Review

Molecular Neuropsychiatry

Mol Neuropsychiatry 2016;2:61–78
DOI: 10.1159/000445802

Received: November 23, 2015
Accepted: March 24, 2016
Published online: May 20, 2016

Genetics of Common Antipsychotic-Induced Adverse Effects

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Key Words
Antipsychotic · Adverse effect · Extrapyramidal symptoms · Genetic association study · Metabolic syndrome · Pharmacogenetics · Polymorphism · Tardive dyskinesia · Weight gain

Abstract
The effectiveness of antipsychotic drugs is limited due to accompanying adverse effects which can pose considerable health risks and lead to patient noncompliance. Pharmacogenetics (PGx) offers a means to identify genetic biomarkers that can predict individual susceptibility to antipsychotic-induced adverse effects (AAEs), thereby improving clinical outcomes. We reviewed the literature on the PGx of common AAEs from 2010 to 2015, placing emphasis on findings that have been independently replicated and which have additionally been listed to be of interest by PGx expert panels. Gene-drug associations meeting these criteria primarily pertain to metabolic dysregulation, extrapyramidal symptoms (EPS), and tardive dyskinesia (TD). Regarding metabolic dysregulation, results have reaffirmed *HTR2C* as a strong candidate with potential clinical utility, while *MC4R* and *OGFR1* gene loci have emerged as new and promising biomarkers for the prediction of weight gain. As for EPS and TD, additional evidence has accumulated in support of an association with *CYP2D6* metabolizer status. Furthermore, *HSPG2* and *DPP6* have been identified as candidate genes with the potential to predict differential susceptibility to TD. Overall, considerable progress has been made within the field of psychiatric PGx, with inroads toward the development of clinical tools that can mitigate AAEs. Going forward, studies placing a greater emphasis on multilocus effects will need to be conducted.

Introduction

Antipsychotic (AP) drugs are the mainstay pharmacological treatment for schizophrenia (SCZ) and related psychotic disorders. APs have also been shown to be effective for the treatment of other psychiatric conditions, including bipolar disorder, treatment-resistant depression, and autism spectrum disorders (ASDs) [1–3]. Despite their demonstrable clinical utility, significant interindividual variation in the therapeutic efficacy and tolerability of APs presents a significant challenge for physicians and their patients.

The introduction of second-generation 'atypical' APs (SGAs; e.g., risperidone) was highly welcomed by the psychiatric community, as these drugs were thought to rep-

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resent a significant improvement over first-generation 'typical' APs (FGAs; e.g., haloperidol). The use of FGAs had been marred by the tendency of these drugs to cause extrapyramidal symptoms (EPS), and with long-term use, tardive dyskinesia (TD), a highly debilitating and potentially irreversible movement disorder [4, 5]. While the risk of developing EPS and TD associated with SGAs is substantially lower, these adverse effects (AEs) still represent an ongoing concern [6, 7]. Moreover, the use of SGAs is often accompanied by weight gain and related cardiometabolic abnormalities, thereby putting patients at a greater risk of developing diabetes and cardiovascular disease [8–10]. Importantly, whether caused by FGAs or SGAs, AP-induced AEs (AAEs) are a major source of patient noncompliance and treatment discontinuation, both of which lead to greater functional impairment, higher rates of relapse, and an increased risk of suicide [11–14]. In view of this, dissecting the underlying factors contributing to interindividual variation in susceptibility to AAEs may facilitate better treatment selection, and thereby improve clinical outcomes.

Pharmacogenetics (PGx) is a field of study and clinical tool that assesses how genetic variability influences drug response and tolerability. Evidence from twin studies implicates a significant genetic component underlying individual differences in susceptibility to AAEs [15, 16]. Therefore, PGx has the potential to significantly improve the treatment of SCZ and other neuropsychiatric disorders. Considering the progress of PGx in the last two decades, it seems inevitable that pharmacogenetic testing – accounting for genetic variability in both pharmacokinetic and pharmacodynamic processes – will eventually play a role in the prescription of APs and other psychotropic drugs. It is hoped that physicians will be able to utilize information from pharmacogenetic tests in order to deliver personalized drug therapies with optimal efficacy and minimal AEs. Although still in the early stages of their predictive capacity, several psychiatric-based PGx tests have already begun to be offered by private companies [for a review, see 17]. Furthermore, several clinical PGx expert panels, such as the Pharmacogenomics Knowledgebase (PharmGKB) and the Clinical Pharmacogenetics Implementation Consortium (CPIC) [18–20], as well as drug regulatory agencies (e.g., US Food and Drug Administration) [21, 22], have begun to propose guidelines to assist physicians in interpreting the clinical significance of information provided by these tests. Finally, recent studies assessing the feasibility and utility of incorporating PGx into standard psychiatric practice have yielded encouraging results [23–27].

Here, we survey the literature published on the PGx of AAEs within the last 5 years (2010–2015), placing emphasis on drug-gene associations replicated in independent samples and which have additionally been listed by expert panels as having potential clinical relevance. Several high-quality reviews providing extensive coverage on the AP PGx literature published prior to 2010 are available [28–31].

Methods

PubMed, Embase (Ovid), and PsycINFO (Ovid) databases were searched using the following combination of key-terms and/or their matched subject headings: ('antipsychotic' OR 'neuroleptic') AND ('pharmacogenetics' OR 'pharmacogenomics' OR 'genetic association study' OR 'polymorphism') AND ('adverse effect' OR 'tardive dyskinesia' OR 'extrapyramidal symptoms' OR 'weight gain'). Our search parameters limited results to include only peer-reviewed articles that were published in English from 2010 to 2015 inclusive. Letters to the editor, editorials, and publications solely related to drug efficacy, or which were otherwise irrelevant to the subject of our review were excluded. The reference lists of retained publications were also screened for other relevant studies. Given the abundance of literature available, emphasis has been placed on independently replicated gene-drug relationships of common AAEs that have additionally been recognized by expert panels as having potential clinical relevance.

Results

Studies meeting our criteria represent two major categories of AAEs: (1) metabolic dysregulation, including weight gain and/or metabolic syndrome (MetS), and (2) movement disorders, including EPS and TD. In total, we have reviewed 53 studies that report on variants within 11 different genes.

Weight Gain and MetS

AP-induced weight gain (AIWG) has an incidence of approximately 30% and is most pronounced among patients treated with the SGAs clozapine and olanzapine [32]. The heritability (h^2) of AIWG is estimated to be 0.6–0.8 [16]. AIWG often coincides with the development of MetS, a complex phenotype characterized by central obesity, insulin resistance, hyperglycemia, dyslipidemia, and hypertension [8]. With respect to AIWG and AP-induced MetS (AP-MetS), we report on variants within genes *HTR2C*, *LEP*, *LEPR*, *MC4R*, *MTHFR*, and *OGFRL1*. Information on gene-drug interactions listed to be of potential clinical significance by expert PGx panels is given in

Table 1. Putative genetic associations with common metabolic AAEs studied from 2010 to 2015 and their related listings by expert PGx panels

Gene	Polymorphism	Putative association	Listings by expert panels	References
HTR2C	rs3813929 (759C/T)	T allele confers protection against AIWG	CPIC: evidence level D[a] PharmGKB: evidence level 2B[b]	[42–55]
	rs1414334 (C/G)	C allele is associated with a higher risk of antipsychotic-induced MetS	CPIC: evidence level D[a] PharmGKB: evidence level 2B[b]	[49, 61–63]
LEP	rs7799039 (2548G/A)	G allele acts dominantly to heighten susceptibility to AIWG	PharmGKB: evidence level 3[c]	[44, 46, 50, 52, 62, 73–78]
LEPR	rs1137101 (Q223R) or (668A/G)	AIWG and related metabolic dysregulation; risk allele is unclear	PharmGKB: variant annotation	[52, 73, 74, 77, 78, 81]
MC4R	rs17782313 (C/T)	C allele linked to higher risk of AIWG	PharmGKB: evidence level 2B[b]	[97, 98]
	rs489693 (A/C)	A allele linked to higher risk of AIWG	PharmGKB: evidence level 2B[b]	[75, 93, 96]
MTHFR	rs1801131 (A1298C)	C allele associated with a greater risk of metabolic AAEs	PharmGKB: evidence level 3[c]	[109, 111, 112]
	rs1801133 (C677T)	T allele associated with a greater risk of metabolic AAEs	PharmGKB: evidence level 3[c]	[81, 106–112]
OGFRL1	rs9346455 (T/G)	T allele linked to higher risk of AIWG	PharmGKB: variant annotation[d]	[115]

References include both positive and negative findings. See references [19, 20] for further information on the PharmGKB and CPIC, as well as the criteria used to assign evidence levels. [a] Considered of interest. [b] Moderate evidence for this association. [c] Low evidence for this association. [d] Listed under *IBA57*.

table 1. A detailed overview of the studies, including information on design, treatment duration, AP use, sample demographics, main results, and associated odds ratios and/or p values (if applicable), is provided in table 2.

HTR2C

Serotonin 2C receptors (5-HT_{2C}Rs) are integral to the regulation of energy homeostasis via their interaction with the melanocortin and leptin signaling pathways [33–35]. The most potent weight-inducing APs are characterized by their high affinity for 5-HT_{2C}Rs and the antagonistic properties they have at these receptors [36]. 5-HT_{2C}R antagonism promotes hyperphagic activity and attenuates energy expenditure [35]. In light of this, the X-linked *HTR2C* gene encoding 5-HT_{2C}Rs has been among the most extensively investigated genes with respect to AP-induced metabolic dysregulation. Results from studies conducted prior to 2010 have pointed to a consistent relationship between the rs3813929 (–759C/T) promoter SNP and AIWG [28, 37]. This SNP has been shown to affect the transcription of *HTR2C*, though the exact impact on gene expression remains unclear [38–41].

Several studies included in our results have replicated the association of –759C/T with AIWG [42–46], though negative and contradictory results were also reported [47–54]. One study involving a heterogeneous psychiatric sample reported that carriers of the *HTR2C* –759T allele were protected against the weight-inducing effects of olanzapine [42]. This association was also confirmed in a pediatric ASD sample treated with risperidone [43]. However, 2 other studies also involving samples of pediatric patients with ASDs could not verify this result [47, 48]. Opgen-Rhein et al. [44] had initially identified a nominally significant association between the –759C/T SNP and AIWG. However, a haplotype analysis revealed that the A-G-C haplotype (of SNPs rs498207, rs3813928, and rs3813929, respectively) was significantly overrepresented in the weight gain group (i.e. ≥7% increase in body weight), while the opposite haplotype (G-A-T) was overrepresented in the control group.

A study by Sicard et al. [45] provides additional support for the involvement of –759C/T in differential susceptibility to AIWG. Haplotype analyses including correlated SNPs rs518147 (G-697C) and rs6318 (Ser23Cys) showed that the C-G-Cys23 haplotype was significantly overrepresented within the weight gain group. Furthermore, a meta-analysis published as part of the same study confirmed the association between the *HTR2C* –759T allele and resistance to AIWG. The effect size was more pronounced when limiting the analysis to studies including all or almost all European subjects and excluding Asian samples. Limiting the analysis to samples with all or almost all European subjects also eliminated signifi-

Table 2. Overview of studies and their main findings related antipsychotic-induced weight gain and/or metabolic syndrome

Gene	Polymorphism(s)	Design, treatment duration	Medication (n)	Sample [diagnosis; n (m/f); ethnicity/race]	Main findings
HTR2C	rs3813929 (759C/T)	prospective 4 weeks	olanzapine (124)	psychotic or mood disorder; n = 124 (62/62); German-Caucasian (124)	olanzapine treatment associated with change in BMI (p = 0.009) and weight (p = 0.008) [42]
HTR2C	rs3813929 (759C/T)	retrospective 8 weeks	risperidone (36)	ASD pediatric sample (5–16 years); n = 32 (28/4); all Caucasian	carriers of the T allele had lower BMI gain (p < 0.001) [43]
HTR2C	rs3813929 (759C/T)	retrospective 12 months	risperidone (45)	ASD pediatric sample; n = 45 (34/11), n = 31 at 12 months; Caucasian (44), African (1)	nonsignificant [47]
HTR2C	rs3813929 (759C/T)	cohort ≥6 months	risperidone (124)	ASD pediatric sample (7–17 years); n = 124 (112/12); mostly European American	nonsignificant [48]
HTR2C	rs3813929 (759C/T) rs3813928 rs498207 rs6318 (Ser23Cys)	retrospective 12 weeks	amisulpride (2) clozapine (24) olanzapine (33) quetiapine (2) risperidone (8) mixed (52)	SCZ or SA; n = 128 (80/48); European (118), Turkish (10)	significant association for rs498207 (p < 0.0049); G-A-T haplotype (of SNPs rs498207, rs3813928, and rs3813929, respectively) overrepresented in group with <7% BWG [44]
HTR2C	rs3813929 (759C/T)	cross-sectional ≥12 months	clozapine (113)	SCZ; n = 113 (81/32); Korean (113)	nonsignificant trend for male weight-gainers vs. male nongainers (p = 0.051) [50]
HTR2C	rs3813929 (759C/T)	retrospective ≥7 months	iloperidone (216)	SCZ; n = 216 (180/36); White (85), Black (106), Asian (17), other (8)	nonsignificant [51]
HTR2C	rs3813929 (759C/T)	cohort naturalistic 95% ≥3 months	aripiprazole (23) clozapine (68) olanzapine (54) quetiapine (31) risperidone (30)	psychotic disorder (89), mood disorder (21), personality disorder (8), other (23); n = 141 (82/59); European-Caucasian	nonsignificant [52]
HTR2C	rs3813929 (759C/T)	clinical trial 8 weeks	olanzapine (205)	bipolar disorder, borderline personality disorder, treatment resistant depression; n = 205; White, Hispanic, Black	nonsignificant [53]
HTR2C	rs3813929 (759C/T)	retrospective 3 months	olanzapine or risperidone	SCZ (77), SA (7), or delusional disorder (17); n = 101; drug-naïve females, Caucasian (101)	nonsignificant [54]
HTR2C	rs3813929 (759C/T) rs518147 (G697C) rs6318 (Ser23Cys)	retrospective 6 weeks	mostly olanzapine or clozapine	chronic SCZ or SA; n = 205 (141/64); European (126), African-American (58), unspecified (21)	C-G-Cys haplotype (for SNPs rs3813929, rs518147, and rs6318, respectively) overrepresented in patients with weight gain (p = 0.0015; OR: 1.93, 95% CI = 1.04–3.56) [45]
HTR2C	rs3813929 (759C/T) rs1414334 (C/G)	meta-analysis	olanzapine (336)	chronic SCZ; n = 336 (140/196); European (149), Croatian (108), Korean (79)	nonsignificant association for –759C/T allele; significant association showing that C allele confers risk of AP-MetS (OR: 2.44, 95% CI = 1.48–4.00; p = 0.0004; $I^2 = 0$) [49]
HTR2C	rs3813929 (759C/T)	meta-analysis	various	SCZ or SA; n = 862; European American, African-American, Asian	T allele confers significant protection against AIWG (p = 0.02); association more pronounced after limiting analysis to all or almost all European samples (p = 0.006) [45]
HTR2C	rs1414334 (C/G)	cross-sectional ≥3 months	olanzapine (43) risperidone (40) clozapine (31) aripiprazole (11) quetiapine (15) FGAs (17) polypharmacy (29)	SCZ (146), SA (23), or psychotic disorder (17); n = 186 (127/59); 93% of participants were of European ancestry while the remaining 7% were of Asian, African, or mixed ancestry	C allele carriership is significantly associated with a greater risk of AP-MetS (OR: 3.73, 95% CI = 1.29–10.79; p = 0.015) [61]
HTR2C	rs1414334 (C/G)	cross-sectional unstated	clozapine (190)	SCZ (clinical diagnosis of F2 group according to ICD-10); n = 190; all European	nonsignificant [62]

Table 2 (continued)

Gene	Poly-morphism(s)	Design, treatment duration	Medication (n)	Sample [diagnosis; n (m/f); ethnicity/race]	Main findings
HTR2C	rs6318 (rs1414334 proxy) rs498177, rs521018, rs5988072, rs2192371, rs12833104	cross-sectional ≥3 months	clozapine (171) olanzapine (91) risperidone (194)	SCZ; n = 456 (299/157); Han Chinese	the rs521018-rs498177 haplotype was significantly associated with AP-MetS, but only in female patients (p = 0.0108) [63]
HTR2C-LEP	rs3813929 (759C/T) rs7799039 (2548G/A)	cross-sectional ≥3 months	clozapine (67) olanzapine (67) risperidone (55) quetiapine (3) polypharmacy (8)	SCZ (139), SA (43), or psychotic disorder (18); n = 200 (134/66); European-Caucasian	combined *HTR2C* –759C/T-*LEP*-2548G/A genotype significantly associated with AIWG (OR: 2.88; 95% CI = 1.05–7.95) [46]
LEP	rs7799039 (2548G/A)	retrospective 12 weeks	clozapine (24) olanzapine (33) other (12) mixed (52)	SCZ or SA; n = 128 (80/48); European (118), Turkish (10)	nonsignificant [44]
LEP	rs7799039 (2548G/A)	cross-sectional ≥12 months	clozapine (113) polypharmacy for 39.8% patients	SCZ; n = 113 (81/32); Korean (113)	BMI gain for AA genotype carriers was significantly greater than carriers of both the AG and GG genotypes (p = 0.048; reported for AA-AG comparison) [50]
LEP	rs7799039 (2548G/A)	cohort, naturalistic 95% ≥3 months	aripiprazole (23) clozapine (68) olanzapine (54) quetiapine (31) risperidone (30)	psychotic disorder (89), mood disorder (21), personality disorder (8), other (23); n = 141 (82/59); European-Caucasian	nonsignificant [52]
LEP	rs7799039 (2548G/A)	cross-sectional unstated	clozapine (190)	SCZ (clinical diagnosis of F2 group according to ICD-10); n = 190; Finnish (190)	nonsignificant [62]
LEP	rs7799039 (2548G/A)	cross-sectional unstated	clozapine (132) olanzapine (41) risperidone (120) quetiapine (52) sulpride (48) haloperidol (47)	SCZ; n = 633 (338/295); 570 included in pharmacogenetic analysis; patients of Taiwanese descent	LEP rs7799039 G allele significantly associated with BMI (p = 0.008), waist circumference (p = 0.014), MetS (p = 0.019), insulin (p = 0.034), and HOMA (p = 0.029) under a dominance genotypic model [73]
LEP	rs7799039 (2548G/A)	retrospective ≥3 months	clozapine (56)	SCZ, SA, or psychotic disorder; n = 56 (44/12); Spanish	nonsignificant [76]
LEP	rs7799039 (2548G/A) rs10954173 rs3828942	prospective ≥6 weeks	clozapine (80) olanzapine (28) risperidone (32) haloperidol (16) other (24)	SCZ; n =181; European (127), African-American (43), other (9)	significant association between haplotype LEP rs7799039G-rs10954173G-rs3828942G with AIWG (p = 0.035); the rs7799039 G allele (p = 0.042) and G allele of rs3828942 (p = 0.032) were associated with greater weight gain [74]
LEP	rs7799039 (2548G/A) rs10244329, rs12706832 rs2071045	cohort 8 weeks	risperidone (181)	ASD pediatric sample; n = 181 (148/33); White (125), Black (26), Hispanic (10), other (16)	significant association: the rs7799039 G allele acts dominantly to increase risk for AIWG ($p = 1.4 \times 10^{-4}$), while AA homozygotes are relatively protected [75]
LEP	rs7799039 (2548G/A)	prospective, longitudinal 12 months	haloperidol olanzapine risperidone ziprasidone aripiprazole quetiapine	drug naïve, first-episode psychosis with DSM-IV criteria meeting SCZ or a SCZ spectrum disorder; n = 205 (118/87); 94% European-Caucasian (Spanish)	nonsignificant [77]
LEPR	rs1137101 (Q223R or 668A/G)	cross-sectional ≥3 months	clozapine (71) olanzapine (68) risperidone (57) other SGA (4)	SCZ (139), SA (43), or other psychotic disorder (18); n = 200 (134/66); European-Caucasian	significant association for female subjects: 70.6% were obese in the *LEPR* 223QQ group vs. 38.5% in the 223QR (OR: 0.11, 95% CI = 0.02–0.54; p = 0.007) and 40.0% in the 223RR (OR: 0.07, 95% CI = 0.01–0.63; p = 0.018) groups [78]

Table 2 (continued)

Gene	Polymorphism(s)	Design, treatment duration	Medication (n)	Sample [diagnosis; n (m/f); ethnicity/race]	Main findings
LEPR	rs1137101 (Q223R or 668A/G)	cohort, naturalistic 95% ≥3 months	aripiprazole (23) clozapine (68) olanzapine (54) quetiapine (31) risperidone (30)	psychotic disorder (89), mood disorder (21), personality disorder (8), other (23); n = 141 (82/59); European-Caucasian	*LEPR* 223R allele was significantly associated with an increased risk of obesity in females (p = 0.03), but not in males [52]
LEPR	rs1137101 (Q223R or 668A/G)	cross-sectional unstated	clozapine (132) olanzapine (41) risperidone (120) other (147)	SCZ; n = 633 (338/295); 570 included in pharmacogenetic analysis; patients of Taiwanese descent	nonsignificant [73]
LEPR	rs1137101 (Q223R or 668A/G)	retrospective ≥6 weeks	clozapine (80) olanzapine (28) risperidone (32) haloperidol (16) other (24)	SCZ; n =181, European (127) African-American (43), other (9)	nonsignificant [74]
LEPR	rs1137101 (Q223R or 668A/G)	prospective, longitudinal 12 months	haloperidol olanzapine risperidone quetiapine	drug naïve, first-episode psychosis with DSM-IV criteria meeting SCZ or a SCZ spectrum disorder; n = 205 (118/87); 94% European-Caucasian (Spanish)	nonsignificant [77]
LEPR	rs1137101 (Q223R or 668A/G)	cross-sectional ≥12 months	olanzapine (62) risperidone (59) paliperidone (24) other APs (61)	n = 206 (137/69); Malaysian (109), Chinese (76), Indian (21)	*LEPR* 223R or 668G allele significantly associated with increased risk of MetS (OR: 0.47, 95% CI = 0.28–0.80, p = 0.005) [81]
MC4R	rs17782313 (C/T) rs2229616 rs11872992 rs8087522	cohort 4–14 weeks	clozapine (99) olanzapine (36) risperidone (40) haloperidol (16) other (33)	chronic SCZ or SA; n = 224 (150/74); European American (157), African-American (56), other (11)	nonsignificant trend with respect to rs17782313 (p = 0.09); nominally significant association for rs8087522 detected in the clozapine-treated European subsample, with the A allele being overrepresented within the weight gain group [97]
MC4R	rs17782313 (C/T)	retrospective 4 weeks	olanzapine (135) quetiapine (102) risperidone (66) amisulpride (58) clozapine (36) paliperidone (28)	SCZ; whole study, n = 345, 61% with an F2 (ICD-10) diagnosis; adjusted subsample (controlling for co-medication), n = 173, 80% with F2 diagnosis; first-episode sample, n = 59; control sample, n = 40	C allele was significantly associated with risk of weight gain in a dose-loading manner (p = 0.045); effect was more pronounced in the adjusted subsample excluding co-medication (p = 0.03); dose-response effect was absent in first-episode subsample, but association was still significant (p = 0.041) [98]
MC4R	rs8087522 rs489693 (A/C) rs11872992 rs8093815	cohort 8 weeks	risperidone (181)	ASD pediatric sample; n = 181 (148/33); White (125), Black (26), Hispanic (10), other (16)	nonsignificant trends for associations of rs8087522 and rs8093815 with AIWG (p = 0.06 and p = 0.07, respectively); nominally significant results for associations of rs11872992 and rs489693 with AIWG (p = 0.03 for both; p_{cor} >0.05) [75]
MC4R	Tag-SNPs	GWAS, cohort 6–12 weeks	cohort 1: quetiapine (36) risperidone (135) aripiprazole (41) olanzapine (45) cohort 2: clozapine (73) cohort 3: various	cohort 1: drug-naïve youths (4–19 years), n = 270; European American (131), African-American (70), other (69) cohort 2: treatment-resistant SCZ, n = 73; all European American cohort 3: SCZ, n = 40	rs489693 A allele showed significant effects in all three cohorts: cohort 1: $p = 2.8 \times 10^{-7}$ cohort 2: $p = 1.4 \times 10^{-4}$ cohort 3: p = 0.007 meta-analytic $p = 5.59 \times 10^{-12}$ [93]
MC4R	rs489693	retrospective 4 weeks	olanzapine (133) quetiapine (102) risperidone (66) clozapine (34) other (83)	whole study, n = 341, ~61% with an F2 (ICD-10) diagnosis; adjusted subsample, n = 169, ~80% with F2 diagnosis; first-episode sample, n = 59; control sample, n = 40	*MC4R* rs489693 A allele was significantly associated with increased risk of AIWG in whole study sample and both of the subsamples [96]
MTHFR	rs1801133 (C677T)	cross-sectional median treatment duration of 6 months	quetiapine (49) risperidone (46) other (10)	SGA-treated sample, n = 105; primarily of European descent (74%)	T allele carriership was significantly associated with a greater prevalence of MetS (p = 0.05) [108]

Table 2 (continued)

Gene	Poly-morphism(s)	Design, treatment duration	Medication (n)	Sample [diagnosis; n (m/f); ethnicity/race]	Main findings
MTHFR	rs1801131 (A1298C) rs1801133 (C677T)	cohort 8.87 ± 3.6 weeks	clozapine or olanzapine (179) risperidone (92) other (77)	n = 347 (183/164); 66 were first-episode patients; European/ Caucasian (281), African-Americans (56), other (11)	nonsignificant association for *MTHFR* A1298C variant in total study sample, clozapine/olanzapine-treated European subsample, and first-episode subsample analyses; nominal association detected for the C677T variant in total study sample analysis ($p = 0.03$; $p_{cor} > 0.05$) [109]
MTHFR	rs1801131 (A1298C) rs1801133 (C677T)	cohort Chinese sample: 8–10 weeks Spanish sample: 3 months	Chinese sample: chlorpromazine risperidone, other Spanish sample: risperidone olanzapine, other	first-episode, drug-naïve SCZ patients; Chinese Han sample, n = 182 (83/99); Spanish sample, n = 72 (53/19)	677CC genotype carriers showed a significantly greater gain in BMI compared to T allele carriers for both the Chinese ($p = 0.012$) and Spanish ($p = 0.017$) samples; findings for the rs1801131 SNP were nonsignificant [110]
MTHFR	rs1801131 (A1298C) rs1801133 (C677T)	cross-sectional variable	primarily SGAs	SCZ (69.3%), SD (11.4%), or SA (19.3%); n = 518 (66.4% male); primarily of European ancestry	significant association detected for *MTHFR* A1298C, with C/C genotype carriers having a 2.4 times higher risk of MetS compared to A/A genotypes (OR: 2.44, 95% CI = 1.25–4.76; $p = 0.009$) [111]
MTHFR	rs1801131 (A1298C) rs1801133 (C677T)	cohort 3 months	clozapine (16) olanzapine (41) risperidone (37) other (30)	SCZ or SA; n = 104 (71/33); European-Caucasian	*MTHFR* 1298C allele was significantly associated with changes to several metabolic parameters after SGA initiation, especially weight gain ($p = 0.006$) and changes in blood glucose ($p = 0.024$) [112]
MTHFR	rs1801133 (C677T)	cross-sectional ≥12 months	olanzapine (62) risperidone (59) paliperidone (24) other APs (61)	SCZ; n = 206 (137/69); Malaysian (109), Chinese (76), Indian (21)	nominally significant: *MTHFR* 677 T allele appeared to confer protection against AP-MetS (OR: 0.59, 95% CI = 0.35–0.99, $p = 0.049$); authors declare that correction for multiple testing was not performed to avoid type 2 error [81]
MTHFR	rs1801133 (C677T)	cross-sectional ≥6 months	various	SCZ spectrum disorder; n = 127; ethnicity unspecified	significant association: for patients using risk medication, T allele carriership (CT/TT) was associated with an increased risk of AP-MetS ($p < 0.001$); *MTHFR* and *COMT* 158 Val interaction was significant ($p = 0.0073$) [107]
OGFRL1	Tag-SNPs	GWAS, cohort discovery sample: 20.5 (±6.2) replication sample: 6.1 (±2.1)	discovery: olanzapine (63) quetiapine (67) risperidone (59) replication: clozapine (69) olanzapine (18)	discovery sample, SCZ, n = 189 (151/38); a subset of patients from the CATIE sample of sole European ancestry; replication sample, SCZ, n = 86 (56/30); all of European ancestry	GWAS yielded a number of signals in association with BMI gain, the strongest of which emerged from the rs9346455 SNP upstream of the OGFRL1 gene ($p = 6.49 \times 10^{-6}$); replication: $p = 0.005$; meta-analytic $p = 1.09 \times 10^{-7}$ [115]

SA = Schizoaffective disorder; SD = schizophreniform disorder.

cant heterogeneity and publication bias that was initially detected.

A more recent meta-analysis only detected a trending association between –759C/T and AIWG, though only 4 studies were included as the authors were specifically interested in olanzapine-induced weight gain [49]. Kang et al. [50] also reported a trend in their study involving a sample of Korean SCZ patients. Five other studies reported neither an association nor a trend [51–55]. As Wallace et al. [41] first pointed out, contradictory reports relating to this association can mainly be attributed to differences in study duration, as the relationship between AIWG and –759C/T is most prominent during the early stages of treatment (<3 months). Indeed, this pattern is largely consistent with the studies reviewed here. Conflicting results may also be attributable to as yet unidentified confounding variables, such as differential RNA editing [56, 57] and the 'flip-flop' phenomenon described by Lin et al. [58]. All things considered, the overall evidence suggests that the *HTR2C* –759C/T polymorphism is an important

mediator of AIWG during the initial stages of treatment. However, further investigation is needed to determine the precise nature of this association, and also to understand how –759C/T may interact with other variables to influence AIWG.

Recent evidence has also reaffirmed an association of the *HTR2C* intragenic rs1414334 (C>G) SNP with a heightened risk of AP-MetS. Carriers of the C allele are more likely to meet criteria for AP-MetS. In agreement with their previous findings [59, 60], a Dutch research group reported an association (when controlling for type 2 error) between the rs1414334 C allele and a higher risk of developing AP-MetS [61]. A recent meta-analysis by Ma et al. [49] was able to corroborate the significance of this association when examining all 3 studies conducted by the Dutch research group. However, negative results of this association have also been reported [62, 63]. Nevertheless, there is an overall greater amount of evidence supporting this association than there is refuting it. Future studies should investigate the clinical utility of this variant as a means to inform and optimize treatment selection.

LEP and LEPR

Leptin plays a critical role in the regulation of energy homeostasis and feeding behavior. In the hypothalamus, particularly the arcuate and ventromedial nuclei, leptin targets leptin receptors encoded by the *LEPR* gene, whereby it transmits a potent anorectic signal [64–66]. Mutations in both *LEP* and *LEPR* are linked to metabolic abnormalities and the occurrence of human obesity [67–69]. The *LEP* –2548G allele, for instance, has been associated with an increased risk of overweight and obesity [69–71]. Taken together, there is a sound theoretical basis supporting the potential involvement of *LEP* and *LEPR* in AP-induced metabolic dysregulation. Indeed, several studies from our review have implicated these genes in metabolic AAEs [46, 52, 72–75]. Still, negative and contradictory results have also been reported [44, 62, 76, 77].

In line with a 2008 report by Yevtushenko et al. [72], Gregoor et al. [46] found that the combined presence of the *LEP* –2548G allele and absence of the *HTR2C* –759T allele was associated with a greater risk of SGA-related obesity. Another study by Gregoor et al. [52] found that baseline obesity risk was significantly greater for females carrying the *LEPR* 223R allele. This result runs contrary to the finding from their 2009 study which instead reported that the 223R allele was associated with lower baseline risk for female obesity [78].

Nurmi et al. [75] have offered compelling evidence in support of the association of the –2548G allele with AIWG. The sample of this study was comprised of risperidone-treated autistic youth who had participated in one of two clinical trials conducted by the NIMH Research Units on Pediatric Psychopharmacology (RUPP). The majority of subjects were drug-naïve and of European ancestry. Genotype analysis revealed a robust result for the *LEP* –2548G allele, which acted dominantly to confer risk of AIWG. Highly significant findings were also identified for the *CNR1* promoter SNP rs806378 and the *CNR1* variant rs1049353. Under a risk-allele dose model, the combination of risk variants associated with *LEP* and *CNR1* attained an impressive effect size ($D = 0.85$; $p = 1.3 \times 10^{-9}$) [75]. Furthermore, the *CNR1* rs806378 finding is in agreement with a previous report from our group [79].

Perez-Iglesias et al. [77] found no association for either the –2548G/A or Q223R SNP with AIWG. Negative findings for associations of –2548G/A or Q223R with AIWG were also reported by 3 other studies [44, 62, 76]. In terms of other metabolic abnormalities, Gregoor et al. [80] found that the absence of the *LEP* –2548G and *LEPR* 223R alleles were independently associated with higher TC/HDL ratios in males and females, respectively. Roffeei et al. [81] reported that the *LEPR* 223R allele was protective against AP-MetS [81]. In summary, the results for the *LEP* –2548G/A variant have been somewhat consistent, whereas those for the *LEPR* Q223R SNP are less straightforward.

MC4R

The gene product of *MC4R*, the melanocortin 4 receptor (MC4-R), is essential for maintaining energy homeostasis and regulating food consumption [82]. MC4-R has also been implicated in molecular pathways regulating sexual arousal, inflammatory response, pain modulation, and blood pressure [83–86]. MC4-R is widely distributed throughout the brain, though it primarily regulates metabolic pathways from within hypothalamic and brain stem nuclei [82, 87]. MCR-4 interacts with both the serotonergic and leptinergic systems [88, 89], and similar to *LEP* and *LEPR*, mutations in the *MC4R* gene or adjacent regions have a well-established role in the expression of congenital and polygenic forms of obesity [90–92]. Recent pharmacogenetic studies have identified the MC4-R gene locus SNPs rs489693 and rs17782313 as potential biomarkers of AIWG.

The rs489693 SNP was first detected in a genome-wide association study (GWAS) conducted by Malhotra et al. [93] in a cohort of SGA-treated, drug-naïve youth. Twen-

ty SNPs surpassed a statistical threshold of $p < 10^{-5}$, all of them located at a single locus, approximately 190 kb downstream of *MC4R*. This locus overlaps with a region that had been previously linked to obesity and BMI by other GWA studies [94, 95]. The association of SNP rs489693 with AIWG was subsequently confirmed in three replication cohorts. Importantly, these cohorts consisted of adult SCZ patients, and one of these cohorts had previous SGA exposure, thereby demonstrating that this association is neither exclusive to pediatric nor drug naïve populations [93]. Furthermore, this association was recently replicated by Czerwensky et al. [96] in a naturalistic study involving a sample of SCZ inpatients. A trending association between rs489693 and BMI gain was also reported by Nurmi et al. [75] in the RUPP study mentioned above.

In a study involving a sample of SCZ patients of primarily European or African ancestry (70 and 25%, respectively), Chowdhury et al. [97] were unable to identify an association between *MC4R* rs17782313 and AIWG at the genotype level. However, an allelic analysis restricted to patients of European ancestry receiving either clozapine or olanzapine revealed a trending association in which the C allele conferred a greater risk of AIWG. Czerwensky et al. [98] were able to corroborate this finding at the genotype level and showed that CC and CT genotype carriers were at a significantly greater risk of AIWG. A haplotype analysis of rs17782313 and rs489693, as well as other SNPs in LD, may yield more robust results. In sum, the *MC4R* locus appears to be a very promising candidate for the prediction of AIWG. Clinical trials will be required to assess the clinical utility of these SNP as biomarkers to predict AIWG.

MTHFR

MTHFR (methylenetetrahydrofolate reductase) encodes an enzyme that catalyzes biochemical reactions important to the folate pathway [99]. Two common *MTHFR* variants, rs1801133 (C677T) and rs1801131 (A1298C), reduce the catalytic activity of MTHFR by 35 and 20%, respectively [100–102]. The attenuation of MTHFR as a consequence of these SNPs has been linked to elevated plasma homocysteine. Hyperhomocysteinemia has been associated with a greater risk of both SCZ and cardiovascular disease [103–105]. Taken together, there is a rationale establishing *MTHFR* as a potential candidate influencing AAEs.

Following up on the results of a previous study [106], Ellingrod et al. [107] found that an interaction between the *MTHFR* 677T and *COMT* 158Val alleles was positively associated with risk of AP-MetS. Interestingly, increasing age was negatively correlated with the likelihood of meeting MetS criteria, suggesting that this interaction exerts a stronger effect on relatively younger patients. Consistent with the studies by Ellingrod et al. [106, 107], Devlin et al. [108] found that pediatric patients with ASDs carrying the 677T allele were at a greater risk of MetS compared to CC homozygotes. Similarly, Kao et al. [109] reported a nominally significant association between the T allele and AIWG. Conflicting results in which the T allele has a protective effect against AP-MetS have also been reported [81, 110]. In addition, other studies have failed to identify an association between MetS and the 677T allele, but have reported positive results for an association with the 1298C allele [111, 112].

In light of the discordant findings, it is unlikely that *MTHFR* plays a major role in the PGx of metabolic AAEs. However, considering the heterogeneity across studies and possible gene interaction effects, it would be premature to completely rule out *MTHFR* as a potentially informative biomarker. There may also be other confounding variables not taken into consideration. For example, dietary folate has been shown to be important in moderating the effects of the *MTHFR* SNPs C677T and A1298C in other contexts (e.g., susceptibility to cancer) and may similarly influence AAEs [113].

OGFRL1

OGFRL1 encodes for opioid growth factor receptor-like 1, a paralog receptor which binds the endogenous opioid met-enkephalin [114]. Our research team recently conducted a GWAS to assess the genetic factors contributing to AIWG within a subset of European participants (n = 189) derived from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) sample [11, 115]. This subsample represented a relatively homogenous group of participants with similar clinical characteristics and treatment. A strong signal was detected at marker rs9346455, approximately 6.6 kb upstream of *OGFRL1*, with greater BMI gain observed among carriers of the G allele. This finding was subsequently replicated in an independent sample to produce a meta-analytic p value of 1.09×10^{-7}. Although not quite reaching genome-wide significance, this finding still represents a robust and promising result. At present, the rs9346455 SNP is not known to have any functional significance, and only a few studies on *OGFLR1* have been published [115]. Because it is unknown if or how opioid growth factor receptor-like 1 is related to energy homeostasis, this result should be interpreted with caution. Future research should aim to

Table 3. Putative genetic associations with antipsychotic-induced TD and EPS studied from 2010 to 2015, and their related listings by expert PGx panels

Gene	Polymorphism	Putative association	Listings by expert panels	References
CYP2D6	CYP2D6*1, *2, *3, *4, *5, *6, *10, *41	PM and IM status associated with a greater risk of TD or EPS	PharmGKB: evidence level 3[a]	[124–131]
DPP6	rs6977820 (T > C)	T allele associated with a greater risk of TD	PharmGKB: evidence level 2B	[149]
DRD2	rs1800497 (Taq1A)	G allele associated with a greater risk of TD	PharmGKB: evidence level 2B[b] CPIC: evidence level D[c]	[136–139]
SLC18A2	rs2015586 (G/C)	C allele associated with a greater risk of TD	unlisted	[129, 140]
HSPG2	rs2445142 (G > C); rs878949 (T > C)[d]	G and T allele associated with a greater risk of TD	PharmGKB: evidence level 3[a]	[145–147]

References include both positive and negative findings. See references [19, 20] for further information on the PharmGKB and CPIC, as well as the criteria used to assign evidence levels. [a] Low evidence for this association. [b] Moderate evidence for this association. [c] Considered of interest. [d] Perfect proxy marker for rs2445142 ($r^2 = 1$).

address these uncertainties and clarify the potential role of *OGFRL1* in AIWG.

To summarize this section, several genetic associations have been consistently replicated for AIWG, and the *HTR2C* intragenic SNP rs1414334 has been verified as a possible predictor of MetS vulnerability. In light of this accumulating evidence, efforts have been undertaken to develop the first gene panels for use in clinical populations [e.g., 116].

EPS and TD

Our review of EPS and TD will focus on the genes encoding cytochrome P450 2D6 *(CYP2D6)*, dopamine receptor D2 *(DRD2)*, heparan sulfate proteoglycan 2 *(HPSG2)*, dipeptidyl aminopeptidase-like protein 6 *(DPP6)*, and vesicular monoamine transporter 2 *(SLC18A2)* genes. See table 3 for an overview of the results and listings by expert PGx panels. Detailed information on the studies is listed in table 4.

CYP2D6

CYP2D6 is a highly polymorphic enzyme involved in the metabolism of over 25% of the pharmaceuticals in clinical use, including the majority of APs [24]. CYP2D6 is predominantly expressed within the liver [117], though constitutive expression has also been detected in various brain regions, suggesting that CYP2D6 may also influence the activity of drugs at their sites of action [118].

Given the highly polymorphic nature of the *CYP2D6* locus, genotypes are typically described using *star allele nomenclature, which indicates an estimate of an individual's corresponding phenotype or metabolizer status [119]. Four different metabolizer phenotypes are commonly identified: (1) poor metabolizer (PM); (2) intermediate metabolizer (IM); (3) extensive metabolizer (EM; the 'wild-type'), and (4) ultrarapid metabolizer. The frequencies of these phenotypes and corresponding genotypes vary considerably between ethnic groups. For additional details on the specific allelic combinations associated with each metabolizer status and the distribution of *CYP2D6* alleles among different ethnic groups, refer to Hicks et al. [21] and references [17, 120], respectively. Numerous studies published prior to 2010 have examined the relationship between *CYP2D6* and EPS/TD, with the majority having supported a significant association between CYP2D6 metabolizer status and susceptibility to EPS/TD [121–123]. Eight studies published since 2010 have been reviewed here [124–131].

Fleeman et al. [124] conducted a meta-analysis of 20 studies reporting data on EPS and/or TD in relation to the CYP2D6 genotype. The majority of studies included clinical samples of patients treated with FGAs. After limiting the analysis to prospective studies only, PMs and IMs were found to have a significantly greater susceptibility to developing TD and AP-induced parkinsonism than EMs. Additionally, PMs had TD symptoms of greater severity than EMs.

Table 4. Overview of studies pertaining to antipsychotic-induced movement disorders

Gene	Polymorphism(s)	Design, treatment duration	Medication (n)	Sample [diagnosis; n (m/f); ethnicity]	Main findings
CYP2D6	EM/UM, IM, PM	meta-analysis	primarily FGAs	SCZ spectrum disorder; association of TD with CYP2D6, n = 1,482 (all studies); n = 336 (prospective); Caucasian, Japanese, Korean, Chinese	analysis of prospective studies showed significant associations between TD and CYP2D6 when comparing wt/wt genotypes with wt/mut and mut/mut + mut/wt (p = 0.008 and p = 0.02, respectively) [124]
CYP2D6	CYP2D6*1, *41, *3, *4, *5, *1xn, *2xn	cross-sectional ≥12 months	FGAs; equivalent ≥100 mg chlorpromazine daily	SCZ; n = 66; European-Caucasian	significant association between a greater ability to metabolize CYP2D6, as measured by increasing number of functional alleles, and tardive dyskinesia ($\chi^2 = 7.65$, d.f. = 1, p = 0.006) [125]
CYP2D6	CYP2D6*1,*3,*4, *10, *41, *1xn, *2xn	clinical trial 8 days	risperidone (50)	SCZ (43), SA (7); n = 50 (39/11); Caucasian	indirect association suggesting that PMs and IMs experienced a higher occurrence of EPS in response to risperidone [128]
CYP2D6	CYP2D6*1, *4, *5, *6, *1xn	RCT 24 h (2×; 2 studies)	haloperidol (25) risperidone (25)	healthy volunteers, n = 25 (17/8); PMs, n = 8; EMs, n = 10; UMs, n = 7; Caucasian	metabolizer status associated with differences in 'EPS' (measured as wakefulness activity by actigraphy) [126, 127]
CYP2D6	unclear	cross-sectional	unclear	SCZ (CATIE subsample); n = 710 (524/186)	nonsignificant [129]
CYP2D6	*1, *3, *4, *5, *6, *2xN	retrospective 8 weeks	risperidone (83)	first-episode SCZ, drug-naïve; n = 83 (17/66)	nonsignificant [130]
CYP2D6	*1,*2,*4,*5,*6B, *10B, *17, *29, *35, *41, *43, *106	naturalistic cohort	risperidone (25)	multiple diagnoses (unstated); n = 24 (16/8); South-African Black (9), White (15)	nonsignificant [131]
DPP6	rs6977820	discovery: GWAS replication: cohort	various	SCZ, discovery, TD, n = 61 (35/26); non-TD, n = 61 (35/26); replication, TD, n = 36 (18/18); non-TD, n = 136 (88/50); all Japanese	discovery: $p = 7.0 \times 10^{-6}$ (< reach genome-wide significance); significant association in replication sample: p = 0.008 (after correction for multiple testing); combined: $p = 4.6 \times 10^{-6}$ [149]
DRD2	rs6277, rs1800497 (Taq1A); rs1800498 (Taq1D); rs1799732 (−141CIns/Del)	cross-sectional ≥1 month	FGAs (37) SGAs (303) both (15) missing (47)	SCZ (277), SA (55), other PDs (70); n = 401; relatively young (median age = 26 years) Caucasian sample	association of Taq1A with TD nonsignificant, though this variant was significantly associated with akathisia (p = 0.001); the −141C variant was significantly associated with TD (p = 0.001) [139]
DRD2	rs6275, rs1800497 (Taq1A) rs1800498 rs1801028	cross-sectional at least 3 months	unclear	SCZ; n = 263 (140/123); Korean	nonsignificant [139]
HSPG2	rs2445142 (G/A)	discovery: GWAS replication: cohort	various	SCZ, discovery, n = 50 TD, n = 50 non-TD; replication, n = 36 TD (18/18), n = 136 non-TD (88/50); all Japanese	nominally significant association with TD attained in genome-wide and replication samples (p = 0.001 and p = 0.002, respectively); combined $p = 2.0 \times 10^{-5}$ [145]
HSPG2	rs2445142 (G/A) rs878949 (surrogate; $r^2 = 1$)	CATIE: prospective Jewish: cross-sectional ≥3 months	various	Jewish-Israeli sample, n = 166 (89/77); CATIE subsample, n = 179 (147/32); European-Caucasian	nominal significant association identified between rs2445142 (or rs878949 as a surrogate) in both samples (p = 0.003 and p = 0.039, respectively), with the G allele being the risk allele [146]
HSPG2	rs2445142, rs2270697	prospective	unclear	most SCZ, PD, or other; n = 168; Caucasian	nonsignificant, including rs2445142 [147]
SLC18A2	rs2015586	cross-sectional	unclear	SCZ (CATIE subsample); n = 710 (524/186); 56% European-American	$p = 9.858 \times 10^{-5}$; result is nonsignificant at genome-wide significance of 5.0×10^{-8} [129]
SLC18A2 and *DRD2*	*SLC18A2*: rs2015586, rs363224 *DRD2*: rs6277	retrospective variable durations	various	SCZ or SCZ spectrum disorder; n = 223; Caucasian (193), African-American (30)	gene-gene interaction involving C allele of rs363224 and the C allele of rs6277 was significantly associated with AIMS scores (p = 0.001); nominal association involving rs2015586 [140]

AIMS = Abnormal Involuntary Movements Scale; mut = mutant; PD = psychotic disorder; RCT = randomized controlled trial; SA = schizoaffective disorder; UM = ultrarapid metabolizer; wt = wild type.

A large-scale candidate gene study utilizing data from the CATIE sample, however, found no association between TD and *CYP2D6* [129]. Interestingly, results from a recent cross-sectional study by Koola et al. [125] suggested that the risk of TD was positively correlated with the number of functional CYP2D6 alleles that an individual carries. The experimenters speculated that active metabolites of FGAs might have toxic pharmacodynamic properties, and that a greater capacity to metabolize FGAs could therefore enhance susceptibility to TD by increasing exposure to these toxic metabolites. Three other studies involving healthy volunteers reported an indirect association between the PM or IM *CYP2D6* phenotypes and a greater risk of developing EPS [126–128]. Finally, 2 studies involving risperidone-treated samples found no association between CYP2D6 metabolizer status and EPS [130, 131].

Owing to difficulties in characterizing *CYP2D6* genotypes, most studies investigating associations with this gene have limited sample sizes and are therefore underpowered. Also, naturalistic and cross-sectional pharmacogenetic studies of CYP2D6 are limited given that numerous factors influencing the activity of this enzyme (e.g., co-medications, diet) remain unaccounted for. The meta-analysis performed by Fleeman et al. [124], which yielded significant results only after excluding cross-sectional and retrospective studies, underscores this point. Accordingly, a greater number of prospective studies, with sample sizes providing adequate power, are needed to clarify the role of CYP2D6 in AP-induced EPS/TD.

Dopamine Receptor D_2

The binding of dopamine D_2 receptors *(DRD2)* is hallmark feature of all APs and is strongly linked to their efficacy in treating the positive symptoms associated with SCZ and related spectrum disorders [132]. Because dopaminergic transmission in the nigrostriatal pathway is essential for adaptive motor control [133], aberrant DA signaling in this pathway is thought to underlie – at least in part – the pathophysiology of TD and EPS [134, 135]. In light of this, various studies have investigated the possibility that variation at the *DRD2* locus could explain individual differences in susceptibility to AP-induced EPS and TD. The *DRD2/ANKK1* marker rs1800497 (TaqIA) has yielded the most consistent findings, with two meta-analyses conducted prior to 2010 supporting an association with TD [136, 137]. However, the two studies included in our review that reexamined this association yielded negative results [138, 139]. Nevertheless, these studies hold little weight in view of the overall evidence, and the association between the TaqIA variant and TD susceptibility continues to be of clinical interest. Future studies should aim to investigate the clinical utility of this variant in guiding treatment selection.

SLC18A2

The *SLC18A2* gene encodes vesicular monoamine transporter 2 (VMAT2), which is involved in regulating the release of numerous neurotransmitters, including dopamine. A recent study by our lab revealed a significant association between the *SLC18A2* rs363224 CC genotype and susceptibility to TD in sample of chronic SCZ patients [140]. An association of TD with an interaction between the *SLC18A2* rs363224 C allele and the putatively functional *DRD2* rs6277 C allele showed an even greater effect size. Several nominally significant results for *SLC18A2* were also reported, the most interesting of which was rs2015586. This SNP was the top signal detected by Tsai et al. [129] in their candidate gene study of TD in the CATIE subsample.

HSPG2

HSPG2 encodes heparan sulfate proteoglycan 2, or perlecan, a highly conserved and essential structural protein originally identified within the basal lamina (i.e. basement membrane) [141]. Perlecan has also been shown to have an important role in endocytosis, as well as in the mediation of cell signaling, migration and proliferation [142, 143].

Using a genome-wide approach, a team of Japanese researchers [144] identified a number of putative associations predisposing to treatment-resistant TD, with the strongest signal emerging from an intronic SNP (rs2445142) located in the *HSPG2* gene. Although none of the associations survived correction for multiple testing, a replication study reanalyzing the top 67 hits in an independent sample was performed [145]. Case and control criteria were stringently defined so as to represent an extreme distribution of the TD phenotype, thereby increasing the power of the sample. A nominally significant association between the HSPG2 SNP rs2445142 and TD was once again detected. As with the discovery sample, the G allele was found to be overrepresented in the treatment-resistant group. Pooling the results from genome-wide and replication samples, the rs2445142-TD association attained an allelic p value of 2.0×10^{-5}. Functional studies of the rs2445142 variant provided further evidence that *HSPG2* is involved in TD [145]. Moreover, this association was later replicated by Greenbaum et al. [146] in two independent samples, one of Jewish-Israeli ances-

try and the other of American-European ancestry. After limiting the control group of the Jewish-Israeli sample to subjects representing an 'extreme' TD-resistant phenotype, a nominally significant association between the risk rs2445142 G allele and TD was detected. A nominal association was also identified in the European-American sample using a surrogate marker (rs878949, $r^2 = 1$) as a proxy for the rs2445142 genotype. A recent prospective study by Bakker et al. [147], however, was unable to verify this association. Still, given the naturalistic design of this study, it is possible that the signal was masked. While the results for *HSPG2* are promising, further replication of this finding is warranted.

DPP6

DPP6 encodes dipeptidyl peptidase protein 6, an auxiliary subunit of kv4.2 voltage-gated potassium channels [148]. Using the same discovery sample and a similar methodological approach to that of the Japanese study on *HSPG2* (though this time utilizing a different SNP array), the same research team detected an association between the *DPP6* intronic SNP rs6977820 and TD [149]. The A allele was found to be overrepresented in treatment-resistant TD cases. However, the association did not reach a genome-wide level of significance (defined at $p < 1.9 \times 10^{7}$). Nevertheless, replication in an independent sample yielded a significant result (allelic $p = 0.008$), giving a combined sample p value of 4.6×10^{6}. Subsequent functional studies conducted by the investigators provided further evidence that the *DPP6* SNP rs6977820 influences susceptibility to TD [149]. In sum, *DPP6* appears to be a promising biomarker for identifying patients at risk of developing treatment-resistant TD.

Discussion

In this review, we surveyed the literature on the PGx of AAEs from 2010 to 2015 inclusive, placing emphasis on independently replicated gene-drug associations that have been supported by expert panels. The studies included in the review assessed genetic associations involving metabolic dysregulation and movement disorders.

With respect to metabolic dysregulation, the studies included in this review have reaffirmed associations of the *HTR2C* –759C/T and *LEP* –2548G/A SNPs with AIWG [e.g., 45, 74]. Furthermore, additional evidence has accumulated in support of an association between the *HTR2C* rs1414334 SNP and AP-MetS [49]. With respect to AIWG, the *MC4R* marker rs489693 arguably represents the most promising finding to have emerged within the last 5 years [75, 93, 96, 97]. Also, a recent GWAS has identified a promising biomarker of AIWG risk at the *OGFRL1* locus [115].

In terms of TD and EPS, a large meta-analysis has provided additional support for an association between abnormal *CYP2D6* metabolizer status and greater susceptibility to AP-induced movement disorders, namely AIP and TD [124]. Research has also implicated variants of the *SLC18A2* gene and an interaction between *SLC18A2* and *DRD2* in TD susceptibility [129, 140]. Finally, *HSPG2* and *DPP6* have emerged as promising candidates for the prediction of TD susceptibility [145, 146, 149].

The studies on *HSPG2* and *DPP6* are noteworthy for reasons other than the results they obtained. The studies that looked at these genes involved a stringent characterization of the phenotypes constituting cases and controls. Enhancements in power attained through extreme phenotype sampling can help to facilitate the identification of risk alleles that are relatively rare or that only exert a modest effect on drug-gene phenotypes [150]. More frequent application of this design strategy could benefit psychiatric PGx by identifying variants that might usually go undetected due to noise within the sample. However, the limitations inherent to this sampling method, such as the requirement for more extensive screening protocols and the potential that detected variant effects may not apply to a broader distribution of the phenotype [151], need to be considered.

Also of interest in this review was the number of studies representing cases in which the consideration of multilocus effects yielded significant findings, while the examination of single markers was shown to yield nominal or nonsignificant results, or significant results with otherwise smaller effect sizes [46, 72, 75, 107, 140]. These studies highlight the genetic complexity of the phenotypes under examination and the need for investigators to place greater emphasis on gene-gene interactions in unravelling the pharmacogenetic determinants of AAEs. Statistical tools and methods for performing analyses of this complexity are becoming increasingly more efficient [152–154]. For example, principles of pathway-analysis are being combined with machine learning techniques in order to detect epistatic effects from high-dimensional GWAS datasets [155]. The application of computerized algorithms including genetic and nongenetic variables to predict AAEs appears to be particularly promising [e.g., 156].

Conclusion

In summary, pharmacogenetic studies of AAEs bear the promise of improving treatment outcomes by allowing physicians to deliver personalized treatments with minimal AEs and optimal efficacy. One important aspect is that gene variants frequently have larger effect sizes in pharmacogenetic phenotypes compared with complex disease risk [157]. Consistent with this, gene variants associated with AIWG appear to have relatively large effect sizes, especially the rs489693 marker at the *MC4R* gene locus [93]. Furthermore, there is general consensus for an association between CYP2D6 abnormal metabolizer status and an increased risk of AAEs, including TD and parkinsonism [124]. The levels of evidence assigned to AAE genetic associations by expert clinical PGx panels and consortia have continued to increase. In addition, drug regulatory agencies, such as the FDA and Health Canada, are beginning to include PGx information on AP drug labels. Nevertheless, the current level of evidence remains limited, and further validation by additional studies is required. Also, further research is needed to identify novel and interacting variants for AAEs. Building up on these efforts will undoubtedly lead to the implementation of genetic testing to predict and thereby reduce the occurrence of AAEs.

Disclosure Statement

The authors declare no conflicts of interest.

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