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Pharmacogenetics of Antidepressants, A Review of Significant Genetic Variants in Different Populations

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Abstract

Major depressive disorder is a highly prevalent disease that is challenging to treat, often requiring medication and dose adjustments. Genetic factors play an important role in psychotropic medication responses. However, the translation of pharmacogenetics findings to clinical recommendations with regards to antidepressant responses is still in its early stages. We reviewed recent primary research articles, meta-analyses, and reviews on the pharmacogenetics of antidepressant treatment for major depressive disorder in different populations. We identified eight genes with likely associations with treatment responses and summarized genetic variants most likely to influence treatment responses. We determined the frequency of these variants in Caucasian, Asian, Hispanic, and African American populations. The genes are related to functions in drug metabolism, transport, signalling, stress response, and neuroplasticity. Clinical recommendations already exist for CYP2D6 and CYP2C19 cytochrome P450 drug metabolism genes. The other genes are: ABCB1 with single nucleotide polymorphisms (SNPs) rs2032583 and rs2235015; FKBP5 with SNPs rs1360780, rs3800373, and rs4713916; GNB3 with SNP rs5443; BDNF with SNP rs6265; HTR2A with SNPs rs7997012 and rs6313; and SLC6A4 with polymorphisms 5-HTTLPR and STin2. There is significant variability of the frequencies of these polymorphisms in the different populations we reviewed. There is also variability in the antidepressant responses between populations carrying the same polymorphism in some cases, indicating a likely polygenic influence. Future studies in the pharmacogenetics of antidepressants would benefit from including more subjects from underrepresented ethnic groups and stratifying results.

Keywords: Pharmacogenetics; Antidepressants; Genetic Variants; Major Depressive Disorder

Introduction

The recent advances of pharmacogenetics, the study of how an individual's genetic make-up affects the response to drugs, have revealed the genetic data that contributes to our knowledge of differences in drug responses between individuals. The next step is to translate the findings into a more personalized treatment [1,2]. Some of the identified genetic variations have large effects and are highly accurate at predicting drug responses. Those 'pharmacogenomic markers' are candidates for determining which patients will benefit from a particular drug. Psychotropic medications are usually the first-line treatment of severe psychiatric disorders, for example, antidepressants, antipsychotics, and mood stabilizers [3]. Variable response to the medication remains a critical issue in psychiatric care and only 50%-60% of treated patients show full or adequate response to psychotropic therapies, even the treatment of the disorders may be traced back for many years [4,5]. Selecting the appropriate dose is often difficult and usually requires long periods of patient assessment and drug titration [6]. In addition, a large number of patients develop drug-induced side effects and even adverse drug reactions, many of which are potentially avoidable if physicians have knowledge of pharmacogenomics and provide the appropriate medication and dosage based on a patient's genetic and/or genomic profile. Initial pharmacogenetics studies on psychotropic drugs have provided optimism for the potential of tests regarding both safety and efficacy [6].

According to the National Institute of Mental Health, 6.7% of adults in the U.S. in 2014 had at least one episode of major depression the previous year. Despite major therapeutic advancements, variability in drug response remains a challenge in treatment of psychiatric disorders, including major depressive disorder. For over 20 years, the pharmacogenetics study of antidepressant treatment has been the source of much hope and frustration for researchers. Our understanding of the complex mechanisms involved in treatment response variability among patients remains poor. Many studies have linked specific genetic polymorphisms to antidepressant efficacy only to face difficulties with replication and confirmation in future studies. Studies estimate that 42% to 50% of antidepressant response is attributable to genetic factors [7,8]. This is the additive effect of common genetic polymorphisms throughout the human genome. Genetic polymorphisms, such as single nucleotide polymorphisms (SNPs), are the most common form of gene variation in the human genome and can act as heritable landmarks for genetic diversity and population structure [9]. At least nine large genome wide association (GWA) studies on patients with major depressive disorders sought to uncover SNPs associated with response to numerous antidepressant treatments [10], for example, the Sequenced Treatment Alternative to Relieve Depression (STAR*D) study, the Munich Antidepressant Response Signature (MARS) project, and the Genome-Based Therapeutic Drugs for Depression (GENDEP) project. However, they were unable to uncover statistically significant associations even when analysed by meta-analysis [11].

This review will focus on antidepressant therapy for patients with depression, even though the efficacy of current antidepressant treatment strategies is hampered by our still-limited understanding

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of the pharmacogenomics. Because a tremendous variation of genetic backgrounds exists among different ethnic groups, we focus on antidepressant pharmacogenetics in different populations. Application of knowledge into how genetics and epigenetics contribute to inter-individual variability has emerged as a promising avenue for advancement of personalized medicine. Drug choice and dosing are increasingly influenced by knowledge of pharmacogenomics, although data have been derived mainly from studies of the Caucasian population and to a much lesser extent other populations.

Due to inter-ethnic heterogeneity, the dosage established in a landmark trial and clinical pharmacogenetics applications for a certain population may not be generalizable to other ethnic populations and a follow-up study is often needed to find the maximum tolerated dose for different populations. This problem even exists in various ethnic sub-populations [12]. For example, European ancestry has gene variants that remain co-inherited through linkage disequilibrium (LD) as a result of fewer recombination events. However, populations with an ancient African ancestry have genomic regions with a greater diversity of gene variation, resulting from a greater number of recombination events and shorter regions of linkage disequilibrium [13]. Studies demonstrated that populations of African ancestry had three times as many rare variants compared with those of European and Asian origin [13], see review [9]. The genetic diversity of different ancestral populations has been shown to have implications for the frequency of not only common variants, but also rare genetic variants. Therefore, it is important to know these genetic variants of absorption, distribution, metabolism and excretion (ADME) genes in different populations, which will reveal pharmacogenetics effects that, might affect populations.

Although the recent studies represent hopeful progress toward the inclusion of different populations among those who will benefit from the implementation of pharmacogenetic principles and tools in drug therapy, there are not yet sufficient data concerning allelic or genotypic frequencies of genetic markers related to drug responses and/or treatment outcomes for their implementation in clinical practice. Thus, there is a need for more research in antidepressant pharmacogenetics in different populations to increase data availability.

Pharmacogenetic screening prior to antidepressant treatment may soon be pragmatic. Until general guidelines can be established linking genetic polymorphisms with treatment response, considering polymorphisms and their frequency in specific populations may be helpful to clinicians either in guiding treatment or determining which patients will benefit more from genetic testing.

Methods

In this review, preclinical, candidate gene and genome wide association studies were cited. However, the primary aim of this paper is to provide an overview of pharmacogenetic studies investigating genetic variants on antidepressant treatment outcomes in different populations. We searched for English language articles published and there were a total of 548 publications on the key words of antidepressants and pharmacogenetics until February 2016 through PubMed (Figure 1). We further limited the search to reviews and identified 207 articles. Of these, we excluded reviews not focused on major depressive disorder and identified 72. We assessed the full-text of 38 of these reviews after determining they were the most relevant to pharmacogenetics of antidepressant treatment for major depressive disorder and had the most recent results regarding the genes investigated in their objectives. We identified twelve genes (CYP2D6, CYP2C19, ABCB1, FKBP5, GNB3, BDNF, HTR2A, SLC6A4, CRHR1, PLCB1, CaMK, and COMT)

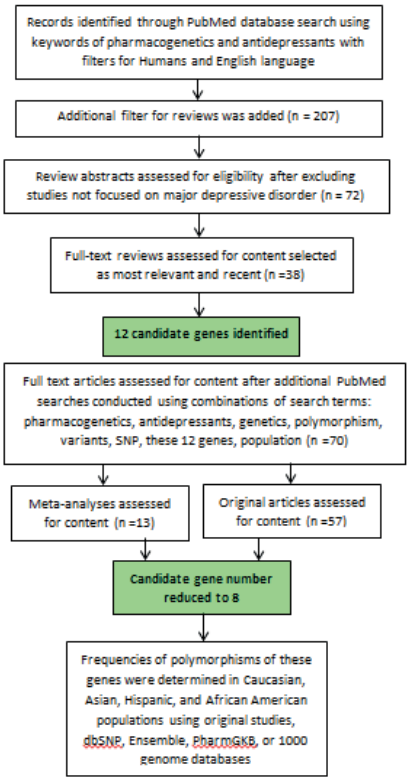

Figure 1: Methods Flow Diagram

from assessment of these publications. Further PubMed searches were conducted using various combinations of the following search terms: genetics, polymorphism, variants, SNP, pharmacogenetics, antidepressant, each individual gene name of these twelve candidate genes and population. We assessed thirteen meta-analyses and 57 original studies from these focused searches. The number of genes was reduced to eight that had consistently significant findings in two or more studies of candidate genes, genome wide association studies and/or meta-analyses (Table 1). Polymorphisms of each gene associated with antidepressant responses were identified and frequencies determined in Caucasian, Asian, Hispanic, and African American populations using original studies, dbSNP, Ensemble, PharmGKB or 1000 genome databases. Using this method, we identified over 108 publications with conclusions pertaining to these eight genes and antidepressant response for treatment of major depressive disorder.

Current Findings

Antidepressant pharmacotherapy is still very primitive; 1 in 3 patients does not fully recover even after several treatment trials. Genetic factors and clinical characteristics contribute to the failure of a favourable treatment outcome [4,5]. A large number of genes are likely to influence the toxicity and response of an individual medication of antidepressant response [1-14,15]. A recent study focused on determination of the effect of the CYP2D6 genotype on the length of hospitalization stay for patients treated for major depressive disorder and found that the hospital stay was significantly longer in deficient CYP2D6 metabolizers compared with functional or supra-functional metabolizers [16]. Importantly, Federal agencies, including the Department of Health and Human Services and the US Food and Drug

Gene	Polymorphisms	Ref.	Ethnicity/ Population	Freq.	Treatment response	Antidepressant	Notes
CYP2D6 Cytochrome P450, Family 2, Subfamily D, Polypeptide 6	*10 (decreased function) -multiple SNPs	[21, 22]	Caucasian	0.028	poor or intermediate metabolizers may experience more side effects than extensive metabolizers, a lower dose or alternate drug may be used ultra rapid metabolizers may need higher drug dose for therapeutic plasma concentrations	several SSRIs and TCAs	*9 and *41 also have decreased function but are consistently rare among populations ultra rapid metabolizers carry multiple copies of functional alleles
			East Asian	0.42			
			Hispanic	0.028			
			African American	0.043			
	*4 (no function) -multiple SNPs	[21, 22]	Caucasian	0.18			*3, *5, and *6 also have no function but are consistently rare among populations *4/*4 is poor metabolizer
			East Asian	0.0045			
			Hispanic	0.11			
			African American	0.06			
CYP2C19 Cytochrome P450, Family 2, Subfamily C, Polypeptide 19	*2 (no function) rs4244285 19154G>A	[21, 22]	Caucasian	0.14	poor or intermediate metabolizers may experience more side effects than extensive metabolizers, a lower dose or alternate drug may be used	several SSRIs and TCAs	*2/*2 is poor metabolizer
			East Asian	0.29			
			Hispanic	0.125[c] (n=67)			
			African American	0.183			
	*3 (no function) rs4986893 17948G>A	[21, 22]	Caucasian	0.002			*3/*3 is poor metabolizer
			East Asian	0.089			
			Hispanic	0.00[b]			
			African American	0.003			
	*17 (increased function) rs12248560 -806C>T	[21, 22]	Caucasian	0.2	Ultra rapid metabolizers may need higher drug dose for therapeutic plasma concentrations		*17/*17 is ultra-rapid metabolizer, consider changing to drug not metabolized by CYP2C19
			East Asian	0.027			
			Hispanic	0.117[c] (n=67)			
			African American	0.194			
ABCB1 ATP-Binding Cassette, Sub-Family B (MDR/ TAP), member 1	rs2032583 C allele	[27, 28]	Caucasian	0.15[a] (n=560)	better remission, TT require higher dosing	P-gp substrates	significant for inpatients, ethnicity mixed
			Asian	0.062[a] (n=614)			
			Hispanic	0.045[a] (n=44)			
			African American	0.157[a] (n=70)			
	rs2235015 T allele	[27, 28]	Caucasian	0.255[a] (n=478)	better remission, GG require higher dosing	P-gp substrates	significant for inpatients, ethnicity mixed
			Asian	0.065[a] (n=568)			
			Hispanic	0.068[a] (n=44)			
			African American	0.385[a] (n=26)			

Gene	Polymorphisms	Ref.	Ethnicity/ Population	Freq.	Treatment response	Antidepressant	Notes
FKBP5 FK506 binding protein 5 gene	rs1360780 T allele (TT)	[30]	Caucasian	0.252[a] (n=322)	better, faster response	SSRI	in mixed ethnic group, Niitsu found beter response in C/C homozygous
		[37]	Asian	0.282 (n=273)	no association	SSRI and SNRI	
			Hispanic	0.219[c] (n=67)			
			African American	0.426[c] (n=66)			
	rs3800373 C allele	[30]	Caucasian	0.253[a] (n=276)	better response	SSRI	no better response in mixed ethnic group
		[37]	Asian	0.274 (n=273)	no association	SSRI and SNRI	
			Hispanic	0.203[c] (n=67)			
			African American	0.478[a] (n=46)			
	rs4713916 A allele	[38]	Caucasian	0.34[a] (n=50)	improved remission	citalopram	
		[37]	Asian	0.229 (n=273)	no association	SSRI and SNRI	
			Hispanic	0.234[c] (n=67)			
			African American	0.13[a] (n=46)			

Gene	Polymorphisms	Ref.	Ethnicity/ Population	Freq.	Treatment response	Antidepressant	Notes
BDNF Brain-Derived Neurotrophic Factor	rs6265, 196G/A Val66Met (vs. Val/ Val)	[40]	Caucasian	0.18-0.30	no association (but small sample size)	SSRI and SNRI	
		[41]			Val/Val have better response to SSRI, Met allele have higher 6 month remission with SNRI/TCA	SSRI, SNRI, TCA	it was a 6 month study - neurogenesis could require long duration for impact
		[40]	Asian	0.41-0.50	better response rate	SSRI and SNRI	more effective with treatment greater than 6 weeks, SNRI has weaker association
			Hispanic	0.195[c] (n=67)			
			African American	0.065[a] (n=46)			
GNB3 Guanine Nucleotide Binding Protein, Beta Polypeptide 3	rs5443 (C825T)	[44]	Caucasian	0.39[a] (n=118)	no significant association	SSRI and SNRI	5 studies on Asians and 2 on Caucasians
			Asian	0.37[a] (n=178)	better efficacy (response rate and remission)		
		[45]	Caucasian		T allele associated with more weight gain and less insomnia	nortriptyline (TCA)	no effect on mood
			Hispanic	0.375[c] (n=67)			
			African American	0.779[c] (n=66)			
HTR2A 5-Hydroxytryptamine (Serotonin) Receptor 2A	rs7997012 G>A	[47]	Caucasian	0.356[a] (n=118)	higher response rate	SSRI and SNRI	
			Asian	0.219[a] (n=178)	no significant association		
			Hispanic	0.320[c] (n=67)			
			African American	0.065[c] (n=66)			
	rs6313 T102C	[47]	Caucasian	0.543[a] (n=514)	higher response rate	SSRI and SNRI	in linkage disequilibrium with rs6311
			Asian	0.489[a] (n=568)	no significant association		
			Hispanic	0.671[c] (n=67)			
			African American	0.63[a] (n=46)			

Gene	Polymorphisms	Ref.	Ethnicity/ Population	Freq.	Treatment response	Antidepressant	Notes
SLC6A4 Solute Carrier Family 6 (Neurotransmitter Transporter), Member 4	5-HTTLPR L allele (44 bp insertion) rs4795541	[48]	Caucasian	0.60 [51]	long allele associated with better response and remission with SSRI treatment (weaker association with all antidepressants classes)	SSRI, non-SSRI, and mixed classes considered	s carriers may have more adverse effects should consider the effect of rs25531 G/A in conjunction
			Asian	0.23 [51]	L/L genotype associated with better remission with mixed antidepressant classes		heterogeneity among studies, weaker association, may need larger sample size
			Hispanic	0.49 [49]			
			African American	0.83 [51]			
	STin2 (12 repeat units of 17 bp vs 10, 9, or 7)	[30]	Caucasian	0.52 [51]	no association		
			Asian	0.93 [51]	12/12 with better response with SSRI	several	high heterogeneity across studies, should consider effect of 5-HTTLPR (linkage disequilibrium)
			Hispanic	NA			
			African American	0.73 [51]			

Table 1: Genetic variants associated with antidepressant treatment responses in different populations.

Administration (FDA) are incorporating pharmacogenomics dosing guidance into the labelling, development, and approval of drugs in a manner that supports gene-based care in more than 110 medications. Of the 32 neuropsychiatric drugs listed, 27 (84%) have CYP2D6 metabolizer status, 3 (9%) identify CYP2C19 metabolizer status and 3 (9%) pertain to other important genetic markers (e.g., HLA-B) [12]. Dosing information is also available for CYP2D6, CYP19, and HLA-B poor metabolizers (PM) [17,18], for example, CYP2D6 is responsible for oxidative metabolism of up to 25% of medications [19], including a large subset of antidepressants and antipsychotic medications. Healthcare providers and patients should be aware of not only benefits, but also risks of those medications.

(Table 1) lists a number of genetic variants associated with antidepressant treatment responses in different populations. If certain populations' genetic variants were not studied, such as Hispanic or African American, then we list allelic frequencies of those variants based on dbSNP, Ensemble, PharmGKB or 1000 genome databases.

CYP450 Genes and Drug Metabolism

Polymorphisms of the genes of the CYP450 family and their effects on drug treatment were the earliest targets of pharmacogenetics studies. In particular, CYP2D6 and CYP2C19 are directly involved in the production of drug metabolizing enzymes for processing xenobiotics including psychotropic medications. The US Food and Drug Administration (FDA) has issued instructions for labelling over 20 psychotropic drugs with recommendations and precautions on their use based on the results of these studies [20]. The drugs include selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs). Evidence based clinical guidelines can be found in the PharmGKB database. The phenotypes resulting from this genetic variability may be classified into four groups: poor metabolizers having decreased enzymatic function, intermediate metabolizers who carry two partially defective alleles or one defective allele, extensive metabolizers with normal function, and ultra-rapid metabolizers with increased enzymatic activity [20]. There are over 100 known allelic variations of CYP2D6 and copy number variations with deletions, duplications, and multiplications [21]. CYP2C19 is also highly polymorphic with over 30 known allelic variations. We have listed some of the most common polymorphisms with significant variation among populations in (Table 1). The *1 allele with normal function for CYP2D6 has a frequency of 34% in East Asians, but 52% in Caucasians [22] (supplementary material). The *10 allele with decreased function is common in East Asians at 42%, but less than 5% in other populations. The *4 allele with no function is very rare in East Asians and has a frequency of 18% in Caucasians. For the CYP2C19 gene, the *2 allele with no function is almost twice as common in East Asians with a frequency of 29%, than in other populations. However, the *17 allele associated with increased function is found in only 2.7% of East Asians and 20% of Caucasians. Poor metabolizers are likely to experience higher side effects while

ultra-rapid metabolizers are likely to have worse outcomes with antidepressant treatment [23]. Genotyping for these polymorphisms is justified in clinical practice in order to optimize drug dosing for efficacy and prevention of side effects. However, many factors complicate the recommendations including patient compliance, environmental circumstances, and comorbidities [24]. Moreover, a patient that carries one polymorphism affecting antidepressant treatment response may also carry others.

ABCB1 and Drug Transport

Another gene, with likely implications for antidepressant treatment response, codes for the ATP-binding cassette, sub-family B (MDR/TAP), member 1 P-glycoprotein (ABCB1) [25]. It is a drug transport protein with a role in efflux across the blood-brain barrier as it is expressed in the luminal layer of brain capillary endothelial cells. ABCB1 influences the concentration in the brain of antidepressants that are substrates of P-glycoprotein which include citalopram, venlafaxine, desipramine, paroxetine, and amitriptyline [26]. Mirtazapine, bupropion, and fluoxetine are not substrates and may serve as alternative psychotropics [25]. Multiple studies with conflicting results have been conducted since an association with treatment was reported in 2008 [25]. A recent meta-analysis of 16 pharmacogenetic studies concluded that two SNPs – rs2032583 and rs2235015 are significantly associated with antidepressant treatment outcome for inpatients with depression when treated with antidepressants that are substrates of P-glycoprotein [27]. The C allele of rs2032583 and the T allele of rs2235015 of the ABCB1 gene lead to better rates of remission [28]. The C allele of rs2032583 is more common in Caucasians and African Americans than in Asians or Hispanics and rs2235015 is most common in African Americans. Another study found the SNP rs1045642 T allele of the ABCB1 gene significantly reduces the dose of escitalopram needed for remission of depression [29]. The frequency of this allele is almost equivalent in Caucasians and Asians, but almost twice as common in Hispanics and very rare in African Americans (Table 1). However, a meta-analysis discovered no significant association between this SNP and treatment efficacy [30]. A study of Mexican Americans with depression yielded an association with remission of three additional polymorphisms: rs3842 (treated with desipramine or fluoxetine), rs17064 (desipramine only), and rs1128503 (fluoxetine only) [31]. For ABCB1, additional research should be conducted in specific populations while taking into account the substrate status of the antidepressant treatment. Understanding the effect of these various SNPs and others may have important clinical applications. Patients carrying unfavourable polymorphisms may benefit from increased dosages of antidepressants or switching to medications that are not substrates for P-glycoprotein. Patients whose inpatient treatment is guided by ABCB1 genotyping may have higher remission rates [32]. Thus ABCB1 genotyping shows promise for future antidepressant clinical guidelines.

FKBP5 and the Hypothalamic-Pituitary-Adrenal Axis

The FK506 binding protein 5 gene (FKBP5) codes for a protein that regulates glucocorticoid receptor sensitivity. In addition, it functions in a multitude of intracellular molecular pathways that may be involved in several neurological pathologies and antidepressant activity including regulation of Act [33]. When this protein binds to the glucocorticoid receptor complex, there is decrease in the affinity for cortisol, affecting the hypothalamic-pituitary-adrenal axis. In a feedback loop, FKBP5 expression is induced by the activation of glucocorticoid receptor. An inefficient negative feedback mechanism leads to prolonged activation of the stress response. Thus, polymorphisms of this gene may disrupt hormonal stress response, important for understanding the environmental effects on psychiatric disease [34]. Certain polymorphisms of the FKBP5 gene are associated with an improved response to antidepressant medication, regardless of antidepressant used [34]. Successful antidepressant treatment response has been directly associated with a decrease in FKBP5 leukocyte mRNA expression [35]. Four SNPs within this gene have been identified as potential candidates for pharmacogenetics: rs1360780, rs3800373, rs4713916, and rs352428 [23]. Polymorphism rs352428 worsens the response to antidepressant treatment in Caucasians [36]. Interestingly, polymorphisms rs1360780 and rs3800373 were found to have an association with improved outcomes from antidepressant treatment in Caucasian populations in meta-analysis [30], but there was no significant association in an Asian population [37] although the frequency of these alleles is similar in both populations. Lekman et al. [38] also found an association of rs4713916 with remission with citalopram treatment in the Caucasian population [38]. This again highlights the importance of studying polymorphisms in specific populations when making recommendations for clinical applications.

BDNF and Neuroplasticity

Brain-derived neurotrophic factor (BDNF) is part of the nerve growth factor family, induced by cortical neurons and necessary for survival of striatal neurons. It is involved in neuro protection and plasticity and plays a role in reversal of hippocampus atrophy during antidepressant treatment. There is a reduction of BDNF in serum and leukocytes of depressed patients that may be reversed with successful treatment [35]. BDNF may be involved in memory and various functions of the hippocampus. The rs6265 Val66Met polymorphism of the BDNF gene was shown to impact the secretion of BDNF in the hippocampus and may be involved in neuronal pathology [39]. Several studies have demonstrated a significant association with this polymorphism and antidepressant response. Asians who carry the Val66Met polymorphism have a better response rate and remission to SSRI treatment; however, this association was not found in a Caucasian population [40]. Another study of the Caucasian population showed a significant association with the Val/Val genotype and response to SSRI while carriers of the Met allele had higher six month remission with serotonin-norepinephrine reuptake inhibitor (SNRI) or tricyclic antidepressant treatment [41]. If this study is replicated and the findings are confirmed, it would have important clinical applications for the Caucasian population, in particular. The efficacy of SSRI versus SNRI or TCA treatment may depend on the genotype of this polymorphism.

GNB3 and the Signalling Cascade

The guanine nucleotide binding protein, beta polypeptide 3 (GNB3) is one of many G proteins essential for signal transduction between receptor and effector proteins. These proteins are responsible for intracellular signalling and have been extensively studied due to their function as molecular switches. G-proteins are the physiological target of approximately 30% of pharmaceuticals on the market [42]. They contain three subunits, α, β, and γ that dissociate to initiate the intracellular signalling cascade. The β subunit is encoded by one of five genes. The polymorphism C825T of GNB3 results in a splice variant leading to a dominant gain of function and increased signalling [43]. It has been linked to antidepressant response in Asian populations [44]. In one study in a Caucasian population, this polymorphism was linked to more weight gain and less insomnia with nortriptyline treatment, but had no effect on mood symptoms of depression [45]. This polymorphism is very common in African Americans according to the 1000 Genomes Project, with a frequency of 77.9% and more studies are necessary for linking this polymorphism to antidepressant efficacy.

HTR2A and the Serotonin Signal

Another critical cell signalling protein is the 5-Hyroxytryptamine (Serotonin) Receptor 2A (HTR2A). It is a postsynaptic receptor for serotonin, coupled to the G-protein signalling cascade that is found throughout the central nervous system. A multitude of studies have been conducted linking polymorphisms of the HTR2A gene with neuropsychiatric phenotypes, with contradictory findings [46]. A recent meta-analysis of studies involving polymorphisms of the gene and antidepressant treatment in major depression found significant association of rs7997012 G>A and rs6313 T>C with good responses to treatment with SSRIs or SNRIs in Caucasians, but no significant association in Asians [47]. Both polymorphisms are fairly common in Caucasians with frequencies of 35.6% for rs7997012 and 54.3% for rs6313; they are slightly less common in Asians with frequencies of 21.9% and 48.9% respectively. Before clinical recommendations for pharmacogenetics testing can be formulated for the HTR2A gene, additional studies are required in other populations.

SLC6A4 and Serotonin Transport

The Solute Carrier Family 6 (Neurotransmitter Transporter) Member 4 (SLC6A4, known as 5 HTT) gene codes for a sodium dependent membrane protein and is responsible for serotonin reuptake into the presynaptic neuron. It is of great interest in the pharmacogenetics of antidepressants because many of the most commonly prescribed antidepressant drugs, SSRIs, disrupt this mechanism. One polymorphism, in particular, 5-HTTLPR, is located in the promoter region of the gene and occurs as a long or short allele (L or S) due to a 44 base pair insertion/ deletion [1]. In a recent meta-analysis, the long (L) allele was associated with better response and remission with SSRI treatment in the Caucasian population [48]. There was a weak association between the L/L genotype and remission in mixed antidepressant classes in the Asian population [48]. There is a large disparity in the frequencies of the L allele with 60% of Caucasians carrying it and only 23% of Asians. An extra-long allele has also been identified, occurring more frequently in Asians, African Americans and non-White Hispanics [49]. SCL6A4 is complex and highly polymorphic. Several SNPs in and around the 5-HTTLPR may affect its expression, including rs25531 G/A which is located upstream of the gene [50]. Subjects with the long (L) allele of the 5-HTTLPR and rs25531- G allele jointly, reduce SCL6A4 expression to about the level of the short allele (S) of the 5-HTTLPR [51]. One small study found an association of L allele carriers with the rs25531A polymorphism had better response to SSRI treatment correlated to serum concentrations [52]. Patients with the L allele and rs25531G had no improved response with higher serum concentrations [52]. Clinically, this variation may be very significant because patients with the L allele of the 5-HTTLPR and rs25531G combination may have no improved response to escalation of SSRI dose, a conclusion that cannot be drawn until the findings are verified in a larger study. Another extensively studied polymorphism of the SLC6A4 is STin2, a variable number tandem repeat (VNTR) within intron two of the gene. High heterogeneity and often contradictory results exist among studies [53]. Nevertheless, there was a possible correlation between the STin2 12/12 genotype and improved response to SSRIs in Asian populations [30]. This polymorphism is about 50% less common in Caucasians while the 5-HTTLPR L allele is almost three times as common as compared with these variants in the Asian population. These three polymorphisms and the possibility of their compounded influence on phenotype should be taken into consideration in future studies.

Conclusions

In this study, we focused on eight genes with significant associations with antidepressant responses in the treatment of depression in multiple studies or meta-analyses. For each gene, we focused on specific polymorphisms with greater likelihood of impacting pharmacogenetic clinical guidelines in the near future as determined by the volume of studies and homogeneity and significance of results. Guidelines for antidepressant treatment with SSRIs and TCAs already exist for two of the genes: CYP2D6 and CYP2C19 [21,22]. Nevertheless, we wanted to highlight the variability of the frequencies of significant polymorphisms of these genes in various populations given that pharmacogenetic testing prior to treatment may be more critical in one population over another. The other genes were: ABCB1 (rs2032583, rs2235015), FKBP5 (rs1360780, rs3800373, rs4713916), GNB3 (rs5443), BDNF (rs6265), HTR2A (rs7997012, rs6313), and SLC6A4 (5-HTTLPR and STin2). We notice lack of pharmacogenetics and genetics studies in minorities, such as Hispanic, Asian and Africa American populations. Although there are some studies in these ethnic groups, sample sizes are too small to draw a conclusive conclusion.

Overwhelmingly, there is a paucity of pharmacogenetics antidepressant studies in populations other than Caucasian and Asian. However, there is sufficient evidence demonstrating ethnic variability in antidepressant response phenotypes with carriers of the identical polymorphisms in the genes we reviewed. We can conclude that this evidence points to polygenic influence with possible linkage disequilibrium affecting treatment outcomes. In order to elucidate the cause of ethnic variability, additional studies should include diverse populations and results should be stratified by ethnicity. The potential for pharmacogenetics to improve treatment outcomes in the realm of psychiatric diseases is undoubtedly vast. A greater focus on population specific outcomes may simplify the challenges remaining in the field.

The path to personalized medicine for all ethnic groups will require that we improve our ability to decipher genotype and sequence data which account for ancestral genetic structure, complex haplotypes, gene-gene interactions, and rare variants to detect and replicate novel pharmacogenetic loci in general and in antidepressant medications [9].

Future Directions

We realize that major challenges for antidepressant pharmacogenetics studies are primarily related to sample size, lack of well-defined pharmacogenetics phenotypes, complex ancestral population structures, and lack of studies in minorities, such as Hispanic, African American, and other minorities [9]. Therefore, future directions need to be 1) good phenotypes for treatment responses: most discomforting is the likelihood that how we define treatment responses to antidepressants as a phenotype may not be easily translatable into a biological phenomenon, 2) to enroll a larger number of subjects from underrepresented ethnic groups into clinical trials for GWAS, admixture mapping, and genotype-stratified trials for antidepressants, 3) to discover other biomarkers, such as copy number variations (CNV), epigenetic modification and future multi-dimensional analysis with pharmacogenetics/pharmacogenomics and epigenetic modification [10-56].

With advanced technology, statistics and bioinformatics analyses, our understanding of the complex genetic factors influencing treatment responses for antidepressant medications in diverse populations will improve, and the costs of genotyping and DNA genotyping and sequencing and the issues of data storage will progress for us to be able to develop genetic biomarker panels to predict the most efficacious

therapies and reduce toxicity for an individual depressive patient in different populations.

Pharmacogenomics has been subject to considerable development during the past 10 years and seems likely to advance even more rapidly in the next decade [57]. We expect that rapid technological advancements in molecular pharmacology and genetics and educating healthcare providers with pharmacogenomics knowledge are facilitating translation of laboratory discoveries into patient care through maximizing drug efficacy, enhancing drug safety, reducing drug toxicity, and an overall cost benefit for individuals and society alike.

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