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Review article

Schizophrenia: genetics, prevention and rehabilitation

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Objective: Genetic factors are largely implicated in predisposing to schizophrenia. Environmental factors contribute to the onset of the disorder in individuals at increased genetic risk. Cognitive deficits have emerged as endophenotypes and potential therapeutic targets for schizophrenia because of their association with functional outcome. The aims of this review were to analyse the joint effect of genetic and environmental (G×E) factors on liability to schizophrenia and to investigate relationships between genes and cognitive endophenotypes focusing on practical applications for prevention and rehabilitation.
Methods: Medline search of relevant studies published between 1990 and 2008.
Results: In schizophrenia, examples of G×E interaction include the catechol-*O*-methyl transferase (COMT) (Val158Met) polymorphism, which was found to moderate the onset of psychotic manifestations in response to stress and to increase the risk for psychosis related to cannabis use, and neurodevelopmental genes such as *AKT1* (serine-threonine kinase), brain-derived neurotrophic factor (BDNF), DTNBP1 (dysbindin) and *GRM3* (metabotropic glutamate receptor 3), which were associated with development of schizophrenia in adulthood after exposure to perinatal obstetric complications. Neurocognitive deficits are recognised as core features of schizophrenia that facilitate the onset of the disorder and have a great impact on functional outcome. Neurocognitive deficits are also endophenotypes that have been linked to a variety of genes [*COMT*, neuregulin (NRG1), *BDNF*, Disrupted-In-Schizophrenia 1 (*DISC1*) and dysbindin] conferring susceptibility to schizophrenia. Recently, it has emerged that cognitive improvement during rehabilitation therapy was under control of *COMT* (Val158Met) polymorphism.
Conclusion: This review could indicate a pivotal role of psychiatric genetics in prevention and rehabilitation of schizophrenic psychoses.

Keywords: endophenotypes; gene; prevention; rehabilitation; review; schizophrenia

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Introduction

Schizophrenia is a severe and disabling mental disorder that compromises psychic activity, emotions, self-perception and social interactions.

A genetic component plays a substantial role in the aetiology of schizophrenia. Relatives of patients with schizophrenia have a 5–10 times increased risk for developing schizophrenia compared with the general population, which progressively decreases in more distant relatives (1). Concordance rates for schizophrenia in monozygotic twin pairs (50–60%) are four-folds higher than those in dizygotic twin pairs (10–15%), which reflects the proportion of shared genes in the two twin groups (2,3). Heritability for schizophrenia has been estimated at 80% (4). Linkage studies found some loci probably associated with schizophrenia on chromosomes 1, 2, 3, 5, 6, 8, 10, 11, 13, 14, 20 and 22 (5–9). To explore the genetic component of schizophrenia, association studies have been addressed mostly to the main transmission systems of

nervous impulses, evidencing possible associations, not always confirmed, between genes for some receptors, biosynthetic enzymes and neurotransmitter transporters (10). Recently, other candidate genes involved in synaptic plasticity and neurotrophic functions have shown a significant association level with schizophrenia (9), as well as genes related to the oligodendrocyte-myelin system (11). Reworking data from linkage and association studies have excluded that schizophrenia is caused by a single gene; disease transmission is more likely polygenic (1,12). Each gene has a small effect and different and, sometimes, contrasting association results; this may imply a diversity of genetic causes in different individuals with schizophrenia (9). A number of overlapping chromosome regions (1q, 2p, 10p, 13q, 18p and 22q) in linkage genome scans for schizophrenia and bipolar illness have led some to speculate on a common genetic diathesis for all psychoses (13). Altogether, these findings, in particular the lack of specificity of susceptibility genes, would lead to reconsider the role of genetics in schizophrenia. In fact, traditional view, genes code for the disorder in a simple, direct way, may be inappropriate as for other mental disorders (14). In recent years, endophenotypes have emerged as promising targets of psychiatry genetics. Adapted from the original meaning of internal, microscopic phenotype, which was introduced in a paper on insect biology, endophenotype is currently used in psychiatry research to define a measurable biological or psychological trait that is common to both individuals with a disease and their non-affected relatives and that may predispose to illness onset (15). Endophenotypes are thought to be closer to genetic underpinning than psychiatric syndromes that are pathophysiologically heterogeneous. As endophenotypes influence the course and outcome of psychiatric disorders (16), they could represent preferential targets for psychopharmacological therapies and psychiatric rehabilitation (17).

Although schizophrenia is often described as a genetic disorder, research has identified a variety of environmental factors that could affect its onset and course: obstetric complications (18), viral infections (19), stressful life events (20) and substance abuse (21). Gene-environment interplay is fundamental for the development of psychosis (22). The Finnish Adoptive Family Study of Schizophrenia found a higher prevalence of psychotic disorders in adopted offspring of schizophrenic patients compared with control adoptees with non-schizophrenic biological parents, but only in the presence of a disturbed environment in adoptive families (23). The study also found that persons with a genetic risk of schizophrenia are especially sensitive to the emotional climate of their family environment. A child-rearing environment with infrequent criticism and clear, straightforward communication appears to be protective against the symptomatic expression of genetic risk (24). The contribution of environmental and genetic factors to the onset of psychosis opens new scenarios for prevention, and the availability of models that explains gene-environment interplay is an emerging need in this field.

The aim of this paper was to review available literature on the genetics of schizophrenia focusing on environmental factors that increase the risk of developing psychosis and neurocognitive and psychophysiological endophenotypes that affect the onset and course of schizophrenic disorders. The article addresses the following topics: (a) relationship between genetic factors and schizophrenia endophenotypes and (b) interaction between genetic and environmental (G×E) factors in the development of schizophrenia. These findings are discussed in view of their implications for prevention and rehabilitation.

Methods

We performed a Medline search including all papers published between January 1990 and April 2008. To retrieve relevant papers, we used keywords such as 'gene', 'schizophrenia', 'endophenotype', 'cognitive deficit', 'executive function', 'working memory', 'P50', 'P300' and 'sensory gating' to investigate gene-endophenotype association; 'gene', 'schizophrenia', 'environment', 'obstetric complications', 'substance abuse', 'cannabis', 'viral infection', 'life-events' and 'stress' were applied as keywords to identify G×E interaction models.

Eligible studies were '*in vitro*' and '*in vivo*' animal and human studies. Review articles were considered for additional studies not retrieved by Medline search.

Results

Relationship between genes and endophenotypes

Following Gottesman and Gould's definition (15), the reasonable criteria for a viable schizophrenia endophenotype are as follows: (a) the endophenotype is a neuropsychological or neurophysiological character associated with schizophrenia; (b) the endophenotype is heritable; (c) the endophenotype is stable and trait related: its appearance is independent of state-related fluctuations in the individuals' conditions, although factors such as

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age may affect the endophenotype; (d) the endophenotype and schizophrenia show cosegregation and (e) the proband's specific endophenotype character is found at higher rates in the proband's relatives than in the general population.

Schizophrenia-related endophenotypes are cognitive functions such as attention, working memory, executive functions and visuospatial memory that are impaired in schizophrenic patients and in their non-schizophrenic relatives (25,26). Cognitive functions are associated with event-related potentials (ERPs): attention is associated with the P50 component of ERPs (27), which is related to sensory gating, whereas working memory and verbal fluency are associated with ERP component P300 (28,29). Both P50 and P300 ERPs are altered in schizophrenic patients and in their healthy relatives (30,31) and can be modified by antipsychotic treatments (32,33). These neuropsychological and electrophysiological endophenotypes have been related to susceptibility genes for schizophrenia.

Catechol-O-methyl transferase. Catechol-*O*-methyl transferase (COMT) enzyme terminates catecholamine activity in the brain by degrading these neurotransmitters. The gene encoding COMT – chromosome 22 (34) – has a functional polymorphism (Val108/158Met) that moderates dopamine availability in the prefrontal cortex (PFC) in an allele-dependent manner: the Met allele, which has a 3–4 times lower enzymatic activity, has been associated to higher dopamine levels in the PFC (35). Several studies have investigated *COMT* (Val108/158Met) polymorphism as a risk factor for schizophrenia: the Val-allele, which has a higher enzymatic activity resulting in lower PFC dopamine levels, has been found to confer susceptibility to schizophrenia in Caucasian populations, while its role in other ethnic groups (e.g. Asians) is more controversial (36). A large number of studies have proven the association of *COMT* (Val108/158Met) variants with cognitive functions in schizophrenic patients and non-affected relatives (37–47). The Val-allele has also been related to P50 sensory gating (48) and schizotypal personality traits (49,50).

Neuregulin 1. The neuregulins (NRGs) are cell-cell signalling proteins that are ligands for receptor tyrosine kinases of the ErbB family (51). The NRG1 proteins have been demonstrated to play important roles during the development of the nervous system (52) and moderate N-methyl-D-aspartate (NMDA) receptor function (53), and these findings support NRG1 involvement in the pathogenesis of schizophrenia (54). Mice with heterozygous deletion of NRG1 transmembrane domain have been characterised by behavioural phenotypes, which are related to human schizophrenia (55,56). *NRG1* is a positional candidate gene on chromosome 8p22-p11 that several genome-wide linkage scans have identified as a susceptibility locus for schizophrenia (57). *NRG1* has proven its association with schizophrenia in a variety of studies, although with conflicting results in Caucasian and Asian samples (58). The intermediate phenotypes of the *NRG1* gene have been poorly investigated. Recently, Stefanis et al. reported a moderate impact of this gene on sustained attention and working memory in the general population (59).

Brain-derived neurotrophic factor. Neurotrophins restore the functions of the damaged neurons and prevent apoptosis in adults, thus they are likely to be implicated in the pathophysiology of several mental disorders including schizophrenia (60). Indeed, abnormal activity of the neurotrophin system has been reported in schizophrenics' brains, in particular increased brain-derived neurotrophic factor (BDNF) levels have been found in the hippocampus and anterior cingulate cortex (61) and decreased BDNF in the PFC (62) of schizophrenic patients compared with healthy controls. The pathophysiological meaning of these findings is not yet fully understood. However, it has been demonstrated that BDNF can regulate the expression of Reelin (63,64), a protein that is involved in migration and positioning of cortical and hippocampal neurons during embryonic development of the brain (65). Both typical and atypical antipsychotics have been shown to reduce BDNF expression in various brain regions of the rat (66,67) and BDNF-like immunoreactivity in the serum of schizophrenics (68,69). The gene encoding BDNF is a putative susceptibility factor for psychosis (70). Two polymorphisms in the *BDNF* gene – Val66-Met and C270T – have been associated with schizophrenia, although their effects seem to be weak (71,72). The Val66Met polymorphism has also been connected with early phases of information processing in schizophrenic samples (73) and with verbal memory in schizophrenics and healthy controls (74).

Disrupted-In-Schizophrenia 1. Disrupted-In-Schizophrenia 1 (*DISC1*) is a gene disrupted by a balanced (1;11) (q42;q14.3) translocation that has been shown to cosegregate with major psychiatric disorders in a large Scottish family (75) DISC1 protein occurs in various subcellular compartments, which include the centrosome, microtubule fractions, postsynaptic

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densities, actin cytoskeletal fractions, the mitochondria and the nucleus (76). Recent studies have clarified that DISC1 is a component of a neurodevelopmentally regulated protein complex that has different functions in the developing and adult brain. In the developing brain, DISC1 has been implicated in neuronal migration (77) and in neurite outgrowth and extension (78). In the adult, DISC1 has been identified in multiple populations of neurons and in structures associated with synaptic function, suggesting that one of its adult functions may be synaptic plasticity (79). DISC1 is present in many of the brain regions known to be abnormal in schizophrenia, such as the PFC, hippocampus and thalamus (80). Mutant truncated DISC1 may contribute to schizophrenia susceptibility by altering neuronal architecture and migration (81). More recently, it has been suggested that DISC1 may interact with phosphodiesterase 4B (PDE4B) and biochemical cycle of 3′,5′-cyclic adenosine monophosphate (cAMP), which appears to be implicated in learning, memory and mood. According to proposed model, DISC1 sequesters PDE4B in resting cells and releases it in an activated state in response to elevated cAMP (82). The association of the *DISC1* gene (chromosome 1p42) with schizophrenia, which was originally reported in a Scottish population, has been replicated in other ethnic groups (80). *DISC1* single nucleotide polymorphisms have shown to be connected with sustained attention and working memory deficits in schizophrenic families (83,84).

DTNBP1. Dysbindin is an evolutionary conserved 40-kDa coiled-coil-containing protein that binds to alpha- and beta-dystrobrevin in muscle and brain. In the brain, dysbindin immunoreactivity is associated with glutamatergic mossy fibre terminals in the cerebellum and hippocampus (85). Although most aspects of its function are still waiting to be elucidated, dysbindin seems to promote neuronal viability and protect cortical neurons against death through phosphoinositide-3 (PI3)-kinase-Akt signalling. (86). Significant dysbindin reductions have been found at presynaptic levels in glutamatergic afferents of the subiculum, hippocampus and dentate gyrus in the brain of schizophrenic patients (87). *DNTBP1* is the gene encoding dysbindin on chromosome 6p22.3. Sequence variations in *DNTBP1* determine reductions in dysbindin messenger RNA levels in the PFC of schizophrenics (88) and mediate the risk for schizophrenia by lowering dysbindin expression (89). A variety of linkage and association studies have supported *DTNBP1* as a susceptibility gene for schizophrenia, although with different haplotypes (90). In samples of schizophrenics, carriers of the *DNTBP1* risk haplotype have been associated to early visual processing deficits and a significantly lower spatial working memory performance (91,92). In addition, genetic variation in *DNTBP1* has been shown to influence general cognitive ability (93).

GRM3. A large body of evidence supports the involvement of the glutamate system in schizophrenia. Glutamatergic NMDA receptor antagonist phencyclidine can cause psychotic symptoms in healthy individuals and exacerbate psychosis in schizophrenics (94). Phencyclidine-evoked motor behaviours in rats are suppressed by glutamate receptor agonists (95), which are currently studied as new agents to treat schizophrenia in phase-2 trials (96). *GRM3*, a metabotropic glutamate receptor modulating synaptic glutamate, has emerged as a promising candidate gene for schizophrenia (97). Variation in *GRM3* mediates glutamate release in the PFC and cognitive functioning in psychotic patients (98).

CHRNA7. Sensory gating is impaired in schizophrenia most likely because of dysregulation of nicotinic cholinergic neurotransmission. Indeed, cigarette smoking and nicotine administration have been shown to reverse sensory gating deficit in individuals with schizophrenia (99) and in relatives of schizophrenics (99) in a transient manner. Nicotine can also reverse diminished inhibitory sensory gating in cocaine addicts (100). One measure of sensory gating abnormalities, diminished inhibition of the P50 evoked response to repeated auditory stimuli, has been linked to the chromosome 15q14 locus of the alpha-7-nicotinic receptor gene (*CHRNA7*) (101). This site has shown linkage to schizophrenia across several studies. Polymorphisms in the core promoter of the gene are associated with schizophrenia and also with diminished inhibition of the P50 response (102,103).

Interaction between G×E factors

In twin studies on schizophrenia, identical twins show average concordance rates of only 50%, although they share 100% of their genes (1). This finding does not necessarily exclude a pure genetic aetiology: it is also possible that non-genetic factors consist entirely of stochastic events affecting gene expression or structure (104). However, there is a general agreement on the contribution of environmental factors to schizophrenia pathophysiology (2). Identification of these factors is hampered by the lack of reliable objective measures for subjective psychological variables, thus

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research has focused on the few measurable environmental variables (22).

Obstetric complications. It is well established that exposure to obstetric complications in the prenatal or perinatal periods increases the risk for schizophrenia with a small but significant effect (18). Complications of pregnancy, abnormal foetal growth and complications of delivery are more often reported in individuals who later develop schizophrenia than in non-schizophrenic controls (105). The pathogenic effect of these events generally lies in a hypoxic damage of foetal and neonatal brains (106–108). Foetal hypoxia is associated with structural brain abnormalities [reduced grey matter and increased cerebrospinal fluid (CSF)] among schizophrenic patients and their non-schizophrenic siblings but not among controls at low genetic risk (109). This is clearly a proof that hypoxic brain damage leading to schizophrenia is mediated by genetic factors. Indeed, brain hypoxia was shown to alter the expression of 20 susceptibility genes for schizophrenia (110). In particular, the most consistent finding was about the *NRG1* gene, which was found to be expressed at higher levels in rats exposed to brain hypoxia within the first postpartum week (111). These models of gene-environment interaction are also confirmed by recent human studies. Thus, Nicodemus et al. reported that a few polymorphisms in the *DTNBP1*, *AKT1*, BDNF and *GRM3* genes increased risk for developing schizophrenia in individuals who were exposed to obstetric complications causing foetal hypoxia (112).

Viral infections. Population studies indicate that exposure to influenza epidemics between the third and seventh month of gestation is associated with schizophrenia in adult life, suggesting that maternal-foetal transmission of influenza virus may be a risk factor for schizophrenia (113). To corroborate this hypothesis, a French study demonstrated that prenatal exposure to influenza virus occurred more frequently in schizophrenic patients than in non-schizophrenic siblings and a control sample (114). The pathogenic effect of influenza viral infection has been studied in rodents. Mice exposed to prenatal human influenza viral infection showed altered levels of neuronal nitric oxide synthase (115), which has been implicated in synaptogenesis and excitotoxicity, abnormal pyramidal cell density and atrophy (116) and increased expression of markers of gliosis (117).

Studies have suggested that also cytomegalovirus (CMV) may play an aetiological role in schizophrenia. Indeed, it has been reported that some patients experiencing initial episodes of schizophrenia had increased levels of immunoglobulin G antibodies against CMV in their sera and CSF (118). Treatment with antipsychotic medications may result in a decrease in CMV antibodies (119), while treatment with antiherpes virus and anti-inflammatory medications may reduce symptoms in some individuals with schizophrenia (120). The onset of schizophrenia following prenatal exposure to viral infections is most likely mediated by genetic factors. In rats, olfactory bulb injection of a neuroadapted influenza A virus strain led to persistent changes in spatial learning and elevated transcriptional activity of the gene encoding synaptic regulatory protein RGS4 (121), which has been pointed to as a schizophrenia liability gene. Some polymorphisms within the chromosomal region 6p-21-p23 have been noted to confer risk for schizophrenia in conjunction with CMV exposure (122).

Substance abuse. Epidemiological data indicate that 30–60% of schizophrenics meet lifetime criteria for substance abuse or dependence (123–126). The 6-month prevalence of substance misuse in schizophrenia is 10–30% (123,126), with alcohol and cannabis having the greatest diffusion (123). In adolescents, regular use of cannabis almost doubles the risk of psychotic outcomes (21). This effect is dose dependent and much stronger in individuals with predisposition for psychosis (127). Family histories of schizophrenia have been more often reported in psychotic patients who were cannabis positive on urinary screening than in controls with psychosis who screened negatively for all substances of abuse (128). Thus, it is necessary to postulate a gene-environment interaction to explain the onset of psychotic symptoms in response to cannabis use. Caspi et al. identified the role of the *COMT* (Val108/158Met) polymorphism in developing psychosis in adulthood after exposure to cannabis during adolescence: individuals who carried the Val-allele were more likely to experience psychotic symptoms or any schizophrenia-like disorder (129). More recently, the Val-allele has been associated not only with psychosis after exposure to delta-9-tetrahydrocannabinol (THC) but also with attention and working memory deficits (130). On the contrary, Zammit et al. reported no effect of the *COMT* gene on association between cannabis and psychosis (131). Another valuable candidate gene is the one encoding *NRG1*. NRG1-deficient knockout mice showed positive correlations with animal models of schizophrenia after administration of THC and increased c-Fos expression in the amygdala, nucleus accumbens and lateral septum

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but only in the subsample exposed to behavioural stimulation (132). These findings might imply a complex interaction between stress, genetic factors and cannabis in substance-induced psychosis but need to be replicated in humans.

Furthermore, amphetamine-induced psychosis has been related to the dysbindin *DTNBP1* gene (133).

Life stress. Exposure to stressful life events facilitates the onset of the first episode of psychosis (20) and triggers depressive exacerbation in the early course of schizophrenia (134). Schizophrenic patients are more vulnerable to the effect of daily life stress (135). This characteristic, which is independent of cognitive deficits, may support an affective pathogenesis of schizophrenia (136).

The *COMT* (Val108/158Met) polymorphism has been demonstrated to modulate the impact of stress on psychotic symptoms. Stefanis et al. used a semi-experimental paradigm to evaluate the effect of stress on psychosis manifestations in a sample of young men at recruitment in the Greek army and noted that carriers of the *COMT* (Val108/158Met) Val-allele experienced higher levels of psychotic symptoms after stress exposure (137). On the contrary, van Winkel et al. reported that psychosis sensitivity to stress was higher in Met/Met homozygotes (138).

Discussion

Gene, environment and prevention

A variety of environmental factors contribute to the onset of schizophrenia. The task of primary prevention is to identify and remove those risks. The benefit of primary prevention for the population's health may be considerable. A recent meta-analysis reported a 40% increased risk for any psychotic outcome in individuals who had ever used cannabis (21): based on this finding, it has been estimated that in UK at least 800 new cases of schizophrenia yearly could be avoided if cannabis was no longer used by individuals at risk for psychosis.

Genetics may have a key role in primary prevention of schizophrenia. Accordingly, the main finding of this review, in line with more authoritative opinions of leading researchers in psychogenetics (139), is that sensitivity to environmental risk factors is under genetic control. Thus, the *COMT* (Val108/158Met) polymorphism has been found to modulate the risk of developing psychosis in individuals who are cannabis users (129) or exposed to stress conditions (137,138). Various genes whose expression is regulated by hypoxia (*AKT1*, *DTNBP1*, BDNF and *GRM3*) have been shown to interact with obstetric complications to influence risk for schizophrenia (112). Although gene-environment models have surfaced to schizophrenia research, their application to prevention activity is still premature. In fact, many gene-environment associations were only reported in animal studies. Other genes were associated with environmental factors in humans, but replication studies are needed. Future research is expected to identify new models of G×E interaction. Morphometry has shown a larger proportion of myelinated fibres with atrophy of axon and swelling of periaxonal oligodendrocyte processes, a lower number of oligodendroglial satellites of pyramidal neurons and a loss of pericapillary oligodendrocytes in the PFC of schizophrenic patients compared with non-schizophrenic controls (140). These white matter abnormalities have been associated with cognitive deficits (141). Preliminary evidence suggests that substance abuse, particularly cannabis, might interfere with the development of frontal white matter in some adolescents, thus leading to less white matter (142). Therefore, it is arguable that oligodendrocyte-myelin-related genes (e.g. MAG; 2,3-cyclic nucleotide 3′-PDE; QKI and SOX10), which have been associated with schizophrenia (11), may affect risk for psychosis in substance abusers (143). Communication deviance has been found to be higher in families with schizophrenic offspring (144–146) and has emerged as a risk factor for schizophrenia by interacting with genetic liability (147,148). Recent studies suggest that communication deviance might be under genetic control (149), although there is no information on implicated genes.

Secondary prevention involves individuals at increased risk for schizophrenia to prevent the onset of the first psychotic episode. Ultra-high-risk individuals with family histories of psychosis and a recent decline in social functioning or subthreshold psychotic manifestations (150,151) develop schizophrenia in 30–40% of cases within 1—2 years of follow-up (152–154). As transition to psychosis does not occur in about two thirds of these subjects, ultra-high-risk criteria may not be specific enough to warrant secondary prevention interventions. Genetics may improve identification of at risk subjects for developing schizophrenia to an acceptable level for secondary prevention activity; this hypothesis needs to be confirmed by future research. The knowledge of gene-endophenotype interaction may increase the feasibility of prophylactic interventions. Thus, cannabis is known to alter sensory gating, thereby causing substance-induced psychosis (155–157). The *COMT*

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gene has been associated to both gating deficits in schizophrenia (48) and onset of psychosis in cannabis users (129). Taken together, these findings would indicate that reducing sensory gating deficits among cannabis users carrying at risk variant (Val-allele) of the *COMT* gene, e.g. by administration of atypical antipsychotics (158) or nicotinic cholinergic agonists (100), might aid in preventing psychotic complications.

Genetics and rehabilitation

In schizophrenic patients, cognitive deficits are not only related to psychopathological dimensions – significant associations have been reported between executive function deficits and negative symptoms (159,160) and between working memory deficits and disorganisation (160,161) – but also affect psychosocial functioning and long-term outcome (162–166). Therefore, reducing cognitive impairment is considered to be one of the main objectives in the treatment of schizophrenia (167).

Cognitive dysfunction can be treated by atypical antipsychotics (168–170). A recent meta-analysis demonstrates that atypicals produce a mild remediation of cognitive deficits in schizophrenia, each atypical having a greater effect on specific cognitive domains (171). Given the moderate efficacy of antipsychotics on cognitive deficits, a relatively large number of schizophrenics could have partial or no improvement in cognitive functions during antipsychotic treatment. Besides antipsychotics, cognitive deficits can also be targeted by training exercises of impaired cognitive functions (172). These cognitive remediation interventions produce moderate improvements in cognitive performance and psychosocial outcomes, with only small effects on the symptoms of schizophrenia (173). The efficacy of cognitive remediation programmes is variable and seems to be dependent on the use of specific components of training (174).

This paper summarised the contribution of genetic factors to cognitive dysfunction in schizophrenic subjects and their relatives. We argue that the same genes that have been related to cognitive deficits may influence cognitive function response to antipsychotic treatment and cognitive remediation therapy. This hypothesis is now supported by some experimental data. Indeed, in a recent study of schizophrenics treated with clozapine, cognitive improvement during antipsychotic therapy was found to be influenced by *COMT* (Val108/158Met) genotype (40). The *COMT* gene is also involved in response to cognitive remediation interventions. Fifty out-patients with chronic schizophrenia were evaluated over a 3-month follow-up on active rehabilitation treatment including cognitive remediation exercises or control treatment with standard rehabilitation alone and genotyped for *COMT* (Val108/158Met) variants: carriers of the Met allele showed a greater improvement in cognitive flexibility and quality of life on active treatment compared with Val/Val homozygotes on control treatment (175).

Further studies are warranted to confirm the impact of the *COMT* gene on cognitive response and to elucidate the role of other 'cognitive' genes.

Conclusions

Schizophrenia has a complex pathophysiology that involves both genetic and environmental factors as well as their interaction. To understand the link between these two categories of susceptibility, adoption studies have clarified that adoptees without a pre-existing genetic liability were not vulnerable to the effects of a disturbed family environment, whereas individuals with a pre-existing genetic liability could only express this liability in the presence of additional adverse environmental factors (23,147,148). In contrast to traditional view, which postulates that genes and environment have independent effects, these findings point to gene-environment interaction accounting for schizophrenia liability. This establishes the role of genetics in prevention of schizophrenia. Available literature suggests that genes do not directly target schizophrenic disorders; instead, they have been linked to cognitive endophenotypes that affect psychosocial functioning and long-term outcome of psychosis. This opens new perspectives for genetics in schizophrenia rehabilitation.

In conclusion, although psychogenetics was born as a branch of biological psychiatry, genetic research on schizophrenia has gone beyond neurobiology to encompass biopsychosocial model.

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