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REVIEW

Pharmacogenetic Correlates of Antipsychotic-Induced Weight Gain in the Chinese Population

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Abstract Antipsychotic-induced weight gain (AIWG) is a common adverse effect of this treatment, particularly with second-generation antipsychotics, and it is a major health problem around the world. We aimed to review the progress of pharmacogenetic studies on AIWG in the Chinese population to compare the results for Chinese with other ethnic populations, identify the limitations and problems of current studies, and provide future research directions in China. Both English and Chinese electronic databases were searched to identify eligible studies. We determined that > 25 single-nucleotide polymorphisms in 19 genes have been investigated in association with AIWG in Chinese patients over the past few decades. *HTR2C* rs3813929 is the most frequently studied single-nucleotide polymorphism, and it seems to be the most strongly associated with AIWG in the Chinese population. However, many genes that have been reported to be associated with AIWG in other ethnic populations have not been included in Chinese studies. To explain the pharmacogenetic reasons for AIWG in the Chinese population, genome-wide association studies and multiple-center, standard, unified, and large samples are needed.

Keywords Pharmacogenetic · Antipsychotic · Weight gain · Single nucleotide polymorphism · Schizophrenia

Introduction

Schizophrenia (SCZ) is a highly heritable mental illness that affects ~1% of the world population [1–3]. Second-generation antipsychotics (SGAs) are the first-line antipsychotics prescribed in clinical practice for the treatment of SCZ, bipolar disorder, and other psychotic disorders [4]. SGAs have fewer or no extrapyramidal symptoms and arguably provide a greater improvement of negative symptoms at clinically effective doses than do first-generation antipsychotics (FGAs). However, patients who use SGAs may exhibit troublesome weight gain [5], obesity, and associated metabolic syndromes (e.g., dyslipidemia, insulin resistance, hyperglycemia, and type II diabetes) [6, 7]. These adverse effects may decrease patient compliance and increase health costs [8, 9], which could be a significant burden on both the physical and financial well-being of patients and their families.

Despite considerable research efforts, the etiology of antipsychotic-induced weight gain (AIWG) remains obscure [10]. Previous studies have indicated that the affinity of SGAs for serotoninergic, dopaminergic, and histaminergic receptors in the central nervous system, particularly their antagonistic effects on serotoninergic 2C and histamine H1 receptors in the hypothalamus, is the cause of AIWG [11, 12]. In rodent studies, hypothalamic

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ghrelin signaling, histamine H1 receptors, and AMP-activated protein kinase signaling have been implicated in AIWG [13, 14]. Lifestyle, genetic effects, medication, demographics, and physiological and pathological status are possible factors associated with AIWG [15–17] (Fig. 1). Genetic studies of twins and siblings revealed similar weight gain after treatment with SGAs [18]. In addition, unrelated individuals treated with the same SGA gained weight as a result of related gene variants [19, 20]. Thus, specific gene polymorphisms might play a vital role in AIWG.

Pharmacogenetics is the interdisciplinary study of gene function and molecular pharmacology and aims to explore the relationships between genetic differences (both congenital and acquired) and drug effects (both therapeutic and adverse) [21]. Because of the variety of factors associated with AIWG, the rapid development of pharmacogenetics will be needed to meet the demands of precision medicine. Genome-wide association studies (GWASs) have been used to identify multiple gene variants associated with AIWG in SCZ patients [22, 23], and the functions of the proteins affected by these variants have also been studied [24]. Zhang *et al.* summarized the pharmacogenomic literature on AIWG in recent decades and reported that 11 single-nucleotide polymorphism (SNPs) in 8 genes were associated with AIWG around the world [25]. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), sponsored by the US National Institute of Mental Health, has published numerous pharmacogenetic studies on AIWG as part of the trial [23, 26–28]. In China, considerable progress has been made toward investigating the pharmacogenetics of AIWG in psychiatric patients; however, an overall review has not been conducted in the Chinese population. We reviewed the pharmacogenetic research on AIWG in the Chinese population with the aim of comparing the findings for Chinese with other ethnic populations, identifying the limitations and problems of current studies, and providing future research directions in China.

Methods

The literature search was conducted in both English and Chinese databases. PubMed, EMBASE, and the Cochrane Library were used to search the literature in English, and the China National Knowledge Infrastructure (CNKI), Wan Fang, and Chongqing VIP Information, were used to search the literature in Chinese. The key words used for the searches included China (also Chinese, Mainland, Hong Kong, Macau, and Taiwan), antipsychotics (also the names of single antipsychotics), single-nucleotide polymorphism (also SNP, mutation, variant, polymorphism, and genetic), and weight gain (also obesity, body mass index, and BMI). The Boolean operators (AND, OR, and NOT) were used in combination with the key words. All literature was searched up to June 30, 2018. The selected studies met the following inclusion criteria: (1) sample composed entirely of Chinese psychiatric patients, (2) patients received single-agent antipsychotic treatment for at least 2 weeks, and (3) data on body weight or BMI or change before and after treatment. Exclusion criteria were as follows: (1) studies of non-psychiatry patients, (2) data did not contain information on changes in weight or BMI before and after treatment, and (3) partially or entirely duplicated studies (only the most comprehensive study was included). As a result, the search produced 986 unduplicated hits from the above databases, and finally 33 reports (29 in English and 4 in Chinese) were included in this review (Fig. 2, Table 1).

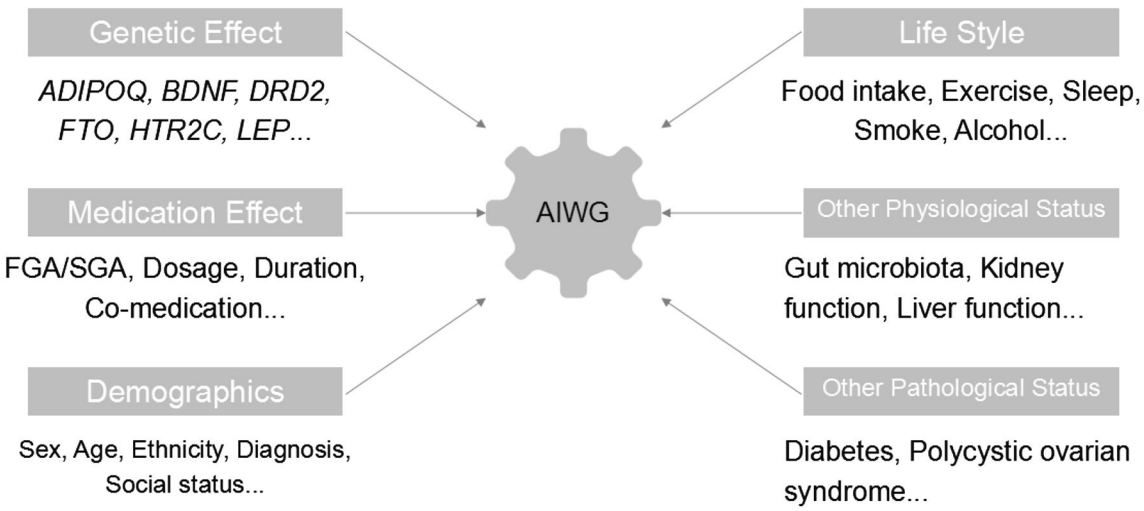

Fig. 1 Possible factors associated with antipsychotic-induced weight gain (AIWG).

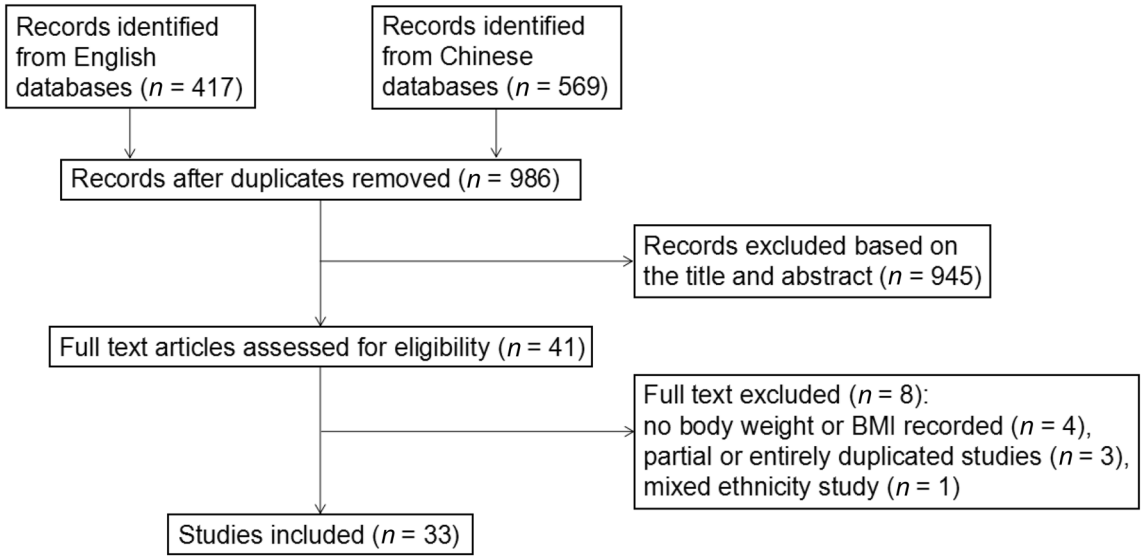

Fig. 2 Literature search strategy.

Genes that Code for Receptors Modulated by Antipsychotics

Serotonin Receptor

The serotonin receptor, a type of G-protein-coupled receptor, regulates the transmission of excitatory and inhibitory neurotransmitters and is a target for a variety of drugs [29]. Among these targets, *HTR2C* is the most-studied serotonin receptor gene in the Chinese population with AIWG. Since the *HTR2C* gene is located on chromosome Xq24, gender-specific heterosis effects have been reported as well [30]. In 2002, Reynolds *et al.* first identified the *HTR2C*-759C>T (rs3813929) polymorphism as a functional SNP associated with AIWG in 123 Chinese patients with first-episode psychosis (OR = 6.01, 95% CI = 1.92–18.79, P = 0.001) [30]. Subsequent studies in Chinese patients confirmed this finding and demonstrated that the T allele is associated with less weight gain than the C allele [31–34]. However, some researchers in China have been unable to replicate this finding [35, 36], consistent with studies in other parts of Asia [37, 38]. The discrepancy within the same population may be due to differences in the clinical status of patients; positive associations were found in first-episode SCZ patients [30–34], while negative associations were found in chronic or refractory patients [35, 36]. The *HTR2C* promoter polymorphism -697C/T (rs518147), with or without rs3813929 in the coding region, has a reported relationship with AIWG (χ^2 = 10.89, P = 0.001) [34], and a recent meta-analysis suggested that the -697C allele might be a risk allele for antipsychotic-induced metabolic syndrome [39]. An additional 5 SNPs in *HTR2C* were not found to have any association with AIWG in the Chinese population [36, 40]. Among them, Cys23Ser (rs6318) was found to be associated with AIWG in many Caucasian studies [41], but the very low frequency of the 23Ser allele in Asians may have contributed to the negative findings in the Chinese population [40, 42].

HTR2A, which is one of the most studied receptors in relation to the antipsychotic response, has a high affinity for SGAs and gene polymorphisms have been reported to be involved in antipsychotic-induced side-effects [43]. The 102T/C (rs6313) polymorphism is a synonymous substitution located in the coding region, and one study reported that, among Chinese patients treated with risperidone, those with the C/C genotype gain less weight by 1.432 kg than do those with the T/T genotype ($P < 0.0001$) [31]. The underlying mechanism is that the C allele downregulates *HTR2A* promoter activity, which may lower the response rate and the adverse effects of antipsychotics [44]. In an earlier Chinese population study, Hong *et al.* failed to find any relationship between rs6313 and body weight change in patients treated with clozapine [40]. Although rs6313 was found to be in linkage disequilibrium with rs6311, Mou *et al.* failed to demonstrate that rs6311 was associated with AIWG in first-episode SCZ patients [45]. In studies of other ethnicities, the results also remain inconsistent [46–48]. As listed in the HapMap project, the minor alleles of rs6313 and rs6311 differ between the Chinese and Caucasian populations, which may produce controversial pharmacogenetic results in different racial studies.

The *HTR6* gene is located on chromosome 1, and the 267C/T (rs1805054) polymorphism has been associated with an improved treatment response for positive and general symptoms in patients receiving risperidone [49].

Table 1 Pharmacogenetic studies of AIWG in the Chinese population.

Study	Gene (SNPs)	*n* (male %)	Age (years)	Diagnosis (FE%)	APs	Duration	Main finding
Dong, 2015 [147]	*RBFOX1* (rs8048076, rs1478697, rs10500331, rs4786847)	328 (49%)	29.1 ± 7.6	SCZ (0)	OLZ	8 weeks	*RBFOX1* rs1478697 polymorphism showed an association with AIWG ($P = 0.0012$)
Fang, 2016 [97]	*BDNF* (rs6265)	308 (66%)	44.6 ± 10.3	SCZ (0)	various APs	4.8 ± 4.0 years	*BDNF* rs6265 polymorphism showed an association with AIWG ($P < 0.01$)
Hong, 2001 [40]	*HTR2A* (rs6313) *HTR2C* (rs6318) *HTR6* (rs1805054) *SLC6A4* (rs25531)	93 (65%)	37.1 ± 8.2	SCZ (0)	CLZ	4 months	NS
Hong, 2002 [57]	*HRH1* (rs2067467)	88 (66%)	37.1 ± 8.2	SCZ (0)	CLZ	4 months	NS
Hong, 2010 [53]	*DRD2* (rs1799978, rs4350392, rs7131056, rs4245148, rs12574471, rs4648318, rs4436578, rs7350522, rs2075652, rs2734833, rs6275, rs2242591) *ANKK1* (rs1800497)	479 (59%)	47.2 ± 13.2	SCZ (0)	CLZ, OLZ, RIS	48.2 ± 27.8 months	*DRD2* rs4436578 polymorphism showed an association with AIWG ($P = 0.001$)
Hu, 2013 [137]	*NRXN3* (rs11624704, rs7154021, rs724373, rs7154021, rs7142344, rs221492, rs221454)	1214 (44.2%)	31.0 ± 10.7	SCZ (27%)	RIS	6 weeks	*NRXN3* rs11624704 and rs7154021 polymorphisms showed associations with AIWG ($P = 0.03$ and $P = 0.008$, respectively)
Huang, 2011 [155]	*TNF* (rs1800629)	500 (60%)	43.9 ± 9.0	SCZ (0)	CLZ, OLZ, RIS	3 months	NS
Lane, 2006 [33]	*HTR1A* (rs1800042) *HTR2A* (rs6313, rs6314) *HTR2C* (rs3813929) *HTR6* (rs1805054) *DRD1* (rs265981, rs4532) *DRD2* (rs1799732, rs1801028) *ANKK1* (rs1800497) *ADRA1A* (rs1048101) *BDNF* (rs6265)	123 (55%)	34.0 ± 9.7	SCZ (0)	RIS	6 weeks	*HTR2A* rs6313, *HTR2C* rs3813929, *HTR6* rs1805054 and *BDNF* rs6265 polymorphisms showed associations with AIWG ($P < 0.0001$, $P = 0.04$, $P = 0.02$, $P = 0.02$, respectively)
Li, 2017 [75]	43 SNPs from 23 genes	339 (39.8)	38.7 ± 11.5	SCZ SAD (25%)	Various APs	12 weeks	*TOX* rs11777927, *ADIPOQ* rs182052, *CDKN2A/B* rs3731245 and rs2811708 polymorphisms showed associations with AIWG ($P = 0.009$, $P = 0.019$, $P = 0.040$, $P = 0.039$, respectively)
Mou, 2005 [45]	*HTR2A* (rs6311)	84 (65%)	25 ± 6	SCZ (100%)	CLP, RIS	10 weeks	NS

Table 1 continued

Study	Gene (SNPs)	*n* (male %)	Age (years)	Diagnosis (FE%)	APs	Duration	Main finding
Mou, 2008 [73]	*LEP* (rs7799039)	84 (65%)	25 ± 6	SCZ (100%)	CLP, RIS	10 weeks	*LEP* rs7799039 polymorphism showed an association with AIWG ($P = 0.045$)
Reynolds, 2002 [30]	*HTR2C* (rs3813929)	123 (50%)	26.6 ± 7.7	SCZ (100%)	Various APs	6 and 10 weeks	*HTR2C* rs3813929 polymorphism showed an association with AIWG ($P = 0.0003$)
Reynolds, 2003 [32]	*HTR2C* (rs3813929)	32 (66%)	NR	SCZ (100%)	CLZ	6 weeks	*HTR2C* rs3813929 polymorphism showed an association with AIWG ($P < 0.02$)
Song, 2014 [115]	*FTO* (rs9939609, rs8050136, rs1421085, rs9939506)	237 (54%)	27.5 ± 7.6	SCZ (100%)	RIS	6 months	*FTO* rs9939609 and rs8050136 polymorphisms showed associations with AIWG ($P < 0.01$ and $P = 0.01$, respectively)
Srisawat, 2013 [130]	*MTHFR* (rs1801133, rs1801131)	182 (46%)	26.2 ± 7.4	SCZ (100%)	Various APs	8 or 10 weeks	*MTHFR* rs1801133 polymorphism showed an association with AIWG ($P = 0.003$)
Tsai, 2002 [35]	*HTR2C* (rs3813929)	80 (65%)	36.7 ± 8.4	SCZ, SAD (0)	CLZ	4 months	NS
Tsai, 2003 [157]	*TNF* (rs1800629)	205 (49%)	37.2 ± 8.4	SCZ (0)	CLZ	4 months	NS
Tsai, 2004 [69]	*ADRB3* (rs4994) *GNB3* (rs5443)	87 (64%)	37.0 ± 8.2	SCZ (0)	CLZ	4 months	NS
Tsai, 2011 [98]	*BDNF* (rs11030101, rs6265, rs12291186, rs2030323)	481 (61%)	43.9 ± 8.9	SCZ (0)	CLZ, OLZ, RIS	3 months	*BDNF* rs11030101 polymorphism showed a modest association with AIWG (P =0.037)
Wang, 2005 [65]	*ADRA2A* (rs1800544)	93 (53%)	38.4 ± 8.1	SCZ (0)	CLZ	14 months	*ADRA2A* rs1800544 polymorphism showed an association with AIWG ($P = 0.025$)
Wang, 2005 [125]	*GNB3* (rs5443)	134 (60%)	38.5 ± 0.7	SCZ (0)	CLZ	13.4 ± 0.5 months	*GNB3* rs5443 polymorphism showed an association with AIWG ($P = 0.002$)
Wang, 2010 [153]	*TNF* (rs1800629)	55 (49%)	37.2 ± 7.8	SCZ (0)	CLZ	8 years	*TNF* rs1800629 polymorphism showed an association with AIWG ($P = 0.0084$)
Wang, 2013 [114]	*FTO* (rs9939609)	236 (38%)	31.9 ± 10.6	SCZ (0)	RIS	4 weeks	*FTO* rs9939609 polymorphism showed an association with AIWG ($P = 0.04$)
Wang, 2015 [36]	768 SNPs from 85 genes	216 (42%)	30.8 ± 8.7	SCZ (0)	RIS	4 weeks	*SLC6A4* rs3813034 polymorphism showed an association with AIWG ($P = 0.000357$)

Table 1 continued

Study	Gene (SNPs)	*n* (male %)	Age (years)	Diagnosis (FE%)	APs	Duration	Main finding
Wu, 2011 [34]	*HTR2C* (rs3813929, rs518147) *LEP* (rs7799039) *ADIPOQ* (rs1501299, rs2241766) *HRH1* (rs2067467)	170 (35%)	23.1 ± 5.2	SCZ (100%)	Various APs	< 1 year	*HTR2C* rs3813929, rs518147, *LEP* rs7799039, *ADIPOQ* rs1501299 polymorphisms showed associations with AIWG ($P < 0.001$, $P = 0.001$, $P = 0.011$, $P = 0.009$, respectively)
Yang, 2012 [83]	*GHRL* (rs696217, rs26802, rs27647, rs26311)	634 (52%)	27.1 ± 7.5	SCZ (0)	Various APs	8 weeks	*GHRL* rs27647 polymorphism showed an association with AIWG ($P = 0.028$)
Yao, 2008 [79]	*LEP* (rs7799039) *LEPR* (rs1137101)	86 (36%)	34.6 ± 10.0	SCZ (0)	Various APs	0.8 ± 1.43 years	NS
Yu, 2016 [22]	GWAS	534 (48%)	26.4 ± 5.3	SCZ (0)	Various APs	8 weeks	*PTPRD* rs109777144 polymorphism showed an association with AIWG ($P_{GWAS} = 9.26E{-}09$)
Zhang, 2002 [31]	*HTR2C* (rs3813929)	117 (50%)	26 ± 8	SCZ (100%)	CLP, RIS	10 weeks	*HTR2C* rs3813929 polymorphism showed an association with AIWG ($P = 0.0001$)
Zhang, 2003 [103]	*ANKK1* (rs1800497)	117 (50%)	26 ± 8	SCZ (100%)	Various APs	10 weeks	NS
Zhang, 2003 [71]	*LEP* (rs7799039)	128 (48%)	26 ± 7	SCZ (100%)	CLP, RIS	10 weeks	*LEP* rs7799039 polymorphism showed an association with AIWG ($P = 0.02$)
Zhang, 2007 [72]	*LEP* (rs7799039)	102 (66%)	47.2 ± 6.3	SCZ (0)	CLZ	18.8 ± 6.7 years	*LEP* rs7799039 polymorphism showed an association with AIWG ($P = 0.039$)
Zhang, 2008 [96]	*BDNF* (rs6265)	196 (66%)	NR	SCZ (100%)	Various APs	18 ± 6 years	*BDNF* rs6265 polymorphism showed an association with AIWG ($P = 0.009$)

Notes: AIWG, antipsychotic-induced weight gain; AP, antipsychotic; CLZ, clozapine; CPZ, chlorpromazine; FE, first episode; NR, not recorded; NS, not significant; OLZ, olanzapine; RIS, risperidone; SAD, schizoaffective disorder; SCZ, schizophrenia; SNP, single nucleotide polymorphism.

Lane *et al.* found that the rs1805054 polymorphism was associated with AIWG after risperidone treatment, and the CC and TC groups gained 1.354 kg and 1.164 kg more weight, respectively, than the TT genotype group ($P = 0.02$ and 0.02, respectively) [33]. However, a previous study conducted in the same population reported a negative finding in clozapine-treated patients [40]. Nowrouzi *et al.* studied *HTR6* rs1805054 in CATIE samples, and no association with weight gain was found in patients treated with various antipsychotics [50]. The discrepancies among *HTR6* pharmacogenetic studies on AIWG may be due to differences in antipsychotic choice [49].

SLC6A4, also known as *HTT*, encodes the serotonin transporter, which transports serotonin from the synaptic cleft to the presynaptic neuron. Wang *et al.* examined 85 genes in 216 Chinese patients treated with risperidone [36]. After correction for multiple comparisons, four *SLC6A4* SNPs (rs3813034, rs1042173, rs4325622 and rs9303628) retained significant associations. The most significant association was rs3813034 with AIWG, and AA homozygotes gained more body weight (8.8% ± 3.6%) than patients with the AC (3.9% ± 5.3%) and CC (1.6% ± 5.6%) genotypes ($P = 0.001$). Hong *et al.* studied the rs25531 polymorphism of *SLC6A4*, but failed to

demonstrate an association with AIWG in Chinese chronic SCZ patients [40]. In a mainly Caucasian and African-American population study, no association between rs1042173 polymorphism and AIWG was reported [50].

Dopamine Receptor

Antipsychotic agents tend to block dopamine receptors in the brain, and anti-dopaminergic activity seems to be the defining feature of all clinical antipsychotics [51]. Therefore, gene polymorphisms influencing the density, expression, and activity of dopamine receptors may be a key factor in the regulation of treatment and adverse responses [52]. In subsequent research, an association between dopamine receptor gene polymorphisms and AIWG was discovered. Hong *et al.* investigated 12 polymorphisms of the *DRD2* gene in the Chinese population and identified a significant association of rs4436578 with AIWG in 479 chronic patients after long-term SGA treatment [53]. Allelic analysis showed that the C allele was the risk allele for body weight gain (adjusted OR = 1.58, 95% CI = 1.16–2.13, P = 0.003). In a separate antipsychotic analysis, the CC genotype was associated with a greater risk of body weight gain compared with the TT genotype in patients treated with clozapine (adjusted OR = 3.03, 95% CI = 1.11–8.29, P = 0.031) or risperidone (adjusted OR = 9.98, 95% CI = 1.85–53.97, P = 0.008). Another study examined 4 SNPs of the dopamine receptors *DRD1* (rs265981, rs4532) and *DRD2* (rs1799732, rs1801028) in 123 patients; however, no significant association after 6 weeks of treatment was found [33]. This discrepancy may be due to differences in sample size, age, antipsychotic type, and treatment duration. In first-episode psychiatric patients, Lencz *et al.* found that rs1799732 was associated with weight gain after 6 weeks of risperidone or olanzapine treatment [51]. Muller *et al.* examined 37 SNPs of 5 dopamine receptor genes in CATIE samples and found that rs6277 and rs1079598 of the *DRD2* gene had a significant association with weight gain (P = 0.0027 and 0.0003, respectively) [54]. Moreover, after demographic and genotype interaction analysis, medication and ethnic background had an effect on weight gain, while gender and age did not [54].

Histamine Receptor

Antipsychotics are reported to have an affinity for histamine receptors. These receptors, especially the H1 receptor in the central nervous system, function in appetite and cognition, and may be associated with the response to antipsychotics and related adverse effects [55]. Rodent studies have demonstrated that the binding of the histamine H1 receptor in the hypothalamus was associated with olanzapine-induced weight gain [56], and this weight gain was attenuated by histamine H1 receptor agonists [14]. Hong *et al.* identified a novel *HRH1* polymorphism, Glu349Asp (rs2067467), in 2002 [57]; however, they failed to demonstrate that this SNP is associated with AIWG after 4 months in clozapine-treated patients. A similar result was reported in another Chinese cohort of 170 first-episode SCZ patients after treatment with various antipsychotics for less than 1 year [34]. The negative findings may be due to the low frequency of 349Asp, only five out of 88 patients in the Hong *et al.* study had the 349Glu/349Asp genotype, and no patients with the 349Asp allele were identified by Wu *et al.* In addition to rs2067467, several SNPs of *HRH1* have been studied in other ethnicities. Among them, rs346074 and rs346070 were associated with AIWG [58], whereas others continued to yield no association in CATIE samples [59, 60].

Adrenergic Receptor

The adrenergic receptors are targets of catecholamines, which play an important role in energy expenditure [61]. Therefore, genes involved in catecholamine regulation, such as *ADRA1A*, *ADRA2A*, and *ADRB3*, are natural candidates for pharmacogenetic research on AIWG. Although few studies have examined the relationship between *ADRA1A* polymorphism and AIWG [62, 63], Liu *et al.* examined 44 valid SNPs in the *ADRA1A* promoter and intron regions and found that 11 SNPs were associated with BMI changes in 401 Chinese patients with chronic SCZ [64]. The association between SNPs of *ADRA1A* and AIWG was gender-related; females exhibited greater increases in BMI than males (25.7 ± 0.4 *vs* 24.3 ± 0.2 kg/m^2), possibly due to estrogen [64]. The *ADRA2A*-1291C/G polymorphism (rs1800544) was examined in 93 chronic SCZ patients, and the results demonstrated that the GG carriers exhibited a higher mean body weight than the CC carriers (OR = 4.21, 95% CI = 1.58–11.19, P = 0.023) [65]. In other Asian studies, similar results were found among the Malaysian and Korean populations, but not in a mixed-ethnicity study [38, 46, 66]. Although numerous reports have demonstrated that the *ADRB3* gene variant Trp64Arg (rs4994) has effects on obesity or BMI changes [67, 68], no association was found between rs4994 and AIWG in the Chinese population [69]. The failure to find an association may be due to the small sample size (n = 87) and the low Arg allele frequency (11%), so a replicated study is needed in Chinese patients.

Genes that Code for Satiety-Influencing Hormones and Related Neuroendocrine Pathways

LEP and LEPR

Leptin is an adipocyte-specific hormone, and high serum leptin levels and leptin resistance have been reported in the obese population. Leptin (*LEP*) and leptin receptor (*LEPR*) gene variants may have effects on satiety, body weight, and energy expenditure [70]. SNPs of *LEP* and *LEPR* have been investigated in several Chinese studies, and most have been found to be associated with AIWG [34, 71–75]. The *LEP* –2548G/A polymorphism (rs7799039) has been associated with AIWG, whereas the A allele was considered the risk allele in some but not all these studies. Zhang *et al.* found that individuals with the A/A genotype gained less weight than those with the A/G or G/G genotype (both $P = 0.05$) among 102 patients treated with clozapine for over 2 years [72]. The gender effect on the *LEP* gene in BMI was significant ($F_{2,99} = 3.38$, $P = 0.034$), and weight gain in males but not females was strongly affected by genotype. Li *et al.* also considered the G allele to be the risk allele for weight gain in risperidone-treated patients ($P = 0.002$), but without adjustment due to the small sample size [75]. Possible explanations for this discrepancy include differences in sample size, gender ratio, antipsychotic choice, and study duration. The Gln223Arg polymorphism (rs1137101) is the most studied SNP of the *LEPR* gene [76–78], however, two Chinese studies both reported negative findings [74, 79]. According to HapMap outcomes, the frequency of the rs1137101-A allele is much lower in the Chinese population (13%) than in other ethnicities (42%), which may cause different results for different populations.

GHRL

The *GHRL* gene encodes the ghrelin-obestatin preproprotein, and is located on chromosome 3, band p25.3. Ghrelin plays a vital role in both appetite regulation and energy distribution, while obestatin is an anorectic peptide that may affect food intake [80]. In rodent studies, olanzapine has been reported to increase peripheral ghrelin levels, activate the ghrelin hormone secretagogue receptor in the hypothalamus, and increase appetite and weight gain [81, 82]. Yang *et al.* investigated four *GHRL* variants (rs696217, rs26802, rs27647, and rs26311) in Chinese SCZ patients and found that the SNP rs27647 (-604 G/A) had a significant impact on weight and BMI during SGA treatment ($P < 0.001$) [83]. Furthermore, homozygous AA carriers exhibited changes in body weight (2.61 ± 3.46 kg *vs* 0.55 ± 3.85 kg, $P = 0.039$) and BMI (1.15 ± 1.21 kg/m^2 *vs* 0.21 ± 1.42 kg/m^2, $P = 0.013$) that were significantly greater than those seen in homozygous GG carriers [83]. In a recent study, *GHRL* rs696217 was associated with both weight gain ($P = 0.001$) and appetite change ($P = 0.042$) in a Korean population treated with various antipsychotics [48]. As listed in the HapMap database, the rs696217-T frequency is 19.1% in the east Asian population, which is higher than the frequencies in the European (8.8%) and American (5.0%) populations.

MC4R

Melanocortin receptor 4 (MC4R) is involved in food intake regulation, energy balance, and obesity [84], and is related to the serotonergic and leptinergic systems [85, 86]. The *MC4R* gene is located on chromosome 18, and variants in the gene or near its locus can cause heritable obesity [87]. In Chinese studies, rs17782313 and rs2229616 of the *MC4R* gene were examined in a mixed sample of monotherapy- and polypharmacy-treated patients. The latter SNP exhibited a weak association with BMI ($P = 0.014$) [74]. Li *et al.* screened 43 SNPs from 23 genes in the Chinese population, and among them, rs6567160 and rs489693 of *MC4R* were found to be associated with risperidone-induced weight gain ($P = 0.006$ and 0.018, respectively) [75]. However, because the samples included non-single-agent antipsychotic-treated patients and were not adjusted to account for its small size, those two reports in the Chinese population did not provide convincing pharmacogenetic evidence for AIWG. In Caucasian studies, rs2229616 was found to have no association in CATIE samples [88], while rs17782313 was reported to have a significant influence on SGA-related weight gain. Notably, rs489693 of *MC4R* was initially detected by a GWAS in a sample of drug-naïve young patients treated with SGAs [89]. Twenty SNPs located near the *MC4R* locus exceeded the $P < 10^{-5}$ statistical threshold, and three were investigated for replication in three separate cohorts. Ultimately, the rs489693 SNP was significantly associated with AIWG. A similar result was replicated in subsequent studies [90, 91], but unfortunately not in the Chinese population.

BDNF

Brain-derived neurotrophic factor (BDNF) functions in the development, maintenance, and plasticity of the central and peripheral nervous systems and mediates the beneficial effects of energetic challenge and peripheral metabolism [92]. The *BDNF* gene is located on chromosome 11, and the Val66Met (rs6265) variant is the most extensively studied polymorphism [93–95]. However, conflicting allelic associations of rs6265 with AIWG in the Chinese population have been reported. Lane *et al.* found that Met/

Met homozygotes gained less weight by 0.806 kg than Val/Val homozygotes ($P = 0.02$) among 123 SCZ patients receiving risperidone treatment [33]. By contrast, Zhang *et al.* found that Met/Met homozygosity correlated with more weight gain than Val/Val homozygotes ($F = 4.84$, $P = 0.01$) in a study of 196 SCZ patients after at least 10 years of antipsychotic treatment [96]. Furthermore, gender showed a significant effect on BMI in male patients ($F = 5.48$, $P = 0.004$), but not in females ($F = 2.01$, $P = 0.13$). Subsequently, Fang *et al.* replicated results similar to those of Zhang *et al.* – in 308 SCZ patients, rs6265 was reported to have an association with AIWG ($F = 5.29$, $df = 2, 261$, $P < 0.01$) [97]. In addition, Tsai *et al.* failed to find an association between rs6265 and AIWG [98], while Li *et al.* found that rs6265 was associated with a change in waist-to-hip ratio rather than body weight [75]. There are some possible reasons for these discrepancies in studies of the same ethnicity. First, Lane *et al.* only studied risperidone-treated patients, but the patients in Zhang *et al.* and Fang *et al.* received FGAs or SGAs. Previous network meta-analysis demonstrated that different antipsychotics have different effects on body weight gain [4], which may explain the different results to some extent. Second, since the association of rs6265 with AIWG was gender-related, the inclusion of more males in the studies by Zhang *et al.* and Fang *et al.* made their results more convincing. Third, the treatment duration of 6 weeks in Lane *et al.*'s report was much shorter than those in the studies by Zhang *et al.* and Fang *et al.* (> 10 years and > 1 year, respectively). In most Caucasian studies, *BDNF* Val66Met demonstrated a significant association with AIWG with various diagnoses [93, 95, 99], although not in Spanish acute SCZ patients treated with risperidone [94]. The Val frequency in the Chinese Han population differs from those in the American and European populations [100], which is a possible explanation for the differences among pharmacogenetic studies of different races. In addition to rs6265, rs11030101 of the *BDNF* gene was reported to have a modest effect on weight gain ($P = 0.037$) in 481 SCZ patients, and the body weight change of TT carriers (11.3% ± 18.0%) was higher than that of TA (4.6% ± 16.3%) or AA (2.9% ± 15.4%) carriers [98].

ANKK1

The ANKK1 protein belongs to the Ser/Thr protein kinase family, and is involved in signal transduction pathways [101]. The *ANKK1* gene is linked closely to the *DRD2* gene on chromosome 11, and the TaqIA polymorphism (rs1800497) of *ANKK1* was formerly considered to be located in the promoter region of the *DRD2* gene since TaqIA variants influence DRD2 receptor expression [101]. A previous study demonstrated that the TaqIA variant was associated with obesity [102], and subsequent studies in Caucasians reported similar results for AIWG [54, 103]. However, three studies focused on the TaqIA polymorphism in the Chinese population reported contradictory results, finding no significant association [33, 47, 104]. The possible reason for the difference between these studies of Chinese and Caucasians may be the frequency of the rs1800497-A allele, which has a higher frequency in Chinese (44%) than in Caucasian (19%) populations according to HapMap.

Genes that Code for Lipid Metabolism

ADIPOQ

Adiponectin is a protein hormone produced in adipose tissue that is involved in the regulation of glucose and fatty-acid oxidation. Encoded by the *ADIPOQ* gene, adiponectin is associated with obesity, cancer, and type 2 diabetes [105–107]. Wu *et al.* investigated rs1501299 and rs2241766 of the *ADIPOQ* gene and found the 276G/T polymorphism (rs1501299) was associated with weight gain in 170 first-episode SCZ patients [34]. The 276G allele was considered the risk allele ($\chi^2 = 6.812$, $P = 0.009$) [34]. Another group found that rs1501299 was not associated with AIWG but was associated with waist-to-hip ratio change in 339 Chinese patients [75]. In addition, Li *et al.* reported that another *ADIPOQ* SNP, rs182052, was associated with AIWG and that individuals with the AA allele gained more weight than those with the AG+GG allele ($P = 0.019$) [75]. The relationship between *ADIPOQ* polymorphisms and AIWG remains controversial in studies of other ethnicities. Jassim *et al.* found that six *ADIPOQ* SNPs, including rs1501299, were associated with BMI change in the German population; however, this result could not be replicated in CATIE and Finnish samples [108–110]. No association of rs182052 with AIWG was found in mixed Asian samples or in CATIE samples [46, 109].

FTO

The fat-mass and obesity-associated (*FTO*) gene is located on human chromosome 16, and its polymorphisms have been correlated with obesity in GWASs [111]. The *FTO* rs9939609 variant has been found to be significantly associated with obesity, type 2 diabetes, various cancers, and Alzheimer's disease [112, 113]. In the Chinese population, Wang *et al.* found that this *FTO* variant was significantly associated with BMI change after 4 weeks of risperidone treatment, and the T allele was identified as the risk allele ($t = 2.07$, $P = 0.04$) [114]. In another study of

risperidone-treated patients, Song *et al.* examined 4 *FTO* variants and found that 3 of them (rs9939609, rs8050136, and rs9930506) were associated with weight gain after 6 months of treatment (P = 0.004, 0.019, and 0.034, respectively) [115]. After controlling for potential confounding variables, the rs9930506 polymorphism was the only SNP that showed a significant association, and TT homozygotes gained less weight than AT+AA carriers ($P < 0.01$). In addition, strong linkage disequilibrium between rs9939609 and rs8050136 was found in this study ($r^2 > 0.33$) [115]. The same antipsychotic was used in a study of a Chinese population similar in size, but a contradictory result was obtained. The samples in the Wang *et al.* study were chronic patients, and their antipsychotic history before enrollment was not available, which reduces the credibility of the results compared with Song *et al.*'s study [114, 115]. In a study of CATIE samples, Shing *et al.* investigated the same SNPs of the *FTO* gene, but none had statistically significant associations with AIWG [116]. This result was replicated in an Asian study [46], in which *FTO* rs9939609 exhibited a significant association with AIWG in chronic SCZ patients. As listed in the HapMap database, Chinese populations had lower rs9939609-A and rs8050136-A frequencies than European populations.

INSIG2

Both INSIG2 and its related isoform INSIG1 are endoplasmic reticulum proteins that function by blocking the processing of sterol regulatory element binding proteins (SREBPs) [117]. The rs7566605 SNP of *INSIG2* was suggested to be associated with obesity [118], but the first study of an association of rs7566605 with AIWG yielded a negative result with CATIE samples [119]. Twenty-one *INSIG2* SNPs were examined by Le Hellard *et al.*, and three of them (rs17587100, rs10490624, and rs17047764) were strongly associated with AIWG [120]. In subsequent studies, the aforementioned 4 SNPs were investigated in CATIE and European samples, but no association with AIWG was found [121, 122]. In 2011, Kuo *et al.* found that rs7566605 had a weak association with changes in BMI (OR = 1.74, P = 0.035) and waist circumference (OR = 1.83, P = 0.026) in Chinese patients after treatment with single or combined antipsychotics [74]. Another two SNPs were studied in this report: rs17587100 was significantly associated with fasting plasma glucose, while rs889904 was not associated with either BMI or biochemical assessments. A meta-analysis demonstrated that the rs7566605 polymorphism was significantly associated with obesity in the Caucasian but not in the non-Caucasian population [123]. Although the underlying mechanism is unknown, this meta-analysis may explain part of the discrepancy between studies.

Genes that Code for Neurotransmitter Turnover and Methylation Enzymes

GNB3

The human *GNB3* gene, which encodes the Gβ3 subunit of heterotrimeric G proteins, is an important regulator of alpha subunits and of certain signal transduction receptors and effectors [124]. Only a few reports link the C825T polymorphism (rs5443) of *GNB3* with AIWG in the Chinese population: Tsai *et al.* reported a negative finding in 87 SCZ patients treated with clozapine for 4 months [69], but Wang *et al.* found that rs5443 retained a significant association with weight gain in 134 chronic SCZ patients after long-term clozapine treatment [125]. The mean body weight change of patients in Wang *et al.*'s study was higher in TT carriers (9.6 ± 1.4 kg) than in CC (3.2 ± 1.4 kg) and CT (5.3 ± 0.8 kg) carriers (P = 0.002 and 0.015, respectively) [125]. A recent meta-analysis also demonstrated that rs5443 affects weight gain, as TT carriers gained significantly more weight than CC/CT carriers [25]. The same polymorphism was investigated in Japanese, Korean, and Caucasian populations, but a significant association with weight gain was only found in the Japanese population after olanzapine treatment [63, 126, 127].

MTHFR

Methylenetetrahydrofolate reductase is encoded by the *MTHFR* gene, and some variants of *MTHFR* may confer susceptibility to AIWG, metabolic syndrome, and cancer [128]. The *MTHFR* C677T polymorphism (rs1801133) may influence serum folate and homocysteine levels, which may cause recurrent pregnancy loss, dementia, and SCZ [129]. In a recent prospective study conducted by Srisawat *et al.*, two SNPs of the *MTHFR* gene (rs1801133 and rs1801131) were investigated [130]. Although strong linkage disequilibrium of rs1801133 and rs1801131 was found (r^2 = 0.127), only the C677T (rs1801133) polymorphism had a significant association with AIWG. After 8 or 10 weeks of antipsychotic treatment, patients with the 677CC allele had a greater BMI change than CT/TT carriers (1.58 ± 1.25 kg/m^2 *vs* 1.04 ± 1.16 kg/m^2, P = 0.012) [130]. These results were replicated in studies of other ethnicities, which demonstrated that the *MTHFR* rs1801133 variant might influence AIWG and that the 677C allele is the risk allele [131, 132].

NRXN3

Neurexins are a family of presynaptic single-pass transmembrane proteins that act as synaptic organizers in mammals [133]. *NRXN3*, which is located on human chromosome 14, spans 1,618.5 kb and contains 24 exons. This gene is the largest and most extensively alternatively spliced of the three *NRXN* genes (*NRXN1*, *NRXN2*, and *NRXN3*) [134]. Several studies have reported that the *NRXN1* polymorphism is associated with SCZ [134] and that *NRXN3* might be a novel locus related to physical obesity [135, 136], but to date, there has only been one study focused on AIWG. In a study of risperidone treatment, seven *NRXN3* SNPs were investigated, and two (rs11624704 and rs7154021) were identified as susceptibility SNPs for modest weight gain in Chinese SCZ patients (P = 0.03 and 0.008, respectively) [137]. The BMI change was higher in the rs11624704 AA group (2.65% ± 0.24%) than in the AC group (1.80% ± 0.12%), and higher in the rs7154021 TT group (2.16% ± 0.26%) than in the CT group (1.36% ± 0.41%). However, to date, there has been no replication study in Chinese psychiatric patients or those of other ethnicities.

PTPRD

Protein tyrosine phosphatase receptor-type δ (PTPRD) is composed of a cell adhesion molecule-like extracellular domain and two cytoplasmic protein tyrosine phosphatase domains [138]. The *PTPRD* gene is located at 9p24.1-p23, and its variants have been implicated in SCZ, mood instability, type 2 diabetes, and cancer in GWASs [139–143]. In a GWAS involving 534 SCZ patients, Yu *et al.* found that *PTPRD* rs10977144 (P_{GWAS} = 9.26E-−9) and rs10977154 (P_{GWAS} = 4.53E−08) met the genome-wide significance threshold for AIWG after treatment with various SGAs for 8 weeks [22]. Replication was conducted subsequently in another independent cohort, and both rs10977144 ($P_{Replicated}$ = 4.31E−03) and rs10977154 ($P_{Replicated}$ = 6.33E−03) were further validated. This GWAS also found that polymorphisms of *GFPT2*, *ACTR3*, *TCP11*, *LOC391738*, *KCNK1*, *RNLS*, and other genes were associated with AIWG in Chinese patients [22]. A replication study is still needed in AIWG studies of Chinese and other ethnicities.

RBFOX1

RBFOX1, also known as ataxin 2-binding protein 1, functions as an alternative splicing factor, and gene variants may cause heritable neurodegenerative diseases such as autism and epilepsy [144]. In GWASs, rs10500331 and rs4786847 of *RBFOX1* were considered to confer susceptibility to obesity in adults [145, 146]. In a recent AIWG study, Dong *et al.* examined 4 *RBFOX1* SNPs (rs10500331, rs4786847, rs8048076, and rs1478697) in 328 Chinese SCZ patients [147]. After 8 weeks of olanzapine treatment, rs8048076 and rs1478697 were found to be associated with significant weight gain (P = 0.0273 and 0.0012, respectively). However, after meta-analysis of the discovery and replication cohorts, only rs1478697 remained statistically significant (P_{meta} = 3.63E−05), and the AA genotype showed greater weight gain than the other two genotypes (F = 4.921, df = 2, P = 0.008). In a recent study, the *RBFOX1* gene was found to have an association with the antipsychotic response in Caucasian and African-American patients [148]. Therefore, the association of *RBFOX1* gene variants with AIWG still remains to be investigated.

Genes that Code for Antipsychotic-Activated Immune Factors

TNF

Tumor necrosis factor (TNF) is a monocyte-derived cytotoxin that plays a role in the regulation of immune cells [149], and has been implicated in inflammation, HIV-1 susceptibility, cancer, obesity, and Alzheimer's disease [150, 151]. Several *TNF* gene variants have been shown to be correlated with BMI, obesity, and glucose and lipid metabolism. Among them, the SNP -308 G/A (rs1800629) had the strongest correlations [152]. In a sample of clozapine-treated Chinese patients, Wang *et al.* found that rs1800629 was significantly associated with BMI gain and that this change was lower in A allele carriers than in GG homozygotes. (−1.8% ± 8.4% *vs* 3.3% ± 3.5%, P = 0.0084) [153]. However, in two other Chinese population studies, no association was found between rs1800629 and AIWG [154, 155]. The discrepancy in studies of the same ethnic group may be of two possible reasons. First, the sample size in Wang *et al.* (n = 55) was much smaller than the other two reports (n = 205 and n = 500, respectively), which may cause a type I error. Another reason is the treatment duration; the patients in Wang *et al.*'s study were treated for much longer (> 8 years) than those in the other two reports (4 months and 3 months, respectively). Over such long periods, body weight may be affected by various factors other than antipsychotics. In studies of other ethnicities, negative results were reported in both CATIE and Japanese samples [63, 156].

TOX

Tox (thymocyte selection-associated HMG-box) is a highly conserved transcription factor that is strongly expressed in the thymus. Tox was identified as a multifunctional, off-switch transcription factor controlling brain development, neural stem cell differentiation, and dendritogenesis [157]. The *Tox* gene is located at 8q12.1, and its SNPs have been studied in type 2 diabetes, myopia, and cancers [158–161]. The only study related to *Tox* polymorphisms and AIWG reported that in patients treated with various antipsychotics, SNP rs11777927 was significantly associated with weight gain ($P = 0.009$) after 12 weeks of treatment in a Chinese population [75]. A replication study is needed in Chinese SCZ patients and those of other ethnicities.

CDKN2A/B

CDKN2A/B (cyclin-dependent kinase inhibitor 2A/B) is located on chromosome 9, band p21.3. The proteins it encodes act as tumor suppressors [162]. Previous studies of its polymorphisms have focused on associations with many kinds of tumor and diabetes [158, 163–165]. In a recent study of multiple SNPs, rs3731245 and rs2811708 of the *CDKN2A/B* gene were significantly associated with AIWG, especially risperidone-induced weight gain in Chinese patients ($P = 0.040$ and 0.039, respectively) [75]. A replication study is needed, and the mechanism by which *CDKN2A/B* affects AIWG awaits investigation.

Conclusion and Future Perspective

Antipsychotics are widely used in the treatment of SCZ [4]. Although the general curative effect of SGAs is superior to that of FGAs, SGAs can induce body weight gain, which has severe adverse effects on physical and psychological health [5]. Over the past few decades, there has been a substantial expansion of pharmacogenetic research on AIWG worldwide. Numerous studies have been conducted in Chinese populations with encouraging results. To the best of our knowledge, the present review is the first overall review of the pharmacogenetic associations of AIWG in the Chinese population. Thirty-three unduplicated reports of Chinese psychiatric patients treated with single-agent antipsychotics were included; they reported associations of > 25 SNPs in 19 genes distributed on 13 chromosomes with AIWG (Table 2). The first functional polymorphism to be implicated in body weight gain in the Chinese population was rs3813929 of the *HTR2C* gene [30]. Therefore, *HTR2C* has been the most studied gene in Chinese people. Many SNPs of *HTR2C* have been investigated in Chinese reports, and two SNPs (rs3813929 and rs518147) were reported to have an association with AIWG [30–34]. The consistent results have provided strong evidence of associations of *HTR2C* genetic variants with AIWG in the Chinese population. The second most studied genes are *LEP* and *BDNF*; four out of five studies found an association of the *LEP* rs7799039 polymorphism with AIWG [34, 71–73], and three out of five studies found an association of the *BDNF* rs6265 polymorphism with AIWG [33, 96, 97]. However, both studies generated controversial results in risk allele analysis. The weakest evidence for genetic variants with AIWG is for the 'orphan' SNPs such as *NRXN3*, *TOX*, and *RBFOX1*. These SNPs were not replicated in subsequent studies, even in the Chinese population.

Pharmacogenetic studies in the Chinese population have many similarities and differences with those in other ethnicities. The candidate-gene approach has been widely used in Chinese studies as well as in studies of other ethnic groups [26, 36, 48, 75]. The candidate genes are mainly antipsychotic affinity receptor-encoding genes (e.g., *HTR2C*, *DRD2*, *ADRA1A*, and *HRH1*), endocrine regulation-related genes (e.g., *GHRL*, *ADIPOQ*, and *LEP*), and neural development-related genes (e.g., *BDNF* and *NRXN3*). In the last 5 years, two GWASs of AIWG have been performed. One was by Yu *et al.* [22], who found that the *PTPRD* rs10977144 polymorphism had the strongest association ($P = 9.26\text{E}{-}09$) with AIWG in the Chinese population. The other was by Brandl *et al.* in CATIE samples [23], and revealed that rs9346455 of the *OGFRL1* gene was significantly associated with AIWG ($P = 6.49\text{E}{-}06$). Discrepant results were obtained in these GWASs conducted in different populations, as is common in studies of different ethnic groups due to the diverse allele frequencies (Table 2). In global pharmacogenetic studies, the *HTR2C*, *MC4R*, and *LEP* genes had consistent associations with AIWG [25, 29, 42]. However, only *HTR2C* has been consistently implicated in AIWG in the Chinese population [30–34]. Although the *LEP* and *BDNF* genes have been studied extensively in Chinese patients, the results remain inconsistent. Only one study found an association of the *MC4R* gene with risperidone-induced BMI change in the Chinese population, but age and gender were not adjusted in this study due to sample size limitations [75]. Recent studies have reported that cytokine and mitochondrial gene variants may influence AIWG in other ethnic populations [5, 166]. There have been no studies of the correlations between these gene mutations and AIWG in the Chinese population, so this may be a suitable direction for future study. Moreover, some gene polymorphisms, such as those of *ADRB3*, *CNR1*, *MDR1*, and *SNAP25*, have never been fully studied in Chinese samples. These polymorphisms could be examined or replicated in future Chinese AIWG studies.

Table 2 Associations between AIWG and genotype in the Chinese population.

Gene	Chr.	rs#	Major allele	Minor allele	MAF in CHB (*vs* in EUR)	Risk allele	Summary of result	Ref.
ADIPOQ	3	rs1501299	G	T	0.335 (0.279)	G	G allele more weight gain than T allele (χ^2 = 6.812, P = 0.009)	[34]
		rs182052	G	A	0.471 (0.605)	A	AA allele more weight gain than AG+GG allele (P = 0.019)	[75]
ADRA2A	10	rs1800544	G	C	0.354 (0.739)	G	GG allele more weight gain than CC allele (OR = 4.21, 95% CI = 1.58–11.19, P = 0.023)	[65]
BDNF	11	rs6265	G	A	0.495 (0.803)	A	Met/Met homozygote less weight gain than Val/Val (t = 2.31, P = 0.02)	[33]
						G	Met/Met homozygote more BMI gain than Val/Val (5.2 ± 3.9 *vs* 2.1 ± 2.4 kg/m^2, P = 0.01)	[96]
						G	Met/Met homozygote more BMI gain than Val/Val (χ^2 = 5.29, P < 0.01)	[97]
		rs11030101	A	T	0.296 (0.463)	T	TT allele more weight gain than AA+AT allele (11.3 ± 18.0 *vs* 2.9 ± 15.4 and 4.6 ± 16.3 kg, P = 0.037)	[98]
CDKN2A/B	9	rs3731245	G	A	0.184 (0)	A	AA allele more weight gain than AG+GG allele (P = 0.040)	[75]
		rs2811708	G	T	0.228 (0.276)	T	TT allele more weight gain than TG+GG allele (P = 0.039)	[75]
DRD2	11	rs4436578	T	C	0.427 (0.130)	C	C allele more weight gain than TT allele (OR = 1.58, 95% CI = 1.16–2.13, P = 0.003)	[53]
FTO	16	rs9939609	T	A	0.155 (0.414)	T	TT allele more BMI gain than AA+AT allele (t = 2.07, P = 0.040)	[114]
			T	A		A	TT allele less weight gain than AA/AT allele (P < 0.01)	[115]
		rs8050136	C	A	0.150 (0.414)	A	CC allele less weight gain than AA+AC allele (P = 0.01)	[115]
GHRL	3	rs27647	T	C	0.121 (0.379)	A	AA allele more weight and BMI change compared with AG+GG allele (2.61 ± 3.46 *vs* 0.18 ± 3.35 and 0.55 ± 3.85 kg, P = 0.039; 1.15 ± 1.21 *vs* 0.04 ± 1.18 and 0.21 ± 1.42 kg/m^2, P = 0.013, respectively)	[83]
GNB3	12	rs5443	T	C	0.461 (0.307)	T	TT allele more weight gain than CC or CT allele (9.6 ± 1.4 *vs* 3.2 ± 1.4 and 5.3 ± 0.8 kg, P = 0.003 and P = 0.027, respectively)	[126]
HTR2A	13	rs6313	T	C	0.495 (0.564)	T	CC allele less weight gain than TT allele (t = −4.14, P < 0.0001)	[33]
HTR2C	X	rs3813929	C	T	0.138 (0.157)	C	T allele less weight gain than C allele (OR = 6.01, 95% CI = 1.92–18.79, P = 0.001)	[30]
						C	T allele less BMI change than C allele (0.41 ± 1.02 *vs* 1.38 ± 1.21 kg/m^2, P = 0.0001)	[31]
						C	T allele less BMI change than C allele (0.32 ± 0.68 *vs* 1.12 ± 0.88 kg/m^2, P < 0.02).	[32]
						C	T allele less weight gain than C allele (t = −2.08, P = 0.04)	[33]
						C	C allele more weight gain than T allele (χ^2 = 14.363, P < 0.001)	[34]
		rs518147	G	C	0.150 (0.320)	G	G allele more weight gain than C allele (χ^2 = 10.89, P = 0.001)	[34]
HTR6	1	rs1805054	C	T	0.243 (0.116)	C	TC or CC allele more weight gain than TT allele (t = 2.40, P = 0.02; t = 2.45, P = 0.02, respectively)	[33]
LEP	7	rs7799039	A	G	0.243 (0.558)	A	AA allele more BMI gain than AG+GG allele (OR = 1.941, 95% CI = 1.175–3.207, P = 0.006)	[71]
						G	AA allele less BMI change than AG+GG allele (2.6 ± 3.5 *vs* 4.4 ± 3.5 kg/m^2, P = 0.0014)	[72]
						A	AA allele more BMI gain than AG+GG allele (χ^2 = 6.428, P = 0.004)	[34]

Table 2 continued

Gene	Chr.	rs#	Major allele	Minor allele	MAF in CHB (*vs* in EUR)	Risk allele	Summary of result	Ref.
						A	A allele more weight gain than G allele (χ^2 = 4.031, P = 0.045)	[73]
MTHFR	1	rs1801133	C	T	0.466 (0.365)	C	CC allele more BMI change than CT/TT allele (1.58 ± 1.25 *vs* 1.04 ± 1.16 kg/m^2, P = 0.012)	[130]
NRXN3	14	rs11624704	A	C	0.068 (0.136)	A	AA allele more weight gain than AC allele (t = −2.179, P = 0.03)	[137]
		rs7154021	T	C	0.049 (0.053)	T	TT allele more weight gain than CT allele (t = 2.654, P = 0.008)	[137]
PTPRD	9	rs10977144	C	T	0.087 (0.070)	T	CC allele less weight gain than CT+TT allele (P_{GWAS} = 9.26E−09)	[22]
RBFOX1	16	rs1478697	A	G	0.146 (0.379)	A	AA allele more weight gain than AG+GG allele (F = 4.921, df = 2, P = 0.008).	[147]
SLC6A4	17	rs3813034	C	A	0.146 (0.565)	A	AA allele more weight gain than AC+CC allele (9.6 ± 1.4 *vs* 3.2 ± 1.4 and 5.3 ± 0.8 kg, P = 0.001)	[36]
TNF	6	rs1800629	G	A	0.092 (0.134)	G	GG allele more weight gain than AA+AG allele (9.5 ± 10.1 *vs* −5.3 ± 22.5 kg, P = 0.0084)	[153]
TOX	8	rs11777927	T	A	0.369 (0.194)	A	AA allele more weight gain than AT+TT allele (P = 0.009)	[75]

Notes: BMI, body mass index; CHB, Han Chinese in Beijing, China; Chr, chromosome; EUR, European; MAF, minor allele frequency; Ref., reference.

Although substantial research has been conducted, some limitations remain in current Chinese studies. First, China is a large country with a very large population, and most studies of SNPs and AIWG have been restricted to a couple of hospitals in several cities. Recently, some multi-center studies of gene polymorphisms and AIWG in the Chinese population have been performed [22, 36, 97, 137, 147], but most of the reports included samples from north China and seldom included the southern population. The insufficient communication and transfer of samples among hospitals in China may limit the representativeness of studies of the Chinese population. Therefore, wider and deeper scientific cooperation with multi-center participation is needed. Second, the collection of samples depends on the actual situation in each hospital, and no universal standards are followed. Regional preferences were evident in the samples in previous pharmacogenetic studies. For example, studies in Taiwan region mainly included chronic SCZ patients treated with clozapine and of older age, studies in Nanjing and Changsha preferred first-episode drug-naïve SCZ patients and younger patients, and studies in northern China conducted in recent years preferred multi-center studies and larger sample sizes. In addition, antipsychotic use before enrollment, treatment duration, sample size, gender ratio, food intake, and exercise time varied among these studies, and these non-genetic factors may provide inconsistent results in the same ethnic population [4, 10, 167]. Taking rs6265 of the *BDNF* gene as an example, five Chinese studies including patients with different clinical status reported a relationship of the rs6265 polymorphism with AIWG. Three of them found an association between rs6265 and AIWG, but Lane *et al.* obtained a result opposite to those of Zhang *et al.* and Fang *et al.* in terms of which genotype was associated with greater weight gain [33, 96, 97]. The other two reports had negative findings, but Li *et al.* found that rs6265 was associated with waist-to-hip ratio [75, 98]. Single-molecule DNA sequencing technologies have advanced rapidly in recent years, and whole-genome and whole-exome analysis have been applied in pharmacogenetic studies of antipsychotics. However, most studies used the candidate-gene approach and tested only one SNP or several SNPs in the Chinese population, and only one GWAS has been performed [22]. The polygenic score generated from a GWAS is the best predictor of a trait when considering the variation of multiple genetic variants [168]. In non-GWASs, a polygenic score is difficult to calculate, and traits can only be verified by multiple replications. Therefore, future studies can make greater use of DNA sequencing technologies, and the results may reveal the underlying direction of the associations of SNPs or copy number variants with AIWG.

In conclusion, we attempted to review the progress of pharmacogenetic studies of AIWG in the Chinese population and compare the results from Chinese and other ethnic groups. Furthermore, we aimed to uncover the limitations

of current Chinese studies and point out future research directions. More than 25 SNPs in 19 genes have been reported to be associated with AIWG in Chinese patients over the past few decades. The *HTR2C* gene has been most consistently associated with AIWG in the Chinese population. In future studies, the inconsistent and unconvincing results in current Chinese studies need to be replicated, and genes that have been reported to be associated with AIWG in other ethnic groups should be investigated. In addition, to explain the pharmacogenetic reasons for AIWG in the Chinese population, GWAS and multi-center, standard, unified, and large-size samples are needed.

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Conflict of interest The authors declare that they have no conflict of interest.

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