Genetic Testing for Antipsychotic Pharmacotherapy

Subjects: Genetics & Heredity

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Genetic testing is increasingly utilized to identify genetic biomarkers for optimizing the efficacy and tolerability of psychotropic drugs, especially antidepressants. However, genetic testing is also being requested to enhance the effectiveness of antipsychotic drugs, which is especially true for the treatment-refractory schizophrenia population, who frequently experience irrational polypharmacy at high dosages with significant adverse effects, generally without much therapeutic benefit.

Keywords: genetic testing ; antipsychotic ; pharmacotherapy ; schizophrenia

1. Introduction

Genetic testing is increasingly utilized to identify genetic biomarkers for optimizing the efficacy and tolerability of psychotropic drugs, especially antidepressants. Most clinically meaningful findings have been reported using genetic factors affecting the pharmacokinetics (PKs) of antipsychotic drugs, such as genetic polymorphisms in the drug-metabolizing cytochrome-P450 (CYP) enzymes to identify and/or predict effective and tolerable dosages of an antipsychotic drug. Despite these limitations, PG studies investigating PD genetic factors may be helpful to enhance the effectiveness of antipsychotic drugs with more success in the treatment-refractory population.

2. Pharmacogenetic Studies

The data from PG studies are clinically utilized at the individual level to predict and optimize the response to antipsychotic drugs while preventing or minimizing adverse events. A drug's response or tolerability can be affected by genetic polymorphisms in PK factors, which determine the concentration of a drug at its site(s) of action, and PD factors, which determine a drug's response or tolerability at its molecular targets. However, these distinctions are rather arbitrary, as changes in a drug's concentration at the site of action (i.e., PKs) are always associated with changes in a drug's efficacy and/or tolerability (i.e., PDs) at its site(s) of action.

2.1. Pharmacokinetic (PK) Genetic Biomarkers

Genetic variance in drug-metabolizing enzymes, such as CYP enzymes, represents most of the PK biomarkers. The genetic polymorphisms of CYP enzymes have produced one of the most replicated and clinically relevant findings in patients who develop adverse effects on routinely administered dosages of an antipsychotic drug. As compared to extensive metabolizers, patients that are ultra-rapid metabolizers require higher doses and those who are intermediate metabolizers require lower doses of drugs that are substrates for this enzyme due to altered elimination. If antipsychotic doses are not corrected for this genetic variance, ultra-rapid metabolizers for CYP2D6 may experience decrease or loss in efficacy and poor metabolizers may develop higher levels of antipsychotic drugs resulting in adverse effects, such as extrapyramidal symptoms (EPS) and hyperprolactinemia [1]. These differences may be explained by small sample sizes and a lower frequency of poor metabolizer alleles for CYP2D6 alleles in these ethnic groups as compared to Caucasians.

Deficient activity of CYP enzyme1A2has also been associated with adverse effects due to an increase in plasma levels of antipsychotic drugs that are substrates for this enzyme, such as clozapine and olanzapine [2][3][4]. In contrast, patients with high inducibility of CYP1A2, as observed with smoking in some patients, may end up with subtherapeutic levels of clozapine and olanzapine [5]. One study associated genetic variance in CYP3A4 activity with the efficacy of risperidone, an antipsychotic drug [6], while other studies produced negative results [7][8]. However, polymorphism in a specific transporter, P-glycoprotein (also known as multiple drug resistance-1 (MDR1) or ATP-binding cassette subfamily B member1 gene [9]) has been correlated with efficacy as well as tolerability of risperidone [10] and clozapine [11].

2.2. Pharmacodynamic (PD) Biomarkers

Antipsychotic efficacy across different antipsychotic drugs has been strongly linked with genetic variance in dopamine-2 receptors (DRD2). Polymorphisms of the promotor regions of DRD2, DRD3, and DRD4 have also been linked with antipsychotic efficacy [12][13][14][15][16]. Another biomarker repeatedly associated with antipsychotic efficacy is catechol-o-methyl transferase (COMT), which primarily metabolizes dopamine [17][18][19][20] This finding was also supported by a meta-analysis [21], which showed that patients with met/met homozygosity were more likely to respond to antipsychotic drugs, especially the newer ones.

Another HTR2A genotype, 1438-A/A, has been correlated with antipsychotic response in various ethnic groups. Lack of antipsychotic efficacy and treatment resistance for negative symptoms were found in a French cohort with 5-HT2A−1438-A Another polymorphism in serotonin receptor, HTR1A (i.e.,5-HT1A−1019G), has been associated with lower antipsychotic efficacy in various ethnic groups [22][23][24]. Although multiple other reports have also observed association between specific PD markers and antipsychotic efficacy, these findings are without replication and questionable clinical utility [25][26][27][28][29][30][31][32][33][34].

Some studies have examined the pharmacogenetics of commonly used antipsychotic drugs, such as clozapine, risperidone, and olanzapine. Several studies have examined dopamine receptor polymorphisms to explain clozapine's unique efficacy and have found replicated genetic variance in DRD1 [35][36], DRD2 [37][38], DRD3 [39][40], and DRD4 [41][42] to be associated with clozapine efficacy. Association between clozapine's efficacy and genetic variance in the dopamine transporter protein (DAT) has been supported by one study [43] but not the other [15]. Despite several studies producing negative results with polymorphisms in various serotonin targets [44][45][46][47][48][49][50][51][52][53], the overall data support the critical role of the serotonin system in clozapine's efficacy.

Risperidone is another second-generation antipsychotic drug, which has shown decreased antipsychotic efficacy in patients with DRD2 Ser311 [54] variant associated with the reduced response at DRD2 receptors [55]. Nevertheless, this relationship between COMT variant and antipsychotic efficacy points towards the importance of dopamine levels in antipsychotic response. However, unlike clozapine, no correlation was reported between risperidone response andDRD4variance [56]. Other genetic findings with risperidone have been in single studies and will not be reviewed here [22][13][57][58][59][60][61][62][63][64][65].

variantD3Ser9Gly [66][67], which has also been associated with antipsychotic efficacy of risperidone and clozapine [66][67]. However, this finding was not replicated in Indian patients [68], suggesting ethnic differences in response. However, once again, this olanzapine response was not associated with HRT2A and HRT2C variants in the Indian population [67][68], highlighting the ethnic differences in antipsychotic response. Glutamate metabotropic receptor-3 polymorphism [69] associated with better olanzapine response in only one study, a positive olanzapine's response with calcium channel variant, calcium voltage-gated channel subunit alpha1 C, rs1006737 was replicated in two studies [70][71].

Although aripiprazole is classified as one of the newer second-generation antipsychotic drugs, it is the first antipsychotic drug with partial agonist activity at D2 receptors and 5HT1A receptors [72]. A couple of studies have documented an association betweenD2TaqI variants and the efficacy of aripiprazole in Korean and Chinese patients [73][74]. In summary, there is inadequate genetic data to compare clinically meaningful differences in genetically mediated antipsychotic response between different antipsychotic drugs, perhaps with the exception of clozapine.

The genetic data for antipsychotic tolerability is not as consistent as those for antipsychotic efficacy, except for weight gain. The margin for controversial results is much higher than those from the efficacy studies, as documented below.

Thus, the poor metabolizers for CYP2D6 have a higher risk for developing EPS due to increased plasma levels of antipsychotic drugs that are CYP2D6 substrates [75][76][77][78][79][80][81][82][83][84][85][86][7][87][2] The results examining relationship between EPS and DRD3 polymorphisms are also controversial; some studies supported the relationship [7][88][89][90][91][92][93][94][95][96][97], but some did not [98][88][89][99][100][101][102], while some strangely reported paradoxical results [103][104][105]. A couple of studies found a direct association between two variants of dopamine metabolizing enzyme, COMT (G158A and A-278G) and risk for TD [106][107]. [108][88][109] and polymorphisms of dopamine-related enzymes, monoamine oxidase A, and monoamine oxidase B [108][110].

Genetic variance in the serotonergic system has also produced inconsistent results; some reports have documented associations between HRT2A polymorphisms and TD [89][105][111][112], and some have not [98][113][114][115]. , one study produced negative results [103]. No clear associations were observed between EPS and genes involved in oxidation and stress, such as manganese superoxide dismutase [116][117][118], nitric oxide synthase [119][120][121], glutathione S-

transferase [122], and glutathione peroxidase [123]. Only marginal associations were reported with polymorphism in nicotinamide adenine dinucleotide phosphate (NADPH), dehydrogenase quinone, nitric oxide synthase 3 [124][125], and glutathione S-transferase μ1 [7].

Although there is not much research investigating the role of genetic variance on antipsychotic-induced hyperprolactinemia, any DRD2 polymorphism that increases the risk for EPS will also increase the risk for hyperprolactinemia, as both adverse effects are mediated by D2R blockade. In this context, one study did report 40% higher prolactin levels in patients with DRD2*A1 allele than those without [126]. Interestingly, this increase in prolactin was also observed with clozapine, which is least likely to increase prolactin levels [126].

Although the genetic mechanisms underlying weight gain due to HTR2C polymorphisms are not completely clear, several HRT2C gene haplotypes have been associated with weight gain and metabolic syndrome [127][128][129][130]. Increased negative feedback due to increased levels of leptin observed in patients with haplotype B may explain the resistance against weight gain [131]. Although a meta-analysis revealed a 100% increase in risk for weight gain in patients with HRT2C -759 C allele [132], there were studies that did not find any correlation between the presence of the -759 C allele and weight gain [133][134][135][136][137]. Genetic variance in other serotonin receptors, such as HRT2A 102-T/C, have also been associated with weight gain, obesity, and lipid levels [127][138][139], except one study [140].

Although earlier studies did find an association between weight gain and genetic variance in DRD2 [138][141] or DRD3 [138], one recent study did observe a positive relationship between weight gain and DRD2 variants rs6277 In addition, a functional promoter region variant in DRD2 was implicated in a study of antipsychotic drug-induced weight gain during early psychosis with minimal prior exposure to antipsychotic drugs [142]. Ins/Del in the DRD2 promoter gene demonstrated substantially more weight gain than noncarriers after 6 weeks of treatment with risperidone or olanzapine. Another study reported an association between an increase in body mass index and a DRD4 variable number tandem repeat allele during antipsychotic treatment [143].

Few studies have reported a significant correlation between genetic polymorphism in melanocortin 4 receptors (MC4R) and antipsychotic-induced weight gain [144][145], which is also supported by a genome-wide association study [146] (**Table 1**). Genetic variance in other adrenergic receptors, such as 5HT1A, have also been associated with changes in body mass index [147]. Leptin appears to play an important role in mediating antipsychotic drug-induced weight gain, as reflected by the association between a leptin gene variant, −2548-A/G, and weight gain, despite the different direction of these results [148][136][149][150][151]. Results with leptin studies were also inconclusive across various ethnic groups, such as Indians [107] and Germans [130].

Table 1. Genetic biomarkers for antipsychotic response and adverse effects.

Antipsychotic Response					
Gene	**Polymorphism**	**Risk Allele**	**Functional Outcome**	**Clinical Outcome**	**Statistical Significance**
DRD2	**-141C Ins/Del (rs1799732)**	**Del**	**Decreased DRD2 expression**	**Lower antipsychotic response**	**Odds ratio = 0.65 95% confidence interval = 95% CI: 0.43–0.97 [152]**
HTR1A	**C-1019G**	**G**	**Increased HTR1A expression**	**G/G homozygosity with lesser negative symptom improvement [131][22][23][24]**	***p* = 0.003**
HTR2A	**T-102-C (rs6313)**	**C**	**Decreased HTR2A expression**	**C/C homozygosity with lower antipsychotic response**	**Odds ratio = 0.61 95% confidence interval = 0.43–8.5 [153]**
COMT	**Val 158Met**	**Val**	**Faster metabolism resulting in lower levels of dopamine**	**Lower antipsychotic response [21]**	**Odds ratio = 1.37; 95% confidence interval = 1.02–1.85)**
Weight Gain					

Antipsychotic Response					
HTR2C	**C-759T (rs3813929)**	**C**	**Lesser expression of HTR2C receptors [154]**	**>7% weight gain over baseline with C allele**	**Odds ratio = 1.64; 95% confidence interval = 0.73–3.69 in chronic subjects [127][128][129][130]; Odds ratio = 5.40 95% confidence interval = 2.08–14.01 during early psychosis [127][128][129][130].**
MC4R	**Rs489693**	**A**	**Unknown**	**AA homozygotes gained about 3 kg more weight than other genotypes [146]**	**Odds Ratio (95% confidence interval)**
Tardive Dyskinesia					
CYP2D6	**Presence of at least one dysfunctional alleles**	**One of 3, 4, 5, 6, or 10 alleles**	**Decreased CYP2D6 enzyme activity**	**Increased risk for tardive dyskinesia**	**1.83 95% CI: 1.09–3.08) [75][76][77][78][79][80][81][82][83][84][85][86][7][87][2]**
HTR2A	**T102C**	**C**	**Decreased HTR2A expression and binding**	**Presence of tardive dyskinesia**	**1.64 95% CI: 1.17–2.32 [155]**
DRD2	**Taq1A (rs1800497)**	**C, A2**	**Increased DRD2 receptors and binding**	**Presence of tardive dyskinesia**	**1.30 95% CI: 1.09–1.55 [156]**
Agranulocytosis					
HLADQB1	**G6672C (rs1133322494)**	**G**	**? autoimmune effect**	**Clozapine discontinuation due to ANC < 500 cells/mm^3**	**Odds ratio = 16.9 [157]**

One study reported a correlation between antipsychotic-induced weight gain and polymorphism in insulin-induced gene 2 [158], but a couple of other studies did not [130][159]. Similarly, the association between guanine nucleotide-binding protein subunit beta-3 polymorphism and weight gain in Indians [68] was not replicated in other ethnic groups, such as Koreans [160], Taiwanese [161], and Caucasians [162]. One study failed to find any association between the histamine-1 receptor gene and antipsychotic-induced weight gain [163]. However, associations have been reported between weight gain and/or metabolic syndrome and apolipoprotein E [164], brain-derived neurotrophic factor [138][165], cannabinoid receptor-1 [166],CYP2D6[138][167], multidrug resistance 1 [137], methylenetetrahydrofolate reductase [168][169], peroxisome proliferator-activated receptor-γ [170], synaptosomal-associated protein25[171], and tumor necrosis factor [172][173].

Agranulocytosis is a rare but severe and potentially lethal adverse effect associated with clozapine use. Pharmacogenetic studies have reported strong associations between polymorphisms in the major histocompatibility complex and clozapine-induced agranulocytosis [174][175][176]. Two cohorts from a clozapine study found significantly high odds ratios (16.9) for agranulocytosis in patients with a human leukocyte antigen (HLA)-DQB1, which is a single-nucleotide polymorphism (i.e., 6672G > C) with high specificity and sensitivity rates [157] (**Table 1**). However, similar to results from the genetic studies investigating antipsychotic-induced TD, involvement of oxidative genes in bone marrow toxicity has also produced inconsistent results, as reflected by a marginal association with NADPH quinone 2

3. Pharmacogenomic (PGx) Studies

These studies have primarily explored the effects of genetically mediated PD differences in a drug's response and/or adverse effects through a systematic assessment of genes, their products, and individual variation in gene expression and function. This may be the reason why most GWAS studies with antipsychotic drugs are primarily based on post hoc analyses from a large effectiveness trial, CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) [177][178][179][180][181]. Another GWAS found 20 statistically significant polymorphisms at a single locus near the melanocortin 4 receptor (MC4R) gene associated with weight gain in patients undergoing the first trial with antipsychotic drugs, which is consistent with a region previously identified by large-scale GWAS of obesity in the general population [146].

Antipsychotic treatment in a subset of 738 schizophrenia patients from the CATIE study [180] polymorphisms localized within or close to the genes, ETS homologous factor, solute carrier family 26 member 9 (SLC26A9), DRD2, G protein-coupled receptor 137B, carbohydrate sulfotransferase 8, and interleukin1-alpha (IL1A) was associated with improvements

in various neurocognitive domain areas. A significant result was also found for the variant rs286913 in the ETS homologous factor related to the effects of ziprasidone on vigilance.

4. Commercially Available Genetic Assays

These assays offer genetic testing for multiple genetic biomarkers (combinatorial assays) for treatment response and/or tolerability identified in other studies to facilitate the selection of effective psychotropic medications. Although there is no specific genetic assay for antipsychotic drugs, combinatorial genotyping of genetic biomarkers is used to optimize the efficacy and tolerability of antipsychotic drugs, especially in the treatment-refractory population. CYP2C19.AmpliChip™is the only FDA-approved genetic test, which is a microarray-based product to assess the activity of CYP2D6 and CYP2C19 and can be helpful in a large number of psychiatric patients as multiple psychotropic drugs are metabolized by these two CYP enzymes. Following are the major resources and genetic assay companies that offer genetic testing for psychotropic drugs.

The GeneSight®(Myriad Health®, South San Francisco, CA, USA) combinatorial assays provide coverage for about 50 PK alleles, including those for CYP2D6, CYP2C19, CYP2C9, CYP2B6, CYP3A4, and CYP1A2, On the basis of information on these genetic biomarkers, an individualized report is created which divides psychotropic medications into a green bin for recommended use, a yellow bin for use with caution, and a red bin use with extreme caution and frequent monitoring.

GeneceptTMassay (Genomind®) also provides testing for PK biomarkers (CYP2D6, CYP2C19, CYP3A4) and PD markers, (5HT transporter, 5HT2C receptors, DRD2, COMT, CACNA1C, ANK3, and MTHFR). Like the GeneSight report, each patient's results are provided to the ordering clinician, along with suggested therapeutic options.

Drug-Metabolizing Enzymes and Transporters (DMET™) Plus Solution is one of the largest commercially available genetic assays for about 2000 PK variants across multiple genes. The DMET™ Plus Solution was developed as a platform to identify genetic variance and has not been tested for its efficacy in enhancing clinical outcomes with psychotropic drugs.

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