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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-methytransferase (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)
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A Review of Molecular Genetic Studies of Neurocognitive Deficits in Schizophrenia

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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-methytransferase (*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 (*ANKK1*) (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 cingulated 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 proteint 1 (*DTNBP1*) 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 ~~two~~seven 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 three~~wo~~ of the ~~three~~ four studies above showed modest significant association between *DTNBP1* 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 a important role in the regulation of morphogenesis in CNS development, neuronal proliferation, migration, differentiation, and cognition (98-100). In term 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 (5*HTT*, 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 (*FNBP1L*) 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.

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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.

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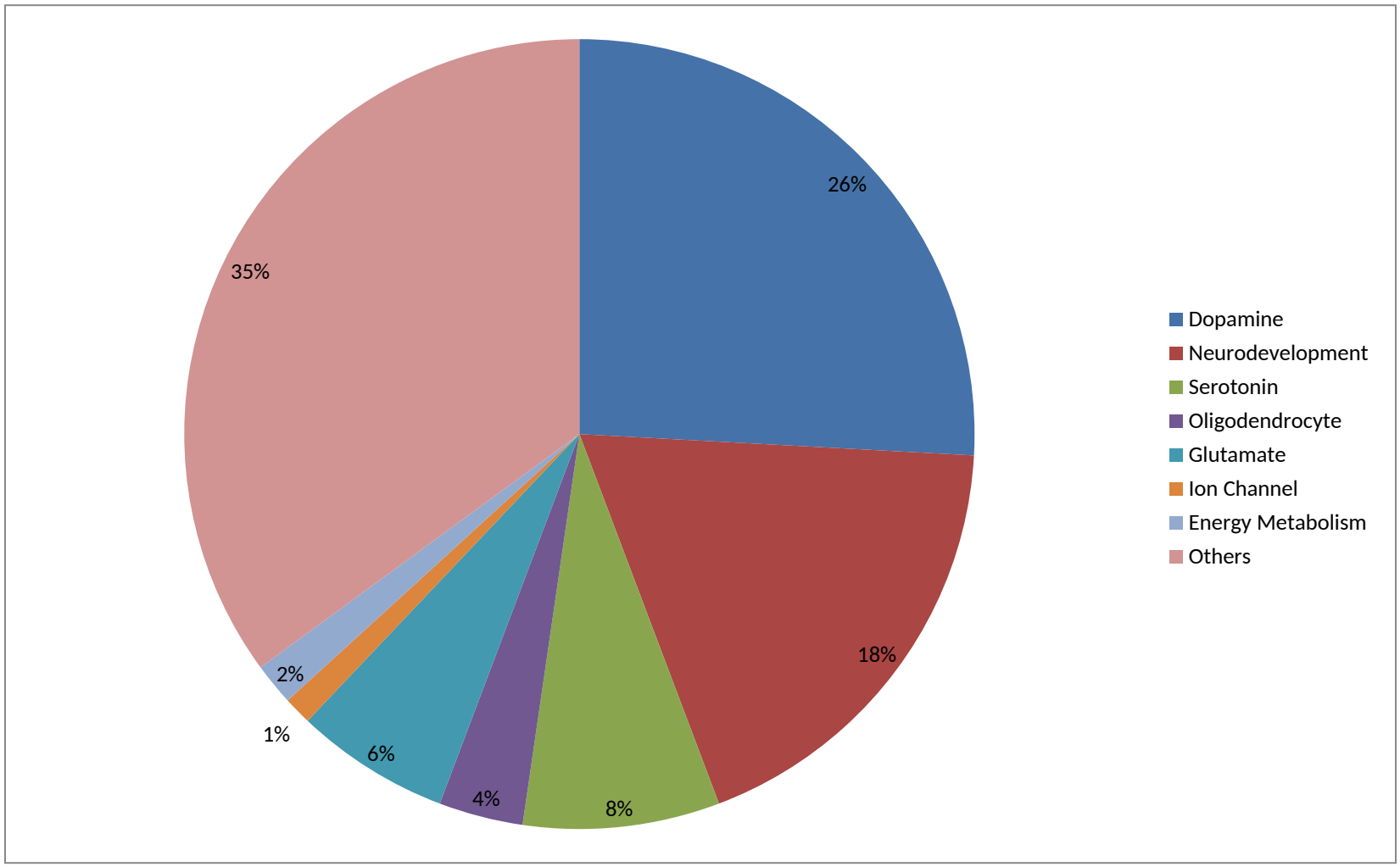

Figure 1. Candidate gene studies according to their biomolecular systems. Dopaminergic system genes have been examined the most in genetic studies of cognition in schizophrenia given the important role of dopamine in the etiology of schizophrenia and cognition. Neurodevelopmental genes are amongst the 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	*COMT*	23	12	11	2	-	Executive function, theory of mind, reaction time, processing speed, attention, IQ, spatial working memory, attentional flexibility and planning	(1-25)
	DAT/SLC6A3	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)
	DRD1	-	-	-	1	-	- Speed of information processing, attention/vigilance, verbal learning and memory, working memory, reasoning and problem solving, set shifting, and verbal comprehension	(23)
	DRD2	2	0	2	1	-	-	(2, 22, 23)
	DRD3	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)
	DRD4	1	1	0	-	-	Working memory, verbal fluency	(5)
	DRD5	1	1	0	-	-	Visual voluntary attention	(27)
	DBH	2	1	1	-	-	Immediate memory	(20, 28)
	SLC18A2	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)
	ANKK1	-	-	-	1	-	-	(23)
	PPP1R1B	-	-	-	1	-	-	(23)
Neuro	*DISC1*	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)
	DTNBP1	4	3	1	1	-	Attention/vigilance domain, spatial working memory, IQ	(23, 33-36)
	BDNF	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)
	NRG1	2	2	0	2	-	Processing speed, visuomotor speed, attention, long-term episodic memory, short-term memory	(17, 23, 46, 47)
	NRG3	2	2	0	-	-	Visuomotor speed, processing speed, mental flexibililty, executive function, sustained attention	(48, 49)
	NRN1	1	1	0	-	-	General intellectual ability	(50)
	SNAP-25	1	1	0	-	-	Verbal memory, attention, executive function	(51)
	PRODH	1	0	1	1	-	-	(23, 52)
	P2RX7	-	-	-	1	-	-	(23)
	NPY	-	-	-	1	-	-	(23)
	NQO1	-	-	-	1	-	-	(23)
	GST-1	-	-	-	1	-	-	(23)
	GST-2	-	-	-	1	-	-	(23)
Serotonin	*5HTT*	2	1	1	1	-	Executive function, attention	(17, 21, 53)
	HTR1A	1	1	0	1	-	Theory of mind	(17, 23, 54)
	HTR2A	5	3	2	2	-	Voluntary and involuntary attention, executive function, verbal fluency	(1, 17, 23, 37, 55-57)
	NET	2	0	2	-	-	-	(6, 7)

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

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

System	Gene	N	Candidate Gene Studies		Significant		Cognitive Domains	Reference
			Positive	Negative	Multi-gene	GWAS		
	MTHFR	1	1	-	1	-	IQ, spatial working memory, attentional flexibility and planning	(23, 24)
	MTR	-	-	-	1	-	-	(23)
	MTRR	-	-	-	1	-	-	(23)
	EHMT1	-	-	-	1	-	-	(23)
	EHMT2	-	-	-	1	-	-	(23)
	PRDM2	-	-	-	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 (5*HTT*), 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 (*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 dehydogenase, 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 phosphatise 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*), saitohin (*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*).

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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	*COMT*	+/-	+/-	+/-[9]	+/-	Executive function, theory of mind, reaction time, processing speed, attention	(1-20, 22-25, 83-85)
	DAT/SLC6A3	+/-	+/-	+/-[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)
	DRD1	+		-[9]		- Speed of information processing, attention/vigilance, verbal learning and memory, working memory, reasoning and problem solving, set shifting, and verbal comprehension	(23)
	DRD2	-	+/-	+/-[9]	-	-	(2, 22, 23, 85, 88-91)
	DRD3	+/-	+/-	+/-[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)
	DRD4	+	+/-	+	+/-	Working memory, verbal fluency	(5, 60, 85)
	DRD5	+	+/-	-[2]		Visual voluntary attention	(27)
	DBH	+/-	+/-	-	+	Immediate memory	(20, 28, 92, 93)
	SLC18A2	+/-	+/-	-[1]		- Speed of information processing, attention/vigilance, verbal learning and memory, working memory, reasoning and problem solving, set shifting, and verbal comprehension	(20)
	ANKK1	-	+/-	-[9]		-	(23)
	PPP1R1B	-	+/-	+/-[9]		-	(23, 94)
Neuro	*DISC1*	+	+/-	+/-[9]		Verbal fluency, verbal working memory, short- and long-term memory, short-term visual memory, visual search, attention	(1, 17, 23, 29-32)
	DTNBP1	+/-	+/-	+/-[9]		Attention/vigilance domain, spatial working memory, IQ	(23, 33-36)
	BDNF	+/-	+/-	+/-[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)
	NRG1	+	+/-	-[3,9]	+	Processing speed, visuomotor speed, attention, long-term episodic memory, short-term memory	(17, 23, 46, 47)
	NRG3	+	+/-		+	Visuomotor speed, processing speed, mental flexibililty, executive function, sustained attention	(48, 49, 95)
	NRN1	+	+/-	-[3]		General intellectual ability	(50)
	SNAP-25	+	+/-	+[1]	+	Verbal memory, attention, executive function	(51, 96)
	PRODH	-	+/-	+/-[9]		-	(23, 52, 97)
	P2RX7	-	-	-[9]	-	-	(23, 98)

	NPY	-	+/-	-[9]	-	-	(23)
	NQO1	-	-	-[9]	+/-	-	(23)
	GST-1	-		-[9]		-	(23)
	GST-2	-		-[9]		-	(23)
Serotonin	*5HTT/SLC6A4*	+/-	+/-	+	+/-	Executive function, attention	(17, 21, 53, 99)
	HTR1A	+	+/-			Theory of mind	(17, 54)
	HTR2A	+/-	+/-	-[9]	+[4]/-	Voluntary and involuntary attention, executive function, verbal fluency	(1, 17, 23, 37, 55-57, 83)
	NET/SLC6A2	-	-			-	(6, 7)
Oligodendrocyte	*QKI*	-	-	-[5]	+	-	(46, 100)
	MAG	+	+/-	+[5]		Processing speed, visuomotor speed, attention	(46)
	CNP	-	+/-	-[5]		-	(46)
	OLIG2	-	+/-	+[5]	+[4]/-	-	(46, 101)
	ERBB4	-	+/-	+[5]	+	Verbal learning, abstraction, visuospatial memory	(17, 20, 46)
Glutamate	*GRIN2A*	-	+/-	+		-	(58)
	GRIN2B	+/-	+/-	+	+/-	Immediate and delayed recall (verbal memory)	(1, 17, 58)
	GRM1	+	+			Attention, verbal learning, abstraction, visuospatial memory, spatial processing	(17, 21, 86)
	GRM3	+	+/-	+/-[9]		Enhanced performance	(23, 58, 87)
	SLC1A2	+	+/-			Attention, abstraction, spatial memory	(17)
	DAOA	+	+/-	+[6]/-[9]	+[4]	Verbal memory	(23, 59, 60)
	GAD1	-	+/-	-[9]		-	(23)
Ion channel	*CACNA1C*	+/-	+	-[3]	+	Logical memory	(1, 61, 88, 89)
	SCN2A	+		-[2]		Cognitive ability (g)	(62, 90)
Energy metabolism	*LYRM4*	+				Verbal memory	(63)
	FARS1	+				Verbal memory	(63)
	ATP2C2	-				-	(1)
Others	*ANK3*	+	+/-	+/-[3]	+/-	Working memory, verbal memory, attention	(64, 91, 92, 102)
	TCF4	+	+/-	+[7]		Reasoning, problem-solving, attention-related tasks	(65, 66)
	CNNM2	-	+	-		Social cognition	(67, 103)
	CSMD1	+	+	+		General cognitive ability, memory cognition	(68, 69, 104, 105)
	STH	+	-		+/-	Executive function	(25, 70)
	ACT	-	-		+	-	(71, 106)
	DCDC2	-	-			-	(1)
	DYX1C1	-				-	(1)
	KIAA0319	+				Verbal learning and recall	(1)
	NAGPA	-				-	(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)
PKNOX1	-				-	(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)

ROBO1	-		-[9]		-	(23)
CHRM3	-		-[9]		-	(23)
TBX1	-	+/-	-[9]		-	(23)
ADRA2C	-		-[9]		-	(23, 130)
FKBP5	+	-	-[9]		- Speed of information processing, attention/vigilance, verbal learning and memory, working memory, reasoning and problem solving, set shifting, and verbal comprehension	(23)
DNMT3B	+	+	-[9]	+/-	- Speed of information processing, attention/vigilance, verbal learning and memory, working memory, reasoning and problem solving, set shifting, and verbal comprehension	(23, 131, 132)
CNR1	-	+/-	-[9]		-	(23, 133)
MTHFR	+/-	+/-	-[9]	+/-	-	(23, 24, 133-137)
MTR	-	+	-[9]	+/-	-	(23, 134)
MTRR	-	-	-[9]		-	(23, 134, 138, 139)
EHMT1	-		-[9]		-	(23)
EHMT2	-	-	-[9]		-	(23)
PRDM2	-		-[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
COMT	22q11.21	Val158Met (rs4680)	343 schizophrenia patients	Brief Assessment of Cognition in Schizophrenia, WCST, CPT	• Significant effects on processing speed and executive functions • *COMT* × *STH* Q7R interaction on executive functions with *COMT* Val/Val and *STH* 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	• 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	• 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	• *COMT* × *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* × *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	MATRICS battery with WAIS-III: category fluency, digit symbol, TMTA, WMS-III,	• 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,	• No association	Nicodemus et al., 2013 (6)
			209 schizophrenia and 172 healthy people	ToM: second-order false belief, faux pas stories	• 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	• 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	• No association	Bombin et al., 2008 (9)
			Meta-analysis: 1910 patients and controls • 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	• 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
			• 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) • Joober et al. (2002) • Bilder et al. (2002) • Egan et al. (2001)			
			50 DSM-IV schizophrenia patients and responders to one adequately dosed antipsychotic for 3 months • Placebo vs. active (both with SRT)	BACS, WCST, CPT	• 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)	• Val158Met-*DRD4* -521C/T Val/Val+C/C and Met/Met+T/T with better performance on verbal fluency • Val158Met-*DRD4* 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	• 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	• 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	• 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	• 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	• 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	• 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	• 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	• 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	• Met allele with better performance in the processing speed and attention domain but not with executive and visuoperceptual 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	• 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)		• 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	• 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,	• 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	• 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	• Significant effect of verbal and visuospatial working memory performance	Zilles et al., 2012 (8)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
			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	
		VNTR *	124 DSM-IV schizophrenia patients (60 males; mean age 27 years; mean age at onset 23 years)	WCST	• No association	Rybakowski et al., 2006 (14)
			120 Caucasian volunteers (75 DSM-IV schizophrenia [34 males], 45 healthy controls [17 males])	WCST	• No association	Szekeres et al., 2004 (24)
DRD3	3q13.3	Ser9Gly (rs6280)			• 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)	
			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	Bombin et al., 2008 (9)

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)
		TaqIA (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
			healthy controls	WCST		
DRD4	11p15.5	-809G/A (rs936461) -521C/T *	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)	• *COMT* Val158Met-rs936461 Val-G haplotype with best results on working memory and Met-A haplotype with worst performance • *COMT* Val158Met-*DRD4* -521C/T Val/Val+C/C and Met/Met+T/T with better performance on verbal fluency	Alfimova et al., 2006 (12)
DRD5	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)	• 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)
DBH	9q34.2	5'–Ins/Del	195 DSM-IV first-episode psychosis	RBANS – Form A	• 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)
SLC18A2	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)
DISC1	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	• 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	• *DISC1-TRAX* 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	• 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	
DTNBP1	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	• 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	• 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	• 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,	• 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)
BDNF	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*)	• 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	• No association	Nicodemus et al., 2013 (6)
			657 DSM-IV schizophrenia patients and 445 healthy controls	RBANS (immediate memory, attention, language, visuospatial/constructional performance, delayed memory)	• Cognitive test scores were significantly lower in schizophrenic than control subjects except for visuospatial/constructional 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 • (*HTR2A* 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	• No association	Ho et al., 2007 (40)
			293 DSM-IV schizophrenia patients and 144 healthy volunteers	RAV, WAIS-R	• 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	• 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)
SNAP-25	20p12-p11.2	*MnlI* (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)
PRODH	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)
NRG1	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	• 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	• 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	• 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	• 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 • 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 (β=0.523, 95% CI 0.070-0.976, *P*=0.025) and G allele of rs10883866 (β=0.687, 95% CI 0.195-1.178, *P*=0.007) with degraded-stimulus continuous performance task and better performance in schizophrenia	2011 (49)
NRN1	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	• 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)		• 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 (SLC6A4)	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 (≥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,	• No association	Nicodemus et al., 2013 (6)
		T102C (rs6313)	89 schizophrenia patients, 91 unaffected relatives, and 163 controls	Voluntary and involuntary visual attention	• T allele with more time for performing the test • T-(*BDNF* 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	• 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)	• 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	• 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)
LYRM4 FARS2	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	• 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)
QKI	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	• No association	Voineskos et al., 2013 (46)
MAG	19q13.1	rs756796 rs756596 rs720308 rs720309 rs2301600			• *MAG* rs2301600 and rs720309, *NRG1* SNP8NRG221533 and SNP8NRG243177, and *ERBB4* 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) • *MAG* rs2301600 and rs720309, and *NRG1* SNP8NRG221533 in schizophrenia with the same tasks as above (P=0.01)	
CNP	17q21	rs2070106			• No association	
OLIG2	21q22.11	rs1059004 rs9653711			• No association in schizophrenia	
ERBB4	2q33.3-q34	rs839523			• *OLIG2* rs1059004 and *ERBB4* 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	
ANK3	10q21	rs10761482 rs10994336	163 first-episode schizophrenia patients (antipsychotic-naïve) and 42 healthy subjects (sex and age-	N-back task	• 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	• 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)
TCF4	18q21.1	rs9960767	173 first-episode psychosis patients	MCCB, WMS-III, WAIS-III, TMT (TMTA and TMTB)	• 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	• 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	• 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	• 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		
STH	17q21.1	Q7R *	343 schizophrenia patients	Brief Assessment of Cognition in Schizophrenia, WCST, CPT	• Significant effects on executive functions • *COMT* rs4680 × *STH* interaction on executive functions with *COMT* Val/Val and *STH* R carriers performing worse	Bosia et al., 2014 (1)
		128A/G *	220 DSM-IV schizophrenia patients and responders (≥30%	WCST	• 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*=0.015) • 6.4% variance explained verbal memory performance • No differences in attentional control, working memory, and spatial memory	
ACT (SERPINA3)	14q32.1	Ala-15Thr *	175 DSM-IV schizophrenia inpatients and 114 healthy controls	CDR, MMSE	• No difference between schizophrenia and control • No significant difference with cognitive impairment	Chiu et al., 1999 (66)
EPO	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	• Carriers of *EPO* rs1617640 and *EPOR* STR(GA)n low repeat sum showed superior performance in cases • No differences for *EPOR* STR(GA)n in healthy controls	Kästner et al., 2012 (67)
EPOR	19p13.2	STR(GA)n			•	
(WWC1) KIBRA	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	• 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)	
ATP2C2	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)
DCDC2	6p22.1	rs2274305			• No association	
DYX1C1	15q21.3	rs600753			• No association	
KIAA0319	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)	
NAGPA	16p13.3	rs887854			• No association	
CLSTN2	3q23	rs17348572 rs7632885 rs10804675			• No association	
WWC1 (KIBRA)	5q34	rs17551608 rs3822659 rs3733980 rs3203960			• No association	
ATRNL1	10q26	rs10885721			• No association	
C20orf196	20p12.3	rs1699233			• No association	
CRTC3	15q26.1	rs8033595			• No association	
DIP2C	10p15.3	rs3740304 rs2288681			• No association	
NFKBIL1	6p21.3	rs2230365			• No association	
PDE1C	7p14.3	rs3213709 rs2302450 rs1860790			• No association	

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
PKNOX1	21q22.3	rs234781			• No association	
SPATA7	14q31.3	rs3179969			• No association	
ZNF804A	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
					indices than controls • 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	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 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	• 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)
ADCY8	8p24	rs12545028	194 DSM-IV schizophrenia	WMS, CVLT, category fluency	• 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	• 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	• 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	• 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			• No association	
GRIN2A	16p13.2	rs1868291			• No association	

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
PRKCA	17q22-q23.2	rs8074995	years) DSM-IV and ICD-10 schizophrenia patients and 172 normal (59% males; mean age 40.7 years) controls		• rs8074995 with RAVLT (*P*=0.02)	
RGS4	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	• 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		
NOS1	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	• 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)
MTHFR	1p36.22	rs1801133 (C677T)	90 DSM-IV schizophrenia patients and 55 healthy controls	CANTAB: Motor Control, Pattern Recognition Memory and Spatial	• *MTHFR* × *COMT* 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 • *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* × *MTHFR* interaction with IQ (P=0.035), worse performance with *COMT* Met carriers and *MTHFR* T carriers (P=0.021)	
46 Candidate Genes: ***RGS4,*** ***NRG1,*** ***DTNBP1,*** ***PIP5K2A,*** ***G72/DAOA,*** ***DISC1,*** ***HT2A,*** ***AKT1,*** ***LRRTM1,***	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,	• *DRD1* rs265981 allele G (P=0.010), *DRD3* rs6280 allele C (P=0.031), *SLC6A3* rs456082 allele C, rs463379 allele G, rs464049 allele C, *BDNF* rs988748 allele G, *FGF2* rs7700205 allele C, *SLC18A2*	Simons et al., 2013 (75)

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
FGF2, FGFR1, GPM6A, PRODH, GRM3, GABRA6, GAD1, NOS1, RGS2, ROBO1, CHRM3, TBX1, COMT, ANKK1, DRD1, DRD2, DRD3, SLC6A3, PPP1R1B, SLC18A2, CNR1, ADRA2C, FKBP5, BDNF, P2RX7, NPY, NQO1, GST-1, GST-2, MTHFR, MTR, MTRR, DNMT3B, EHMT1,				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, *FKBP5* rs1334894 allele G, *DNMT3B* rs2424913 allele T, and rs406193 allele C with worse cognitive performance in patients • *SLC18A2* rs363227 allele T with poorer cognitive functioning in siblings (P=0.04)	

Gene	Chromosome	Polymorphism	Sample	Cognition	Result	Reference
EHMT2, PRDM2						
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	• Multiple significant associations with cognitive domains including continuous performance (i.e., *DISC1*, *GRM1*), letter-number span (i.e., *DISC1*, *ERBB4*, *HTR2A*), verbal learning (i.e., *ERBB4*, *HTR1A*, *GRM1*, *NRG1*, *SLC1A2*, *GRIN2B*, *COMT*), abstraction (i.e., *ERBB4*, *NRG1*, *SLC1A2*), face memory (i.e., *ERBB4*, *5HTT*, *GRM1*, *COMT*), spatial memory (i.e., *ERBB4*, *GRM1*, *SLC1A2*), and spatial processing (i.e., *5HTT*, *GRM1*, *NRG1*, *HTR2A*)	Greenwood et al., 2011 (76)
GWAS • ***SCN2A***	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,	• rs10174400 (P=9.27×10^{-10}) and rs10182570 (P=2.56×10^{-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	• 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
GWAS meta-analysis • ***MIR137*** • ***MPC2*** • ***SDCCAG8*** • ***ZNF804A*** • ***PCGEM1*** • ***ZSWIM6*** • ***MAD1L1*** • ***CSMD1*** • ***LSM1*** • ***CNNM2*** • ***NT5C2*** • ***NRGN*** • ***TCF4***	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 • *MAD1L1* rs12666575 (*P*=0.032) and *CNNM2* rs7914558 (*P*=0.040) schizophrenia risk alleles with lower cognitive ability • *LSM1* rs16887244 (*P*=0.017) and *NRGN* rs12807809 (*P*=0.040) schizophrenia risk allele with higher cognitive ability	Lencz et al., 2014 (79)
GWAS	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)			
CAM Pathway HLA-DQA1	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	• Increased CAM pathway polygenic risk scores with poorer performance on measures of memory and attention • *HLA-DQA1* rs9272105 (strongest signal) with attentional control but not memory	Hargreaves et al., 2013 (81)
GWAS • ***RASGRF2*** • ***PLCG2*** • ***LMO1*** • ***CSMD1*** • ***PRKG1***	Whole genome	HumanHap660 Bead Array • rs401758 • rs7185362 • rs484161 • rs2469383 • rs7898516	98 chronic schizophrenia patients and 60 matched controls	Memory cognition (details in Chinese)	• *RASGRF2* rs401758 (P=8.03×10^{-5}), *PLCG2* rs7185362 (P=4.54×10^{-5}), *LMO1* rs484161 (P=9.80×10^{-7}), *CSMD1* rs2469383 (P=2.77×10^{-6}), and *PRKG1* rs7898516 (P=6.94×10^{-5})	Xiang et al., 2012 (82)

* rs number not available.

Abbreviations for genes: serotonin transporter (5*HTT*), 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 (*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 dehydogenase, 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 phosphatise 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*), saitohin (*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 (BVMT-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- and Merkfähigkeitstest (VLMT), Weschsler 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).

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A Review of Molecular Genetic Studies of Neurocognitive Deficits in Schizophrenia

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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.