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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.

Keywords: Genetics; schizophrenia; neurocognition; cognitive deficits; candidate gene studies; genome-wide association studies (GWASs)

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 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. 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). 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). Eight studies in addition to a multi-gene study and a meta-analysis including seven studies from our search were detected. 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) 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, 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 of the four studies above showed modest significant association between *DTNBP1* variants and poor cognitive performance in schizophrenia patients, and 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 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).*

Gene	N	Candidate Gene Studies		Significant		Cognitive Domains
		Positive	Negative	Multi-gene	GWAS	
COMT	23	12	11	2	-	Executive function, theory of mind, reaction time, processing speed, attention, IQ, spatial wor memory, attentional flexibility and planning
DAT/SLC6A3	4	0	4	1	-	- Speed of information processing, attention/vigilance, verbal learning and memory, wor memory, reasoning and problem solving, set shifting, and verbal comprehension
DRD1	-	-	-	1	-	- Speed of information processing, attention/vigilance, verbal learning and memory, wor memory, reasoning and problem solving, set shifting, and verbal comprehension
DRD2	2	0	2	1	-	-
DRD3	3	1	2	1	-	Perseveration - Speed of information processing, attention/vigilance, verbal learning and memory, wor memory, reasoning and problem solving, set shifting, and verbal comprehension
DRD4	1	1	0	-	-	Working memory, verbal fluency
DRD5	1	1	0	-	-	Visual voluntary attention
DBH	2	1	1	-	-	Immediate memory
SLC18A2	1	0	1	-	-	- Speed of information processing, attention/vigilance, verbal learning and memory, wor memory, reasoning and problem solving, set shifting, and verbal comprehension
ANKK1	-	-	-	1	-	-
PPP1R1B	-	-	-	1	-	-
DISC1	5	5	0	2	-	Verbal fluency, verbal working memory, short- and long-term memory, short-term visual mem visual search, attention
DTNBP1	4	3	1	1	-	Attention/vigilance domain, spatial working memory, IQ
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, wor memory, reasoning and problem solving, set shifting, and verbal comprehension
NRG1	2	2	0	2	-	Processing speed, visuomotor speed, attention, long-term episodic memory, short-term mem
NRG3	2	2	0	-	-	Visuomotor speed, processing speed, mental flexibililty, executive function, sustained attentio
NRN1	1	1	0	-	-	General intellectual ability
SNAP-25	1	1	0	-	-	Verbal memory, attention, executive function
PRODH	1	0	1	1	-	-
P2RX7	-	-	-	1	-	-
NPY	-	-	-	1	-	-
NQO1	-	-	-	1	-	-
GST-1	-	-	-	1	-	-
GST-2	-	-	-	1	-	-
5HTT	2	1	1	1	-	Executive function, attention

Gene	N	Candidate Gene Studies		Significant		Cognitive Domains
		Positive	Negative	Multi-gene	GWAS	
HTR1A	1	1	0	1	-	Theory of mind
HTR2A	5	3	2	2	-	Voluntary and involuntary attention, executive function, verbal fluency
NET	2	0	2	-	-	-
QKI	1	0	1	-	-	-
MAG	1	1	0	-	-	Processing speed, visuomotor speed, attention
CNP	1	0	1	-	-	-
OLIG2	1	0	1	-	-	-
ERBB4	1	0	1	1	-	Verbal learning, abstraction, visuospatial memory
GRIN2A	1	0	1	-	-	-
GRIN2B	2	1	1	1	-	Immediate and delayed recall (verbal memory)
GRM1	-	-	-	1	-	Attention, verbal learning, abstraction, visuospatial memory, spatial processing
GRM3	1	1	0	1	-	Enhanced performance
SLC1A2	-	-	-	1	-	Attention, abstraction, spatial memory
DAOA	1	1	0	1	1	Verbal memory
GAD1	-	-	-	1	-	-
CACNA1C	2	1	1	-	-	Logical memory
SCN2A	-	-	-	-	1	Cognitive ability
LYRM4	1	1	0	-	-	Verbal memory
FARS1	1	1	0	-	-	Verbal memory
ATP2C2	1	0	1	-	-	-
ANK3	2	2	0	-	-	Working memory, verbal memory, attention
TCF4	1	1	0	-	-	Reasoning, problem-solving, attention-related tasks
CNNM2	1	0	1	-	-	Social cognition
CSMD1	1	1	0	-	1	General cognitive ability, memory cognition
STH	2	2	0	-	-	Executive function
ACT	1	0	1	-	-	-
DCDC2	1	0	1	-	-	-
DYX1C1	1	0	1	-	-	-
KIAA0319	1	1	0	-	-	Verbal learning and recall
NAGPA	1	0	1	-	-	-
ZNF804A	4	3	1	-	-	Verbal learning and recall, verbal and spatial working memory, verbal episodic memory, v memory
CLSTN2	1	0	1	-	-	-
WWC1	2	0	2	-	-	-
ATRNL1	1	0	1	-	-	-
C20orf196	1	0	1	-	-	-
CRTC3	1	0	1	-	-	-
DIP2C	1	0	1	-	-	-
NFKBIL1	1	0	1	-	-	-
PDE1C	1	0	1	-	-	-
PKNOX1	1	0	1	-	-	-
SPATA7	1	0	1	-	-	-
ADCY8	2	0	2	-	-	-
CAMK2G	2	0	2	-	-	-
PRKACG	1	0	1	-	-	-
PRKCA	1	1	0	-	-	Verbal memory
HEY1	-	-	-	-	1	Working memory

Gene	N	Candidate Gene Studies		Significant		Cognitive Domains
		Positive	Negative	Multi-gene	GWAS	
MAD1L1	-	-	-	-	1	Cognitive ability
LSM1	-	-	-	-	1	Cognitive ability
CAM	-	-	-	-	1	Memory, attention
HLA-DQA1	-	-	-	-	1	Attention
RASGRF2	-	-	-	-	1	Memory cognition
PLCG2	-	-	-	-	1	Memory cognition
LMO1	-	-	-	-	1	Memory cognition
PRKG1	-	-	-	-	1	Memory cognition
EPO	1	1	0	-	-	Processing speed, short-term memory, and tasks requiring distinct fine motor component
EPOR	1	1	0	-	-	Processing speed, short-term memory, and tasks requiring distinct fine motor component
RGS4	1	1	-	1	-	Face and verbal memory speed
PIP5K2A	-	-	-	1	-	-
AKT1	-	-	-	1	-	-
LRRTM1	-	-	-	1	-	-
FGF2	-	-	-	1	-	- Speed of information processing, attention/vigilance, verbal learning and memory, wor memory, reasoning and problem solving, set shifting, and verbal comprehension
FGFR1	-	-	-	1	-	-
GPM6A	-	-	-	1	-	-
GABRA6	-	-	-	1	-	-
NOS1	1	1	-	1	-	General cognitive ability, verbal and spatial working memory
RGS2	-	-	-	1	-	-
ROBO1	-	-	-	1	-	-
CHRM3	-	-	-	1	-	-
TBX1	-	-	-	1	-	-
ADRA2C	-	-	-	1	-	-
FKBP5	-	-	-	1	-	- Speed of information processing, attention/vigilance, verbal learning and memory, wor memory, reasoning and problem solving, set shifting, and verbal comprehension
DNMT3B	-	-	-	1	-	- Speed of information processing, attention/vigilance, verbal learning and memory, wor memory, reasoning and problem solving, set shifting, and verbal comprehension
CNR1	-	-	-	1	-	-
MTHFR	1	1	-	1	-	IQ, spatial working memory, attentional flexibility and planning
MTR	-	-	-	1	-	-
MTRR	-	-	-	1	-	-
EHMT1	-	-	-	1	-	-
EHMT2	-	-	-	1	-	-
PRDM2	-	-	-	1	-	-

* 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*).

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

ystem	Gene	Schizophrenia Cognition	Schizophrenia Disease Risk	Healthy	Dementia	Cognitive Domains	References
Dopamine	*COMT*	+/-	+/-	+/-[9]	+/-	Executive function, theory of mind, reaction time, processing speed, attention	(120-139, 141 144, 202-204)
	DAT/SLC6A3	+/-	+/-	+/-[9]	+/-	- Speed of information processing, attention/vigilance, verbal learning and memory, working memory, reasoning and problem solving, set shifting, and verbal comprehension	(120, 126, 142 145, 179, 205 206)
	DRD1	+		-[9]		- Speed of information processing, attention/vigilance, verbal learning and memory, working memory, reasoning and problem solving, set shifting, and verbal comprehension	(142)
	DRD2	-	+/-	+/-[9]	-	-	(121, 141,142 204, 207-210)
	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	(139, 141,142 145)
	DRD4	+	+/-	+	+/-	Working memory, verbal fluency	(124, 179, 204)
	DRD5	+	+/-	-[2]		Visual voluntary attention	(146)
	DBH	+/-	+/-	-	+	Immediate memory	(139, 147,211 212)
	SLC18A2	+/-	+/-	-[1]		- Speed of information processing, attention/vigilance, verbal learning and memory, working memory, reasoning and problem solving, set shifting, and verbal comprehension	(139)
	ANKK1	-	+/-	-[9]		-	(142)
	PPP1R1B	-	+/-	+/-[9]		-	(142, 213)
leuro	*DISC1*	+	+/-	+/-[9]		Verbal fluency, verbal working memory, short- and long-term memory, short-term visual memory, visual search, attention	(120, 136, 142 148-151)
	DTNBP1	+/-	+/-	+/-[9]		Attention/vigilance domain, spatial working memory, IQ	(142, 152-155)
	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	(120, 142, 156 164, 204)
	NRG1	+	+/-	-[3,9]	+	Processing speed, visuomotor speed, attention, long-term episodic memory, short-term memory	(136, 142, 165 166)
	NRG3	+	+/-		+	Visuomotor speed, processing speed, mental flexibililty, executive function, sustained attention	(167, 168, 214)
	NRN1	+	+/-	-[3]		General intellectual ability	(169)
	SNAP-25	+	+/-	+[1]	+	Verbal memory, attention, executive function	(170, 215)
	PRODH	-	+/-	+/-[9]		-	(142, 171, 216)
	P2RX7	-	-	-[9]	-	-	(142, 217)
	NPY	-	+/-	-[9]	-	-	(142)
	NQO1	-	-	-[9]	+/-	-	(142)
	GST-1	-		-[9]		-	(142)
	GST-2	-		-[9]		-	(142)
erotonin	*5HTT/SLC6A4*	+/-	+/-	+	+/-	Executive function, attention	(136, 140, 172 218)
	HTR1A	+	+/-			Theory of mind	(136, 173)
	HTR2A	+/-	+/-	-[9]	+[4]/-	Voluntary and involuntary attention, executive function, verbal fluency	(120, 136, 142 156, 174-176 202)
	NET/SLC6A2	-	-			-	(125, 126)
Oligodendrocyte	*QKI*	-	-	-[5]	+	-	(165, 219)
	MAG	+	+/-	+[5]		Processing speed, visuomotor speed, attention	(165)
	CNP	-	+/-	-[5]		-	(165)
	OLIG2	-	+/-	+[5]	+[4]/-	-	(165, 220)

	ERBB4	-	+/-	+[5]	+	Verbal learning, abstraction, visuospatial memory	(136, 139, 165)
Glutamate	*GRIN2A*	-	+/-	+		-	(177)
	GRIN2B	+/-	+/-	+	+/-	Immediate and delayed recall (verbal memory)	(120, 136, 177)
	GRM1	+	+			Attention, verbal learning, abstraction, visuospatial memory, spatial processing	(136, 140, 205)
	GRM3	+	+/-	+/-[9]		Enhanced performance	(142, 177, 206)
	SLC1A2	+	+/-			Attention, abstraction, spatial memory	(136)
	DAOA	+	+/-	+[6]/-[9]	+[4]	Verbal memory	(142, 178, 179)
	GAD1	-	+/-	-[9]		-	(142)
on channel	*CACNA1C*	+/-	+	-[3]	+	Logical memory	(120, 180, 207-208)
	SCN2A	+		-[2]		Cognitive ability (g)	(181, 209)
Energy metabolism	*LYRM4*	+				Verbal memory	(182)
	FARS1	+				Verbal memory	(182)
	ATP2C2	-				-	(120)
Others	*ANK3*	+	+/-	+/-[3]	+/-	Working memory, verbal memory, attention	(183, 210, 211-221)
	TCF4	+	+/-	+[7]		Reasoning, problem-solving, attention-related tasks	(184, 185)
	CNNM2	-	+	-		Social cognition	(186, 222)
	CSMD1	+	+	+		General cognitive ability, memory cognition	(187, 188, 223-224)
	STH	+	-		+/-	Executive function	(144, 189)
	ACT	-	-		+	-	(190, 225)
	DCDC2	-	-			-	(120)
	DYX1C1	-				-	(120)
	KIAA0319	+				Verbal learning and recall	(120)
	NAGPA	-				-	(120)
	ZNF804A	+/-	+/-	+/-		Verbal learning and recall, verbal and spatial working memory, verbal episodic memory, visual memory	(120, 191-193, 226-229)
	CLSTN2	-		+/-		-	(120, 230, 231)
	WWC1	-	+	+/-	+/-	-	(120, 194, 232-235)
	ATRNL1	-				-	(120)
	C20orf196	-				-	(120)
	CRTC3	-				-	(120)
	DIP2C	-				-	(120)
	NFKBIL1	-	-			-	(120)
	PDE1C	-				-	(120)
	PKNOX1	-				-	(120)
	SPATA7	-				-	(120)
	ADCY8	-				-	(120, 177)
	CAMK2G	-			-	-	(120, 177)
	PRKACG	-				-	(177)
	PRKCA	+	+/-	+		Verbal memory	(177, 236)
	HEY1	+				Working memory	(195)
	MAD1L1	+	+			Cognitive ability	(196, 237)
	LSM1	+	+/-			Cognitive ability	(196, 238, 239)
	CAM	+				Memory, attention	(197)
	HLA-DQA1	+	-		+/- (A2)	Attention	(197, 240-242)
	RASGRF2	+				Memory cognition	(188)
	PLCG2	+				Memory cognition	(188)
	LMO1	+				Memory cognition	(188)
	PRKG1	+	-		+/-	Memory cognition	(188, 243, 244)
	EPO	+				Processing speed, short-term memory, and tasks requiring distinct fine motor component	(198)

	EPOR	+				Processing speed, short-term memory, and tasks requiring distinct fine motor component	(198)
	RGS4	+/-[1]	+/-	+[1]/-[9]	-	-	(142, 199, 245)
	PIP5K2A	-	+/-	-[9]		-	(142)
	AKT1	-	+/-	-[9]		-	(142)
	LRRTM1	-	+	-[9]		-	(142, 246)
	FGF2	+	-	-[2]/-[9]		- Speed of information processing, attention/vigilance, verbal learning and memory, working memory, reasoning and problem solving, set shifting, and verbal comprehension	(142)
	FGFR1	-		-[9]		-	(142)
	GPM6A	-	+	-[9]		-	(142, 247)
	GABRA6	-	+/-	-[9]		-	(142)
	NOS1	+/-	+/-	+/-[2,9]	+/-	General cognitive ability, verbal and spatial working memory	(142, 200)
	RGS2	-	+	-[9]		-	(142, 248)
	ROBO1	-		-[9]		-	(142)
	CHRM3	-		-[9]		-	(142)
	TBX1	-	+/-	-[9]		-	(142)
	ADRA2C	-		-[9]		-	(142, 249)
	FKBP5	+	-	-[9]		- Speed of information processing, attention/vigilance, verbal learning and memory, working memory, reasoning and problem solving, set shifting, and verbal comprehension	(142)
	DNMT3B	+	+	-[9]	+/-	- Speed of information processing, attention/vigilance, verbal learning and memory, working memory, reasoning and problem solving, set shifting, and verbal comprehension	(142, 250, 251)
	CNR1	-	+/-	-[9]		-	(142, 252)
	MTHFR	+/-	+/-	-[9]	+/-	-	(142, 143, 252 256)
	MTR	-	+	-[9]	+/-	-	(142, 253)
	MTRR	-	-	-[9]		-	(142, 253, 257 258)
	EHMT1	-		-[9]		-	(142)
	EHMT2	-	-	-[9]		-	(142)
	PRDM2	-		-[9]		-	(142)

* 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.