• Review •

Research in China on the molecular genetics of schizophrenia

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Summary: Schizophrenia is a complex disease caused by genetic and environmental factors with a global heritability of more than 80%. By the end of the 1970s, Chinese scientists reported a heritability of schizophrenia of 82.9% in the Chinese Han population. Continuous improvements in research techniques and the recruitment of larger samples have made it possible for Chinese scientists to identify a number of candidate susceptibility genes for schizophrenia. This article reviews the results in genetic research of schizophrenia by Chinese scientists over the last five decades.

1. Introduction

Schizophrenia (SZ) is a severe mental disorder characterized by decrements in cognitive functioning, emotional responsiveness, and behavior. The global lifetime prevalence of this disorder is about 1%. The first onset of SZ is usually during adolescence or adulthood, typically between 15 and 35 years of age. About 50% of SZ patients develop this disorder between 20 and 30 years of age, and smaller fractions of patients develop it before 10 years of age (childhood-onset SZ) or between 40 and 50 years of age (late-onset SZ). In most patients the progression is continuous, with episodes of recurrent symptoms interspersed with periods of partial remission. Consequently, the illness is usually chronic and the prognosis is poor in terms of social development and cognitive functioning. Although the exact pathogenesis of SZ remains unclear there is general consensus that the onset and course of schizophrenia is controlled by both genetic and environmental factors. The genetic basis of SZ has been a topic of intense research worldwide; family, twin, and adoption studies have demonstrated that the heritability of SZ is greater than 80%.

In China SZ has been recognized as a major public health issue. A substantial body of research has developed that aims to clarify the molecular genetic mechanisms underlying the disorder. Improved research techniques and large samples of patients have made it possible to identify a number candidate susceptibility genes for SZ in China. The current article reviews the progress in this field made by Chinese scientists.

2. Classical genetics

In the 1970s, the *Shanghai Polygenic Inheritance Collaborative Research Group* investigated the heritability of SZ in Chinese individuals using classical genetic methods (i.e., family surveys, twin and adoption studies) and estimated a heritability of 82.9% in the Chinese population. Subsequent studies reported heritability for schizophrenia of 63 to 78% in Chinese individuals[1] and heritability of 70% in Chinese children.[2] Similar to results from international studies, these heritability estimates for SZ became widely accepted in China. But the genetic complexity of schizophrenia and the limitations of research techniques and equipment in China in the 1970s and 1980s made it impossible to conduct more detailed studies of potential susceptibility genes for SZ. By the early 1990s molecular biological techniques had advanced in China, so Chinese neuroscientists started to explore the genes associated with SZ.

3. Family linkage analysis

In the late 1980s, Jiang and colleagues[3] con-ducted a pioneer linkage study in China to locate SZ susceptibility genes in 11 families using HLA antibodies and blood groups (i.e., ABO, P, MN, and Rh) as genetic markers, but they found no association between SZ and these markers, with logarithms of odds (LOD) scores between 0.083 and -0.296. In a subsequent study[4] they analyzed the restriction-fragment length polymorphisms (RFLPs) of the Ha-ras-1 genes in 14 SZ patients and 12 controls by enzymatic restriction and Southern blotting and found a significant association between SZ susceptibility and a 1.7-kb restriction fragment, with a relative risk of 14.47. In 2001, Yu et al.[5] conducted a linkage disequilibrium analysis using microsatellite markers and PCR techniques among male SZ patients in 70 families and found a significant association between SZ and HSU93305 (a locus on the short arm of the X chromosome). One year later, in 2002, Deng et al.[6] performed gene scans for 137 sib-pair families with SZ based on 28 microsatellite

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markers on chromosome 6 and found a relationship between D6S1960 and the positive symptoms of SZ (LOD, 1.39), and a relationship between D6S291 and both the general pathology symptoms of SZ (LOD, 2.5) and the negative symptoms of SZ (LOD, 1.56). Their findings suggested the existence of SZ susceptibility genes on the short arm of chromosome 6. Chen et al.[7] investigated 60 sibling pairs with chronic SZ and 120 patients with sporadic SZ using 60 unaffected sibling pairs and 120 controls as the respective controls; they found significantly higher frequencies of 264 bp and 278 bp alleles at D6S296 in the sibling pairs with chronic SZ than in the control pairs (264 bp, χ^2=18.84, p<0.01; 278 bp, χ^2=4.59, p<0.05, respectively). Cai et al.[8] performed a linkage analysis and quantitative trait locus study of SZ susceptibility genes for 32 families with familial SZ by analyzing 29 microsatellite markers distributed on chromosome 1. They detected an association between SZ and D1S206 (LOD, 1.71, p=0.046) and D1S425 (LOD, 1.37, p=0.086), suggesting the presence of SZ susceptibility genes on the long arm of chromosome 1. Their results also suggested that the negative symptoms of SZ may be related to independent quantitative trait loci in the chromosomal region 1q21-23. Tang et al.[9] studied a number of candidate chromosomal regions (e.g., 1q21-22, 1q32-44, 5q21-33, 6p24-22, 8p22-21, 10p15-11, 11q23-24, 11p15, 12q23-24, 13q32-34, 22q11-12, 9q34, 16p13, 12q13, 17q25 and 19q13) for a SZ family with 26 members by capillary electrophoresis and only detected an association between SZ and one chromosomal region (i.e, 11q22.1-24.2). In contrast, Zhu et al.[10] and Chen et al.[11] performed microsatellite scans for 119 SZ patients and 119 controls and found positive associations between SZ and several chromosomal regions (i.e., D13S265, D21S1256, D1S2878, D8S264, and D9S273; see Table 1).

4. Genetic association analysis

The progress of molecular biological techniques and, particularly, the use of single nucleotide polymorphisms (SNPs) as genetic markers has greatly improved the efficiency of genotyping and expedited the application of genetic association analysis. In the late 1990s, based on the mechanisms of action of antipsychotic medications, studies on candidate genes for SZ were focused on 5-hydroxytryptamine (5-HT) and dopamine (DA) receptors. The most commonly used designs for association studies were case-control analyses and family-based transmission disequilibrium tests.

Table 1. Family linkage analysis

Chromosome	Gene/Locus	Finding	Sample size	Method	Reference
1	D1S206, D1S425	Association, (p=0.046)	32 families with familial SZ	Genome scanning	Cai[8]
1	D1S2878	Positive association (D1S2878, p<0.01)	119 SZ patients and 119 normal controls	Capillary electrophoresis	Chen[11]
6	28 microsatellite markers	Positive associations (D6S1960, Lod=1.39; D6S291, Lod=2.5)	137 sibling pair families with SZ	Microsatellite scanning	Deng[6]
6	D6S274, D6S296	Significantly higher frequencies of D6S296 alleles (264bp and 278bp) in sibling pairs with chronic SZ than in normal sibling pairs (264bp: χ^2=18.84, p<0.01; 278bp: χ^2=4.59, p<0.05)	60 sibling pairs with chronic SZ and 60 normal sibling pairs; 120 patients with sporadic SZ and 120 normal controls	PCR-RFLP	Chen[7]
6	20 microsatellite markers	Positive associations with D6S289 (p<0.01) and D6S460 (p<0.01)	119 SZ patients and 119 normal controls	Capillary electrophoresis	Zhu[12]
8	14 microsatellite markers	Positive association with D8S264 (p<0.05)	119 SZ patients and 119 normal controls	Capillary electrophoresis	Wei[13]
9p21, 9q21	20 microsatellite markers	Positive association with D9S273 (p<0.01)	119 SZ patients and 119 normal controls	Capillary electrophoresis	Zhu[10]
13q31.3	14 microsatellite markers	Positive association with D13S265 (p<0.01)	119 SZ patients and 119 normal controls	Capillary electrophoresis	Chen[14]
13q	7 microsatellite markers	Positive associations with D13S170 (p=0.0195), D13S265 (p=0.0273), and D13S159 (p=0.0488)	4 high-SZ-risk families	Microsatellite scanning	Luo[15]
21	5 microsatellite markers	Positive association with D21S1256	119 SZ patients and 119 normal controls	Capillary electrophoresis	Zhou[16]
Xp1	HS212G6, HS884M20, HSU93305	Association between SZ and HSU93305	70 SZ patients	PCR-RFLP	Yu[5]
	1q21-22, 1q32-44, 5q21-33, 6p24-22, 8p22-21, 10p15-11, 11q23-24, 11p15, 12q23-24, 13q32-34, 22q11-12, 9q34, 16p13, 12q13, 17q25, 19q13	Positive association with 11q22.1-24.2	A SZ-risk family with 26 members	Capillary electrophoresis	Tang[9]

Subsequent work investigated candidate genes related to various theories about the causes of SZ (e.g., the glutamate hypothesis, neurodevelopmental hypothesis, neurodegenerative hypothesis, immune abnormality hypothesis). Within a relatively short period of time several groups produced results about the association of various genes with SZ. With the exception of chromosomes 16 and Y, all other chromosomes have been examined for linkage with SZ. Table 2 summarizes the genes that have been extensively studied in China.

4.1 Neurotransmitter-related genes

4.1.1 Dopamine receptor D (DRD) genes

The DRD system consists of two families: the D1-like

Table 2. Extensively analyzed genes for association with schizophrenia

Physiological system	Gene	Chromosome and region	Polymorphism locus
Neurotransmitter system	5-HT receptors	Chromosomes 1, 5, 11, 13, and X	T102A, A1438G, 5-HT1A-C(-1019)G, 5-HT2CR(-697C), 5-HT2cR Cys23Ser, 5-HT6(rs3790756 and rs4912138), 5HTR2C-759C/T, 5-HTR2C-759C/T, 5-HTR4 (rs888957(C/T), VNTR locus (5-HTTLPR), etc
	DA system	Chromosomes 3, 4, 5, and 11	-141C deletion, (48bp-VNTR), TaqI A polymorphism -48A/G, 697G→C, -A241G, ser9Gly, (CT/GT/GA)n, etc.
	Glutamate receptor (GLUR)	Chromosomes 3 and 7	rs2227283(G/A), rs6922753, D7S644, D7S2555, D7S2481, rsl6915130, GRM7-CNVS, etc
	Cholecystokinin (CCK)	Chromosome 3	-45C/T, 1270, etc
Neurotransmitter metabolic enzyme system	COMT	Chromosome 22	136-Bcl I, Val108/158Met, rs4633-rs4680, rs3751082, etc
	MAOs	X	(CA)n, (GT)n, rs1799836, rs6323, -941G/T and -1460C/T, promoter VNTR, etc
Neurodevelopment-related system	NTF-3	Chromosome 12	Gly/Glu dinucleotide repeat polymorphism, etc
	NRG1	Chromosome 8	rs2954041, SNP8NRG221533(C/T), SNP8NRG243177(C/T), rs3924999(A/G), rs3735774(A/G), rs2954041(G/T), rs2919390(G/T), rs6988339(A/G), etc
	BDNF	Chromosome 11	C270T, G196A, (GT)n, Val66Met, Met66Met, etc
Tumor- and immune-related systems	Human leukocyte antigen (HLA)	Chromosome 6	rs 2239800
	Interleukins (ILs)	Chromosomes 1 and 2	
	Tumor necrosis factor (TNF)		G308A, C863A, G252A, CC857T, T1031C, etc
	TXNIP	Chromosome 5	rs7211, rs9245, etc
	APC	Chromosome 5	rs2229992, rs42427, rs465899, etc
Other systems	Apolipoprotein (APO) system	Chromosomes 2, 6, 11, and 12	
	Regulator of G protein signaling 4 (RGS4)	Chromosome 1	rs2344671, rs12753561, rs10759, etc
	Disrupted-in-schizophrenia-1 (DISC1)	Chromosome 1	rs821616, rs821597, rs2295959, etc
	Acid ceramidise (ASAH1)	Chromosome 8	rs3753118, rs3753116, rs7830490, etc
	Cytochrome P450 (CYP) enzymes	Chromosomes 7, 15, and 22	CYP1A: C734A, CYP2D6: C188T, +10B defect, G/A1934, rs1344706, C100T, G681A etc
	Methylenetetrahydrofolate reductase (MTHFR)	Chromosome 1	C677T, A1298C, etc

family receptors and the D2-like family receptors. The D1-like family receptors include the DRD1 and DRD5 genes. The D2-like family receptors include the DRD2, DRD3, and DRD4 genes. Between 2000 and 2005 research on the DRD systems in Chinese SZ patients focused on the DRD2, DRD3, and DRD4 genes. Studies first examined DRD2 because of the well-established linear relationship between the effects of antipsychotic medications and their binding affinities to DRD2. These studies investigated the A-241G polymorphism, TaqIA RFLP, C ins/del mutation in the promoter region (position -141), and the (CA)n dinucleotide-repeat polymorphism in intron 1. However, these studies did not find a significant relationship between SZ and DRD2, and only one study (with 101 families) found an association between the DRD2-A241G genotype and the clinical characteristics of SZ (e.g., delusion score, hallucination score, emotional abnormalities, thought form abnormalities, aphasia and the duration of symptoms).[17]

DRD3 is mainly expressed in the ventral parts of the basal ganglia (e.g., nucleus accumbens). Most studies in China have focused on the Ser9Gly polymorphism of the DRD3 gene. Three out of eight studies[18-20] found associations between the Ser9Gly polymorphism and SZ, while the other five failed to detect an association.

The DRD4 gene is also a major candidate susceptibility gene for SZ because of its predominant expression in the frontal cortex and the high affinity of DRD4 receptors to clozapine, a potent atypical antipsychotic medication. Studies in China have focused on a 48-bp repeating sequence in the third exon of the DRF4 gene, known as 48-bp variable number tandem repeat (VNTR). In 2000, Luo et al.[21] discovered an association between 48-bp VNTR and refractory SZ in a study of 104 SZ patients and 76 controls. In another study of 510 patients and 171 controls in 2001, Tang et al.[22] observed SZ to be related to four repeats of 48-bp VNTR (X^2=13.00, df=1, p<0.001). However, this association was not confirmed in smaller subsequent studies of 38 patients and 76 controls[23] and 162 patients and 162 controls.[24]

After 2005 studies in China increasingly focused on the genes encoding DRD1, DRD5, and DA transporter 1 (DAT1). In 2005, Hu et al.[25] reported a higher frequency of the DRD1 AA genotype in SZ patients than in controls (X^2=6.621, p<0.01), suggesting that the allele A was a susceptibility gene for SZ. In 2011, Zhu et al.[26] studied 385 SZ patients and 350 controls and found an association between SZ and two SNP of the DRD1 gene (i.e., rs686 and rs10063995). However, in another study of 373 patients and 379 controls,[27] Zhang et al. failed to detect an association between SZ and DRD1 SNPs (i.e., rs4532, rs5326, rs2168631, rs6882300 and rs267418). Compared with the extensive research on DRD1, few studies have investigated the DRD5 gene in Chinese individuals, and the studies that do exist have small sample sizes; no significant associations have been found between DRD5 and SZ in Chinese patients.[28, 29]

In 2010, Huang et al.[30] performed genotyping for 352 Chinese SZ patients and 311 controls to identify six promoter polymorphisms of the DAT1 gene (i.e., rs6413429, rs2652511, rs2975226, rs6347 and rs27072) and a VNTR of this gene. They found a positive association between SZ and two polymorphisms (rs2652511 and rs2975226) and an association between SZ and a promoter region haplotype (rs2652511-rs2975226-rs6413429).

4.1.2 5-HTR receptors

Human 5-HTR receptors are divided into seven subtypes. One of these subtypes, the 5-HT2A receptor (5-HTR2A), is the target of many antipsychotic medications. Therefore, the 5-HTR2A gene has been the target of extensive research, much of which has focused on the T102C polymorphism. In a 1997 study of 223 patients and 162 controls, Luo et al.[31] first reported that the A1/A1 genotype at the T102C locus was a risk factor for SZ. Some subsequent studies supported this finding,[32,33] but most did not. Zhang et al.[34] conducted a small-scale study and found an association (p<0.05) between 5-HTR2A-A1438G and tardive dyskinesia in chronic SZ, but subsequent larger studies failed to confirm this association. Yi et al.[35] reported an association between SZ and the 5-HTR6 gene (X^2=5.16, p<0.05). A research group at Shanghai Jiao Tong University performed several studies with large samples and found that a repeating sequence (STin2) in the 5-HT transporter (5-HTT) gene was associated with SZ in Chinese patients,[36] but they found no significant associations between SZ and other loci of this gene.[37,38] Studies in China have also investigated the relationship between SZ and 5-HT polymorphisms (e.g., 5-HT1A-C-1019G, 5-HTR1B, 5-HTR2C, 5-HTR4), but the results are inconclusive. A few studies suggested that the polymorphisms of the genes encoding 5-HTT[39] and 5-HTR3A[40] may be useful for predicting the therapeutic response of Chinese patients with SZ to treatment with risperidone.

4.1.3 Neurotransmitter metabolic enzymes

After release into the extracellular space, neurotransmitters are degraded by their metabolic enzymes. The genes encoding these enzymes have also been considered candidate susceptibility genes for SZ. Existing studies have focused on the genes encoding catechol-O-methyltransferase (COMT, an enzyme catalyzing dopamine) and monoamine oxidases (MAOs, key enzymes in the catabolism of monoamine neurotransmitters).

Many studies have focused on the Val158Met polymorphisms of the COMT gene. In 2002, Tang et al.[41] investigated 476 SZ patients and 207 controls, and identified associations between early-onset SZ and the Val158Met polymorphism. Shen Yan's research group revealed that COMT may play important roles

in the development of paranoid SZ[42,43] and that the COMT gene may be associated with the negative symptoms of chronic SZ.[44] Kang et al.[45] examined the relationship between the P300 event-related potential (ERP) component and the Val158Met polymorphism in Chinese SZ patients and found significantly shorter P300 latencies (at Cz and Pz) in Met homozygotes than those in Val/Met carriers and Val/Val carriers, and significantly shorter P300 latencies (Cz and Pz) in Val/Met carriers than in Val/Val carriers; taken together these results suggest a relationship between the Val158Met polymorphism and P300 abnormalities in patients with SZ. Other studies suggested that this polymorphism may be implicated in cognitive functions,[46] propensity for violence,[47] and tardive dyskinesia[48] in Chinese SZ patients, although a few studies failed to detect such relations.[49,50] Additionally, Liu et al.[51] and Lü et al.[52] reported that SZ is associated with the 900 ins/del and the 287A/G polymorphisms of the COMT gene. In a relatively small-scale study (82 patients and 88 controls) in 2003 Jiang et al.[53] observed an association between SZ and the gene encoding monoamine oxidase B (MAOB), but there was no association between SZ and the gene encoding monoamine oxidase A (MAOA). Subsequently, Wei et al.[54] reported an association between SZ and the rs1799836 polymorphism of the MAOB gene (p=0.00001). Shi et al.[55] performed genetic association analysis for 212 SZ patients and 168 controls, but they detected no association between SZ and the MAOA gene polymorphism. However, a study of Chinese SZ patients in Taiwan[56] reported that SZ was associated with the 941T/G polymorphism of the MAOA gene in male patients, but not in female patients.

4.2 Neuroimmune- and endocrine-related genes

In the mid-1990s the emergence of the immune hypothesis of SZ lead to the realization that genes related to the immunoendocrine system may be SZ susceptibility genes. Human leukocyte antigens (HLAs) are an important component of the human immune system. The genes encoding the HLAs are located on the short arm of chromosome 6. Some large-sample nuclear-family studies and case-control association analyses in China have suggested a relation between SZ and the HLA class-II genes in immune cells.[57,58] Yu et al.[59] analyzed 190 nuclear families with SZ and suggested an association between the rs2239800 SNP of the HLA-DQA1 gene and positive symptoms in SZ. Yu et al.[60] subsequently confirmed this association in 195 nuclear families.

The results from other studies on the association between SZ and HLA class-II genes are inconclusive.[58-61] Yang et al.[61] analyzed 277 SZ patients and 355 controls and observed significant associations between SZ and HLA class-I genes, but a subsequent study[62] of 355 patients and 321 controls failed to confirm these associations. The potential relationship between SZ and genes encoding other immune factors (e.g., IL-2R, L-1β, IL-10, and TNF-α) has also been examined, but the results are inconsistent.

Cholecystokinin (CCK) is a peptide hormone responsible for stimulating the digestion of fat and proteins. The promoter region polymorphisms (i.e., -333G/T and -286A/C) of the CCK receptor gene have also been suggested as susceptibility genes for SZ.[63] Song et al.[64] studied 94 nuclear families with SZ and identified the CCK gene as an important factor affecting the severity of negative symptoms in SZ. Lü et al.[65] analyzed 77 nuclear families and another 32 SZ patients and found an association between the CCK gene polymorphism and the positive symptoms of SZ; this association was confirmed in a subsequent study[66] of 207 female SZ patients and 202 female controls. In contrast, several other studies[67,68] failed to confirm such an association. In addition, Itokawa[69] suggested that the polymorphism of the neuropeptide Y (NPY) gene is associated with SZ, but a subsequent study of 583 Chinese SZ patients failed to find this association. [70] The inconsistency between these studies may be partially attributed to their relatively small sample sizes.

4.3 Cancer-related genes

International epidemiological surveys have revealed that SZ patients have lower incidences of cancers than the general population, suggesting a potential antagonism between SZ and cancers. Using DNA microarray analysis, Cui et al.[71] discovered significantly different expression of the adenomatous polyposis coli (APC) and thioredoxin interacting protein (TXNIP) genes in the peripheral blood leukocytes of Chinese SZ patients compared to controls. The APC gene is a key factor in the Wnt signaling pathway and is located in 5q21-22, a chromosomal region reported to host many SZ susceptibility genes. The TXNIP gene is located in 1q21.1 (another region containing SZ susceptibility genes) and participates in cell proliferation and differentiation. In particular, this gene also participates in suppressing tumor metastasis and is involved in neuron damage. In another study,[72] the same research group analyzed 169 nuclear families and found significant associations between SZ and three SNPs of the APC gene (rs2229992, χ^2=4.23, p<0.05; rs42427, χ^2=4.15, p<0.05; rs465899 χ^2=8.49, p<0.01), and a significant association between SZ and the APC haplotypes from rs2229992-rs42427-rs465899 (χ^2=44.376, p<0.05). Subsequently, this group investigated[73] 182 nuclear families and identified associations between SZ and the APC rs7211 SNP (χ^2=6.32, p=0.012), as well as between SZ and the haplotypes from rs7211-rs9245 (χ^2=5.01, df=1, p=0.024).

4.4 Neurodevelopment-related genes and others

After 2000, with the development of the neurodevelopment hypothesis for SZ, a series of

neurodevelopment-related genes were investigated as possible SZ susceptibility genes. Brain-derived neurotrophic factor (BDNF) is a protein with important functions in the growth, survival, and differentiation of neurons and has vital roles in the hippocampus and the dopaminergic system. Studies have focused on the C270T, Val66Met, and (GT)n dinucleotide-repeat polymorphisms of the BDNF gene. In 2005, He et al.[74,75] reported an association between SZ and the C270T polymorphism. The association was confirmed by subsequent studies.[76-78] Xiu et al.[79] identified the G196A and C270T polymorphisms of this gene as risk factors in SZ patients who were smokers. Two studies[80,81] found no direct association between SZ susceptibility and the Val66Met polymorphism in Chinese patients, but both studies found that the polymorphism was related to the age of onset of SZ. Xu et al.[82] performed case-control association analysis and meta-analysis for Chinese patients but detected no association between SZ susceptibility and the C270T or Val66Met polymorphism. In another study, these authors[83] identified an association between BDNF (GT)n dinucleotide-repeat polymorphism and SZ, and associations between the polymorphism and chlorpromazine-induced extrapyramidal adverse effects and therapeutic response to treatment with risperidone. Collectively, the available results on Chinese patient groups support the roles of the BDNF gene in the pathogenesis of SZ.

Neuregulin 1 (NRG1) is another protein essential for the development and differentiation of neurons. Only a few studies have investigated the relation between NRG1 and SZ in Chinese individuals. A study of 258 nuclear families with SZ[84] and another study examining 315 patients and 347 controls[85] found an association between NRG1 and SZ in Chinese patients.

Methylenetetrahydrofolate reductase (MTHFR) is a key methyl transferase affecting the development of the nervous system and also the principal methyl donor in the human body. The C/T polymorphism at the 677 bp (T677C) of the MTHFR gene has been found to affect the enzymatic activity of MTHFR. Several case-control studies have supported the association between SZ susceptibility and the T677C polymorphism in Chinese individuals.[86,87] The study by Yang et al.[86] with 100 first-episode SZ patients and 100 controls suggested that T677C polymorphism is associated with SZ, a finding that was confirmed by the study of Feng et al.[88] among 123 patients and 123 controls. But Shi et al.[89] did not detect this association in a study of 106 nuclear families with SZ.

Regulator of G protein signaling 4 (RGS4) is a protein that participates in neuron differentiation and modulates serotonergic (5-HTergic) receptors and metabolic glutamate receptors. The RGS4 gene is located in a chromosomal region containing candidate SZ genes, and its expression is regulated by dopaminergic neurotransmitters. In two studies (one including 386 SZ patients and 390 controls[90]; the other 315 patients and 347 controls[84]) Yue et al. found associations between SZ and two polymorphisms of the RGS4 gene (rs12753561: χ^2=8.97, p=0.002; rs10759: χ^2=13.77, F=0.002, p=0.002). In a study of 504 SZ patients and 531 controls, So et al.[91] analyzed the relation between SZ and four rGS4 SNPs (rs10917670(G/A), rs951436(G/T), rs951439(A/G), rs2661319(A/G). Their results suggested that the GGGG haplotype may be a risk factor for the development of SZ, but studies by Zhang et al.[92] and Guo et al.[93] did not confirm these results.

Neurotrophin-3 (NTF3) is a protein closely related to the survival, proliferation, and migration of neurons. International studies have revealed the association between SZ susceptibility and the G304A polymorphism of the NTF3 gene. Few studies, however, have examined the role of NFT3 in Chinese SZ patients. Wu et al.[94] compared 80 patients with 81 controls and found an association between SZ and the Gly-63/Glu-63 polymorphism of the NTF3 gene. Du et al.[95] confirmed this association (χ^2=6.86, p<0.05) in a larger-scale study in children with SZ. Studies on other NTF-3 gene polymorphisms, such as the dinucleotide-repeat polymorphism examined by Deng et al.,[96] failed to detect an association with SZ in Chinese patients.

Disrupted-in-schizophrenia-1 (DISC1) is a multifunctional regulator of cell activities, such as neuronal axis and dendrite outgrowth. The DISC1 gene, first discovered in a family with SZ in Scotland, is characterized by a balanced (t[1;11] q[42.1;14.3]) chromosomal translation. In 2007, Qu et al.[97] compared 313 SZ patients and 317 controls, and identified associations between SZ susceptibility and two DISC1 gene SNPs (rs821616: χ^2=7.8006, p=0.0052; rs821597: χ^2=9.5404, p=0.0020). These findings were confirmed in a subsequent study[98] of 466 patients and 551 controls (rs821616: χ^2=7.063, p=0.008; rs821597: χ^2=6.009, p=0.014); this second study also reported that the GA haplotype was a risk factor for SZ (χ^2=6.01, p=0.014). Several small-scale case-control studies [99,100] also found an association between the rs821616 polymorphism and SZ. But another study[101] of 560 patients and 576 controls failed to detect significant associations between SZ and the two loci; this study found a weak association between the rs2295959 polymorphism and SZ in the female patients (χ^2=6.188, p=0.0135, OR=0.728, 95% confidence level: 0.567–0.935).

N-acylsphingosine amidohydrolase 1 (ASAH1, also known as acid ceramidase) is a critical enzyme that catalyzes sphingomyelin synthesis and participates in brain neuronal development and in the metabolism of sphingomyelin. The ASAH1 gene is located in 8p22-21.3, a 'hotspot' region of SZ susceptibility genes. Zhang et al.[102] investigated ASAH1 SNPs in 254 SZ families and identified two haplotypes (rs3753118T-rs7830490A and rs3753118T-rs3753116G-rs7830490A) that were risk

factors for SZ. In another study, they also identified[103] linkage between the SNPs and the quantitative traits loci (QTL) in SZ (rs3753118: p=0.030; rs3753116: p=0.030; rs7830490: p=0.036).

The roles of other genes in SZ have also been examined in Chinese patients, such as the genes encoding proline dehydrogenase (PRODH), tryptophan hydrogenase (TPH), apolipoprotein D(APOD), apolipoprotein E(APOE), neuronal acetylcholine receptor subunit α-7(CHRNA7), and dopamine β–hydroxylase(DBH). For example, Yue et al.[104] detected an association between SZ susceptibility and the PRDH gene in a study of 330 patients and 334 controls. This association was confirmed by another study of paranoid SZ patients.[105] Three separate studies[106-108] suggested that TPH gene polymorphisms may be associated with SZ susceptibility in female patients, male patients, and minority ethnic groups of Chinese citizens.

Despite a large number of studies, the available studies on candidate SZ susceptibility genes for Chinese individuals have a common limitation of relatively small sample sizes. Consequently, results from these studies need to be verified by larger scale in-depth research.

5. Expression of schizophrenia-related genes

In the 2000s, the development of DNA microarrays provided an effective tool for clarifying the genetic mechanisms of SZ. Cui et al.[71] first analyzed the peripheral blood leukocyte gene expression patterns of six Chinese patients with SZ and six controls using cDNA microarrays with 8,464 genes. Compared with the patterns of the controls, the SZ patients showed 31 differentially expressed genes (DEGs, 29 down-regulated; the other 2 up-regulated). These DEGs (Table 3) included cancer suppressor genes, cancer-related genes, and neurodevelopment-related genes. Subsequently, this research group compared the gene expression patterns of 30 drug-naïve, first-episode SZ patients, 30 medicated patients with recurrent SZ, and 30 controls. They confirmed changes in the expression levels of APC, TXN1, and ASH1 genes by quantitative real-time PCR and were the first to report the relationship of the three genes to SZ.[72,102,94]

The emergence of quantitative real-time PCR around 2005 offered more opportunities for genetic research. Correspondingly, many studies in China have applied quantitative (or semi-quantitative) real-time PCR to investigate the expression of candidate SZ susceptibility genes in peripheral blood cells, such as genes related to the dopamine system and immune factors. Liu et al.[109] analyzed the expression of the genes encoding interleukin 1β (IL-1β), tumor necrosis factor α (TNF-α), and tyrosine hydrogenase (TH) in 30 SZ patients, 25 control siblings, and 30 controls. The expression levels of L-1β, TNF-α, and TH were similar in the SZ patients and their siblings, but substantially lower in the controls, suggesting the presence of dopaminergic hyperfunction and inflammatory cytokine overexpression in SZ patients. In another study, Liu et al.[110] compared the expression levels of the nitric oxide synthase (NOS) gene in 63 SZ patients, 54 control siblings, and 51 controls. Their results indicated a NOS overexpression in the SZ patients that was positively correlated with the severity of positive symptoms.

Despite these positive results, the exact relations between SZ susceptibility gene expression in the peripheral blood and the expression in the central nervous system (e.g., to what extent the former represents the latter) remains unclear. So after 2007 the number of studies solely focused on the expression of SZ susceptibility genes rapidly decreased. One exception is the 2010 study by Zhang et al.[111] which found increased DRD1 gene expression in patients with first-episode SZ compared with controls, a positive correlation between the level of DRD1 expression and the severity of negative symptoms, and an inverse relationship between the level of DRD1 expression level and the level of aggressiveness of the patient. Another exception is the study by Zhang et al.[112] that found no significant association between SZ and the expression of the G72 gene.

6. Genome-wide association studies (GWASs)

With rapid development of DNA microarray techniques, particularly since 2007, several GWASs have been conducted to investigate the genetic mechanisms of SZ. In 2011 two research groups in China independently conducted large-sample GWASs in Chinese SZ patients. As shown in Table 4, Shi et al.[113] analyzed 546,561 SNPs in 3,570 individuals with schizophrenia and 6,468 controls using Affymetrix 6.0 microarrays and discovered associations between SZ and five SNPs on chromosomes 1 and 8. Yue et al.[114] analyzed 620,901 SNPs and copy number variations in 746 individuals with schizophrenia and 1,599 controls using Illumina 610 microarrays and independently validated the findings in 4,027 patients and 5,603 controls, identifying significant associations between SZ and 6 SNPs on chromosomes 6 and 11. However, there was no overlap in the identified SNPs between these two large-sample studies.

7. Challenges and prospects in molecular genetics of schizophrenia

7.1 Challenges

Chinese scientists have conducted a large number of studies on the molecular genetics of SZ and have identified or confirmed a large number of susceptibility genes. However, many of these studies are repetitive or superficial and most of them have relatively small sample sizes so the results all need to be verified by multiple, large-scale studies. The two available GWASs studies used large samples but they still had inconsistent

Table 3. Summary of 31 differentially expressed genes screened by DNA microarray assays

No.	UniGene ID	Ganbank accession number	Chromosomal region	Gene name	Gene description (or encoded protein)	Mean expression ratio
1	Hs.165263	HSU89278	1p34.3	PHC2/EDR2/HPH2	Human polyhomeotic 2 homolog (HPH2)	0.331
2	Hs.75823	HSU16954	1q21.1	AF1q	Fused gene (human acute lymphoblastic leukemia gene and chromosome 1q)	0.244*
3	Hs.179526	S73591	1q21.1	TXNIP/VDUP1/ TBP2	Brain-expressed HHCPA78 homologue (from human promyelocytic leukemia cell line HL-60)	0.267*
4	Hs.429504	A141346	1q23.3	GAS5	Human growth arrest-specific transcript 5	0.242*
5	Hs.82425	AF07807	1q25.2	ARPC5/ARC16	Human actin Apr2/3 complex 16 kDa subunit (ARC16) (participate in actin polymerization in cells)	0.339
6	Hs.170171	HSGLUSYN/Y00387	1q31	GLUL/GLNS	Human glutamine synthase	0.337
7	Hs.21599	AB015132	2q32	KLF7/UKLF	Ubiquitous human Kruppel-like factor	0.339
8	Hs.75290	HUMARF4/M36341	3p21.2-p21.1	ARF4	Human ADP-ribosylation factor 4 (ARF4)	0.481
9	Hs.169793	HSRPL32/XO3342	3p25-24	RPL32	Human ribosomal protein L32	0.260*
10	Hs.66394	AB00068	4p16.3	RNF4/SNURF	Human ring-finger protein 4 mRNA (RES4-26)	0.182*
11	Hs.75081	HUMFAPAPC/m74088	5q21-22	APC	Adenomatous polyposis coli (APC) gene	2.184*
12	75627	HSCK14R/X13334	5q31.1	CD14	Leukocyte differentiation antigen of myeloid cell-specific leucine-rich glycoprotein (CD14 gene)	0.281*
13	Hs.318720	HUMMHDRW01	6p21.1-p22.3	HLA-DRB4	Human histocompatibility complex class II HLA-DRw53-beta (DR4, w4)	0.342
14	Hs.236774	HSARGICG/X64282	6p21.3	HMGN4	Human tRNA-arginine (tRNA-Arg) gene (anticodon: ICG) and pseudogene of tRNA-valine (tRNA-val) (anticodon: CAC)	0.353
15	Hs.375570	HUMMHDRWA/ M2043	6p21.3	HLA-DRB1	Human histocompatibility complex class II HLA-DR-beta (DR2-DQw1/DR4 DQw3)	0.317
16	Hs.227777	HSU48296	6q12	PTP4A1/PRL1	Human protein tyrosine phosphatase (hPTPCAAX1)	0.351
17	Hs.232400	HUMHNRNP/D28877	7p15.2-p14	HNRPA2B1	Human heterogeneous nuclear ribonucleoprotein A2B1(hnRNPA2/B1)	2.223*
18	Hs.75811	HSU70063	8p22-21.3	ASAH1/PHP	Human aci ceramidase	0.377*
19	Hs.248107	HSEDG3/X83864	9q22.1-22.2	EDG3	Human sphingolipid G-protein-coupled receptor gene (endothelial differentiation gene 3, EDG3 gene)	0.396
20	Hs.79334	HSE4BP4RN/X64318	9q22.1-22.3	NFIL3/E4BP4/ IL3BP1	Human adenovirus E-4 binding protein (E4BP4) gene, [i.e., nuclear factor, interleukin 3 regulated (NFIL3)]	0.260*
21	Hs.433394	HSTUBAG/X01703	12q12-14.3	TUBA3	Human α-tubulin 3 (b alpha i)	0.305*
22	Hs.278270	HUMPRA/L24804	12q13.13	TEBP/P23	Human p23 protein (a component of progesterone receptor complexes, a ubiquitous conserved protein)	0.497
23	Hs.416087	AF087693	12q21.2	LIN7A/VELI1/ MALS-1/TIP-33	Human VELI 1 mRNA (involved in synaptic vesicle exocytosis, synaptic function and plasticity, and neuron formation)	0.414
24	Hs.116875	AB020880	12q24.11	SART3	Human squamous cell carcinoma antigen (SART-3)	0.231*
25	Hs.8116	HSFERTBPS/Y09232	12q24.13	-	Human Fertilin α pseudogene	0.231*
26	Hs.79971	HSZPHSAL2/X98834	14q11.1-q12.1	SALL2	Human zinc finger protein Hsal2 (or sal-2)	0.263*
27	Hs.1742	HUMORFA01/X98834	15q26.1	IQGAP1/ KIAA0051	Also known as human KIAA0051 gene. One IO motif of the protein encoded by this gene contains GTPase-activating-like protein. The encoded protein interacts with the cytoskeleton components, cell adhesion molecules, and signal molecules to modulate cell morphology.	0.338
28	Hs.9691	HUMG13A/L22075	17q24.3	GNA13/G13	Human guanine nucleotide binding protein subunit α-13 (G13)	0.417
29	Hs.180877	HSHH3X3B/Z48950	17q25	H3F3B	Human histone hH3.3B	0.388
30	Hs.119475	HUMCIRPA/D78134	19p13.3	CIRBP	Human cold inducible RNA binding protein (CIRP)	0.509
31	Hs.6113	AF061939	20q13.1	STAU	Human staufen protein gene, alternatively spliced. The gene encodes a double-strand-RNA-binding protein (STAU) that participates in RNA localization during translation.	0.338*

* the CY5/CY3 fluorescence ratios are smaller than 0.5 or bigger than 2.0 [71]
Source: the ID, location, name, and description of differentially expressed genes in SZ patients, and mean CY5/CY3 fluorescence ratios[72]

Table 4. Two available genome-wide association studies on Chinese SZ patients

Research group (reference)	Analysis platform	Sample		Loci with positive associations (p-value)
Shi[113]	Affymetrix SNP 6.0microarrays	Patients: 3750	Controls: 6468	**Chromosome 1**
		NC: 1578	NC: 1592	rs10489202 (9.50×10^{-9})
		CC: 1238	CC: 2856	rs1060041 (5.31×110^{-7})
		SC: 934	SC: 2020	rs11586522 (1.17×10^{-4})
				Chromosome 8
				rs16887244(1.27×10^{-10})
				rs1488935(5.06×10^{-9})
Yue[114]	Illuminal Humamn 610-Quad microarrays	Patients: 768	Controls: 1733	**Chromosome 6**
				rs1635(5.53×10^{-12})
				rs2142731(5.14×10^{-10})
				Chromosome 11
				rs11038167(1.09×10^{-11})
				rs11038172(7.21×10^{-10})
				rs835784(2.71×10^{-11})

NC, Nothern China; CC, Central China; SC, Southern China

results; this may have been due to different recruitment procedures or heterogeneity within the samples.

Furthermore, the GWAS methodology has several weaknesses: a) Simultaneously analyzing tens of thousands of loci inevitably results in severe error accumulation that may not be fully resolved by using statistical corrections for multiple testing. There is no standard method available to differentiate true positives from false positives; b) As a multifactorial disorder, SZ is only weakly associated with individual genes so these weak associations may be missed; c) The GWAS may not be appropriate for complex diseases like SZ that probably involve the interaction of different genes; d) Microarrays for GWAS may have flaws that adversely affect the accuracy of genotyping analysis; e) Effective research strategies and statistical methods for GWAS are, as yet, imperfect.

7.2 Prospects: exome sequencing, whole-genome sequencing, and applications

Since 2000, the introduction of the Roche 454, Illumina Solexa, and ABI SOLiD platforms has marked the appearance of second-generation sequencing technologies. The rapid advance of high-throughput sequencing platforms multiplies sequencing speed and reduces cost. This technical progress has made exome sequencing and whole-genome sequencing possible, thereby allowing accurate localization of pathogenic genes of SZ. Relevant studies are underway worldwide, including in China, but no results have been reported. We believe that in the next several years these second-generation sequencing technologies will lead to breakthrough discoveries in the molecular genetics of SZ in China and elsewhere.

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