A, Skibinska M, Szczepankiewicz A, Kapelski P, Leszczynska-Rodziewicz A, et al. Prefrontal cognition in schizophrenia and bipolar illness in relation to Val66Met polymorphism of the brain-derived neurotrophic factor gene. *Psychiatry and clinical neurosciences*. 2006;60(1):70-6.
40. Ahmed AO, Mantini AM, Fridberg DJ, Buckley PF. Brain-derived neurotrophic factor (BDNF) and neurocognitive deficits in people with schizophrenia: a meta-analysis. *Psychiatry research*. 2015;226(1):1-13.
41. Egan MF, Weinberger DR, Lu B. Schizophrenia, III: brain-derived neurotrophic factor and genetic risk. *The American journal of psychiatry*. 2003;160(7):1242.
42. Ho BC, Andreasen NC, Dawson JD, Wassink TH. Association between brain-derived neurotrophic factor Val66Met gene polymorphism and progressive brain volume changes in schizophrenia. *The American journal of psychiatry*. 2007;164(12):1890-9.
43. Chung S, Chung HY, Jung J, Chang JK, Hong JP. Association among aggressiveness, neurocognitive function, and the Val66Met polymorphism of brain-derived neurotrophic factor gene in male schizophrenic patients. *Comprehensive psychiatry*. 2010;51(4):367-72.
44. Lu W, Zhang C, Yi Z, Li Z, Wu Z, Fang Y. Association between BDNF Val66Met polymorphism and cognitive performance in antipsychotic-naïve patients with schizophrenia. *Journal of molecular neuroscience : MN*. 2012;47(3):505-10.
45. Zhang XY, Chen DC, Xiu MH, Haile CN, Luo X, Xu K, et al. Cognitive and serum BDNF correlates of BDNF Val66Met gene polymorphism in patients with schizophrenia and normal controls. *Human genetics*. 2012;131(7):1187-95.
46. Voineskos AN, Felsky D, Kovacevic N, Tiwari AK, Zai C, Chakravarty MM, et al. Oligodendrocyte genes, white matter tract integrity, and cognition in schizophrenia. *Cerebral cortex*. 2013;23(9):2044-57.
47. Alfimova MV, Abramova LI, Aksenova EV, Golubev SA, Frolova LF, Ganisheva TK, et al. [The association between the NRG1 gene polymorphism and cognitive functions in patients with schizophrenia and healthy controls]. *Zhurnal nevrologii i psikiatrii imeni SS Korsakova / Ministerstvo zdravookhraneniia i meditsinskoj promyshlennosti Rossiiskoi Federatsii, Vserossiiskoe obshchestvo nevrologov [i] Vserossiiskoe obshchestvo psikiat*. 2011;111(6):53-7.

48. Meier S, Strohmaier J, Breuer R, Mattheisen M, Degenhardt F, Muhleisen TW, et al. Neuregulin 3 is associated with attention deficits in schizophrenia and bipolar disorder. *The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum*. 2013;16(3):549-56.
49. Morar B, Dragovic M, Waters FA, Chandler D, Kalaydjieva L, Jablensky A. Neuregulin 3 (NRG3) as a susceptibility gene in a schizophrenia subtype with florid delusions and relatively spared cognition. *Molecular psychiatry*. 2011;16(8):860-6.
50. Chandler D, Dragovic M, Cooper M, Badcock JC, Mullin BH, Faulkner D, et al. Impact of Neuritin 1 (NRN1) polymorphisms on fluid intelligence in schizophrenia. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 2010;153B(2):428-37.
51. Golimbet VE, Alfimova MV, Gritsenko IK, Lezheiko TV, Lavrushina OM, Abramova LI, et al. [The association of the SNAP-25 gene polymorphism with verbal memory and attention in patients with major psychosis and healthy people]. *Zhurnal neurologii i psikiatrii imeni SS Korsakova / Ministerstvo zdravookhraneniia i meditsinskoi promyshlennosti Rossiiskoi Federatsii, Vserossiiskoe obshchestvo nevrologov [i] Vserossiiskoe obshchestvo psikiat*. 2009;109(1):59-63.
52. Li T, Ma X, Hu X, Wang Y, Yan C, Meng H, et al. PRODH gene is associated with executive function in schizophrenic families. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 2008;147B(5):654-7.
53. Bosia M, Anselmetti S, Pirovano A, Ermoli E, Marino E, Bramanti P, et al. HTTLPR functional polymorphism in schizophrenia: executive functions vs. sustained attention dissociation. *Progress in neuro-psychopharmacology & biological psychiatry*. 2010;34(1):81-5.
54. Bosia M, Anselmetti S, Bechi M, Lorenzi C, Pirovano A, Cocchi F, et al. Effect of 5-HT1A-receptor functional polymorphism on Theory of Mind performances in schizophrenia. *Psychiatry research*. 2011;188(2):187-90.
55. Uçok A, Alpsan H, Cakir S, Saruhan-Direskeneli G. Association of a serotonin receptor 2A gene polymorphism with cognitive functions in patients with schizophrenia. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 2007;144B(5):704-7.
56. Alfimova MV, Golimbet VE, Mitiushina NG. [Polymorphism of the serotonin receptor (5-HTR2A) gene and verbal fluency in normalcy and schizophrenia]. *Molekuliarnaia biologii*. 2003;37(1):68-73.
57. Chen RY, Sham P, Chen EY, Li T, Cheung EF, Hui TC, et al. No association between T102C polymorphism of serotonin-2A receptor gene and clinical phenotypes of Chinese schizophrenic patients. *Psychiatry research*. 2001;105(3):175-85.
58. Jablensky A, Morar B, Wiltshire S, Carter K, Dragovic M, Badcock JC, et al. Polymorphisms associated with normal memory variation also affect memory impairment in schizophrenia. *Genes, brain, and behavior*. 2011;10(4):410-7.
59. Donohoe G, Morris DW, Robertson IH, McGhee KA, Murphy K, Kenny N, et al. DAOA ARG30LYS and verbal memory function in schizophrenia. *Molecular psychiatry*. 2007;12(9):795-6.
60. Lin WY, Wu BT, Lee CC, Sheu JJ, Liu SH, Wang WF, et al. Association analysis of dopaminergic gene variants (Comt, Drd4 And Dat1) with Alzheimer s disease. *Journal of biological regulators and homeostatic agents*. 2012;26(3):401-10.
61. Hori H, Yamamoto N, Fujii T, Teraishi T, Sasayama D, Matsuo J, et al. Effects of the CACNA1C risk allele on neurocognition in patients with schizophrenia and healthy individuals. *Scientific reports*. 2012;2:634.
62. Dickinson D, Straub RE, Trampush JW, Gao Y, Feng N, Xie B, et al. Differential Effects of Common Variants in SCN2A on General Cognitive Ability, Brain Physiology, and messenger RNA Expression in Schizophrenia Cases and Control Individuals. *JAMA psychiatry*. 2014.

63. Jablensky A, Angelicheva D, Donohoe GJ, Cruickshank M, Azmanov DN, Morris DW, et al. Promoter polymorphisms in two overlapping 6p25 genes implicate mitochondrial proteins in cognitive deficit in schizophrenia. *Molecular psychiatry*. 2012;17(12):1328-39.
64. Zhang C, Cai J, Zhang J, Li Z, Guo Z, Zhang X, et al. Genetic modulation of working memory deficits by ankyrin 3 gene in schizophrenia. *Progress in neuro-psychopharmacology & biological psychiatry*. 2014;50:110-5.
65. Albanna A, Choudhry Z, Harvey PO, Fathalli F, Cassidy C, Sengupta SM, et al. TCF4 gene polymorphism and cognitive performance in patients with first episode psychosis. *Schizophrenia research*. 2014;152(1):124-9.
66. Zhu X, Gu H, Liu Z, Xu Z, Chen X, Sun X, et al. Associations between TCF4 gene polymorphism and cognitive functions in schizophrenia patients and healthy controls. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2013;38(4):683-9.
67. Rose EJ, Hargreaves A, Morris D, Fahey C, Tropea D, Cummings E, et al. Effects of a novel schizophrenia risk variant rs7914558 at CNNM2 on brain structure and attributional style. *The British journal of psychiatry : the journal of mental science*. 2014;204(2):115-21.
68. Donohoe G, Walters J, Hargreaves A, Rose EJ, Morris DW, Fahey C, et al. Neuropsychological effects of the CSMD1 genome-wide associated schizophrenia risk variant rs10503253. *Genes, brain, and behavior*. 2013;12(2):203-9.
69. Xiang B, Wu JY, Ma XH, Wang YC, Deng W, Chen ZF, et al. [Genome-wide association study with memory measures as a quantitative trait locus for schizophrenia]. *Zhonghua yi xue yi chuan xue za zhi = Zhonghua yixue yichuanxue zazhi = Chinese journal of medical genetics*. 2012;29(3):255-9.
70. Bosia M, Buonocore M, Guglielmino C, Pirovano A, Lorenzi C, Marcone A, et al. Saitohin polymorphism and executive dysfunction in schizophrenia. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*. 2012;33(5):1051-6.
71. Chiu HJ, Hong CJ, Chen JY, Wang YC, Lin CY, Bai YM, et al. Alpha-1-antichymotrypsin polymorphism in schizophrenia: frequency, age at onset and cognitive function. *Neuropsychobiology*. 1999;40(2):71-4.
72. Walters JT, Corvin A, Owen MJ, Williams H, Dragovic M, Quinn EM, et al. Psychosis susceptibility gene ZNF804A and cognitive performance in schizophrenia. *Archives of general psychiatry*. 2010;67(7):692-700.
73. Hashimoto R, Ohi K, Yasuda Y, Fukumoto M, Iwase M, Iike N, et al. The impact of a genome-wide supported psychosis variant in the ZNF804A gene on memory function in schizophrenia. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 2010;153B(8):1459-64.
74. Hargreaves A, Morris DW, Rose E, Fahey C, Moore S, Cummings E, et al. ZNF804A and social cognition in patients with schizophrenia and healthy controls. *Molecular psychiatry*. 2012;17(2):118-9.
75. Vassos E, Bramon E, Picchioni M, Walshe M, Filbey FM, Kravariti E, et al. Evidence of association of KIBRA genotype with episodic memory in families of psychotic patients and controls. *Journal of psychiatric research*. 2010;44(12):795-8.
76. Knowles EE, Carless MA, de Almeida MA, Curran JE, McKay DR, Sprooten E, et al. Genome-wide significant localization for working and spatial memory: Identifying genes for psychosis using models of cognition. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 2014;165(1):84-95.
77. Lencz T, Knowles E, Davies G, Guha S, Liewald DC, Starr JM, et al. Molecular genetic evidence for overlap between general cognitive ability and risk for schizophrenia: a report from the Cognitive Genomics consorTium (COGENT). *Molecular psychiatry*. 2014;19(2):168-74.

78. Hargreaves A, Anney R, O'Dushlaine C, Nicodemus KK, Gill M, Corvin A, et al. The one and the many: effects of the cell adhesion molecule pathway on neuropsychological function in psychosis. *Psychological medicine*. 2013;1-11.
79. Kastner A, Grube S, El-Kordi A, Stepniak B, Friedrichs H, Sargin D, et al. Common variants of the genes encoding erythropoietin and its receptor modulate cognitive performance in schizophrenia. *Mol Med*. 2012;18:1029-40.
80. Prasad KM, Almasy L, Gur RC, Gur RE, Pogue-Geile M, Chowdari KV, et al. RGS4 polymorphisms associated with variability of cognitive performance in a family-based schizophrenia sample. *Schizophrenia bulletin*. 2010;36(5):983-90.
81. Donohoe G, Walters J, Morris DW, Quinn EM, Judge R, Norton N, et al. Influence of NOS1 on verbal intelligence and working memory in both patients with schizophrenia and healthy control subjects. *Archives of general psychiatry*. 2009;66(10):1045-54.
82. Fernandes CP, Christoforou A, Giddaluru S, Ersland KM, Djurovic S, Mattheisen M, et al. A genetic deconstruction of neurocognitive traits in schizophrenia and bipolar disorder. *PloS one*. 2013;8(12):e81052.
83. Sagud M, Muck-Seler D, Mihaljevic-Peles A, Vuksan-Cusa B, Zivkovic M, Jakovljevic M, et al. Catechol-O-methyl transferase and schizophrenia. *Psychiatria Danubina*. 2010;22(2):270-4.
84. Raz N, Lustig C. Genetic variants and cognitive aging: destiny or a nudge? *Psychology and aging*. 2014;29(2):359-62.
85. Savitz J, Solms M, Ramesar R. The molecular genetics of cognition: dopamine, COMT and BDNF. *Genes, brain, and behavior*. 2006;5(4):311-28.
86. Zheng C, Shen Y, Xu Q. Association of intron 1 variants of the dopamine transporter gene with schizophrenia. *Neuroscience letters*. 2012;513(2):137-40.
87. Colzato LS, Pratt J, Hommel B. Dopaminergic Control of Attentional Flexibility: Inhibition of Return is Associated with the Dopamine Transporter Gene (DAT1). *Frontiers in human neuroscience*. 2010;4:53.
88. Liu L, Fan D, Ding N, Hu Y, Cai G, Wang L, et al. The relationship between DRD2 gene polymorphisms (C957T and C939T) and schizophrenia: A meta-analysis. *Neuroscience letters*. 2014;583C:43-8.
89. Small GW, Noble EP, Matsuyama SS, Jarvik LF, Komo S, Kaplan A, et al. D2 dopamine receptor A1 allele in Alzheimer disease and aging. *Archives of neurology*. 1997;54(3):281-5.
90. Colzato LS, van den Wildenberg WP, Hommel B. The genetic impact (C957T-DRD2) on inhibitory control is magnified by aging. *Neuropsychologia*. 2013;51(7):1377-81.
91. Rodriguez-Jimenez R, Hoenicka J, Jimenez-Arriero MA, Ponce G, Bagney A, Aragues M, et al. Performance in the Wisconsin Card Sorting Test and the C957T polymorphism of the DRD2 gene in healthy volunteers. *Neuropsychobiology*. 2006;54(3):166-70.
92. Combarros O, Warden DR, Hammond N, Cortina-Borja M, Belbin O, Lehmann MG, et al. The dopamine beta-hydroxylase -1021C/T polymorphism is associated with the risk of Alzheimer's disease in the Epistasis Project. *BMC medical genetics*. 2010;11:162.
93. Dai D, Wang Y, Yuan J, Zhou X, Jiang D, Li J, et al. Meta-analyses of 10 polymorphisms associated with the risk of schizophrenia. *Biomedical reports*. 2014;2(5):729-36.
94. Meyer-Lindenberg A, Straub RE, Lipska BK, Verchinski BA, Goldberg T, Callicott JH, et al. Genetic evidence implicating DARPP-32 in human frontostriatal structure, function, and cognition. *The Journal of clinical investigation*. 2007;117(3):672-82.
95. Wang KS, Xu N, Wang L, Aragon L, Ciubuc R, Arana TB, et al. NRG3 gene is associated with the risk and age at onset of Alzheimer disease. *Journal of neural transmission*. 2014;121(2):183-92.

96. Guerini FR, Agliardi C, Sironi M, Arosio B, Calabrese E, Zanzottera M, et al. Possible Association between SNAP-25 Single Nucleotide Polymorphisms and Alterations of Categorical Fluency and Functional MRI Parameters in Alzheimer's Disease. *Journal of Alzheimer's disease : JAD*. 2014;42(3):1015-28.
97. Roussos P, Giakoumaki SG, Bitsios P. A risk PRODH haplotype affects sensorimotor gating, memory, schizotypy, and anxiety in healthy male subjects. *Biological psychiatry*. 2009;65(12):1063-70.
98. Arlt S, Demiralay C, Tharun B, Geisel O, Storm N, Eichenlaub M, et al. Genetic risk factors for depression in Alzheimer's disease patients. *Current Alzheimer research*. 2013;10(1):72-81.
99. O'Hara R, Marcus P, Thompson WK, Flournoy J, Vahia I, Lin X, et al. 5-HTTLPR short allele, resilience, and successful aging in older adults. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry*. 2012;20(5):452-6.
100. Bertram L, McQueen MB, Mullin K, Blacker D, Tanzi RE. Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database. *Nature genetics*. 2007;39(1):17-23.
101. Allen NC, Bagade S, McQueen MB, Ioannidis JP, Kavvoura FK, Khoury MJ, et al. Systematic meta-analyses and field synopsis of genetic association studies in schizophrenia: the SzGene database. *Nature genetics*. 2008;40(7):827-34.
102. Cassidy C, Buchy L, Bodnar M, Dell'elce J, Choudhry Z, Fathalli F, et al. Association of a risk allele of ANK3 with cognitive performance and cortical thickness in patients with first-episode psychosis. *Journal of psychiatry & neuroscience : JPN*. 2014;39(1):31-9.
103. Aberg KA, Liu Y, Bukszar J, McClay JL, Khachane AN, Andreassen OA, et al. A comprehensive family-based replication study of schizophrenia genes. *JAMA psychiatry*. 2013;70(6):573-81.
104. Havik B, Le Hellard S, Rietschel M, Lybaek H, Djurovic S, Mattheisen M, et al. The complement control-related genes CSMD1 and CSMD2 associate to schizophrenia. *Biological psychiatry*. 2011;70(1):35-42.
105. Koiliari E, Roussos P, Pasparakis E, Lencz T, Malhotra A, Siever LJ, et al. The CSMD1 genome-wide associated schizophrenia risk variant rs10503253 affects general cognitive ability and executive function in healthy males. *Schizophrenia research*. 2014;154(1-3):42-7.
106. Dou C, Zhang J, Sun Y, Zhao X, Wu Q, Ji C, et al. The association of ACT -17 A/T polymorphism with Alzheimer's disease: a meta-analysis. *Current Alzheimer research*. 2013;10(1):63-71.
107. Fernandes CP, Westlye LT, Giddaluru S, Christoforou A, Kauppi K, Adolfsson R, et al. Lack of association of the rs1344706 ZNF804A variant with cognitive functions and DTI indices of white matter microstructure in two independent healthy populations. *Psychiatry research*. 2014;222(1-2):60-6.
108. Lencz T, Szeszko PR, DeRosse P, Burdick KE, Bromet EJ, Bilder RM, et al. A schizophrenia risk gene, ZNF804A, influences neuroanatomical and neurocognitive phenotypes. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2010;35(11):2284-91.
109. Stefanis NC, Hatzimanolis A, Avramopoulos D, Smyrnis N, Evdokimidis I, Stefanis CN, et al. Variation in psychosis gene ZNF804A is associated with a refined schizotypy phenotype but not neurocognitive performance in a large young male population. *Schizophrenia bulletin*. 2013;39(6):1252-60.
110. Walter H, Schnell K, Erk S, Arnold C, Kirsch P, Esslinger C, et al. Effects of a genome-wide supported psychosis risk variant on neural activation during a theory-of-mind task. *Molecular psychiatry*. 2011;16(4):462-70.
111. Sedille-Mostafaie N, Sebesta C, Huber KR, Zehetmayer S, Jungwirth S, Tragl KH, et al. The role of memory-related gene polymorphisms, KIBRA and CLSTN2, on replicate memory assessment in the elderly. *Journal of neural transmission*. 2012;119(1):77-80.

112. Laukka EJ, Lovden M, Herlitz A, Karlsson S, Ferencz B, Pantzar A, et al. Genetic effects on old-age cognitive functioning: a population-based study. *Psychology and aging*. 2013;28(1):262-74.
113. Papassotiropoulos A, Stephan DA, Huentelman MJ, Hoerndli FJ, Craig DW, Pearson JV, et al. Common Kibra alleles are associated with human memory performance. *Science*. 2006;314(5798):475-8.
114. Schaper K, Kolsch H, Popp J, Wagner M, Jessen F. KIBRA gene variants are associated with episodic memory in healthy elderly. *Neurobiology of aging*. 2008;29(7):1123-5.
115. Almeida OP, Schwab SG, Lautenschlager NT, Morar B, Greenop KR, Flicker L, et al. KIBRA genetic polymorphism influences episodic memory in later life, but does not increase the risk of mild cognitive impairment. *Journal of cellular and molecular medicine*. 2008;12(5A):1672-6.
116. Need AC, Attix DK, McEvoy JM, Cirulli ET, Linney KN, Wagoner AP, et al. Failure to replicate effect of Kibra on human memory in two large cohorts of European origin. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 2008;147B(5):667-8.
117. MacLeod CA, Donaldson DI. PRKCA polymorphism changes the neural basis of episodic remembering in healthy individuals. *PloS one*. 2014;9(5):e98018.
118. Ruderfer DM, Fanous AH, Ripke S, McQuillin A, Amdur RL, Gejman PV, et al. Polygenic dissection of diagnosis and clinical dimensions of bipolar disorder and schizophrenia. *Molecular psychiatry*. 2014;19(9):1017-24.
119. Ma L, Tang J, Wang D, Zhang W, Liu W, Liu XH, et al. Evaluating risk loci for schizophrenia distilled from genome-wide association studies in Han Chinese from Central China. *Molecular psychiatry*. 2013;18(6):638-9.
120. Huang L, Hu F, Zeng X, Gan L, Luo XJ. Further evidence for the association between the LSM1 gene and schizophrenia. *Schizophrenia research*. 2013;150(2-3):588-9.
121. Li T, Underhill J, Liu XH, Sham PC, Donaldson P, Murray RM, et al. Transmission disequilibrium analysis of HLA class II DRB1, DQA1, DQB1 and DPB1 polymorphisms in schizophrenia using family trios from a Han Chinese population. *Schizophrenia research*. 2001;49(1-2):73-8.
122. Schwab SG, Hallmayer J, Freimann J, Lerer B, Albus M, Borrmann-Hassenbach M, et al. Investigation of linkage and association/linkage disequilibrium of HLA A-, DQA1-, DQB1-, and DRB1-alleles in 69 sib-pair- and 89 trio-families with schizophrenia. *American journal of medical genetics*. 2002;114(3):315-20.
123. Guan S, Zhang X, Xu Q, Ye L, Jin S, Wang Z, et al. Lack of genetic association of the HLA-DQA1(0501 variant with schizophrenia in a Chinese population. *Psychiatry research*. 2013;208(1):97-8.
124. Zhao Z, Webb BT, Jia P, Bigdeli TB, Maher BS, van den Oord E, et al. Association study of 167 candidate genes for schizophrenia selected by a multi-domain evidence-based prioritization algorithm and neurodevelopmental hypothesis. *PloS one*. 2013;8(7):e67776.
125. Fallin MD, Szymanski M, Wang R, Gherman A, Bassett SS, Avramopoulos D. Fine mapping of the chromosome 10q11-q21 linkage region in Alzheimer's disease cases and controls. *Neurogenetics*. 2010;11(3):335-48.
126. Chowdari KV, Mirnics K, Semwal P, Wood J, Lawrence E, Bhatia T, et al. Association and linkage analyses of RGS4 polymorphisms in schizophrenia. *Human molecular genetics*. 2002;11(12):1373-80.
127. Francks C, Maegawa S, Lauren J, Abrahams BS, Velayos-Baeza A, Medland SE, et al. LRRTM1 on chromosome 2p12 is a maternally suppressed gene that is associated paternally with handedness and schizophrenia. *Molecular psychiatry*. 2007;12(12):1129-39, 057.

128. Boks MP, Hoogendoorn M, Jungerius BJ, Bakker SC, Sommer IE, Sinke RJ, et al. Do mood symptoms subdivide the schizophrenia phenotype? Association of the GMP6A gene with a depression subgroup. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 2008;147B(6):707-11.
129. Campbell DB, Lange LA, Skelly T, Lieberman J, Levitt P, Sullivan PF. Association of RGS2 and RGS5 variants with schizophrenia symptom severity. *Schizophrenia research*. 2008;101(1-3):67-75.
130. Kohli U, Muszkat M, Sofowora GG, Harris PA, Friedman EA, Dupont WD, et al. Effects of variation in the human alpha2A- and alpha2C-adrenoceptor genes on cognitive tasks and pain perception. *European journal of pain*. 2010;14(2):154-9.
131. Murakami S, Uchijima M, Shimoda A, Kaneko S, Kobayashi K, Hattori N. Hepadnavirus enhancer and its binding proteins. *Gastroenterologia Japonica*. 1990;25 Suppl 2:11-9.
132. Pezzi JC, Ens CM, Borba EM, Schumacher-Schuh AF, de Andrade FM, Chaves ML, et al. DNA methyltransferase haplotype is associated with Alzheimer's disease. *Neuroscience letters*. 2014;579:70-4.
133. Yeh TK, Hu CY, Yeh TC, Lin PJ, Wu CH, Lee PL, et al. Association of polymorphisms in BDNF, MTHFR, and genes involved in the dopaminergic pathway with memory in a healthy Chinese population. *Brain and cognition*. 2012;80(2):282-9.
134. de Lau LM, van Meurs JB, Uitterlinden AG, Smith AD, Refsum H, Johnston C, et al. Genetic variation in homocysteine metabolism, cognition, and white matter lesions. *Neurobiology of aging*. 2010;31(11):2020-2.
135. Ravaglia G, Forti P, Maioli F, Scali RC, Arnone G, Talerico T, et al. Common polymorphisms in methylenetetrahydrofolate reductase (MTHFR): relationships with plasma homocysteine concentrations and cognitive status in elderly northern italian subjects. *Archives of gerontology and geriatrics Supplement*. 2004(9):339-48.
136. Schiepers OJ, van Boxtel MP, de Groot RH, Jolles J, Bekers O, Kok FJ, et al. Genetic variation in folate metabolism is not associated with cognitive functioning or mood in healthy adults. *Progress in neuro-psychopharmacology & biological psychiatry*. 2011;35(7):1682-8.
137. Visscher PM, Tynan M, Whiteman MC, Pattie A, White I, Hayward C, et al. Lack of association between polymorphisms in angiotensin-converting-enzyme and methylenetetrahydrofolate reductase genes and normal cognitive ageing in humans. *Neuroscience letters*. 2003;347(3):175-8.
138. Roffman JL, Brohawn DG, Nitenson AZ, Macklin EA, Smoller JW, Goff DC. Genetic variation throughout the folate metabolic pathway influences negative symptom severity in schizophrenia. *Schizophrenia bulletin*. 2013;39(2):330-8.
139. Lajin B, Alhaj Sakur A, Michati R, Alachkar A. Association between MTHFR C677T and A1298C, and MTRR A66G polymorphisms and susceptibility to schizophrenia in a Syrian study cohort. *Asian journal of psychiatry*. 2012;5(2):144-9.

Table 2. Molecular genetic studies of cognition across healthy to disease spectrum.*

System	Gene	Schizophrenia Cognition	Schizophrenia Disease Risk	Healthy	Dementia	Cognitive Domains	References
Dopamine	<i>COMT</i>	+/-	+/-	+/- ⁹	+/-	Executive function, theory of mind, reaction time, processing speed, attention	(1-20, 22-25, 83-85)
	<i>DAT/SLC6A3</i>	+/-	+/-	+/- ⁹	+/-	- Speed of information processing, attention/vigilance, verbal learning and memory, working memory, reasoning and problem solving, set shifting, and verbal comprehension	(1, 7, 23, 26, 60, 86, 87)
	<i>DRD1</i>	+		₉		- Speed of information processing, attention/vigilance, verbal learning and memory, working memory, reasoning and problem solving, set shifting, and verbal comprehension	(23)
	<i>DRD2</i>	-	+/-	+/- ⁹	-	-	(2, 22, 23, 85, 88-91)
	<i>DRD3</i>	+/-	+/-	+/- ^{1,9}	-	Perseveration - Speed of information processing, attention/vigilance, verbal learning and memory, working memory, reasoning and problem solving, set shifting, and verbal comprehension	(20, 22, 23, 26)
	<i>DRD4</i>	+	+/-	+	+/-	Working memory, verbal fluency	(5, 60, 85)
	<i>DRD5</i>	+	+/-	₂		Visual voluntary attention	(27)
	<i>DBH</i>	+/-	+/-	-	+	Immediate memory	(20, 28, 92, 93)
	<i>SLC18A2</i>	+/-	+/-	₁		- Speed of information processing, attention/vigilance, verbal learning and memory, working memory, reasoning and problem solving, set shifting, and verbal comprehension	(20)
	<i>ANKK1</i>	-	+/-	₉		-	(23)
	<i>PPP1R1B</i>	-	+/-	+/- ⁹		-	(23, 94)
	<i>DISC1</i>	+	+/-	+/- ⁹		Verbal fluency, verbal working memory, short- and long-term memory, short-term visual memory, visual search, attention	(1, 17, 23, 29-32)
	<i>DTNBP1</i>	+/-	+/-	+/- ⁹		Attention/vigilance domain, spatial working memory, IQ	(23, 33-36)
	<i>BDNF</i>	+/-	+/-	+/- ⁹	+/-	Voluntary and involuntary attention, verbal memory, visuospatial skills, working memory - Speed of information processing, attention/vigilance, verbal learning and memory, working memory, reasoning and problem solving, set shifting, and verbal comprehension	(1, 23, 37-45, 85)
Neuro	<i>NRG1</i>	+	+/-	_{3,9}	+	Processing speed, visuospatial speed, attention, long-term episodic memory, short-term memory	(17, 23, 46, 47)
	<i>NRG3</i>	+	+/-		+	Visuospatial speed, processing speed, mental flexibility, executive function, sustained attention	(48, 49, 95)
	<i>NRN1</i>	+	+/-	₃		General intellectual ability	(50)
	<i>SNAP-25</i>	+	+/-	+ ¹	+	Verbal memory, attention, executive function	(51, 96)
	<i>PRODH</i>	-	+/-	+/- ⁹	-	-	(23, 52, 97)
	<i>P2RX7</i>	-	-	₉	-	-	(23, 98)

	<i>NPY</i>	-	+/-	-.9	-	-	(23)
	<i>NQO1</i>	-	-	-.9	+/-	-	(23)
	<i>GST-1</i>	-		-.9		-	(23)
	<i>GST-2</i>	-		-.9		-	(23)
Serotonin	<i>5HTT/SLC6A4</i>	+/-	+/-	+	+/-	Executive function, attention	(17, 21, 53, 99)
	<i>HTR1A</i>	+	+/-			Theory of mind	(17, 54)
	<i>HTR2A</i>	+/-	+/-	-.9	+4/-	Voluntary and involuntary attention, executive function, verbal fluency	(1, 17, 23, 37, 55-57, 83)
	<i>NET/SLC6A2</i>	-	-			-	(6, 7)
Oligodendrocyte	<i>QKI</i>	-	-	-.5	+	-	(46, 100)
	<i>MAG</i>	+	+/-	+.5		Processing speed, visuomotor speed, attention	(46)
	<i>CNP</i>	-	+/-	-.5		-	(46)
	<i>OLIG2</i>	-	+/-	+.5	+4/-	-	(46, 101)
Glutamate	<i>ERBB4</i>	-	+/-	+.5	+	Verbal learning, abstraction, visuospatial memory	(17, 20, 46)
	<i>GRIN2A</i>	-	+/-	+		-	(58)
	<i>GRIN2B</i>	+/-	+/-	+	+/-	Immediate and delayed recall (verbal memory)	(1, 17, 58)
	<i>GRM1</i>	+	+			Attention, verbal learning, abstraction, visuospatial memory, spatial processing	(17, 21, 86)
	<i>GRM3</i>	+	+/-	+/- ⁹		Enhanced performance	(23, 58, 87)
	<i>SLC1A2</i>	+	+/-			Attention, abstraction, spatial memory	(17)
	<i>DAOA</i>	+	+/-	+.6/- ⁹	+ ⁴	Verbal memory	(23, 59, 60)
	<i>GAD1</i>	-	+/-	-.9		-	(23)
	<i>CACNA1C</i>	+/-	+	-.3	+	Logical memory	(1, 61, 88, 89)
	<i>SCN2A</i>	+		-.2		Cognitive ability (g)	(62, 90)
Energy metabolism	<i>LYRM4</i>	+				Verbal memory	(63)
	<i>FARS1</i>	+				Verbal memory	(63)
	<i>ATP2C2</i>	-				-	(1)
Others	<i>ANK3</i>	+	+/-	+/- ³	+/-	Working memory, verbal memory, attention	(64, 91, 92, 102)
	<i>TCF4</i>	+	+/-	+.7		Reasoning, problem-solving, attention-related tasks	(65, 66)
	<i>CNNM2</i>	-	+	-		Social cognition	(67, 103)
	<i>CSMD1</i>	+	+	+		General cognitive ability, memory cognition	(68, 69, 104, 105)
	<i>STH</i>	+	-		+/-	Executive function	(25, 70)
	<i>ACT</i>	-	-		+	-	(71, 106)
	<i>DCDC2</i>	-	-			-	(1)
	<i>DYX1C1</i>	-				-	(1)
	<i>KIAA0319</i>	+				Verbal learning and recall	(1)
	<i>NAGPA</i>	-				-	(1)
	ZNF804A	+/-	+/-	+/-		Verbal learning and recall, verbal and spatial working memory, verbal episodic memory, visual memory	(1, 72-74, 107-110)

CLSTN2	-		+/-	-	(1, 111, 112)
WWC1	-	+	+/-	+/-	(1, 75, 113-116)
ATRNL1	-			-	(1)
C20orf196	-			-	(1)
CRTC3	-			-	(1)
DIP2C	-			-	(1)
NFKBIL1	-	-		-	(1)
PDE1C	-			-	(1)
PKNX1	-			-	(1)
SPATA7	-			-	(1)
ADCY8	-			-	(1, 58)
CAMK2G	-			-	(1, 58)
PRKACG	-			-	(58)
PRKCA	+	+/-	+	Verbal memory	(58, 117)
HEY1	+			Working memory	(76)
MAD1L1	+	+		Cognitive ability	(77, 118)
LSM1	+	+/-		Cognitive ability	(77, 119, 120)
CAM	+			Memory, attention	(78)
HLA-DQA1	+	-		+/- (A2) Attention	(78, 121-123)
RASGRF2	+			Memory cognition	(69)
PLCG2	+			Memory cognition	(69)
LMO1	+			Memory cognition	(69)
PRKG1	+	-		+/- Memory cognition	(69, 124, 125)
EPO	+			Processing speed, short-term memory, and tasks requiring distinct fine motor component	(79)
EPOR	+			Processing speed, short-term memory, and tasks requiring distinct fine motor component	(79)
RGS4	+/- ¹	+/-	+1/- ⁹	-	(23, 80, 126)
PIP5K2A	-	+/-	- ⁹	-	(23)
AKT1	-	+/-	- ⁹	-	(23)
LRRTM1	-	+	- ⁹	-	(23, 127)
FGF2	+	-	-2/- ⁹	- Speed of information processing, attention/vigilance, verbal learning and memory, working memory, reasoning and problem solving, set shifting, and verbal comprehension	(23)
FGFR1	-		- ⁹	-	(23)
GPM6A	-	+	- ⁹	-	(23, 128)
GABRA6	-	+/-	- ⁹	-	(23)
NOS1	+/-	+/-	+/- ^{2,9}	+/- General cognitive ability, verbal and spatial working memory	(23, 81)
RGS2	-	+	- ⁹	-	(23, 129)

<i>ROBO1</i>	-		9	-	(23)
<i>CHRM3</i>	-		9	-	(23)
<i>TBX1</i>	-	+/-	9	-	(23)
<i>ADRA2C</i>	-		9	-	(23, 130)
<i>FKBP5</i>	+	-	9	-	(23)
<i>DNMT3B</i>	+	+	9	+/-	(23, 131, 132)
<i>CNR1</i>	-	+/-	9	-	(23, 133)
<i>MTHFR</i>	+/-	+/-	9	+/-	(23, 24, 133-137)
<i>MTR</i>	-	+	9	+/-	(23, 134)
<i>MTRR</i>	-	-	9	-	(23, 134, 138, 139)
<i>EHMT1</i>	-		9	-	(23)
<i>EHMT2</i>	-	-	9	-	(23)
<i>PRDM2</i>	-		9	-	(23)

* The list of genes in this table has been cross-referenced with the genetic databases in schizophrenia www.alzgene.org (100) and Alzheimer's disease www.szgene.org (101) and updated with references from PubMed for schizophrenia risk genes, dementia risk genes, and genes affecting normal cognition.

“+” indicates previous significant association(s), “-” indicates prior negative association(s), and “+/-” indicates previous positive and negative associations.

¹ This study reported a significant association between SNP(s) across this gene and cognitive function(s) in the combined psychosis and healthy control sample.

² This study detected a significant association between SNP(s) across this gene only in schizophrenia patients and their unaffected relatives but not in healthy controls.

³ This study found significant association between SNP(s) across this gene only in schizophrenia patients but not in healthy controls.

⁴ This study found significant association between this gene and psychosis in patients with Alzheimer's disease.

⁵ This study reported significant associations for *MAG* in schizophrenia patients and healthy controls but in different cognitive domains and for *OLIG2* and *ERBB4* in only healthy controls; *QKI* and *CNP* were not significant in either sample.

⁶ This study found significant association between *DAOA* and cognitive function regardless of disease status (psychosis patients and healthy controls).

⁷ This study found significant association between *TCF4* and cognitive function in schizophrenia patients and healthy controls but opposite alleles associated with cognitive better performance.

⁸ This study with two independent samples found significant associations between *NOS1* and cognitive function in Irish controls but not in Irish schizophrenia patients, and German schizophrenia patients but not controls.

⁹ This study found significant association between SNP(s) across this gene only in schizophrenia patients but not in their unaffected relatives or healthy controls.

Supplementary Table 1. Molecular genetic studies of cognitive deficits in schizophrenia.

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
<i>COMT</i>	22q11.21	Val158Met (rs4680)	343 schizophrenia patients	Brief Assessment of Cognition in Schizophrenia, WCST, CPT	<ul style="list-style-type: none"> • Significant effects on processing speed and executive functions • <i>COMT</i> × <i>STH</i> Q7R interaction on executive functions with <i>COMT</i> Val/Val and <i>STH</i> R carriers performing worse 	Bosia et al., 2014 (1)
			188 DSM-IV psychotic (94 schizophrenia and 94 schizoaffective disorder) patients	ANART, BVMT-R, HVLT-R, CPT-IP, WAIS-III, Digit Symbol and Symbol Search subtests, D-KEFS	<ul style="list-style-type: none"> • Met allele with better learning/memory ($P=0.034$) and D-KEFS abstraction ($P=0.038$) 	Twamley et al., 2014 (2)
			429 DSM-IV Australian schizophrenia and/or schizoaffective disorder patients	RBANS, COWAT, LNS, WTAR	<ul style="list-style-type: none"> • Val homozygotes with worse cognitive performance in the absence of childhood adversity • Val homozygotes and history of abuse with better executive function • Met carriers and history of physical abuse with worse positive symptoms • Met carriers and history of emotional 	Green et al., 2014 (3)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
					neglect with worse negative symptoms	
			90 DSM-IV schizophrenia patients and 55 healthy controls	CANTAB: Motor Control, Pattern Recognition Memory and Spatial Recognition Memory, Intra-Extra Dimensional Set Shifting Task, Stockings of Cambridge, Spatial Working Memory, WAIS-III to assess IQ	<ul style="list-style-type: none"> • $COMT \times MTHFR$ rs1801133 interaction on spatial working memory ($P=0.048$) and planning ($P=0.026$) in cases and controls • $COMT$ Val/Val and $MTHFR$ C/C individuals with more spatial working memory errors ($P=0.033$) and solving fewer Stockings of Cambridge problems ($P=0.025$) in both groups • $COMT \times MTHFR$ interaction with IQ ($P=0.035$), worse performance with $COMT$ Met carriers and $MTHFR$ T carriers ($P=0.021$) 	Kontis et al., 2013 (4)
			74 DSM-IV schizophrenia spectrum disorder patients (44 schizophrenia, 16	MATRICES battery with WAIS-III: category fluency, digit symbol, TMTA, WMS-III,	<ul style="list-style-type: none"> • No association 	Lopez-Garcia et al., 2013 (5)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
			schizoaffective disorder, 4 delusional disorder, 5 brief psychotic disorder, and 5 schizotypal personality disorder), 48 non-psychotic first-degree relatives, and 67 healthy controls	HVLT-R, BVMT-R, DPX task (modified version of the expectancy AX-CPT)		
			194 DSM-IV schizophrenia patients, 164 unaffected siblings, and 307 healthy controls	WMS, CVLT, category fluency task, TASA corpus,	<ul style="list-style-type: none"> • No association 	Nicodemus et al., 2013 (6)
			209 schizophrenia and 172 healthy people	ToM: second-order false belief, faux pas stories	<ul style="list-style-type: none"> • No association in schizophrenia • Met allele in females (schizophrenia and controls) with worse performance than Val/Val genotype in males 	Alfimova et al., 2013 (7)
			32 ICD-10 schizophrenia, 22 bipolar I disorder, 26 OCD, and 20 healthy individuals	Sternberg paradigm (delayed match-to-sample task), 4 tasks testing verbal and visuospatial working memory	<ul style="list-style-type: none"> • No association 	Zilles et al., 2012 (8)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
			97 DSM-IV patients (28 schizophrenia, 8 schizophreniform disorder, 17 bipolar disorder, 13 psychosis not otherwise specified, and 18 other affective disorders with psychotic symptoms) and 90 healthy controls	WAIS-III (digits forward, digits backward, number-letter sequencing), TMTA, TMTB, Stroop 1 words, Stroop 2 colours, CPT, TAVEC (total learning, short term free recall, long term free recall, discrimination), FAS, COWAT, WCST	<ul style="list-style-type: none"> No association 	Bombin et al., 2008 (9)
			Meta-analysis: 1910 patients and controls <ul style="list-style-type: none"> Szöke et al. (2006) Rybakowski et al. (2006a) Minzenberg et al. (2006; 67 DSM-III-R schizotypal personality disorder, 154 non-schizotypal personality disorder, and 60 unrelated normal controls) 	WCST	<ul style="list-style-type: none"> No association in schizophrenia Met/Met genotype with better performance than Val/Val in healthy controls ($d=0.29$, 95% CI 0.40-0.26, $P=0.03$) 	Barnett et al., 2007 (10)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
			<ul style="list-style-type: none"> • Ho et al. (2005) • Galderisi et al. (2005) • Bruder et al. (2005; healthy volunteers) • Rosa et al. (2004) • Tsai et al. (2003; 120 Chinese healthy female volunteers) • Malhotra et al. (2002; 73 healthy volunteers) • Joobert et al. (2002) • Bilder et al. (2002) • Egan et al. (2001) 			
			<p>50 DSM-IV schizophrenia patients and responders to one adequately dosed antipsychotic for 3 months</p> <ul style="list-style-type: none"> • Placebo vs. active (both with SRT) 	BACS, WCST, CPT	<ul style="list-style-type: none"> • Met carriers on active treatment with greater improvement for WCST performance when compared with Val/Val on placebo ($P=0.01$) 	Bosia et al., 2007 (11)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
			150 schizophrenia patients, 83 relatives, and 118 mentally healthy subjects with no family history of psychosis	Verbal memory, executive functions, and peculiarities of associative processes (details not shown)	<ul style="list-style-type: none"> • Val158Met-<i>DRD4</i> - 521C/T Val/Val+C/C and Met/Met+T/T with better performance on verbal fluency • Val158Met-<i>DRD4</i> rs936461 Val-G haplotype with best results on working memory and Met-A haplotype with worst performance 	Alfimova et al., 2006 (12)
			318 participants (66 DSM-IV schizophrenia or schizoaffective disorder, 94 DSM-IV bipolar disorder, and 158 healthy controls or relatives)	TMT (TMTA and TMTB), WCST	<ul style="list-style-type: none"> • No association 	Szöke et al., 2006 (13)
			124 DSM-IV schizophrenia patients (60 males; mean age 27 years; mean age at onset 23 years)	WCST	<ul style="list-style-type: none"> • Val/Val genotype with better results on all domains of WCST in males ($P=0.044$) but worse in females ($P=0.042$) 	Rybakowski et al., 2006 (14)
			159 DSM-III-R or DSM-IV schizophrenia patients (74.21%	WCST, WAIS-R, TMT, N-back test	<ul style="list-style-type: none"> • No association 	Ho et al., 2005 (15)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
			male; mean age 26.5 years) and 84 healthy volunteers (40.48% male; mean age 27.0 years)			
			60 deficit/non-deficit DSM-IV schizophrenia pairs (56 with deficit schizophrenia and 41 males vs. 50 with non-deficit and 35 males)	NES, CPT-AX, WCST	<ul style="list-style-type: none"> • Significant main effect accounting for 6.6% of cognitive performance variance ($F=3.28$, $d.f.=2.91$, $P<0.04$) • Val/Val genotype with worse WCST and CPT-AX when compared to Met carriers • Val/Val genotype with worse NES motor scores than Met carriers in deficit schizophrenia ($P<0.005$) 	Galderisi et al., 2005 (16)
			26 (18 males; 25 Caucasians and 1 Hispanic; mean age of 41.4 years) schizophrenia or schizoaffective disorder patients	Competing Programs Task	<ul style="list-style-type: none"> • Val with slower reaction time when compared to Met homozygotes ($P<0.05$) • Met homozygotes with greater accuracy for imitation but not reversal response, 	Nolan et al., 2004 (17)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
					lower trials to criterion ($P<0.05$), and greatest sensitivity to conflict than Val homozygotes	
			89 schizophrenia spectrum disorder patients (48 schizophrenia, 14 psychotic mood disorder, 11 schizoaffective disorder, 8 schizophreniform disorder, 5 brief psychotic disorder, 2 delusional disorder) and their family members (total 356 individuals)	WCST	<ul style="list-style-type: none"> Val/Val genotype with more perseverative errors in healthy siblings ($P=0.007$) but not in schizophrenia spectrum disorder patients 	Rosa et al., 2004 (18)
			74 DSM-IV schizophrenia or schizoaffective disorder patients (59 males; mean age 37 years), 108 siblings (46 males; mean age 37 years), and 68 controls (41 males;	N-back task, CPT “1-9 Distractibility Version”, WAIS-R	<ul style="list-style-type: none"> Val/Val genotype with lowest (n-back) and slowest performance in controls, siblings and patients Met/Met genotype with highest performance 	Goldberg et al., 2003 (19)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
			mean age 35 years)			
			104 DSM-IV schizophrenia patients and 96 unrelated healthy volunteers (94 patients and 31 controls with neuropsychological testing)	WCST	<ul style="list-style-type: none"> Met allele with better WCST performance in the combined patient and control group and trend in schizophrenia ($P=0.07$) 	Joober et al., 2002 (20)
			58 DSM-IV schizophrenia or schizoaffective disorder patients who are defined as treatment resistant (persistent positive symptoms despite adequate treatment with conventional antipsychotics and poor social/vocational functioning level >2 years and PANSS >60 at baseline)	WCST, Category Fluency, Letter Fluency, Block Design, Visual Reproductions I, Visual Reproductions II, Paragraph Recall I, Paragraph Recall II, Word list Learning I, Word List Learning II, TMT (TMTA and TMTB), Digit Symbol, Tapping Left, Tapping Right	<ul style="list-style-type: none"> Met allele with better performance in the processing speed and attention domain but not with executive and visuo-perceptual functions, declarative verbal learning and memory, simple motor ability, or global neurocognitive function ($P=0.01-0.04$) 	Bilder et al., 2002 (21)
			175 DSM-IV schizophrenia or schizoaffective disorder patients (138 males; mean	WCST, WAIS-R	<ul style="list-style-type: none"> Accounted for 4.1% of variance in executive function performance ($P=0.001$) 	Egan et al., 2001 (22)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
			age 36.1 years), 219 unaffected siblings (97 males; mean age 35.6 years), and 55 controls (23 males; mean age 33.9 years)		<ul style="list-style-type: none"> Val/Val genotype with worse performance than Val/Met and Met/Met ($P<0.002$) Met allele with perseverative errors ($P=0.001$) 	
		Val158Met (rs4680) rs4646315 rs9332377	601 Indian DSM-IV schizophrenia case-parent trios and 468 controls; 119 north Indian trio replication sample	TMT for 260 cases and 302 parents	<ul style="list-style-type: none"> No association 	Kukshal et al., 2013 (23)
DAT (SLC6A3)	5p15.3	rs6350 (Asn38Asn)	194 DSM-IV schizophrenia patients, 164 unaffected siblings, and 307 healthy controls	WMS, CVLT, category fluency task, TASA corpus,	<ul style="list-style-type: none"> No association 	Nicodemus et al., 2013 (6)
		rs403636	601 Indian DSM-IV schizophrenia case-parent trios and 468 controls; 119 north Indian trio replication sample	TMT for 260 cases and 302 parents	<ul style="list-style-type: none"> No association 	Kukshal et al., 2013 (23)
		VNTR *	32 ICD-10 schizophrenia, 22 bipolar I disorder, 26 OCD, and 20	Sternberg paradigm (delayed match-to-sample task), 4 tasks testing verbal and	<ul style="list-style-type: none"> Significant effect of verbal and visuospatial working memory performance 	Zilles et al., 2012 (8)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
DRD3	3q13.3	VNTR *	healthy individuals	visuospatial working memory	with 10-repeat homozygote showing worse 'visuospatial rehearsal' performance than 9-repeat carriers (corrected for disease status) – unable to conclude for schizophrenia patients alone	Rybakowski et al., 2006 (14)
			124 DSM-IV schizophrenia patients (60 males; mean age 27 years; mean age at onset 23 years)	WCST	• No association	
			120 Caucasian volunteers (75 DSM-IV schizophrenia [34 males], 45 healthy controls [17 males])	WCST	<ul style="list-style-type: none"> • No association • Ser/Ser genotype with fewer categories completed and more perseverative errors than Ser/Gly ($P<0.01$) • Ser/Ser genotype with non-responders ($P=0.0018$) 	Szekeres et al., 2004 (24)
			97 DSM-IV patients (28 schizophrenia, 8 schizophreniform disorder, 17	WAIS-III (digits forward, digits backward, number-letter sequencing), TMTA, TMTB,	• Significant difference for executive functioning domain ($P=0.002$) with no group effects	

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
			bipolar disorder, 13 psychosis not otherwise specified, and 18 other affective disorders with psychotic symptoms) and 90 healthy controls	Stroop 1 words, Stroop 2 colours, CPT, TAVEC (total learning, short term free recall, long term free recall, discrimination), FAS, COWAT, WCST		
		rs7631540 rs2046496 rs2134655 rs324030	601 Indian DSM-IV schizophrenia case-parent trios and 468 controls; 119 north Indian trio replication sample	TMT for 260 cases and 302 parents	• No association	Kukshal et al., 2013 (23)
DRD2	11q23.2	Not provided	209 schizophrenia patients and 172 healthy people	Second-order false belief and faux pas stories	• No associations	Alfimova et al., 2013 (7)
		<i>TaqIA</i> (rs1800497)	97 DSM-IV patients (28 schizophrenia, 8 schizophreniform disorder, 17 bipolar disorder, 13 psychosis not otherwise specified, and 18 other affective disorders with psychotic symptoms) and 90	WAIS-III (digits forward, digits backward, number-letter sequencing), TMTA, TMTB, Stroop 1 words, Stroop 2 colours, CPT, TAVEC (total learning, short term free recall, long term free recall, discrimination), FAS, COWAT,	• No association	Bombin et al., 2008 (9)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
<i>DRD4</i>	11p15.5	-809G/A (rs936461) -521C/T *	healthy controls 150 schizophrenia patients, 83 relatives, and 118 mentally healthy subjects with no family history of psychosis	WCST Verbal memory, executive functions, and peculiarities of associative processes (details not shown)	<ul style="list-style-type: none"> • <i>COMT</i> Val158Met-rs936461 Val-G haplotype with best results on working memory and Met-A haplotype with worst performance • <i>COMT</i> Val158Met-<i>DRD4</i> -521C/T Val/Val+C/C and Met/Met+T/T with better performance on verbal fluency 	Alfimova et al., 2006 (12)
<i>DRD5</i>	4p16.1	CT/GT/GA microsatellites	152 schizophrenia patients (81 males; mean age 34.7 years) and 81 mentally healthy individuals without family history of schizophrenia (54 males; mean age 31.8 years)	Short-term memory (reproduction of spoken words with 2 series of 10 words), long-term memory (16 words and to draw picture for each word, verbal fluency (generation of words from 2 semantic categories), attention and working memory (serial counting from 200 to 100 by 2 and 5)	<ul style="list-style-type: none"> • 2 allele 7 with lower word generation (visual voluntary attention) than 1 allele 7 in schizophrenia ($P=0.018$) and their relatives ($P=0.006$) 	Golimbet et al., 2008 (25)
<i>DBH</i>	9q34.2	5'-Ins/Del	195 DSM-IV first-episode psychosis	RBANS – Form A	<ul style="list-style-type: none"> • 19bp Del allele and Del/Del homozygous 	Hui et al., 2013 (26)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
			schizophrenia patients (drug-naïve) and 304 healthy controls		with lower immediate memory score in patients ($P<0.05$) but not in healthy controls	
		rs6271	601 Indian DSM-IV schizophrenia case-parent trios and 468 controls; 119 north Indian trio replication sample	TMT for 260 cases and 302 parents	• No association	Kukshal et al., 2013 (23)
<i>SLC18A2</i>	10q25.3	rs363399 rs363338 rs10082463 rs363285	601 Indian DSM-IV schizophrenia case-parent trios and 468 controls; 119 north Indian trio replication sample	TMT for 260 cases and 302 parents	• rs363285 with TMTB ($P=0.025$)	Kukshal et al., 2013 (23)
<i>DISC1</i>	1q42.1	rs2492367 rs6675281 rs12133766	194 DSM-IV schizophrenia patients, 164 unaffected siblings, and 307 healthy controls	WMS, CVLT, category fluency task, TASA corpus,	• rs12133766 with verbal fluency in male probands ($P=0.049$) and healthy males only ($P=0.018$)	Nicodemus et al., 2013 (6)
		rs1322784 rs2255340 rs2738864 hCV1650723 * hCV9628138 *	250 schizophrenia patients	WRAT-III, WAIS Digits Forward (auditory attention), CPT-I/P (visual attention), TMT-A & TMT-B (rapid visual search),	• rs2255340 genotype with rapid visual search ($P=0.002$) and verbal working memory ($P=0.010$), explaining 3-4% of the variance	Burdick et al., 2005 (27)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
				Digits Backward (working memory), CVLT (verbal learning), COWAT (executive functioning)		
		rs751229 rs1572899 rs1934909 rs1538976 rs4079841 rs999710 rs821597 rs821616 rs1411776	252 schizophrenia patients, 311 unaffected siblings, 368 parents, and 238 healthy controls	WMS-R, CVLT, WCST, N back, CPT, letter fluency, WAIS-R, WRAT	<ul style="list-style-type: none"> rs821616 Ser/Ser with reduced performance on WMS Logical Memory II subsection ($P=0.02$) in schizophrenia and lower WCST category scores across all diagnoses ($P=0.04$) 	Callicott et al., 2005 (28)
		rs1615409 rs766288 rs751229 rs3738401 rs6675281 rs3890280 rs1000731	236 DSM-III-R or DSM-IV schizophrenia subjects (6 MZ and 1 DZ concordant for schizophrenia, 20 MZ and 32 DZ discordant for schizophrenia, and 28 MZ and 31 DZ normal twin pairs)	WAIS-R	<ul style="list-style-type: none"> <i>DISC1-TRAX</i> haplotype with short-/long-term memory impairment and reduced gray matter density in the prefrontal cortex 	Cannon et al., 2005 (29)
		rs1073507 rs1630250 rs1615344 rs1615409	746 DSM-IV schizophrenia patients including 356 unaffected	WMS-R, CVLT, WAIS-R	<ul style="list-style-type: none"> DISC1 HEP3 (rs751229-rs3738401) haplotype with poorer 	Hennah et al., 2005 (30)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
		rs766288 rs1655285 rs1982095 rs3738398 rs751229 rs3738401 1872C/T * rs3890280 rs1000731 rs1000730 rs734551 rs1015100 rs999710 rs999709 rs999708 rs1073180 rs1073179 rs821616 2879A/G * rs1411771 5320A/G * 6070C/T * rs980989 6347A/G *	offsprings (subset of 215 families with 1437 individuals and 400 affected; 390 males; average age 50.2 years)		performance on short-term visual memory and attention	
<i>DTNBPI</i>	6p22.3	rs2619539 rs3213207 rs1011313 rs760761 rs1018381 rs2619528 rs2619522	122 DSM-IV schizophrenia patients and 119 healthy subjects	Korean version of WAIS, word fluency, TMT (TMTA and TMTB), RAVLT, CPT-DS, span of apprehension	<ul style="list-style-type: none"> • No differences between schizophrenia and controls • No interaction with cognitive measures • rs760761 ($P=0.00015$) and 	Baek et al., 2012 (31)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
					rs1018381 ($P=0.00004$) with performance of “attention/vigilance” domain after multiple testing correction whereas rs2619539 did not survive correction in combined patient and healthy subjects	
		39 tagging SNPs (1 removed after QC): rs3213207 rs2619545 rs1011313 rs2619547 rs2619528 rs2619522 rs1018381 rs1997679 rs909706 rs9476886 rs2743852 rs2619538	508 (371 males) European (>75% Anglo-Irish) DSM-IV and ICD-10 schizophrenia patients (155 with pervasive cognitive deficit and 121 with relatively spared cognition) and 172 controls (102 males)	NART, SILS, visual CPT-DS and CPT-IP, FAS version of COWAT, RAVLT, IT task, EHI	<ul style="list-style-type: none"> No association with schizophrenia diagnosis or any cognitive measures 	Peters et al., 2008 (32)
		rs2619539 rs3213207 rs2619538	52 DSM-IV schizophrenia or schizoaffective disorder patients	CANTAB, WMS, CPT, simple go/no-go task, WTAR	<ul style="list-style-type: none"> C-A-T haplotype (rs2619539-rs3213207-rs2619538) with lower spatial working memory performance 	Donohoe et al., 2007 (33)
		rs909706	183 Caucasian	WAIS-R, CPC-I/P,	<ul style="list-style-type: none"> CTCTAC risk 	Burdick et

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
		rs1018381 rs2619522 rs760761 rs2619528 rs1011313	schizophrenia or schizoaffective disorder patients	CVLT, COWAT, TMT A & B	haplotype with greater decline in IQ ($P=0.05$)	al., 2007 (34)
<i>BDNF</i>	11p13	Val66Met (rs6265)	1890 schizophrenia (972 Met carriers and 918 Val homozygotes)	MCCB (processing speed, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving), language and general intelligence (g)	<ul style="list-style-type: none"> Non-significant difference between genotype groups and most neurocognitive domains 	Ahmed et al., 2015 (35)
			194 DSM-IV schizophrenia patients, 164 unaffected siblings, and 307 healthy controls	WMS, CVLT, category fluency task, TASA corpus	<ul style="list-style-type: none"> No association 	Nicodemus et al., 2013 (6)
			657 DSM-IV schizophrenia patients and 445 healthy controls	RBANS (immediate memory, attention, language, visuospatial/constructive performance, delayed memory)	<ul style="list-style-type: none"> Cognitive test scores were significantly lower in schizophrenic than control subjects except for visuospatial/constructive index Schizophrenia Met carriers with 	Zhang et al., 2012 (36)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
					attention impairment • Val allele with better visuospatial/constructional performance in both schizophrenic and healthy subjects	
			112 antipsychotic-naïve schizophrenia patients and 63 healthy controls	WAIS-R (verbal and performance IQ), WMS-R, WCST	• Schizophrenia Met carriers showed higher percentage of WCST perseverative errors ($P=0.007$), especially in males ($P=0.014$) but no in females ($P=0.09$)	Lu et al., 2012 (37)
			51 male DSM-IV schizophrenia patients who had committed homicide, 50 male DSM-IV schizophrenia patients without homicide, and 50 healthy male controls	WAIS, RAVLT learning, RAVLT delayed recall, RAVLT delayed recognition, RCFT copy, RCFT immediate recall, RCFT delayed recall, WCST NCC, WCST perseverative responses %, WCST perseverative errors %	• No association	Chung et al., 2010 (38)
			89 schizophrenia patients, 91 unaffected relatives, and 163 controls	Voluntary and involuntary visual attention	• Val/Val genotype with higher scores of both voluntary and involuntary attention • (<i>HTR2A</i> T102C)T-	Alfimova et al., 2008 (39)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
					Met with lower scores of voluntary attention and higher scores of involuntary attention	
			119 patients with first-episode CASH (Comprehensive Assessment of Symptoms and History) diagnosis of DSM schizophrenia or schizophrenia-spectrum disorders	Verbal memory domain, speed/attention domain, problem solving domain, language domain, and visuospatial domain	<ul style="list-style-type: none"> • No association 	Ho et al., 2007 (40)
			293 DSM-IV schizophrenia patients and 144 healthy volunteers	RAV, WAIS-R	<ul style="list-style-type: none"> • Met allele carriers with poorer verbal memory performance and visuospatial impairment in schizophrenia 	Ho et al., 2006 (41)
			129 DSM-IV/ICD-10 schizophrenia patients (66 males; mean age 27 years; mean age of onset 23 years) and 111 DSM-IV/ICD-10 bipolar disorder patients (37 males; mean age 43 years;	WCST, N-back test	<ul style="list-style-type: none"> • No association with WCST • Val/Val genotype with higher correct reactions (working memory) in N-back test 	Rybakowski et al., 2006 (42)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
			mean age of onset 31 years)			
			203 schizophrenia patients and their healthy siblings, and healthy controls	WRAT reading comprehension, WAIS-R category fluency, and WCST perseverative errors	• Individuals with one or two Met allele(s) had lower abilities to perform tasks of learning and memory	Egan et al., 2003 (43)
<i>SNAP-25</i>	20p12-p11.2	<i>MnII</i> (rs3746544)	66 major psychosis patients, 75 relatives, and 136 controls	Verbal memory, attention, executive functions	• TT genotype with worse performance on most tasks	Golimbet et al., 2009 (44)
<i>PRODH</i>	22q11.21	1945T/C 1852G/A	167 Chinese Han DSM-IV first-episode schizophrenic families with 167 first-episode patients (80 males)	Stroop test, TMT (TMTA and TMTB), Tower of Hanoi, WCST-M, WAIS-R (Chinese version), WMS-R	• No association	Li et al., 2008 (45)
<i>NRG1</i>	8p12	SNP8NRG243177 SNP8NRG221533	60 DSM-IV schizophrenia patients and 60 healthy controls	EXIT, letter number span, Stroop ratio, letter cancellation, finger taps (dominant and non-dominant hands), grooved pegboard (dominant and non-dominant hands), RBANS	<ul style="list-style-type: none"> • SNP8NRG221533 and SNP8NRG243177, MAG rs2301600 and rs720309, and ERBB4 rs839523 with processing speed, visuomotor speed and attention in schizophrenia, visuomotor speed and verbal memory in controls ($P=0.02$) • SNP8NRG221533, 	Voineskos et al., 2013 (46)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
					MAG rs2301600 and rs720309 in schizophrenia with the same tasks as above ($P=0.01$)	
		478B14-848 * 420M9-1395 *	338 Russian schizophrenia patients, 162 unaffected relatives, and 316 healthy controls	Semantic verbal fluency, working and episodic memory	<ul style="list-style-type: none"> • Allele 0 of 478B14-848 with long-term episodic memory in schizophrenia • Allele 0 of 420M9-1395 with short-term memory in schizophrenia 	Alfimova et al., 2011 (47)
NRG3	10q22-q23	rs6584400	358 DSM-IV schizophrenia (214 males; average age 35.78 years) and 111 DSM-IV bipolar disorder (55 males; average age 42.30 years) patients; OPCRIT for psychotic symptoms	TMT (TMTA and TMTB), CSP-DS	<ul style="list-style-type: none"> • Minor allele with higher OPCRIT scores ($r=0.110$, $P=0.037$) in schizophrenia but not bipolar disorder ($P=0.885$) • A carriers with faster TMTA and TMTB in schizophrenia ($P<0.05$) and bipolar disorder ($P<0.05$) • Bipolar disorder faster than schizophrenia in TMTA ($P=0.001$) and TMTB ($P<0.001$) 	Meier et al., 2013 (48)
		rs6584400	411 European	Battery of	<ul style="list-style-type: none"> • No association with 	Morar et al.,

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
		rs10883866	(>75% Anglo-Irish) DSM-IV/ICD-10 schizophrenia inpatients (180 with pervasive cognitive deficit and 148 with relatively spared cognition) and 223 non-psychiatric controls	neurocognitive tests: general cognitive ability (premorbid and current IQ), learning and episodic verbal memory, executive function, speed of information processing and focused sustained attention	schizophrenia diagnosis <ul style="list-style-type: none"> • rs6584400 and delusional factors in spared cognition group (OR=1.67, 1.10-2.53, $P=0.02$) • No effect on general intelligence or verbal memory • A allele of rs6584400 ($\beta=0.523$, 95% CI 0.070-0.976, $P=0.025$) and G allele of rs10883866 ($\beta=0.687$, 95% CI 0.195-1.178, $P=0.007$) with degraded-stimulus continuous performance task and better performance in schizophrenia 	2011 (49)
<i>NRN1</i>	6p25.1	rs1475157 rs605865 rs642883 rs686628 rs9405890 rs9379002 rs4960155 rs10484320 rs3763180	508 (371 males) Australian (>75% Anglo-Irish) DSM-IV and ICD-10 schizophrenia patients (155 with pervasive cognitive deficit and 121 with relatively	SILS, WAIS-R, NART	<ul style="list-style-type: none"> • No association with schizophrenia diagnosis • G allele of rs1475157 ($P=0.005$, $P=0.047$ after multiple testing correction) with lower SILS scores in schizophrenia 	Chandler et al., 2010 (50)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
		rs582262 C-318delA * rs11285278 rs645649 rs107738 rs582186 rs3749860 rs2208870 rs17363382 rs6597175	spared cognition) and 172 controls (102 males)		<ul style="list-style-type: none"> • G allele rs9405890 ($P=0.001$, $P=0.027$ after multiple testing correction) with higher SILS scores in schizophrenia • G-A haplotype of rs1475157-rs9405890 with lower current SILS IQ ($P=0.001$) and the opposite A-G haplotype with higher IQ ($P=0.003$) 	
5HTT (<i>SLC6A4</i>)	17q11.2	HTTLPR	32 ICD-10 schizophrenia, 22 bipolar I disorder, 26 OCD, and 20 healthy individuals	Sternberg paradigm (delayed match-to-sample task), 4 tasks testing verbal and visuospatial working memory	• No association	Zilles et al., 2012 (8)
			223 schizophrenia patients	WCST, CPT	• High activity long (L) allele with better executive performances and poorer attention	Bosia et al., 2010 (51)
HTR1A	5q11.2-q13	-1019C/G (rs6295)	118 (75 males) DSM-IV schizophrenia patients and responders ($\geq 30\%$ reduction in PANSS) to one	WAIS-R, WCST, BACS, ToM Picture Sequencing Task	• CC genotype and higher ToM task score ($F=4.13$, $d.f.=2$, $P=0.019$)	Bosia et al., 2011 (52)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
			adequately dosed antipsychotic for 3 months			
HTR2A	13q14-q21	T102C (rs6313) rs6314	194 DSM-IV schizophrenia patients, 164 unaffected siblings, and 307 healthy controls	WMS, CVLT, category fluency task, TASA corpus,	<ul style="list-style-type: none"> • No association 	Nicodemus et al., 2013 (6)
		T102C (rs6313)	89 schizophrenia patients, 91 unaffected relatives, and 163 controls	Voluntary and involuntary visual attention	<ul style="list-style-type: none"> • T allele with more time for performing the test • T-(<i>BDNF</i> Val66Met)Met with lower scores of voluntary attention and higher scores of involuntary attention 	Alfimova et al., 2008 (39)
			82 DSM-IV schizophrenia patients (47 males; mean duration of illness 6.7 years)	BPRS, CPT, WCST	<ul style="list-style-type: none"> • T allele with lower hit rate in CPT • T/C genotype with more commission errors in CPT and fewer correct responses in WCST 	Uçok et al., 2007 (53)
			108 schizophrenia or schizotypic disorder patients and 97 mentally healthy individuals	Verbal fluency (details not shown)	<ul style="list-style-type: none"> • A2/A2 homozygotes with lower verbal fluency in male schizophrenia patients (N=67) 	Alfimova et al., 2003 (54)
			471 DSM-IV Chinese Han	Semantic verbal fluency (animal	<ul style="list-style-type: none"> • No association • Trend between T/C 	Chen et al., 2001 (55)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
			schizophrenia patients (334 males; mean age 42.3 years) and 523 unrelated healthy controls	category), motor co-ordination soft neurological signs examination from Cambridge Neurological Inventory, Stroop test (“colour task” and “colour-word task”), WAIS	genotype and better verbal fluency and less motor co-ordination soft neurological signs	
NET (SLC6A2)	16q12.2	1287A/G * -182T/C *	318 participants (66 DSM-IV schizophrenia or schizoaffective disorder, 94 DSM-IV bipolar disorder, and 158 healthy controls or relatives)	TMT (TMTA and TMTB), WCST	• No association	Szöke et al., 2006 (13)
		1287A/G *	124 DSM-IV schizophrenia patients (60 males; mean age 27 years; mean age at onset 23 years)	WCST	• No association	Rybakowski et al., 2006a (14)
CACNA1C	12p13.3	rs1544514	194 DSM-IV schizophrenia patients, 164 unaffected siblings, and 307 healthy controls	WMS, CVLT, category fluency task, TASA corpus,	• No association	Nicodemus et al., 2013 (6)
		rs1006737	202 Japanese	WMS-R, WAIS-R,	• A allele carriers with	Hori et al.,

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
			DSM-IV schizophrenia from a total sample of 552 patients (304 males; mean age 43.7 years) and 706 controls	WCST	worse logical memory performance in schizophrenia ($P=0.006$) but not in controls	2012 (56)
<i>LYRM4</i> <i>FARS2</i>	6p25.1	1170 tagging SNPs: rs7752203 rs4141761 rs17736905 rs2503812	507 European (>75% Anglo-Irish) DSM-IV and ICD-10 schizophrenia patients and 282 controls; independent replication sample with 288 schizophrenia cases and 172 controls	CVLT-II, RAVLT-DW	<ul style="list-style-type: none"> rs17736905 with pervasive cognitive deficit schizophrenia ($P=0.029$) and rs2503812 with RAVLT-DW ($P=0.026$) after multiple testing correction rs7752203-rs4141761 G-A haplotype with poor memory and high cognitive deficit in schizophrenia 	Jablensky et al., 2012 (57)
<i>QKI</i>	6q26	rs2784865	60 DSM-IV schizophrenia patients and 60 healthy controls	EXIT, letter number span, Stroop ratio, letter cancellation, finger taps (dominant and non-dominant hands), grooved pegboard (dominant and non-dominant hands), RBANS	<ul style="list-style-type: none"> No association 	Voineskos et al., 2013 (46)
<i>MAG</i>	19q13.1	rs756796 rs756596 rs720308 rs720309 rs2301600			<ul style="list-style-type: none"> <i>MAG</i> rs2301600 and rs720309, <i>NRG1</i> SNP8NRG221533 and SNP8NRG243177, and <i>ERBB4</i> rs839523 with processing speed, visuomotor speed and attention in 	

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
					schizophrenia, visuomotor speed and verbal memory in controls ($P=0.02$) <ul style="list-style-type: none"> • <i>MAG</i> rs2301600 and rs720309, and <i>NRG1</i> SNP8NRG221533 in schizophrenia with the same tasks as above ($P=0.01$) 	
<i>CNP</i>	17q21	rs2070106			<ul style="list-style-type: none"> • No association 	
<i>OLIG2</i>	21q22.11	rs1059004 rs9653711			<ul style="list-style-type: none"> • No association in schizophrenia 	
<i>ERBB4</i>	2q33.3-q34	rs839523			<ul style="list-style-type: none"> • <i>OLIG2</i> rs1059004 and <i>ERBB4</i> rs839253 predicting performance on tasks related to memory, language, executive function, visuospatial ability, visuomotor speed and dexterity, and working memory ($P=0.05$) only in controls 	
<i>ANK3</i>	10q21	rs10761482 rs10994336	163 first-episode schizophrenia patients (antipsychotic-naïve) and 42 healthy subjects (sex and age-	N-back task	<ul style="list-style-type: none"> • Schizophrenia patients with poorer performance than healthy controls ($P<0.01$) • rs10994336 T/T genotype with lower 	Zhang et al., 2014 (58)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
			matched)		accuracy rate and more reaction time at 2-back task in schizophrenia patients	
		rs10994336 rs1938526	173 (first-episode psychosis) DSM-IV affective (bipolar disorder, major depressive disorder with psychosis) or non-affective psychotic disorders (schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, psychosis not otherwise specified)	WMS-III (Logical Memory for verbal memory, Visual Reproduction for visual memory immediate/delayed recall and recognition, Spatial Span for working memory) WAIS-III (IQ, Digit Span for working memory, Digit Symbol for processing speed, Block Design for reasoning and problem solving), TMTA and TMTB, D2 Test of Attention concentration performance for attention	<ul style="list-style-type: none"> • Significant differences between rs1938526 genotype groups on working memory ($P=0.006$), verbal memory ($P=0.015$), and attention ($P=0.019$) • Identical pattern adding diagnosis as covariates 	Cassidy et al., 2014 (9)
<i>TCF4</i>	18q21.1	rs9960767	173 first-episode psychosis patients	MCCB, WMS-III, WAIS-III, TMT (TMTA and TMTB)	<ul style="list-style-type: none"> • C carriers with lower cognitive ability in reasoning and problem-solving ($P=0.038$) 	Albanna et al., 2014 (59)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
		rs2958182	580 ICD-10 schizophrenia patients and 498 healthy controls	WAIS-Revised including the forward and backward digit span tasks, ANT, Stroop task, DPX task, N-back task	<ul style="list-style-type: none"> • Risk (T) allele with better performance on cognitive tasks in schizophrenia patients but with worse performance in controls • Genotype and disease ($P=0.011$), attention-related tasks (WAIS: $P=0.032$; ANT: $P=0.020$; reaction time: $P=0.036$; Stroop: $P=0.032$; DPX: $P=0.002$) 	Zhu et al., 2013 (60)
CNNM2	10q24.32	rs7914558	400 schizophrenia patients and 160 healthy controls	Measures of neuropsychological function and social cognition	<ul style="list-style-type: none"> • No association • Dosage effect of risk allele with attributional style in social cognition across both schizophrenia and healthy subjects ($P<0.05$) 	Rose et al., 2014 (61)
CSMD1	8p23.2	rs10503253	378 Irish DSM-IV schizophrenia patients and 171 healthy controls; 205 German DSM-IV schizophrenia patients and 533 healthy controls	Irish: WAIS-III (11 verbal/performance subtests for vocabulary, comprehension, information, digit span, arithmetic, similarities, block	<ul style="list-style-type: none"> • Schizophrenia risk A allele with poorer performance in general cognitive ability and memory but not attentional control 	Donohoe et al., 2013 (62)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
				design, picture completion, picture arrangement, object assembly, and digit symbol coding), CPT-IP German: WMS-III (verbal and visual episodic memory with logical memory and faces subtests), CANTAB (letter number sequencing task and spatial working memory task, WMS-R (Digit Span and Spatial Span score), N-back task, CPT 3-7 version		
<i>STH</i>	17q21.1	Q7R *	343 schizophrenia patients	Brief Assessment of Cognition in Schizophrenia, WCST, CPT	<ul style="list-style-type: none"> • Significant effects on executive functions • <i>COMT</i> rs4680 $\times$ <i>STH</i> interaction on executive functions with <i>COMT</i> Val/Val and <i>STH</i> R carriers performing worse 	Bosia et al., 2014 (1)
		128A/G *	220 DSM-IV schizophrenia patients and responders ($\geq 30\%$	WCST	<ul style="list-style-type: none"> • Significant predictor of WCST performance ($P=0.007$) in 	Bosia et al., 2012 (63)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
			reduction in PANSS) to one adequately dosed antipsychotic for 3 months, 48 frontotemporal dementia patients, and 47 healthy subjects		schizophrenia patients • G allele with poor performances on WCST ($P=0.044$)	
DAOA	13q33.2	2 Affymetrix chips with ~262,000 and ~238,000 SNPs • rs1570709 • rs9586843 • rs7324448 • rs1575633 • rs7329966	178 DSM-IV schizophrenia-spectrum disorders patients (158 schizophrenia, 13 schizoaffective disorder, and 7 schizophreniform disorder) and 144 healthy controls	WRAT-III (premorbid intellectual capacity), WAIS-R (Digit Span for auditory attention and verbal working memory), CPT-Identical Pairs Version (sustained attention and vigilance), CVLT (verbal learning and memory), TMTA and TMTB (visual-motor speed and executive control)	• GCGGC carrier with better performance on semantic fluency than non-carriers regardless of disease status	Opgen-Rhein et al., 2008 (64)
		rs2391191 (M15; Arg30Lys)	93 Irish DSM-IV schizophrenia patients (from 373 cases and 812 controls)	WMS-III, CANTAB (Paired Associate Learning task, IED), CPT, N-back task, WTAR	• Arg allele with poorer episodic memory performance for immediate ($P=0.028$) and delayed recall	Donohoe et al., 2007 (65)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
					<p>($P=0.015$)</p> <ul style="list-style-type: none"> • 6.4% variance explained verbal memory performance • No differences in attentional control, working memory, and spatial memory 	
<i>ACT</i> (<i>SERPINA3</i>)	14q32.1	Ala-15Thr *	175 DSM-IV schizophrenia inpatients and 114 healthy controls	CDR, MMSE	<ul style="list-style-type: none"> • No difference between schizophrenia and control • No significant difference with cognitive impairment 	Chiu et al., 1999 (66)
<i>EPO</i>	7q22.1	rs1617640 rs564449	1054 DSM-IV schizophrenia or schizoaffective disorder patients and 1142 healthy controls	MMSE, Digit Symbol-Coding (Zahlen-Symbol-Test), WAIS, Dotting and Tapping from Mac-Quarrie Test for Mechanical Ability, VLMT	<ul style="list-style-type: none"> • Carriers of <i>EPO</i> rs1617640 and <i>EPOR</i> STR(GA)n low repeat sum showed superior performance in cases • No differences for <i>EPOR</i> STR(GA)n in healthy controls 	Kästner et al., 2012 (67)
<i>EPOR</i>	19p13.2	STR(GA)n			<ul style="list-style-type: none"> • 	
(<i>WWC1</i>) <i>KIBRA</i>	5q34	rs17070145	544 (166 probands with schizophrenia or bipolar disorder, 201 unaffected relatives, and 177 healthy controls)	WMS-R for episodic memory, immediate and delayed logical memory and immediate and delayed visual reproduction	<ul style="list-style-type: none"> • No association • Nominal significant for both immediate and delayed logical memory in unaffected relatives ($P=0.020$) and 	Vassos et al., 2010 (68)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
					healthy controls only ($P=0.025$) • Trend for delayed visual memory in patients ($P=0.05$)	
<i>ATP2C2</i>	16q24.1	rs2303853	194 DSM-IV schizophrenia patients, 164 unaffected siblings, and 307 healthy controls	WMS, CVLT, category fluency task, TASA corpus	• No association	Nicodemus et al., 2013 (6)
<i>DCDC2</i>	6p22.1	rs2274305			• No association	
<i>DYX1C1</i>	15q21.3	rs600753			• No association	
<i>KIAA0319</i>	6p22.3-p22.2	rs807534 rs807541 rs4576240			• rs807534 with verbal learning and recall in female siblings ($P=0.041$) and healthy females only ($P=0.032$)	
<i>NAGPA</i>	16p13.3	rs887854			• No association	
<i>CLSTN2</i>	3q23	rs17348572 rs7632885 rs10804675			• No association	
<i>WWC1 (KIBRA)</i>	5q34	rs17551608 rs3822659 rs3733980 rs3203960			• No association	
<i>ATRNL1</i>	10q26	rs10885721			• No association	
<i>C20orf196</i>	20p12.3	rs1699233			• No association	
<i>CRTC3</i>	15q26.1	rs8033595			• No association	
<i>DIP2C</i>	10p15.3	rs3740304 rs2288681			• No association	
<i>NFKBIL1</i>	6p21.3	rs2230365			• No association	
<i>PDE1C</i>	7p14.3	rs3213709 rs2302450 rs1860790			• No association	

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
<i>PKNOX1</i>	21q22.3	rs234781			• No association	
<i>SPATA7</i>	14q31.3	rs3179969			• No association	
<i>ZNF804A</i>	2q32.1	rs1366842 rs12477430	194 DSM-IV schizophrenia patients, 164 unaffected siblings, and 307 healthy controls	WMS, CVLT, category fluency task, TASA corpus	• rs1366842 with verbal learning and recall in male probands ($P=0.033$) and healthy males only ($P=0.042$)	Nicodemus et al., 2013 (6)
		rs1344706	418 schizophrenia or schizoaffective disorder patients and 200 healthy controls	Theory of Mind with “Eyes of the Mind” task and “Hinting task”, attributional style with “Interpersonal social attributions questionnaire”	• No association for Theory of Mind • A allele carriers with higher personalizing bias in controls	Hargreaves et al., 2012 (69)
			113 DSM-IV schizophrenia patients and 184 healthy controls	WMS-R for verbal memory, visual memory, attention and concentration, and delayed recall	• Diagnosis with verbal memory ($P<0.001$), visual memory ($P<0.001$), attention and concentration ($P<0.001$), and delayed recall ($P<0.001$) • Diagnosis-genotype interaction with visual memory ($P=0.0048$) • Schizophrenia patients with lower scores on all memory	Hashimoto et al., 2010 (70)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
					<p>indices than controls</p> <ul style="list-style-type: none"> • Genotype effect in schizophrenia patients ($P=0.018$) but not in controls • T/T genotype with significantly lower performance on visual memory than T/G ($P=0.0046$) in schizophrenia patients 	
			2 independent samples: 297 Irish DSM-IV schizophrenia patients and 165 controls, 251 German DSM-IV schizophrenia patients and up to 1472 controls	<p>Irish: WAIS-III for general cognitive functioning (IQ), WMS-III for episodic memory, WMS-III and CANTAB for verbal and spatial working memory, and CPT for vigilant attention</p> <p>German: WAIS-R for IQ, WMS-R for verbal and visual episodic memory, WAIS-R and WMS-R for working memory, and CPT for vigilant attention</p>	<ul style="list-style-type: none"> • Irish: AA genotype with better verbal ($P=0.046$) and spatial ($P=0.045$) working memory, AA and AC genotypes with better verbal episodic memory (AA: $P=0.01$; AC: $P=0.02$) in schizophrenia patients • German: AA genotype with better performance on above tests 	Walters et al., 2010 (71)
<i>ADCY8</i>	8p24	rs12545028	194 DSM-IV schizophrenia	WMS, CVLT, category fluency	<ul style="list-style-type: none"> • No association 	Nicodemus et al., 2013

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
			patients, 164 unaffected siblings, and 307 healthy controls	task, TASA corpus		(6)
		rs263249	336 European (>75% Anglo-Irish; 80% males; mean age 33.9 years; mean length of illness 9.8 years) DSM-IV and ICD-10 schizophrenia patients and 172 normal (59% males; mean age 40.7 years) controls	NART, SILS, WAIS-R, CPT-DS, CPT-IP, FAS version of COWAT, RAVLT, IT task	<ul style="list-style-type: none"> • No association 	Jablensky et al., 2011 (72)
GRIN2B	12p12	rs3026160	194 DSM-IV schizophrenia patients, 164 unaffected siblings, and 307 healthy controls	WMS, CVLT, category fluency task, TASA corpus	<ul style="list-style-type: none"> • No association 	Nicodemus et al., 2013 (6)
		rs12828473 rs220599	336 European (>75% Anglo-Irish; 80% males; mean age 33.9 years; mean length of illness 9.8 years) DSM-IV and ICD-10	NART, SILS, WAIS-R, CPT-DS, CPT-IP, FAS version of COWAT, RAVLT, IT task	<ul style="list-style-type: none"> • rs220599 T allele with poorer immediate and delayed recall (RAVLT) ($P=0.008-0.02$) 	Jablensky et al., 2011 (72)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
			schizophrenia patients and 172 normal (59% males; mean age 40.7 years) controls			
CAMK2G	10q22	rs2675671	194 DSM-IV schizophrenia patients, 164 unaffected siblings, and 307 healthy controls	WMS, CVLT, category fluency task, TASA corpus	• No association	Nicodemus et al., 2013 (6)
		rs11000787	336 European (>75% Anglo-Irish; 80% males; mean age 33.9 years; mean length of illness 9.8 years) DSM-IV and ICD-10 schizophrenia patients and 172 normal (59% males; mean age 40.7 years) controls	NART, SILS, WAIS-R, CPT-DS, CPT-IP, FAS version of COWAT, RAVLT, IT task	• No association	Jablensky et al., 2011 (72)
GRM3	7q21.1-q21.2	rs2189814 rs6465084	336 European (>75% Anglo-Irish; 80% males; mean age 33.9 years; mean length of illness 9.8	NART, SILS, WAIS-R, CPT-DS, CPT-IP, FAS version of COWAT, RAVLT, IT task	• rs2189814 C allele with enhanced performance ($P=0.007$),	Jablensky et al., 2011 (72)
PRKACG	9q13	rs3730386	years; mean length of illness 9.8		• No association	
GRIN2A	16p13.2	rs1868291			• No association	

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
<i>PRKCA</i>	17q22-q23.2	rs8074995	years) DSM-IV and ICD-10 schizophrenia patients and 172 normal (59% males; mean age 40.7 years) controls		<ul style="list-style-type: none"> rs8074995 with RAVLT ($P=0.02$) 	
<i>RGS4</i>	1q23.3	rs10917670 rs951436 rs951439 rs28757216 rs28757217 rs6427711 rs2661319 rs10799897 rs10759	37 multiplex, multigenerational Caucasian families with DSM-IV schizophrenia (at least 2 affected first-degree relatives, 16% with schizophrenia diagnosis)	Computerized neurocognitive battery (Penn Conditional Exclusion Test for abstraction and mental flexibility, Penn Continuous Performance Test for attention, Penn Word Memory Test for verbal memory, Penn Face Memory Test for face memory, Visual Object Learning Test for spatial memory, Judgment of Line Orientation for spatial processing, Emotion Intensity Discrimination Test for emotion)	<ul style="list-style-type: none"> rs10917670 with face and verbal memory speed ($P=0.0003$) in the total sample 	Prasad et al., 2010 (73)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
				processing, and clicking progressively smaller squares for sensorimotor dexterity		
<i>NOS1</i>	12q24.22	rs6490121	2 independent samples: 349 Irish DSM-IV schizophrenia patients and 230 controls, 232 German DSM-IV schizophrenia patients and 1344 controls	Irish: WAIS-III for general cognitive functioning (IQ), WMS-III for verbal and visual episodic memory, WMS-III and CANTAB-Expedio Version for verbal and spatial working memory, and CPT for attentional control German: WAIS-R for IQ, WMS-R for verbal and visual episodic memory, WMS-R and N-back task for verbal and spatial working memory, and CPT for attentional control	<ul style="list-style-type: none"> • GG genotype with poorer verbal IQ in both Irish ($P=0.04$) and German ($P=0.01$) cases and controls • GG genotype with poorer verbal ($P<0.001$) and spatial ($P=0.008$) working memory in Irish controls but not in patients • Significant association between working memory score in patients ($P=0.005$) but not in controls 	Donohoe et al., 2009 (74)
<i>MTHFR</i>	1p36.22	rs1801133 (C677T)	90 DSM-IV schizophrenia patients and 55 healthy controls	CANTAB: Motor Control, Pattern Recognition Memory and Spatial	<ul style="list-style-type: none"> • <i>MTHFR</i> $\times$ <i>COMT</i> rs4680 interaction on spatial working memory ($P=0.048$) 	Kontis et al., 2013 (4)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
				Recognition Memory, Intra-Extra Dimensional Set Shifting Task, Stockings of Cambridge, Spatial Working Memory, WAIS-III to assess IQ	and planning ($P=0.026$) in cases and controls <ul style="list-style-type: none"> • <i>COMT</i> Val/Val and <i>MTHFR</i> C/C individuals with more spatial working memory errors ($P=0.033$) and solving fewer Stockings of Cambridge problems ($P=0.025$) in both groups • <i>COMT</i> $\times$ <i>MTHFR</i> interaction with IQ ($P=0.035$), worse performance with <i>COMT</i> Met carriers and <i>MTHFR</i> T carriers ($P=0.021$) 	
46 Candidate Genes: <i>RGS4</i> , <i>NRG1</i> , <i>DTNBPI</i> , <i>PIP5K2A</i> , <i>G72/DAOA</i> , <i>DISC1</i> , <i>HT2A</i> , <i>AKT1</i> , <i>LRRTM1</i> ,	Candidate genes	152 SNPs in 43 genes (quality controlled from 179 SNPs)	1120 patients with DSM-IV non-affective psychotic disorder, 1057 siblings, 919 parents and their siblings, and 590 unrelated controls	WAIS-III (Digit Symbol Coding for processing speed, CPT-HQ for attention/vigilance, Word Learning Task for verbal learning and memory) WAIS-III Arithmetic for working memory,	<ul style="list-style-type: none"> • <i>DRD1</i> rs265981 allele G ($P=0.010$), <i>DRD3</i> rs6280 allele C ($P=0.031$), <i>SLC6A3</i> rs456082 allele C, rs463379 allele G, rs464049 allele C, <i>BDNF</i> rs988748 allele G, <i>FGF2</i> rs7700205 allele C, <i>SLC18A2</i> 	Simons et al., 2013 (75)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
<i>FGF2,</i> <i>FGFR1,</i> <i>GPM6A,</i> <i>PRODH,</i> <i>GRM3,</i> <i>GABRA6,</i> <i>GAD1,</i> <i>NOS1,</i> <i>RGS2,</i> <i>ROBO1,</i> <i>CHRM3,</i> <i>TBX1,</i> <i>COMT,</i> <i>ANKK1,</i> <i>DRD1,</i> <i>DRD2,</i> <i>DRD3,</i> <i>SLC6A3,</i> <i>PPP1R1B,</i> <i>SLC18A2,</i> <i>CNR1,</i> <i>ADRA2C,</i> <i>FKBP5,</i> <i>BDNF,</i> <i>P2RX7, NPY,</i> <i>NQO1, GST-1,</i> <i>GST-2,</i> <i>MTHFR,</i> <i>MTR,</i> <i>MTRR,</i> <i>DNMT3B,</i> <i>EHMT1,</i>				WAIS-III Block Design for reasoning and problem solving, Reponse-Shifting Task for set shifting (modified version of Competing Programs Task), WAIS-III Information (verbal comprehension)	rs363393 allele A, rs363338 allele C, rs363227 allele T, <i>FKBP5</i> rs1334894 allele G, <i>DNMT3B</i> rs2424913 allele T, and rs406193 allele C with worse cognitive performance in patients • <i>SLC18A2</i> rs363227 allele T with poorer cognitive functioning in siblings ($P=0.04$)	

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
<i>EHMT2</i> , <i>PRDM2</i>						
94 Candidate Genes	Candidate genes	1,536 single-nucleotide polymorphism custom-made array	534 individuals from 130 families (DSM-IV schizophrenia)	University of Pennsylvania Computerized Neurocognitive Battery	<ul style="list-style-type: none"> Multiple significant associations with cognitive domains including continuous performance (i.e., <i>DISC1</i>, <i>GRM1</i>), letter-number span (i.e., <i>DISC1</i>, <i>ERBB4</i>, <i>HTR2A</i>), verbal learning (i.e., <i>ERBB4</i>, <i>HTR1A</i>, <i>GRM1</i>, <i>NRG1</i>, <i>SLC1A2</i>, <i>GRIN2B</i>, <i>COMT</i>), abstraction (i.e., <i>ERBB4</i>, <i>NRG1</i>, <i>SLC1A2</i>), face memory (i.e., <i>ERBB4</i>, <i>5HTT</i>, <i>GRM1</i>, <i>COMT</i>), spatial memory (i.e., <i>ERBB4</i>, <i>GRM1</i>, <i>SLC1A2</i>), and spatial processing (i.e., <i>5HTT</i>, <i>GRM1</i>, <i>NRG1</i>, <i>HTR2A</i>) 	Greenwood et al., 2011 (76)
GWAS • <i>SCN2A</i>	Whole genome • 2q24.3	GWAS • rs10174400 • rs10182570	Discovery cohort: 339 DSM-IV schizophrenia patients and 363 community control	WAIS, verbal memory, visual memory, N-back, processing speed, card sorting,	<ul style="list-style-type: none"> rs10174400 ($P=9.27 \times 10^{-10}$) and rs10182570 ($P=2.56 \times 10^{-9}$) with cognitive ability 	Dickinson et al. 2014 (77)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
			individuals Full sibling sample: 147 sibling pairs	working memory span, and cognitive ability		
GWAS • HEY1	Whole genome	~1 million SNPs (Illumina HumanHap550v3, HumanExon510Sv1 , Human1Mv1, and Human1M-Duov3 BeadChips)	1,269 Mexican American individuals from extended pedigrees (75 families; 37% males; mean age 44.78 years) with 33% life-time depression, 18% recurrent depression, 19% anxiety disorders, 2% hypomania, 0.5% dysthymia, 32% alcohol disorders, 13% substance disorders, 0.7% schizoaffective disorders, and 0.5% schizophrenia	WASI, TMTA, TMTB, letter fluency, facial memory, digit span backwards and forwards, digit symbol memory, CVLT learn, CVLT delay, category fluency, emotion recognition, CPT false alarms, CPT hits, SCAP, CVLT semantic	<ul style="list-style-type: none"> rs723686 (chromosome 8q21.13) with working memory ability in schizophrenia and schizophrenia risk ($P=0.00728$) 	Knowles et al., 2014 (78)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
<i>GWAS meta-analysis</i> • <i>MIR137</i> • <i>MPC2</i> • <i>SDCCAG8</i> • <i>ZNF804A</i> • <i>PCGEM1</i> • <i>ZSWIM6</i> • <i>MAD1L1</i> • <i>CSMD1</i> • <i>LSM1</i> • <i>CNNM2</i> • <i>NT5C2</i> • <i>NRGN</i> • <i>TCF4</i>	Whole genome • 1-21.3 • 1q24.2 • 1q43 • 2q32.1 • 2q32.3 • 5q12.1 • 7p22.3 • 8p23.2 • 8p11.23 • 10q24.32 • 10q24.33 • 11q24.2 • 18q21.2	~900 K SNPs (Affymetrix 6.0) and ~770 K SNPs (Illumina 610 K or Illumina OmniExpress) • rs1625579 • rs10489202 • rs6703335 • rs1344706 • rs17662626 • rs7709645 • rs12666575 • rs10503253 • rs16887244 • rs7914558 • rs1191580 • rs12807809 • rs12966547	5446 (primarily European-American) schizophrenia individuals and 5830 controls (meta-analysis)	MMSE, WAIS-R, CANTAB, N-back task, WCST, Stroop Interference Test, Iowa Gambling Task, WMS, WISC-III, CVLT-II, D-KEFS, RCFT, WASI, Alice Heim 4, Mill Hill Vocabulary A and B, Cattell and Cattell Cultural Fair intelligence tests, Finnish Defesnse Forces Basic Ability Test battery, MCCB (BACS, TMTA, CPT-IP, HVLt-R, BVMT-R, NAB, MSCEIT)	• No genome-wide significance • Schizophrenia patients with lower general cognitive ability than healthy controls • <i>MAD1L1</i> rs12666575 ($P=0.032$) and <i>CNNM2</i> rs7914558 ($P=0.040$) schizophrenia risk alleles with lower cognitive ability • <i>LSM1</i> rs16887244 ($P=0.017$) and <i>NRGN</i> rs12807809 ($P=0.040$) schizophrenia risk allele with higher cognitive ability	Lencz et al., 2014 (79)
<i>GWAS</i>	Whole genome	554,225 SNPs (Illumina Human 610-Quad BeadChip)	>9600 schizophrenia patients, >8,000 bipolar disorder patients, and 670 healthy Norwegian subjects (independent	WASI, CVLT-II, D-KEFS, Cued Discrimination Task	• Strongest genetic enrichments for performance in a colour-interference test and sets associated with memory learning slope	Fernandes et al., 2013 (80)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
			sample)			
<i>CAM Pathway HLA-DQA1</i>	Whole genome enrichment	GWAS • rs9272105	424 DSM-IV psychotic patients (schizophrenia, schizoaffective disorder, bipolar disorder, major depressive disorder with psychotic features, or psychosis not otherwise specified)	WTAR, WAIS-III, WMS-III, CANTAB (Paired Associate Learning Task, Spatial Working Memory Task), CPT-IP, SART	<ul style="list-style-type: none"> Increased CAM pathway polygenic risk scores with poorer performance on measures of memory and attention <i>HLA-DQA1</i> rs9272105 (strongest signal) with attentional control but not memory 	Hargreaves et al., 2013 (81)
<i>GWAS</i> <ul style="list-style-type: none"> <i>RASGRF2</i> <i>PLCG2</i> <i>LMO1</i> <i>CSMD1</i> <i>PRKG1</i> 	Whole genome	HumanHap660 Bead Array <ul style="list-style-type: none"> rs401758 rs7185362 rs484161 rs2469383 rs7898516 	98 chronic schizophrenia patients and 60 matched controls	Memory cognition (details in Chinese)	<ul style="list-style-type: none"> <i>RASGRF2</i> rs401758 ($P=8.03 \times 10^{-5}$), <i>PLCG2</i> rs7185362 ($P=4.54 \times 10^{-5}$), <i>LMO1</i> rs484161 ($P=9.80 \times 10^{-7}$), <i>CSMD1</i> rs2469383 ($P=2.77 \times 10^{-6}$), and <i>PRKG1</i> rs7898516 ($P=6.94 \times 10^{-5}$) 	Xiang et al., 2012 (82)

* rs number not available.

Abbreviations for genes: serotonin transporter (*5HTT*), alpha-1-antichymotrypsin (*ACT*, also known as serine proteinase inhibitor 3 [*SERPINA3*]), adenylate cyclase (*ADCY8*), adrenoceptor alpha 2C (*ADRA2C*), v-akt murine thymoma viral oncogene homolog 1 (*AKT1*), ankyrin 3 (*ANK3*), ankyrin repeat and kinase domain containing 1 (*ANKK1*), ATPase, Ca⁺⁺ transporting, type 2C, member 2 (*ATP2C2*), attractin-like 1 (*ATRNL1*), brain-derived neurotrophic factor (*BDNF*), chromosome 20 open reading frame 196 (*C20orf196*), calcium channel, voltage-dependent, L type, alpha 1C (*CACNA1C*), cell adhesion molecules (CAM), calcium/calmodulin-dependent protein kinase II gamma (*CAMK2G*), cholinergic receptor, muscarinic 3 (*CHRM3*), calsyntenin 2 (*CLSTN2*), cyclin M2 (*CNNM2*), 2',3'-cyclic nucleotide 3'-phosphodiesterase (*CNP*), cannabinoid receptor 1 (brain) (*CNR1*),

catechol-O-methyltransferase (*COMT*), CREB regulated transcription coactivator 3 (*CRTC3*), CUB and Sushi multiple domains 1 (*CSMD1*), D-amino acid oxidase activator (*DAOA*), dopamine transporter (*DAT*, also known as *SLC6A3*), dopamine beta-hydroxylase (*DBH*), doublecortin domain containing 2 (*DCDC2*), DIP2 disco-interacting protein 2 homolog C (Drosophila) (*DIP2C*), disrupted in schizophrenia 1 (*DISC1*), DNA (cytosine-5)-methyltransferase 3 beta (*DNMT3B*), dopamine D1 receptor (*DRD1*), dopamine D2 receptor (*DRD2*), dopamine D3 receptor (*DRD3*), dopamine D4 receptor (*DRD4*), dopamine D5 receptor (*DRD5*), dystrobrevin binding protein 1 (*DTNBPI*), dyslexia susceptibility 1 candidate 1 (*DYX1C1*), euchromatic histone-lysine N-methyltransferase 1 (*EHMT1*), euchromatic histone-lysine N-methyltransferase 2 (*EHMT2*), erythropoietin (*EPO*), erythropoietin receptor (*EPOR*), v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 4 (*ERBB4*), phenylalanyl-tRNA synthetase 2, mitochondrial (*FARS2*), fibroblast growth factor 2 (basic) (*FGF2*), fibroblast growth factor receptor 1 (*FGFR1*), FK506 binding protein 5 (*FKBP5*), gamma-aminobutyric acid (GABA) A receptor, alpha 6 (*GABRA6*), glutamate decarboxylase 1 (brain, 67kDa) (*GADI*), glycoprotein M6A (*GPM6A*), glutamate receptor, ionotropic, N-methyl-D-aspartate, subunit 2A (*GRIN2A*), glutamate receptor, ionotropic, N-methyl-D-aspartate, subunit 2B (*GRIN2B*), glutamate receptor, metabotropic, 3 (*GRM3*), glutathione S-transferase-1 (*GST-1*), glutathione S-transferase (*GST-2*), hairy/enhancer-of-split related with YRPW motif 1 (*HEY1*), human leukocyte antigen (*HLA*), serotonin 1A receptor (*HTR1A*), serotonin 2A receptor (*HTR2A*), LIM domain only 1 (*LMO1*), leucine rich repeat transmembrane neuronal 1 (*LRRTM1*), LSM1 homolog, U6 small nuclear RNA associated (*LSM1*), MAD1 mitotic arrest deficient-like 1 (*MAD1L1*), myelin-associated glycoprotein (*MAG*), MicroRNA 137 (*MIRN137*), mitochondrial pyruvate carrier 2 (*MPC2*), methylenetetrahydrofolate reductase (NAD(P)H) (*MTHFR*), 5-methyltetrahydrofolate-homocysteine methyltransferase (*MTR*), 5-methyltetrahydrofolate-homocysteine methyltransferase reductase (*MTRR*), N-acetylglucosamine-1-phosphodiester alpha-N-acetylglucosaminidase (*NAGPA*), norepinephrine transporter (*NET*, also known as *SLC6A2*), nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor-like 1 (*NFKBIL1*), nitric oxide synthase 1 (neuronal) (*NOS1*), neuropeptide Y (*NPY*), NAD(P)H dehydrogenase, quinone 1 (*NQO1*), neuregulin 1 (*NRG1*), neuregulin 3 (*NRG3*), neurogranin (protein kinase C substrate, RC3) (*NRGN*), neuritin 1 (*NRN1*), 5'-nucleotidase, cytosolic II (*NT5C2*), oligodendrocyte lineage transcription factor 2 (*OLIG2*), purinergic receptor P2X, ligand-gated ion channel, 7 (*P2RX7*), prostate-specific transcript (non-protein coding) (*PCGEM1*), phosphatidylinositol-5-phosphate 4-kinase, type II, alpha (*PIP4K2A*), PBX/knotted 1 homeobox 1 (*PKNOX1*), phospholipase C, gamma 2 (*PLCG2*), protein phosphatase 1, regulator (inhibitor) subunit 1B (*PPP1R1B*), PR domain containing 2, with ZNF domain (*PRDM2*), protein kinase, cAMP-dependent, catalytic, gamma (*PRKACG*), protein kinase C, alpha (*PRKCA*), protein kinase, cGMP-dependent, type 1 (*PRKG1*), proline dehydrogenase (oxidase) 1 (*PRODH*), quaking (*QKI*), Ras-specific guanine nucleotide-releasing factor 2 (*RASGRF2*), regulator of G-protein signalling 2, 24kDa (*RGS2*), regulator of G-protein signalling 4 (*RGS4*), roundabout, axon guidance receptor, homolog 1 (Drosophila) (*ROBO1*), sodium channel, voltage-gated, type II, alpha subunit (*SCN2A*), serologically defined colon cancer antigen 8 (*SDCCAG8*), vesicular monoamine transporter 2 (*SLC18A2*), zinc finger, spermatogenesis associated 7 (*SPATA7*), saitohein (*STH*), synaptosomal-associated protein 25 (*SNAP-25*), T-box 1 (*TBX1*), transcription factor 4 (*TCF4*), translin-associated factor X (*TRAX*), SWIM-type containing 6 (*ZSWIM6*).

Abbreviations for tests: American National Adult Reading Test (ANART), Brief Assessment of Cognition in Schizophrenia (BACS), Brief Visuospatial Memory Test-Revised (BVM-T-R), California Verbal Learning Test (CVLT), Cambridge Automated Test Battery (CANTAB), Clinical Dementia Rating Scale (CDR), confidence interval (CI), Controlled Oral Word Association Task (COWAT), Continuous Performance Task (CPT), CPT-Degraded Stimulus (CPT-DS), CPT-Identical Pairs (CPT-IP), Delis-Kaplan Executive Function System (D-KEFS), Edinburgh Handedness Inventory (EHI), Executive Interview (EXIT), Hopkins Verbal Learning Test-Revised (HVLT-R), F, A, S letters verbal fluency test (FAS), Intra-Extra Dimensional Set Shifting Task (IED), Inspection Time (IT), Letter Number Sequencing (LNS), Operational Criteria Checklist for Psychotic Illness (OPCRIT), NIMH Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB), Mini-Mental Status Examination (MMSE), Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT), Neuropsychological Assessment Battery (NAB), National Adult Reading Test-revised (NART), Neurological Evaluation Scale (NES), Positive and Negative Syndrome Scale (PANSS), quality control (QC), Rey Auditory Verbal Learning Test (RAVLT), RAVLT-Delayed Word recall (RAVLT-DW), Repeatable Battery for Assessment of Neuropsychological Status (RBANS), Rey Complex Figure Test (RCFT), Theory of Mind (ToM), Sustained Attention to Response Task (SART), Social Cognitive Assessment Profile (SCAP), Shipley Institute of Living Scale (SILS), standard rehabilitation treatment (SRT), Touchstone Applied Science Associates, Inc. (TASA), Spanish version of the California Verbal Learning Test (TAVEC), Trail Making Test (TMT), Verbaler Lern- und Merkfähigkeitstest (VLMT), Wechsler Adult Intelligence Scale (WAIS), Wechsler Adult Intelligence Scale-Revised (WAIS-R), Wechsler Abbreviated Scale of Intelligence (WASI), Wechsler Memory Scale (WMS), Wechsler Intelligence Scale for Children (WISC), WMS-Revised (WMS-R), Wechsler Test of Adult Reading (WTAR), Wisconsin Card Sorting Test (WCST).

References:

1. Bosia M, Pigoni A, Pirovano A, Lorenzi C, Spangaro M, Buonocore M, et al. COMT and STH polymorphisms interaction on cognition in schizophrenia. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*. 2014.
2. Twamley EW, Hua JP, Burton CZ, Vella L, Chinh K, Bilder RM, et al. Effects of COMT genotype on cognitive ability and functional capacity in individuals with schizophrenia. *Schizophrenia research*. 2014.
3. Green MJ, Chia TY, Cairns MJ, Wu J, Tooney PA, Scott RJ, et al. Catechol-O-methyltransferase (COMT) genotype moderates the effects of childhood trauma on cognition and symptoms in schizophrenia. *Journal of psychiatric research*. 2014;49:43-50.
4. Kontis D, Theochari E, Fryssira H, Kleisas S, Sofocleous C, Andreopoulou A, et al. COMT and MTHFR polymorphisms interaction on cognition in schizophrenia: an exploratory study. *Neuroscience letters*. 2013;537:17-22.
5. Lopez-Garcia P, Young Espinoza L, Molero Santos P, Marin J, Ortuno Sanchez-Pedreno F. Impact of COMT genotype on cognition in schizophrenia spectrum patients and their relatives. *Psychiatry research*. 2013;208(2):118-24.

6. Nicodemus KK, Elvevag B, Foltz PW, Rosenstein M, Diaz-Asper C, Weinberger DR. Category fluency, latent semantic analysis and schizophrenia: a candidate gene approach. *Cortex; a journal devoted to the study of the nervous system and behavior*. 2013.
7. Alfimova MV, Golimbet VE, Korovaitseva GI, Aksenova EV, Lezheiko TV, Abramova LI, et al. [The association of COMT and DRD2 gene polymorphisms with a cognitive ability to understand others in schizophrenic patients]. *Zhurnal nevrologii i psikiatrii imeni SS Korsakova / Ministerstvo zdravookhraneniia i meditsinskoi promyshlennosti Rossiiskoi Federatsii, Vserossiiskoe obshchestvo nevrologov [i] Vserossiiskoe obshchestvo psikiat*. 2013;113(8):50-6.
8. Zilles D, Meyer J, Schneider-Axmann T, Ekawardhani S, Gruber E, Falkai P, et al. Genetic polymorphisms of 5-HTT and DAT but not COMT differentially affect verbal and visuospatial working memory functioning. *European archives of psychiatry and clinical neuroscience*. 2012;262(8):667-76.
9. Bombin I, Arango C, Mayoral M, Castro-Fornieles J, Gonzalez-Pinto A, Gonzalez-Gomez C, et al. DRD3, but not COMT or DRD2, genotype affects executive functions in healthy and first-episode psychosis adolescents. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 2008;147B(6):873-9.
10. Barnett JH, Jones PB, Robbins TW, Muller U. Effects of the catechol-O-methyltransferase Val158Met polymorphism on executive function: a meta-analysis of the Wisconsin Card Sort Test in schizophrenia and healthy controls. *Molecular psychiatry*. 2007;12(5):502-9.
11. Bosia M, Bechi M, Marino E, Anselmetti S, Poletti S, Cocchi F, et al. Influence of catechol-O-methyltransferase Val158Met polymorphism on neuropsychological and functional outcomes of classical rehabilitation and cognitive remediation in schizophrenia. *Neuroscience letters*. 2007;417(3):271-4.
12. Alfimova MV, Golimbet VE, Gritsenko IK, Lezheiko TV, Abramova LI, Strel'tsova MA, et al. [Dopamine system genes interaction and neurocognitive traits in patients with schizophrenia, their relatives and healthy controls from general population]. *Zhurnal nevrologii i psikiatrii imeni SS Korsakova / Ministerstvo zdravookhraneniia i meditsinskoi promyshlennosti Rossiiskoi Federatsii, Vserossiiskoe obshchestvo nevrologov [i] Vserossiiskoe obshchestvo psikiat*. 2006;106(7):57-63.
13. Szoke A, Schurhoff F, Meary A, Mathieu F, Chevalier F, Trandafir A, et al. Lack of influence of COMT and NET genes variants on executive functions in schizophrenic and bipolar patients, their first-degree relatives and controls. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 2006;141B(5):504-12.
14. Rybakowski JK, Borkowska A, Czerski PM, Dmitrzak-Weglarz M, Skibinska M, Kapelski P, et al. Performance on the Wisconsin Card Sorting Test in schizophrenia and genes of dopaminergic inactivation (COMT, DAT, NET). *Psychiatry research*. 2006;143(1):13-9.
15. Ho BC, Wassink TH, O'Leary DS, Sheffield VC, Andreasen NC. Catechol-O-methyl transferase Val158Met gene polymorphism in schizophrenia: working memory, frontal lobe MRI morphology and frontal cerebral blood flow. *Molecular psychiatry*. 2005;10(3):229, 87-98.

16. Galderisi S, Maj M, Kirkpatrick B, Piccardi P, Mucci A, Invernizzi G, et al. COMT Val(158)Met and BDNF C(270)T polymorphisms in schizophrenia: a case-control study. *Schizophrenia research*. 2005;73(1):27-30.
17. Nolan KA, Bilder RM, Lachman HM, Volavka J. Catechol O-methyltransferase Val158Met polymorphism in schizophrenia: differential effects of Val and Met alleles on cognitive stability and flexibility. *The American journal of psychiatry*. 2004;161(2):359-61.
18. Rosa A, Peralta V, Cuesta MJ, Zarzuela A, Serrano F, Martinez-Larrea A, et al. New evidence of association between COMT gene and prefrontal neurocognitive function in healthy individuals from sibling pairs discordant for psychosis. *The American journal of psychiatry*. 2004;161(6):1110-2.
19. Goldberg TE, Egan MF, Gscheidle T, Coppola R, Weickert T, Kolachana BS, et al. Executive subprocesses in working memory: relationship to catechol-O-methyltransferase Val158Met genotype and schizophrenia. *Archives of general psychiatry*. 2003;60(9):889-96.
20. Joober R, Gauthier J, Lal S, Bloom D, Lalonde P, Rouleau G, et al. Catechol-O-methyltransferase Val-108/158-Met gene variants associated with performance on the Wisconsin Card Sorting Test. *Archives of general psychiatry*. 2002;59(7):662-3.
21. Bilder RM, Volavka J, Czobor P, Malhotra AK, Kennedy JL, Ni X, et al. Neurocognitive correlates of the COMT Val(158)Met polymorphism in chronic schizophrenia. *Biological psychiatry*. 2002;52(7):701-7.
22. Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE, et al. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America*. 2001;98(12):6917-22.
23. Kukshal P, Kodavali VC, Srivastava V, Wood J, McClain L, Bhatia T, et al. Dopaminergic gene polymorphisms and cognitive function in a north Indian schizophrenia cohort. *Journal of psychiatric research*. 2013;47(11):1615-22.
24. Szekeres G, Keri S, Juhasz A, Rimanoczy A, Szendi I, Czimmer C, et al. Role of dopamine D3 receptor (DRD3) and dopamine transporter (DAT) polymorphism in cognitive dysfunctions and therapeutic response to atypical antipsychotics in patients with schizophrenia. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 2004;124B(1):1-5.
25. Golimbet VE, Alfimova MV, Gritsenko IK, Lezheiko TV, Ebstein R. Association of dopamine receptor D5 gene polymorphism with peculiarities of voluntary attention in schizophrenic patients and their relatives. *Bulletin of experimental biology and medicine*. 2008;145(1):65-7.
26. Hui L, Zhang X, Yu YQ, Han M, Huang XF, Chen da C, et al. Association between DBH 19 bp insertion/deletion polymorphism and cognition in first-episode schizophrenic patients. *Schizophrenia research*. 2013;147(2-3):236-40.
27. Burdick KE, Hodgkinson CA, Szeszko PR, Lencz T, Ekholm JM, Kane JM, et al. DISC1 and neurocognitive function in schizophrenia. *Neuroreport*. 2005;16(12):1399-402.

28. Callicott JH, Straub RE, Pezawas L, Egan MF, Mattay VS, Hariri AR, et al. Variation in DISC1 affects hippocampal structure and function and increases risk for schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America*. 2005;102(24):8627-32.
29. Cannon TD, Hennah W, van Erp TG, Thompson PM, Lonnqvist J, Huttunen M, et al. Association of DISC1/TRAX haplotypes with schizophrenia, reduced prefrontal gray matter, and impaired short- and long-term memory. *Archives of general psychiatry*. 2005;62(11):1205-13.
30. Hennah W, Tuulio-Henriksson A, Paunio T, Ekelund J, Varilo T, Partonen T, et al. A haplotype within the DISC1 gene is associated with visual memory functions in families with a high density of schizophrenia. *Molecular psychiatry*. 2005;10(12):1097-103.
31. Baek JH, Kim JS, Ryu S, Oh S, Noh J, Lee WK, et al. Association of genetic variations in DTNBP1 with cognitive function in schizophrenia patients and healthy subjects. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 2012;159B(7):841-9.
32. Peters K, Wiltshire S, Henders AK, Dragovic M, Badcock JC, Chandler D, et al. Comprehensive analysis of tagging sequence variants in DTNBP1 shows no association with schizophrenia or with its composite neurocognitive endophenotypes. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 2008;147B(7):1159-66.
33. Donohoe G, Morris DW, Clarke S, McGhee KA, Schwaiger S, Nangle JM, et al. Variance in neurocognitive performance is associated with dysbindin-1 in schizophrenia: a preliminary study. *Neuropsychologia*. 2007;45(2):454-8.
34. Burdick KE, Goldberg TE, Funke B, Bates JA, Lencz T, Kucherlapati R, et al. DTNBP1 genotype influences cognitive decline in schizophrenia. *Schizophrenia research*. 2007;89(1-3):169-72.
35. Ahmed AO, Mantini AM, Fridberg DJ, Buckley PF. Brain-derived neurotrophic factor (BDNF) and neurocognitive deficits in people with schizophrenia: a meta-analysis. *Psychiatry research*. 2015;226(1):1-13.
36. Zhang XY, Chen DC, Xiu MH, Haile CN, Luo X, Xu K, et al. Cognitive and serum BDNF correlates of BDNF Val66Met gene polymorphism in patients with schizophrenia and normal controls. *Human genetics*. 2012;131(7):1187-95.
37. Lu W, Zhang C, Yi Z, Li Z, Wu Z, Fang Y. Association between BDNF Val66Met polymorphism and cognitive performance in antipsychotic-naïve patients with schizophrenia. *Journal of molecular neuroscience : MN*. 2012;47(3):505-10.
38. Chung S, Chung HY, Jung J, Chang JK, Hong JP. Association among aggressiveness, neurocognitive function, and the Val66Met polymorphism of brain-derived neurotrophic factor gene in male schizophrenic patients. *Comprehensive psychiatry*. 2010;51(4):367-72.
39. Alfimova MV, Lezheiko TV, Golimbet VE, Korovaitseva GI, Lavrushkina OM, Kolesina N, et al. [Investigation of association of the brain-derived neurotrophic factor (BDNF) and a serotonin receptor 2A (5-HTR2A) genes with voluntary and involuntary attention in schizophrenia]. *Zhurnal nevrologii i psikiatrii imeni SS Korsakova / Ministerstvo zdravookhraneniia i meditsinskoi*

promyshlennosti Rossiiskoi Federatsii, Vserossiiskoe obshchestvo nevrologov [i] Vserossiiskoe obshchestvo psikiat. 2008;108(4):62-9.

40. Ho BC, Andreasen NC, Dawson JD, Wassink TH. Association between brain-derived neurotrophic factor Val66Met gene polymorphism and progressive brain volume changes in schizophrenia. *The American journal of psychiatry*. 2007;164(12):1890-9.

41. Ho BC, Milev P, O'Leary DS, Librant A, Andreasen NC, Wassink TH. Cognitive and magnetic resonance imaging brain morphometric correlates of brain-derived neurotrophic factor Val66Met gene polymorphism in patients with schizophrenia and healthy volunteers. *Archives of general psychiatry*. 2006;63(7):731-40.

42. Rybakowski JK, Borkowska A, Skibinska M, Szczepankiewicz A, Kapelski P, Leszczynska-Rodziewicz A, et al. Prefrontal cognition in schizophrenia and bipolar illness in relation to Val66Met polymorphism of the brain-derived neurotrophic factor gene. *Psychiatry and clinical neurosciences*. 2006;60(1):70-6.

43. Egan MF, Weinberger DR, Lu B. Schizophrenia, III: brain-derived neurotrophic factor and genetic risk. *The American journal of psychiatry*. 2003;160(7):1242.

44. Golimbet VE, Alfimova MV, Gritsenko IK, Lezheiko TV, Lavrushina OM, Abramova LI, et al. [The association of the SNAP-25 gene polymorphism with verbal memory and attention in patients with major psychosis and healthy people]. *Zhurnal nevrologii i psikiatrii imeni SS Korsakova / Ministerstvo zdravookhraneniia i meditsinskoi promyshlennosti Rossiiskoi Federatsii, Vserossiiskoe obshchestvo nevrologov [i] Vserossiiskoe obshchestvo psikiat*. 2009;109(1):59-63.

45. Li T, Ma X, Hu X, Wang Y, Yan C, Meng H, et al. PRODH gene is associated with executive function in schizophrenic families. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 2008;147B(5):654-7.

46. Voineskos AN, Felsky D, Kovacevic N, Tiwari AK, Zai C, Chakravarty MM, et al. Oligodendrocyte genes, white matter tract integrity, and cognition in schizophrenia. *Cerebral cortex*. 2013;23(9):2044-57.

47. Alfimova MV, Abramova LI, Aksenova EV, Golubev SA, Frolova LF, Ganisheva TK, et al. [The association between the NRG1 gene polymorphism and cognitive functions in patients with schizophrenia and healthy controls]. *Zhurnal nevrologii i psikiatrii imeni SS Korsakova / Ministerstvo zdravookhraneniia i meditsinskoi promyshlennosti Rossiiskoi Federatsii, Vserossiiskoe obshchestvo nevrologov [i] Vserossiiskoe obshchestvo psikiat*. 2011;111(6):53-7.

48. Meier S, Strohmaier J, Breuer R, Mattheisen M, Degenhardt F, Muhleisen TW, et al. Neuregulin 3 is associated with attention deficits in schizophrenia and bipolar disorder. *The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum*. 2013;16(3):549-56.

49. Morar B, Dragovic M, Waters FA, Chandler D, Kalaydjieva L, Jablensky A. Neuregulin 3 (NRG3) as a susceptibility gene in a schizophrenia subtype with florid delusions and relatively spared cognition. *Molecular psychiatry*. 2011;16(8):860-6.

50. Chandler D, Dragovic M, Cooper M, Badcock JC, Mullin BH, Faulkner D, et al. Impact of Neuritin 1 (NRN1) polymorphisms on fluid intelligence in schizophrenia. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 2010;153B(2):428-37.

51. Bosia M, Anselmetti S, Pirovano A, Ermoli E, Marino E, Bramanti P, et al. HTTLPR functional polymorphism in schizophrenia: executive functions vs. sustained attention dissociation. *Progress in neuro-psychopharmacology & biological psychiatry*. 2010;34(1):81-5.
52. Bosia M, Anselmetti S, Bechi M, Lorenzi C, Pirovano A, Cocchi F, et al. Effect of 5-HT1A-receptor functional polymorphism on Theory of Mind performances in schizophrenia. *Psychiatry research*. 2011;188(2):187-90.
53. Uçok A, Alpsan H, Cakir S, Saruhan-Direskeneli G. Association of a serotonin receptor 2A gene polymorphism with cognitive functions in patients with schizophrenia. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 2007;144B(5):704-7.
54. Alfimova MV, Golimbet VE, Mitiushina NG. [Polymorphism of the serotonin receptor (5-HTR2A) gene and verbal fluency in normalcy and schizophrenia]. *Molekuliarnaia biologii*. 2003;37(1):68-73.
55. Chen RY, Sham P, Chen EY, Li T, Cheung EF, Hui TC, et al. No association between T102C polymorphism of serotonin-2A receptor gene and clinical phenotypes of Chinese schizophrenic patients. *Psychiatry research*. 2001;105(3):175-85.
56. Hori H, Yamamoto N, Fujii T, Teraishi T, Sasayama D, Matsuo J, et al. Effects of the CACNA1C risk allele on neurocognition in patients with schizophrenia and healthy individuals. *Scientific reports*. 2012;2:634.
57. Jablensky A, Angelicheva D, Donohoe GJ, Cruickshank M, Azmanov DN, Morris DW, et al. Promoter polymorphisms in two overlapping 6p25 genes implicate mitochondrial proteins in cognitive deficit in schizophrenia. *Molecular psychiatry*. 2012;17(12):1328-39.
58. Zhang C, Cai J, Zhang J, Li Z, Guo Z, Zhang X, et al. Genetic modulation of working memory deficits by ankyrin 3 gene in schizophrenia. *Progress in neuro-psychopharmacology & biological psychiatry*. 2014;50:110-5.
59. Albanna A, Choudhry Z, Harvey PO, Fathalli F, Cassidy C, Sengupta SM, et al. TCF4 gene polymorphism and cognitive performance in patients with first episode psychosis. *Schizophrenia research*. 2014;152(1):124-9.
60. Zhu X, Gu H, Liu Z, Xu Z, Chen X, Sun X, et al. Associations between TCF4 gene polymorphism and cognitive functions in schizophrenia patients and healthy controls. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2013;38(4):683-9.
61. Rose EJ, Hargreaves A, Morris D, Fahey C, Tropea D, Cummings E, et al. Effects of a novel schizophrenia risk variant rs7914558 at CNNM2 on brain structure and attributional style. *The British journal of psychiatry : the journal of mental science*. 2014;204(2):115-21.
62. Donohoe G, Walters J, Hargreaves A, Rose EJ, Morris DW, Fahey C, et al. Neuropsychological effects of the CSMD1 genome-wide associated schizophrenia risk variant rs10503253. *Genes, brain, and behavior*. 2013;12(2):203-9.
63. Bosia M, Buonocore M, Guglielmino C, Pirovano A, Lorenzi C, Marcone A, et al. Saitohin polymorphism and executive dysfunction in schizophrenia. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*. 2012;33(5):1051-6.

64. Lin WY, Wu BT, Lee CC, Sheu JJ, Liu SH, Wang WF, et al. Association analysis of dopaminergic gene variants (Comt, Drd4 And Dat1) with Alzheimer s disease. *Journal of biological regulators and homeostatic agents*. 2012;26(3):401-10.
65. Donohoe G, Morris DW, Robertson IH, McGhee KA, Murphy K, Kenny N, et al. DAOA ARG30LYS and verbal memory function in schizophrenia. *Molecular psychiatry*. 2007;12(9):795-6.
66. Chiu HJ, Hong CJ, Chen JY, Wang YC, Lin CY, Bai YM, et al. Alpha-1-antichymotrypsin polymorphism in schizophrenia: frequency, age at onset and cognitive function. *Neuropsychobiology*. 1999;40(2):71-4.
67. Kastner A, Grube S, El-Kordi A, Stepniak B, Friedrichs H, Sargin D, et al. Common variants of the genes encoding erythropoietin and its receptor modulate cognitive performance in schizophrenia. *Mol Med*. 2012;18:1029-40.
68. Vassos E, Bramon E, Picchioni M, Walshe M, Filbey FM, Kravariti E, et al. Evidence of association of KIBRA genotype with episodic memory in families of psychotic patients and controls. *Journal of psychiatric research*. 2010;44(12):795-8.
69. Hargreaves A, Morris DW, Rose E, Fahey C, Moore S, Cummings E, et al. ZNF804A and social cognition in patients with schizophrenia and healthy controls. *Molecular psychiatry*. 2012;17(2):118-9.
70. Hashimoto R, Ohi K, Yasuda Y, Fukumoto M, Iwase M, Iike N, et al. The impact of a genome-wide supported psychosis variant in the ZNF804A gene on memory function in schizophrenia. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 2010;153B(8):1459-64.
71. Walters JT, Corvin A, Owen MJ, Williams H, Dragovic M, Quinn EM, et al. Psychosis susceptibility gene ZNF804A and cognitive performance in schizophrenia. *Archives of general psychiatry*. 2010;67(7):692-700.
72. Jablensky A, Morar B, Wiltshire S, Carter K, Dragovic M, Badcock JC, et al. Polymorphisms associated with normal memory variation also affect memory impairment in schizophrenia. *Genes, brain, and behavior*. 2011;10(4):410-7.
73. Prasad KM, Almasy L, Gur RC, Gur RE, Pogue-Geile M, Chowdari KV, et al. RGS4 polymorphisms associated with variability of cognitive performance in a family-based schizophrenia sample. *Schizophrenia bulletin*. 2010;36(5):983-90.
74. Donohoe G, Walters J, Morris DW, Quinn EM, Judge R, Norton N, et al. Influence of NOS1 on verbal intelligence and working memory in both patients with schizophrenia and healthy control subjects. *Archives of general psychiatry*. 2009;66(10):1045-54.
75. Simons CJ, van Winkel R. Intermediate phenotype analysis of patients, unaffected siblings, and healthy controls identifies VMAT2 as a candidate gene for psychotic disorder and neurocognition. *Schizophrenia bulletin*. 2013;39(4):848-56.
76. Greenwood TA, Lazzeroni LC, Murray SS, Cadenhead KS, Calkins ME, Dobie DJ, et al. Analysis of 94 candidate genes and 12 endophenotypes for schizophrenia from the Consortium on the Genetics of Schizophrenia. *The American journal of psychiatry*. 2011;168(9):930-46.
77. Dickinson D, Straub RE, Trampush JW, Gao Y, Feng N, Xie B, et al. Differential Effects of Common Variants in SCN2A on General Cognitive Ability, Brain Physiology, and messenger RNA Expression in Schizophrenia Cases and Control Individuals. *JAMA psychiatry*. 2014.

78. Knowles EE, Carless MA, de Almeida MA, Curran JE, McKay DR, Sprooten E, et al. Genome-wide significant localization for working and spatial memory: Identifying genes for psychosis using models of cognition. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 2014;165(1):84-95.
79. Lencz T, Knowles E, Davies G, Guha S, Liewald DC, Starr JM, et al. Molecular genetic evidence for overlap between general cognitive ability and risk for schizophrenia: a report from the Cognitive Genomics consorTium (COGENT). *Molecular psychiatry*. 2014;19(2):168-74.
80. Fernandes CP, Christoforou A, Giddaluru S, Ersland KM, Djurovic S, Mattheisen M, et al. A genetic deconstruction of neurocognitive traits in schizophrenia and bipolar disorder. *PloS one*. 2013;8(12):e81052.
81. Hargreaves A, Anney R, O'Dushlaine C, Nicodemus KK, Gill M, Corvin A, et al. The one and the many: effects of the cell adhesion molecule pathway on neuropsychological function in psychosis. *Psychological medicine*. 2013:1-11.
82. Xiang B, Wu JY, Ma XH, Wang YC, Deng W, Chen ZF, et al. [Genome-wide association study with memory measures as a quantitative trait locus for schizophrenia]. *Zhonghua yi xue yi chuan xue za zhi = Zhonghua yixue yichuanxue zazhi = Chinese journal of medical genetics*. 2012;29(3):255-9.

A Review of Molecular Genetic Studies of Neurocognitive Deficits in Schizophrenia

Gwyneth Zai ^{1,2,3,4*}, Trevor W. Robbins ^{3,5}, Barbara J. Sahakian ^{3,4}, James L. Kennedy ^{1,2}

¹ *Neurogenetics Section, Centre for Addiction and Mental Health, Toronto, Canada*

² *Department of Psychiatry and Institute of Medical Science, University of Toronto, Toronto, Canada*

³ *MRC/Wellcome Trust Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge, UK*

⁴ *Department of Psychiatry, University of Cambridge, Cambridge, UK*

⁵ *Department of Psychology, University of Cambridge, Cambridge, UK*

HIGHLIGHTS:

- Schizophrenia patients present with impaired cognitive functions.
- Evidence suggests strong genetic etiology for cognitive deficits in schizophrenia.
- Neurotransmitter system genes showed effect on cognitive deficits in schizophrenia.
- Limited evidence suggests the dopaminergic system genes with inconsistent findings.
- Larger samples are required to examine genetic risk of cognition in schizophrenia.