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In Review

Pharmacogenetics of Antipsychotics

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Objective: During the past decades, increasing efforts have been invested in studies to unravel the influence of genetic factors on antipsychotic (AP) dosage, treatment response, and occurrence of adverse effects. These studies aimed to improve clinical care by predicting outcome of treatment with APs and thus allowing for individualized treatment strategies. We highlight most important findings obtained through both candidate gene and genome-wide association studies, including pharmacokinetic and pharmacodynamic factors.

Methods: We reviewed studies on pharmacogenetics of AP response and adverse effects published on PubMed until early 2012. Owing to the high number of published studies, we focused our review on findings that have been replicated in independent studies or are supported by meta-analyses.

Results: Most robust findings were reported for associations between polymorphisms of the cytochrome P450 system, the dopamine and the serotonin transmitter systems, and dosage, treatment response, and adverse effects, such as AP-induced weight gain or tardive dyskinesia. These associations were either detected for specific medications or for classes of APs.

Conclusion: First promising and robust results show that pharmacogenetics bear promise for a widespread use in future clinical practice. This will likely be achieved by developing algorithms that will include many genetic variants. However, further investigation is warranted to replicate and validate previous findings, as well as to identify new genetic variants involved in AP response and for replication of existing findings.

La pharmacogénétique des antipsychotiques

Objectif : Au cours des dernières décennies, des efforts croissants ont été déployés dans des études visant à percer l'influence des facteurs génétiques sur le dosage des antipsychotiques (AP), la réponse au traitement, et la survenue d'effets indésirables. Ces études voulaient améliorer les soins cliniques en prédisant le résultat du traitement par AP, et en donnant lieu ainsi à des stratégies de traitement individualisées. Nous présentons les résultats les plus importants obtenus par des études tant de gènes candidats que d'association pangénomique, notamment les facteurs pharmacocinétiques et pharmacodynamiques.

Méthodes : Nous avons passé en revue les études sur la pharmacogénétique de la réponse aux AP et des effets indésirables publiées dans PubMed jusqu'au début de 2012. Vu le nombre élevé d'études publiées, notre revue a mis l'accent sur les résultats qui ont été reproduits dans des études indépendantes ou qui sont soutenus par des méta-analyses.

Résultats : Les résultats les plus fiables ont été rapportés pour des associations entre les polymorphismes du système du cytochrome P-450, les systèmes des transmetteurs de la dopamine et la sérotonine, et le dosage, la réponse au traitement, et les effets indésirables, comme la prise de poids ou la dyskinésie tardive induites par les AP. Ces associations ont été détectées pour des médicaments spécifiques ou pour des classes d'AP.

Conclusion : Les premiers résultats prometteurs et solides montrent que la pharmacogénétique porte la promesse d'une large utilisation dans une future pratique clinique. Ceci se réalisera probablement en développant des algorithmes qui comporteront de nombreuses variantes génétiques. Cependant, il faut d'autres recherches pour reproduire et valider les résultats précédents, et pour identifier des nouvelles variantes génétiques impliquées dans la réponse aux AP, et pour reproduire les résultats existants.

Since the first observations in the 1950s suggested genetic influences on drug response,[1] pharmacogenetic studies have rapidly evolved over the past decades. Modern laboratory techniques have given insights toward the identification of genetic variants influencing drug efficacy, metabolism, and occurrence of adverse effects. This is giving pharmacogenetics an important role in contemporary psychiatric research, strengthening the notion that the widespread use of genetic tests will become available in future clinical practice.

Besides studies investigating the genetics of outcome to antidepressants and mood stabilizers[2] (see also the In Review paper by Dr Serretti and colleagues[3] in this issue), large efforts have been undertaken in the area of pharmacogenetics of APs. The importance of these efforts is increasing because APs are routinely used in the treatment not only of schizophrenia and related spectrum disorders but also for mood disorders and various other conditions, such as obsessive–compulsive disorder, eating disorders, or behavioural disturbances, associated with dementia. Specific APs may differ regarding alleviating various symptoms; for instance, SGAs may be more effective for the treatment of negative symptoms. APs also differ in their propensity to induce specific adverse effects; for example, SGAs may be associated with a higher risk of significant metabolic disturbances but a lower risk of TD, compared with FGAs.[4] More importantly, large interindividual differences exist among patients. These differences cannot be predicted clinically but they can have serious consequences leading to repeated medication switches owing to intolerability or lack of efficacy. This issue is of particular relevance in patients with schizophrenia who need to be treated over a long period of time and whose adherence is hampered by adverse effects.[5] Also, treatment resistance (that is, a lack of adequate response to medication) occurs in up to 40% of these patients.[6] The possibility of meaningful prediction of individual responses and risks of adverse effects would, therefore, represent a milestone in AP pharmacotherapy.

To date, only a limited number of factors have been identified that are described to be either positively or negatively correlated with outcome of AP treatment. Among those are demographic factors (for example, family history, ethnicity, and gender), clinical factors (for example, duration of untreated psychosis and early response to APs), and environmental factors (for example, smoking habits, concomitant treatment, and diet).[7] The potential influence of genetic factors is underpinned by different studies demonstrating similar treatment response and occurrence of adverse effects in monozygotic twins or first-degree relatives.[8–12]

Most studies conducted to date have used a candidate gene approach, investigating SNPs or changes in larger DNA segments of a gene considered to be involved in the mechanisms of medication response or in a given adverse effect. With further development of laboratory techniques, GWASs and next-generation sequencing are being applied to pharmacogenetic research. Although there are some inconsistencies in the results of some studies, efforts are being made to transfer some promising findings into clinical practice. Our article reviews the most robust pharmacogenetic results, including pharmacokinetic and pharmacodynamic factors, relevant to APs.

Clinical Implications

- Accurate prediction of individual response to AP treatment or individual risk for the occurrence of adverse effects has not yet been achieved. Large efforts have been made to find genetic factors in the hope of improving future patient care.
- Some genetic factors have been identified. However, valid tests with substantial specificity and sensitivity measures have not yet been developed to predict drug metabolism, response to treatment, or most adverse effects.
- Nonetheless, some results are starting to impact patient care through the development of genetic tests.

Limitations

- Lack of independent replication in well-characterized samples limits the clinical applicability of most of these genetic findings.
- Approaches integrating genome-wide, DNA sequencing, epigenetic and environmental factors, methods for prediction of treatment response, and occurrence of adverse effects are required to allow for a more widespread clinical use of pharmacogenetic-based algorithms.

Abbreviations

5-HT	5-hydroxytryptamine (serotonin)
AIWG	AP-induced weight gain
AP	antipsychotic
ATP	adenosine triphosphate
bp	base pair
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CIA	clozapine-induced agranulocytosis
COMT	catechol-*O*-methyltransferase
CYP	cytochrome P450
CYP1A2	CYP, family 1, subfamily A, polypeptide 2
CYP2C19	CYP, family 2, subfamily C, polypeptide 19
CYP2D6	CYP, family 2, subfamily D, polypeptide 6
CYP3A4	CYP, family 3, subfamily A, polypeptide 4
Cys	cysteine
DA	dopamine
del	deletion
DNA	deoxyribonucleic acid
DRB5	MHC, class II, DR beta 5
DRD	DA receptor D
EPS	extra pyramidal symptom
FGA	first-generation AP
GFRA	glial cell derived neurotrophic factor family receptor alpha
Gly	glycine
GNB3	guanine nucleotide binding protein (G protein), beta polypeptide 3
GWAS	genome-wide association study
HLA	human leukocyte antigen
HTR2A	5-HT receptor 2A, G protein-coupled
HTR2C	5-HT receptor 2C, G protein-coupled
IM	intermediate metabolizer
ins	insertion
MC4R	melanocortin 4 receptor
MDR1	multi-drug resistance gene 1
Met	methionine
MHC	major histocompatibility complex
P-gp	permeability glycoprotein
PM	poor metabolizer
rs	reference SNP
SLC	solute carrier
Ser	serine
SGA	second-generation AP
SNP	single-nucleotide polymorphism
TD	tardive dyskinesia
TNF	tumour necrosis factor
Tyr	tyrosine
UM	ultra-rapid metabolizer
Val	valine

Methods

We reviewed studies on pharmacogenetics of AP response and adverse effects published on PubMed until January 2012. Owing to the large amount of available literature, a detailed summary of all studies would go beyond the scope of our review. Also, several recent reviews have focused on AP response and adverse events.[7,13–15] Thus we focused our review on pharmacogenetics findings that have been replicated in independent studies or are supported by meta-analyses. We also included selected studies that highlight new and promising candidate genes in relevant pathways.

Genetics and Pharmacokinetic Factors

Cytochrome Enzymes

Most psychotropics, including APs, are metabolized by cytochrome enzymes, mainly members of the CYP family, which includes *CYP1A2*, *CYP2D6*, *CYP3A4*, and *CYP2C19*. Besides environmental factors, such as induction of the *CYP1A2* enzyme by smoking, genetic variation contributes to the variability in enzyme activity and drug metabolism. The genes encoding CYP enzymes can be highly polymorphic,[16] with more than 80 genetic variations known in *CYP2D6*. For this gene, a distinction is made among extensive metabolizers, with normal enzyme activity having 2 functional alleles; PMs, with low enzyme activity caused by 2 nonfunctional alleles; IMs, with intermediate activity carrying 2 partly defective alleles or 1 nonfunctional allele; and UMs, with more than 2 functional alleles. Similarly, an activity score system was recently proposed.[17] The main polymorphisms causing defective alleles in the population of European descent are *CYP2D6**3, *CYP2D6**4, *CYP2D6**5, and *CYP2D6**6.[18] Genotype distribution differs considerably between ethnicities: 1% to 2% of Europeans are UMs and 5% to 10% are PMs, whereas only 1% to 2% of Asians are PMs, while 30% to 40% of the population in North Africa are UMs but only 1% are PMs.[19] Metabolizer status highly influences the required dosage of substances; for example, it has been demonstrated that carriers of *CYP2D6* defective allele (that is, **3*, **4*, **5*, and **6*) can have up to 80% higher serum concentrations of risperidone, compared with homozygous carriers of the wildtype *CYP2D6*1*.[20] The *1F polymorphism in *CYP1A2* seems to be related to higher inducibility of the enzyme by smoking, leading to reduced clozapine plasma levels.[21] Polymorphisms in *CYP2C19* and *CYP3A4* have also been reported to affect clozapine plasma levels.[22,23]

These data suggest that CYP polymorphisms may affect treatment response. However, there are only a few studies with positive findings, most likely because plasma levels of APs often do not correlate with treatment response. For *CYP1A2*, the *1F polymorphism has been associated with poorer treatment response to clozapine and olanzapine.[24–26] One other study[27] indicated a weak effect of *CYP3A4* polymorphisms on risperidone response. A recent study by Bigos et al[28] reported a highly significant influence of the

Table 1 Polymorphisms associated with AP treatment response supported by a meta-analysis or by 3 or more studies reporting the same allele association

Gene	Polymorphism	Main association finding	Study
CYP1A2	*1F	*1F/*1F genotype associated with lower plasma concentrations and lower response	Laika et al,[24] Ozdemir et al,[25] Eap et al[26]
DRD2	–141C ins/del	Del allele is associated with poorer response	Lencz et al,[66] Wu et al,[67] Zhang et al[68]
	*Taq*IA	A1 allele associated with better response in some studies; but a meta-analysis showed negative results	Suzuki et al,[70] Schafer et al,[71] Yamanouchi et al,[72] Zhang et al[68]
DRD3	Ser9Gly	Meta-analysis with trend for lower response in Ser-allele carriers	Hwang et al[76]
HTR2A	–1438G/A	G allele was associated with poorer response	Arranz et al,[84] Ellingrod et al,[85] Chen et al[177]
	102T/C	T allele was associated with better response in a meta-analysis	Arranz et al[88]
	His452Tyr	Tyr allele was reported to be associated with poor response	Arranz et al,[88] Arranz et al,[178] Masellis et al[179]
5-HTT	5-HTTLPR	Short-allele was demonstrated to be associated with poorer treatment response	Dolzan et al,[95] Arranz et al,[96] Vazquez-Bourgon et al[97]
COMT	Val(108/158)Met	Better improvement of cognitive function was associated with Met allele	Bertolino et al,[104] Woodward et al,[105] Bertolino et al[180]

marker rs472660 in *CYP3A43,* a member of the *CYP3A4* enzyme family encoding the CYP family 3, subfamily A, polypeptide 43, on olanzapine clearance and response. By contrast, several studies investigating the influence of *CYP2D6* polymorphisms on olanzapine response have reported no associations.[29–32]

There are more data available indicating an impact of CYP polymorphisms on side effects: *CYP2D6*3*, *CYP2D6*4*, and *CYP2D6*10*, but not *CYP1A2*1F*, have been associated with increased AIWG.[24,33,34]

Today, most evidence exists for an influence of CYP polymorphisms on motor adverse effects of APs, such as TD. Although some studies reported negative findings,[35–38] there is growing evidence that *CYP2D6* PMs are at higher risk of developing acute EPSs[39,40] or TD[41–43] (see reviews[13,44,45]). Some studies have also associated *CYP1A2*1F* with TD,[42,46] but other studies and a meta-analysis have yielded negative findings.[47,48]

In summary, genetic variation in CYP genes seems to exert a stronger influence on plasma levels and the occurrence of adverse effects than on medication response. As sample sizes of many studies are small and these studies have been performed using different medications and protocols, further investigation is warranted to fully assess clinical implications of these findings. Further, there is still a paucity of studies assessing the cost-effectiveness of CYP genotyping in daily practice,[19,45,49] and further pharmacoeconomic investigations are needed. Despite these limitations, first steps to bring pharmacogenetics advances into clinical practice have been undertaken by offering tests for *CYP2D6* and *CYP2D19* usable for medication monitoring.[50] For information regarding ongoing related investigations in Canada, please see the Pharmacogenetics Research Clinic website.[51,52]

Blood–Brain Barrier Transporters

P-gp is a member of the ATP-binding cassette transporters and is involved in the transmembrane efflux of different substrates, including toxins, peptides, and medications. P-gps are located in different organs, including the blood–brain barrier, where they pump medications back into the plasma.[53] An altered transporter activity influences intracerebral drug concentration and may thereby impact on treatment response as well. Polymorphisms in the encoding gene *MDR1* (synonymous with *ABCB1*, ATP-binding cassette, subfamily B [MDR/transporter associated with antigen processing], member 1 gene) have been investigated in several studies. Although there are negative findings,[54,55] some positive findings exist for the G2677T/A and C3435T polymorphisms. Contradictory results have been reported, with studies showing better treatment response of T allele carriers of both polymorphisms,[56] while others reported worse response in the T allele carriers of C3435T.[57,58] Other studies found no association in the above-mentioned polymorphisms but had positive results for C1236T.[59] Overall, despite ambiguous evidence for the role of *MDR1* polymorphisms in treatment response, probably owing to yet undetected confounding variables (for example, ethnicity), a role of this gene is likely and awaits further clarification.

Regarding AP-induced adverse effects, there has been one study showing no association of *MDR1* polymorphisms with TD,[60] one study demonstrating an association with a specific haplotype and TD,[61] and one study indicating an influence of *MDR1* genotypes on the occurrence of EPSs,[30]

while another study could not find an association with EPSs.[55] There are also hints of an influence of *MDR1* on weight gain[62] and metabolic disturbances caused by APs.[63] Overall, more studies are needed to assess the role of *MDR1* polymorphisms in the occurrence of adverse effects.

Genetics and Pharmacodynamic Factors of Treatment Response

The DA System

The antidopaminergic effect of FGA and SGA is thought to be their main mechanism of action.[64] Therefore, genetic variation in DA receptors influencing receptor density, expression, and activity of the receptor may be an essential factor in regulation of individual treatment response.

As all APs block D_2 receptors,[65] polymorphisms in the *DRD2* gene have been investigated most intensively. The del allele of the –141C ins/del polymorphism in the promoter region is assumed to reduce D_2 density and activity. In several studies, the del allele was associated with poorer response to AP treatment, for example, see Lencz et al[66] and Wu et al.[67] This finding has been confirmed by a recent meta-analysis,[68] despite some studies that failed to find an association with treatment response (for example, see Xing et al[69]). The A1 allele of *Taq*IA polymorphism, which is located 10 kilobases downstream *DRD2*, leads to reduced gene expression and was therefore also hypothesized to influence treatment response. However, previous studies have reported inconsistent findings: while some studies indicated that A1[70–72] or A2[73] are associated with better treatment response, the above-mentioned meta-analysis[68] did not detect any association. Also for other *DRD2* polymorphisms, for example, *Taq*IB,[74] Ser311Cys,[75] or A-241G,[66] a few studies have reported associations, but contradictory results and lack of replication make further investigations necessary.

In *DRD3*, the Gly9 variant of the Ser9Gly polymorphism, changes D_3 receptor density. Thus this impact of this variant on AP treatment response has been studied extensively, with at least 18 published studies.[13] While some studies have indicated better response of the Ser allele, a meta-analysis has reported a nonsignificant trend toward lower response in carriers of Ser allele.[76] Because clozapine also binds to D_4 receptors, a 48-bp variable number tandem repeat in the *DRD4* gene has been investigated in several studies. However, findings have been contradictory,[77,78] and many studies have yielded negative results (for example, see Rietschel et al[79] and Ikeda et al[80]); the role of the polymorphism in treatment response is not fully resolved, to date. Polymorphisms of the *DRD1*[81] and *DRD5*[80] genes have not yet been investigated intensively and their clinical relevance needs to be demonstrated in future studies.

The 5-HT System

Because of the higher affinity of SGAs to 5-HT receptors, compared with FGAs, genes in the serotonergic transmitter system are interesting candidates for investigation of AP treatment response. Several studies have focused on polymorphisms in *HTR2A*, the gene encoding 5-HT_{2A} receptors. The functional –1438A/G SNP in the promoter region of the gene and the SNP 102T/C are in high linkage disequlibrium with each other[82] and –1438A/G has been demonstrated to influence promoter activity.[83] Association studies have repeatedly indicated poorer treatment response in G allele carriers of the –1438A/G SNP,[84,85] although there are negative findings[71] and a study showing better response in G allele carriers.[86] Regarding the 102T/C marker, results are less consistent with some studies (see Anttila et al[87]) and an early meta-analysis focusing on clozapine demonstrating better response in T allele carriers,[88] while later studies investigating other APs found no association[80] or association of the C allele with better symptom improvement.[89] Another polymorphism repeatedly investigated in *HTR2A* is His452Tyr (histidine and Tyr at the 452nd amino acid): the Tyr allele seems to be associated with poorer treatment response,[88] but this has not been observed in all studies.[90]

In *HTR2C*, encoding 5-HT_{2C} receptors, the C/C genotype of the –759C/T SNP, which has been shown to lead to reduced transcription,[91] was described to be associated with improvement of negative symptoms in one study.[92] Also, association of the Ser allele of Cys23Ser has been reported once,[93] but all other studies[90,94] have failed to replicate this finding, indicating no major role of the SNP in treatment response. In the gene encoding solute carrier family 6 (neurotransmitter transporter), member 4 (*SLC6A4*, synonymous with 5-HTT) 5-HT transporters, which terminate 5-HT action by transporting it back into the presynaptic neuron, an association of the short allele of the 44-bp ins/del polymorphism serotonin-transporter-linked polymorphic region (commonly referred to as 5-HTTLPR) with poorer AP response has consistently been demonstrated.[95–97]

Further association with AP treatment response has been described for the G allele of –1019C/G SNP in 5-HT receptor 1A, G protein-coupled (*HTR1A*), encoding 5-HT_{1A} receptors,[98,99] for polymorphisms in the genes encoding subtypes 3A, B, and E of 5-HT_3 receptors[100,101] and for the 267C/T SNP in the gene encoding 5-HT_6 receptors.[102,103] However, this last finding has not been confirmed in all studies.[80]

Other Systems

Other candidate genes that may be involved in regulation of individual treatment response to APs have not been studied as extensively as the above-mentioned genes. However, several studies have suggested an association between response and several genetic variants. For example, the *COMT* gene encodes catechol-*O*-methyltransferase, which is involved in the degradation of monoamines. The Val(108/158)Met polymorphism of this gene influences activity of the enzyme, which is less active in Met/Met carriers. The Met allele has been repeatedly associated with better improvement of cognitive function[104,105] during AP treatment, compared with the Val allele. Other studies[106] have found no association or reported an association of

the Val allele with better response.[107] Therefore, the role of the Val(108/158)Met SNP in the regulation of treatment response is not yet fully understood and deserves further study.

Further, studies reported associations in *GNB3*, encoding the β-subunit of G-protein, with the T allele of the –825C/T polymorphism leading to worse treatment response,[108,109] and in the genes encoding brain-derived neurotrophic factor,[110,111] *GFRA*,[112] oxytocin,[113] and TNF[114]; however, those genes need to be studies more extensively.

In summary, candidate gene studies have delivered some promising results, consisting mainly of associations between genes involved in the DA system and overall treatment response or between genes involved in the serotonergic system and improvement of negative symptoms (Table 1). Therefore, findings suggest a clinical impact of those genetic variants. However, given the relatively small sample sizes and inconsistent results, further studies with larger sample sizes and more homogenous studies are needed before these findings can be incorporated in clinical algorithms.

Genome-Wide Association Studies

During the past few years, the development of technologies has facilitated the investigation of polymorphisms in the whole genome through GWASs. Studies investigating the CATIE sample[5] have reported the association of an intergenetic SNP on chromosome 4p15 with response to APs. Also, borderline significant results have been reported for SNPs in the ankyrin repeat and sterile alpha motif domain containing 1B (*ANKS1B*) and contactin associated protein-like 5 (*CNTNAP5*) genes[115] as well as association of 6 SNPs in or near to the ets homologous factor (*EHF*), solute carrier family 26 (anion exchanger), member 9 (*SLC26A9*), *DRD2*, G protein-coupled receptor 137B (*GPR137B*), carbohydrate (N-acetylgalactosamine 4-0) sulfotransferase 8 (*CHST8*), and interleukin 1, alpha (*IL1A*) genes.[116] In other samples, ATPase, Ca++ transporting, plasma membrane 2 (*ATP2B2*), heparan sulfate (glucosamine) 3-O-sulfotransferase 2 (*HS3ST2*), unc-5 homolog C (C elegans) (*UNC5C*), BCL2-associated athanogene 3 (*BAG3*), phosphodiesterase 7B (*PDE7B*), phosphoribosylaminoimidazole carboxylase, phosphoribosylaminoimidazole succinocarboxamide synthetase (*PAICS*), prostaglandin F2 receptor inhibitor (*PTGFRN*), nuclear receptor subfamily 3, group C, member 2 (*NR3C2*), zinc finger and BTB domain containing 20 (*ZBTB20*), ST6 beta-galactosamide alpha-2,6-sialyltranferase 2 (*ST6GAL2*), phosphatidylinositol-4-phosphate 5-kinase, type I, beta (*PIP5K1B*), ephrin receptor type A6 (*EPHA6*), potassium voltage-gated channel, subfamily H (eag-related), member 5 (*KCNH5*), and adherens junctions associated protein 1 (*AJAP1*) have been reported to be associated with response to risperidone.[117] Similarly, SNPs within neuronal PAS domain protein 3 (*NPAS3*), XK, Kell blood group complex subunit-related family, member 4 (*XKR4*), tenascin R (*TNR*), glutamate receptor, ionotropic, AMPA 4 (*GRIA4*), *GFRA2*, and the nudix (nucleoside diphosphate linked moiety X)-type motif 9 pseudogene 1 (*NUDT9P1*) located in the 5-HT receptor 7, adenylate cyclase-coupled (*HTR7*) gene have been reported to be associated with response to iloperidone.[118] In summary, hypothesis-free GWASs have yielded numerous interesting findings that warrant further investigation.

Genetics and Pharmacodynamic Factors of Adverse Effects

Antipsychotic-Induced Weight Gain

AIWG is observed in up to 30% of patients treated with SGAs. Owing to the higher morbidity and mortality associated with obesity and metabolic syndrome, as well as the social stigmatization and noncompliance that arises from weight gain (extensively reviewed elsewhere[14,119]), this serious adverse effect needs special consideration in clinical practice. However, there is a large variation in the propensity of various APs to cause AIWG,[120] with olanzapine and clozapine causing the most extensive amount of weight gain. Interindividual variability is also influenced by clinical factors, such as sex, baseline weight, and age. However, there are no reliable clinical predictors available in clinical practice. As results of twin studies indicate a genetic influence on AIWG,[11,12,121] numerous candidate studies have been performed during the past few years. Most consistent findings exist for an association between polymorphisms of the *HTR2C* gene and AIWG. The functional polymorphism –759C/T[122] has repeatedly been shown to influence AIWG, with the C allele being overrepresented in patients with higher AIWG (for example, see Reynolds et al,[123] Miller et al,[124] and Opgen-Rhein et al,[125] including 2 meta-analyses, see De Luca et al[126] and Sicard et al[127]). Although negative findings have been reported,[128,129] with one study indicating the opposite allele as a risk variant,[130] to date, the role of this polymorphism is supported by the most robust studies. Other *HTR2C* polymorphisms have been shown to be associated with AIWG as well, including the –995G/A, –1165A/G,[125] and Cys23Ser polymorphisms as part of a high risk haplotype.[127]

Leptin plays a major role in energy homoeostasis. The –2548A/G polymorphism in the encoding gene leptin (*LEP*) has been shown to impact on AIWG, with the G allele being the risk allele in some but not in all studies.[131,132] Nonetheless, negative findings (for example, see Opgen-Rhein et al[125]; for review, see Lett et al[14] and Lee and Bishop[133]) hamper the assessment of the clinical impact of this polymorphism. Other replicated associations include Ddell, Mnll, and Tail polymorphisms in synaptosomal-associated protein, 25kDa (*SNAP25*),[134,135] and in the gene encoding alpha-2-adrenergic receptor, adrenoceptor alpha 2A (*ADRA2A*), with the G/G genotype of –1291C/G being at higher risk for AIWG.[136,137] Similarly, the T allele carriers of the –825C/T polymorphism in the gene encoding β3-subunit of G-protein receptors, that is, *GNB3*, are at higher risk for AIWG.[129,138] Other reported associations, such as polymorphisms in insulin-induced gene 2 (*INSIG2*),[139] have failed to be replicated in other samples.[125,140] Recent studies indicate an influence of *DRD2* polymorphisms,[141,142]

Table 2 Polymorphisms associated with AIWS or EPSs supported by a meta-analysis or by 3 or more studies reporting the same allele association

Gene	Polymorphism	Main association finding	Study
CYP2D6	metabolizer status	PMs were at higher risk for EPSs in several studies	Kobylecki et al,[41] Fu et al,[42] Patsopoulos et al[43]
HTR2C	–759C/T	Two meta-analyzes reported C allele to be associated with larger AIWG	Sicard et al,[127] De Luca et al[181]
LEP	–2548A/G	G allele was associated with higher AIWG in most studies; others showed A allele to be associated	Ellingrod et al,[131] Zhang et al,[132] Templeman et al[182]; Zhang et al[183]
GNB3	–825C/T	T allele was associated with higher AIWG in several studies, and with a nonsignificant trend in a meta-analysis	Ujike et al,[129] Wang et al,[138] Souza et al[184]
DRD2	*Taq*IA	A2 allele was associated with higher risk for TD in 2 meta-analyzes	Bakker et al,[48] Zai et al[154]
DRD3	Ser9Gly	Gly allele was associated with higher risk for TD in several studies	de Leon et al,[60] Steen et al,[155] Al Hadithy et al,[156] Lerer et al,[157] Bakker et al[158]
HTR2A	T102C	C allele was associated with TD in a meta-analysis	Bakker et al,[48] Lerer et al[164]
COMT	Val(108/158)Met	Met allele was protective against TD in a meta-analysis	Bakker et al[48]
MnSOD	Ala-9Val	Val allele was protective against TD in a meta-analysis	Bakker et al[48]

Ala = alanine

cholecystokinin B receptors,[143] and adiponectin.[144] A systematic analysis of the DA D_1–D_5 receptors and the association with weight gain reported a significant finding for the 957C/T polymorphism and 2 weak signals for *DRD3* polymorphisms.[142] Most recent data indicate a strong effect in the region of *MC4R*, the gene encoding the melanocortin 4 receptor, on development of obesity.[145] A GWAS in a cohort of drug-naive adolescents showed significant association of an SNP near this gene with weight gain induced by several APs, which was replicated independently by our group.[146] In a different study, our group has also shown a significant association of another SNP in the promoter region of *MC4R* with AIWG.[147]

A recent GWAS found significant associations of AIWG with SNPs in the Meis homeobox 2 (*MEIS2*), protein kinase, cyclic adenosine monophosphate-dependent, regulatory, type II, beta (*PRKAR2B*), G protein-coupled receptor 98 (*GPR98*), formin homology 2 domain containing 3 (*FHOD3*), ring finger protein 144A (*RNF144A*), astrotactin 2 (*ASTN2*), sex determining region Y-box 5 (SOX5), and activating transcription factor 7 interacting protein 2 (*ATF7IP2*) genes[148] but these findings have not yet been replicated in other studies. Thus further investigation remains necessary. Table 2 presents a summary of the most important genetic findings regarding AIWG. Overall, except for the polymorphism –759C/T of *HTR2C*, with most robust findings obtained in a large number of studies, genetic findings regarding AIWG are not yet applicable in clinical practice.

Agranulocytosis

Agranulocytosis is a serious adverse effect occurring with a wide range of psychotropic medications. While clozapine is the most effective medication for treatment-resistant schizophrenia,[15] it is associated with an incidence of up to 2% of agranulocytosis. Hypothesized mechanisms of CIA include immune-mediated response against neutrophils, enhanced release or destruction of neutrophils, and direct toxicity against bone marrow stromal cells.[149] Association studies investigating genetic factors of CIA have mainly focused on genes building the HLA system. Positive findings exist for the HLA-B38 marker, which is overrepresented in patients affected by CIA as well as a haplotype consisting of *HLA*-B38, DR4, and DQw3.[150] Other HLA-antigens associated with CIA include HLA-DRB5*0201 and HLA-Cw-7 and haplotypes with *HLA*-Cw-B and *HLA*-DRB5-DRB4.[151] In addition, other genes for non-HLA components of the MHC have been investigated. For both *TNF* and heat shock protein replicated positive findings have been reported.[15] There are also associations for genes that are not part of the MHC, for example, myeloperoxidase (*MPO*) and nicotinamide adenine dinucleotide phosphate-oxidase gene polymorphisms.[152,153] First steps toward a clinical use have been made by the temporary release of a commercial test-kit in 2007, that is, PGxPredict:CLOZAPINE (Clinical Data, Inc, New Haven, CT), which included the 6672G/C polymorphism in MHC, class II, DQ beta 1 (*HLA-DQB1*) for detection of high-risk patients carrying the C allele, with high specificity of 98.4% but a low of sensitivity of 21.5%.

TD and EPSs

TD is a serious adverse effect that occurs in roughly 25% of all AP-treated patients. FGAs bear a much higher risk for the development of TD than SGAs. Clinical risk factors include advanced age, dose and duration of medication, and sex.[45] Familial occurrence points to a genetic influence on TD.[10] Candidate genes for TD have been extensively investigated during the past 2 decades, and there are numerous studies supporting the hypothesis of a genetic implication. Besides positive findings for pharmacokinetic factors (see above), there is growing evidence for pharmacodynamic factors having an impact on TD.

In *DRD2*, an increased risk for the development of TD has been described for carriers of the A2 allele of the *Taq*IA polymorphism in 2 meta-analyzes,[48,154] although more studies have delivered negative findings than positive ones.[13] Most robust findings exist for the Ser9Gly polymorphism in *DRD3*, with the Gly allele being associated with higher risk of TD in different ethnicities (for examples, see de Leon et al,[60] Steen et al,[155] Al Hadithy,[156] Lerer et al,[157] and Bakker et al[158]). Nonetheless, results are not unambiguous as negative results also exist,[38,159,160] and one study indicated the opposite allele as risk variant.[161] *DRD4* has not been studied as extensively as *DRD2* and *DRD3*. Nonetheless, there have been positive findings for *DRD4* polymorphisms,[162,163] which need further replication. Several studies have reported associations for polymorphisms in serotonergic genes. A meta-analysis found an association of the C allele in the 102T/C polymorphism of *HTR2A* with TD.[164] Nonetheless, there are numerous negative findings for this SNP as well (for example, see Wilffert et al[165]). Studies also reported positive results with the –1438G/A[166] in *HTR2A* and the Cys23Ser polymorphism in *HTR2C* (for example, see Al Hadithy et al[156]). As there are many studies with negative findings,[38,167] further studies of 5-HT genes remain necessary to evaluate their role in the development of TD. Other significant findings in meta-analyses exist for the Val(108/158)Met polymorphism in *COMT*[48] (with the Met allele being protective against TD) and for manganese superoxide dismutase (*MnSOD*)[44] (with the Val allele of alanine (Ala-9Val) polymorphism being protective against TD[48]). There are single reports of positive results for a few other genes, including different *COMT* polymorphisms,[168] glycogen synthase kinase 3 beta (*GSK3B*), linked to dopaminergic signalling,[169] and nitric oxide synthase 3 (endothelial cell) (*NOS3*).[170]

There has also been reports of an influence of regulator of G-protein signalling 2, 24kDa (*RGS2*) polymorphisms on EPSs.[171,172] A GWAS analyzing the CATIE sample[5,173] reported associations in the gene encoding zinc finger protein 202, (*ZNF202*), in GLI family zinc finger 2 (*GLI2*), a gene encoding a transcription factor involved in embryonal development of the dopaminergic system,[174] and statistical trends for other genes.[175]

In summary, several candidate genes have been found to be involved in TD, and the most robust findings were obtained in dopaminergic genes. Table 2 summarizes the most important genetic findings. As TD and EPSs are mainly mediated by the influence of APs on the DA system, those findings are hardly surprising. However, to date, there is no definite evidence on the genetics of TD, and further research is needed to develop predictive tests that can be used in clinical practice.

Summary and Outlook

During the past 20 years, pharmacogenetic studies have identified many genetic variants implicated in serum levels, response to APs, and occurrence of adverse effects. While some of these results have been replicated in independent samples, and therefore are likely to represent true associations, negative studies have also been published, albeit, often in smaller and likely underpowered studies. Currently, most promising findings involve associations between DA receptor polymorphisms and response, or *HTR2C* SNPs and AIWG. There are several possible explanations for these inconsistencies: differences in study design, small effect sizes of most SNPs, small sample sizes, incomplete coverage of most genes, lack of control of environmental and clinical confounders, or varying definition of outcome parameters. Conflicting results may also be due to an insufficient incorporation of gene–gene and gene–environment interactions. Therefore, new approaches, beyond candidate gene studies and GWASs are needed: DNA-sequencing, gene expression studies, novel bioinformatic approaches, animal studies, epigenetic approaches, and large and prospectively assessed samples will illuminate underlying genetic mechanisms.

Although widespread clinical use of pharmacogenetics will likely take several more years of investigation, some findings are starting to be clinically applied. These include the assessment of drug metabolizer status and inclusion of other pharmacodynamics genes with promising findings showing superiority to treatment as usual.[176]

Those tests are still relatively expensive and need to be improved by adding more gene variants. They also need to be implemented in ways that allow their use in clinical routine (that is, rapid processing and convenient costs), and physicians need to learn how to use their results in their practice. However, the clinical availability of these few tests suggests that pharmacogenetics is becoming a reality in patient care and will help to individualize and substantially improve treatment in the near future.

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