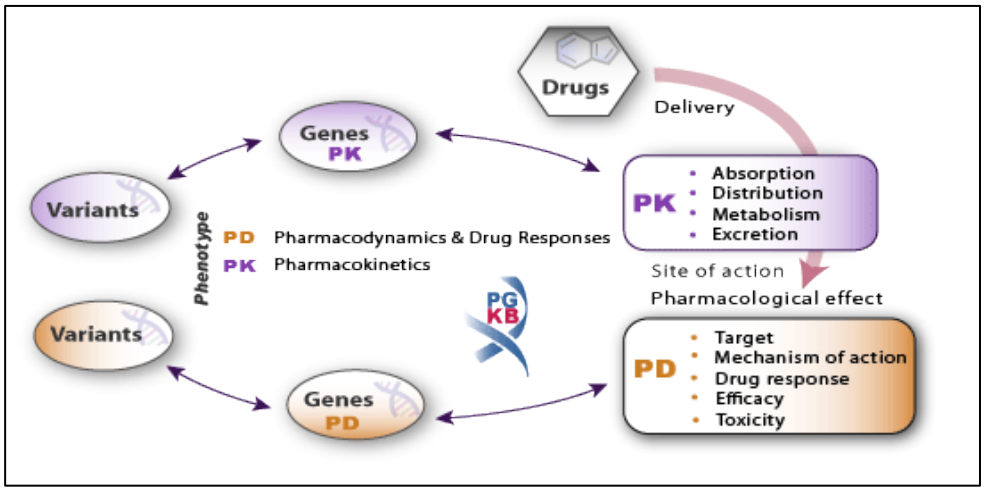
Pharmacogenomics of Depression Therapy

Emily Witt HUMBIO 158G March 14, 2014

The lifetime prevalence of depression in the US is a staggering 17%[1]. This numbing statistic is accentuated by the fact that approximately 10-20% of these patients will demonstrate resistance to anti-depressant therapy, and, consequently, be diagnosed with treatment resistant depression[1]. Yet, with the advent of pharmacogenomics, the study of how genomic variation influences drug response[2], many are beginning to suggest that perhaps the solution to treating these seemingly untreatable patients lies not in the search of better therapies, but in the search of how to better match the specific patient with the ideal therapy based on his or her own genome.

Pharmacogenomics is generally defined as "the study of inter-individual variations in whole-genome or candidate gene single-nucleotide polymorphism (SNP maps), haplotype markers and alterations in gene expression that might be correlated with pharmacological function and therapeutic response."[15] It consists of analyzing two central processes: pharmacokinetics, how the drug is metabolized, absorbed, distributed throughout the body and then excreted, and pharmacodymnamics, the effect of the drug[7]. Ultimately, it rests on the hypothesis that understanding which gene variants a person has that predispose him or her to a malfunction in either of these two pathways is critical for prescribing the best drug.



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Major depressive disorder is distinguished by the DSM-V as having five or more of the following symptoms for longer than two weeks: feelings of worthlessness, excessive or inappropriate guilt, significant weight change, psychomotor agitation, difficulty concentrating, sleep disturbance, recurrent thoughts of death or suicide, or pervasive loss of energy and fatigue[13]. The most common treatments are psychotherapy and pharmaceuticals, though some severe cases warrant more extreme forms of treatment such as electroconvulsive therapy and deep brain stimulation[1]. With respect to pharmaceuticals, predominantly monoamine reuptake inhibiters, the majority of patients are subjected to a "trial and error process" for finding the most effective medication, which leads to a high probability of relapse and a high degree of frustration for the patient[3]. Furthermore, side effects have been estimated to affect between 40-90% of patients[8]. As a result, a large proportion of patients discontinue the use of antidepressants, antipsychotics and mood stabilizers citing side effects or symptom relapse[4].

Common Antidepressants

Class	Antidepressants
Selective serotonin reuptake inhibitors (SSRIs)	Citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), sertraline (Zoloft)
Serotonin norepinephrine reuptake inhibitors (SNRIs)	Desvenlafaxine (Pristiq), duloxetine (Cymbalta), milnacipran (Ixel), venlafaxine (Effexor)
Norepinephrine dopamine reuptake inhibitors (NDRIs)	Bupropion (Wellbutrin)
Tricyclic antidepressants (TCAs)	Amitriptyline (Elavil), clomipramine (Anafranil), desipramine (Norpramin), imipramine (Tofranil), nortriptyline (Aventyl)
Tetracyclic antidepressants (TetCAs)	Mianserin (Norval), mirtazapine (Remeron)
Monoamine oxidase inhibitors (MAOIs)	Phenelzine (Nardil), selegiline (L-deprenyl, Emsam)

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GWAS: Starting with a genome wide approach

Unfortunately, results from the major GWAS that have been conducted regarding antidepressant treatment outcomes have been inconclusive. Thus far, three primary studies have been conducted using a genome-wide approach: the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, the Munich Antidepressant Response Signature (MARS) study and the Genome-based Therapeutic Drugs for Depression (GENDEP) study[6]. The STAR*D study, the largest antidepressant as of 2011, analyzed 1953 patients who were all treated with citalopram, 883 were considered responders, defined by a 50% or greater reduction in the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR), while 608 were considered non-responders[4]. Only three intronic SNPs with p values less than $1x\ 10^{-5}$ identified as being associated with response and remission: rs6966038 near the Ubiquitin protein ligase E3C (*UBE3C*) gene ($p=4.65x10^{-7}$), rs6127921 near the Bone morphogenic protein 7 (*BMP7*) gene ($p=3.45x10^{-6}$), and rs809736 near the RAR-related orphan receptor alpha (*RORA*) gene ($p=8.19x10^{-6}$)[5]. The genotyping platform that was used in the study has been criticized, however, and the results have not been replicated.[6]

The subsequent MARS study was significantly smaller, analyzing only 339 patients[6]. It searched for genetic markers of early partial responders, indicated by a 25% or greater reduction based on the Hamilton Depression Rating Scale (HAM-D) score after two weeks of treatment, responders, those with 50% or more reduction of symptoms after five weeks, or remitters, those with a score of 10 or less after five weeks[6]. Early partial response was associated with the rs6989467 SNP in the Cadherin 17 (*CDH17*) gene ($p=7.6x10^{-7}$) and all three phenotypes were associated with the rs1502174 SNP in the Ephrin type-B receptor gene ($p=7.6x10^{-7}$)[6].

Finally, the GENDEP study, the first to be specifically conducted with a pharmacogenetic purpose, analyzed 394 patients treated with escitalopram and 312 treated with nortriptyline based on the percent change in Montogomer-Asberg Depression Ration Scale (MADRS) after 12 weeks[6]. Two primary markers of interest were detected. The rs2500535 SNP in the interleukin 11gene ($p=3.56x10^{-8}$) was associated with responders to nortriptyline and the rs1126757 SNP in the Uronyl 2-sulphotransferase gene ($p=2.83x10^{-6}$) was associated with responders to citalopram[6].

In all of these studies, there were no polymorphisms that reached the level of what is considered by the field to be genome wide significant ($p<10^{-8}$). As depression has been shown to have a moderate genetic component, it appears unlikely that the inconsistency in GWAS results indicated a lack of genetic influence[6]. Rather, the substantial individuality in the experience of the disorder and the complex gene-environment etiology hinder the ability to identify common genetic variants associated with treatment outcomes[6]. As Laje and McMahon importantly note, there area myriad complicating factors involved in the disease expression, and it may be unrealistic to attempt to create a single GWAS study that accounts for all of the variability in phenotypes[6]. Nevertheless, studies of specific polymorphisms have had more success in identifying variants that may predict treatment response.

Candidate Genes

The most well investigated genetic factor associated with depression therapy has been variation in serotonin receptors and transporters, as many anti-depressants target serotonin pathways[7,8,12]. The majority of research in this field has surrounded the 5-HTTLPR polymorphism of the serotonin (5-HT) transporter gene *SLC6A4*, which, since its identification in the early 1990s, has become the most extensively studied genetic variation in psychiatry[7,8]. The gene, located on chromosome 17q11.1-q12, is thought to be involved in mood regulation[8]. The

polymorphism of the coding sequence consists of a 44 base pair insertion/deletion, for which people with the short variant have a reduction in transcription efficiency of the 5-HTT promoter[7]. People with the with the l allele have been shown to have twice the expression of *SLC6A4* as people with the s allele, and, therefore, greater 5-HTT expression and increased serotonin uptake[7]. In a meta-analysis of 1435 patients, there was a significant association of the homozygous s variant with remission rate ($P<0.0001$) and an association of both the homozygous s variant and heterozygous variant with response rate ($P=0.0002$)[8]. The data indicate allele frequencies vary based on ethnicity as 42% of Caucasians have been shown to carry the s allele, whereas 79% of Asians carry the l allele[8]. When analyzed with respect to treatment response, it was shown that the individuals in both Asian and Caucasian populations with the l variant show a better remission rate and faster response rate[8]. Furthermore, combined odds ratios from nine studies, for a total of 2642 subjects, demonstrated that there was a significantly reduced risk of side effects ($p=0.0005$) for those with the l allele with respect to all antidepressants, which was even more significant when only treatment with SSRIs was considered ($p=0.00001$)[8].

A related polymorphism within intron 2 (STin2) has been show to influence *SLC6A4* transcription in a synergistic manner with 5-HTTLPR[8]. The polymorphism rs25531 consists of a variable copy number (9, 10 or 12) of tandem repeats 16-17 base pairs long, and has been shown to be a significant marker of treatment response in Asian, but not Caucasian, populations[8]. In a Korean sample, the variant with 12 copies was associated with higher gene expression and better response rate[8]. Interestingly, the people with the 12 STin2 variant who were also homozygous for the s variant of 5-HTTLPR, were shown to have the highest response rate in this cohort[8]. However, another analysis found the 12 variant led to a better response rate for Asian subjects with the l allele, but for Caucasian subjects with the s allele[8]. The high degree of heterogeneity

indicates more evidence is needed to identify which variant may predict better treatment response.

Variations in the serotonin receptors 1A (5-HT1A) and 2A(5-HT2A) have also been investigated as candidates for regulation of the effects of antidepressants, as the majority of drugs aim to modulate the levels of serotonin at the synaptic cleft[7,8,12]. The 1A receptor is located on both the pre- and post- synaptic neurons and is encoded by *HTR1A*, an intronless gene 1200 base pairs long on chromosome 5q.11.2-13[8]. The rs6295 (C-1019G) functional polymorphism is in the promoter region and has been linked to changes in expression and function of the 1A receptor, via the regulation of *HTR1A* transcription[8]. For individuals with the G allele, which is estimated to be approximately 50% of Caucasian and 21% Asians, it is believed that the repressor of the gene is prevented from binding, leading to elevated levels of 5-HTR1A[8]. This does little to help elucidate the phenotypic ramifications of the G allele, however, as the overall effect will vary based on whether decreased expression occurs primarily pre or post synaptically.

In contrast to the 1A receptor, the 5-HT2A receptor is encoded by a gene with two introns and three exons on chromosome 13q14-q21[8]. Two primary SNPs in the serotonin 2A receptor, rs6313 (102T/C) and rs6311 (1438A/G), are in linkage disequilibrium and have demonstrated a significant association with the incidence of side effects[8]. For rs6311, a higher risk of side effects has been linked to the G/G phenotype (odds ratio 1.91, $p=0.0006$), which was even more significant when assessed for side effects linked to only SSRIs (odds ratio 2.33, $p<0.0001$)[8]. Greater amounts of gastrointestinal symptoms, nausea, and sexual dysfunction have all been linked to this SNP[8]. While there was a mild predictive effect for treatment response in Asian populations, it was not significant enough to be generalized to larger populations[8].

With respect to the genes connected to the pharmacokinetic processes of genes, the variation in toxicity and tolerability of the drug has been associated with the variation two primary enzyme super-families: the cytochrome P450 (CYP450), enzymes responsible for metabolizing antidepressants, and the ATP binding cassette (ABC) transporter, enzymes that mediate the passage of antidepressants across the blood brain barrier[8]. The CYP450 group consists of over 50 enzymes, encoded by more than 63 genes, that are predominantly found in the liver[8]. *CYP2D6, CYP2C19, CYP3A4* and *CYP1A2* have all been associated with antidepressant drug metabolism[8]. Allelic variants for *CYP2D6* and *CYP2C19,* in particular, have been linked to different metabolizer status (poor, intermediate, extensive and ultra-rapid metabolizers), for tricyclic antidepressants, SSRIs and SNRIs[3]. CYP2D6 ultra-rapid metabolizers of tricyclic antidepressants have a higher likelihood of failing pharmacotherapy with these drugs and are recommended to use other options, and poor metabolizers have a higher likelihood of side effects[17]. Similarly, CYP2C19 intermediated poor metabolizers have an increased probability of adverse reactions and should avoid TCAs[17]. SSRIs are thought to inhibit CYP450 isoenzymes and caution with use is recommended though the FDA is still standardizing its guidelines.

In ABC family, the *ABCB1* gene product, P glycoprotein, is expressed in the blood brain barrier, mediating access of antidepressants to the central nervous system[9]. It is an ATP-dependent pump responsible for the efflux of xenobiotic drugs that may limit the uptake and accumulation of lipophilic drugs such as amitriptyline, nortriptyline, citalopram, venlafaxine, sertraline, and trimipramine[3]. The polymorphisms rs20232582 and rs1045642 have been shown to alter P-glycoprotein expression and function[9]. The G allele at position 2677 (rs20232582) and the C allele at 3435 (rs1045642) have been linked to better response to antidepressants [2,9]. Recently, it has been suggested that the effects these polymorphisms may vary based on the class of

antidepressant used[9], but more investigation is needed analyzing specific antidepressant with specific treatment and side effect outcome measures to clarify the role of *ABCB1* variations.

Polymorphisms in other auxiliary proteins involved in the synthesis and metabolism of serotonin have also been connected to treatment outcomes. Tryptophan hydroxylase is an enzyme involved in serotonin biosynthesis that has two isoforms, TPH1 and TPH2, encoded by genes at positions 11p15.3-p14 and 12q.21.1, respectively[8]. TPH1 is predominantly located in peripheral organs and expressed less commonly in the brain than TPH2[8]. Still, the 218 A/C polymorphism located in intron 7 of *TPH1* has been posited to interfere with TPH transcription, and has been associated with a worse remission rate than C/C, though results are mixed[8].

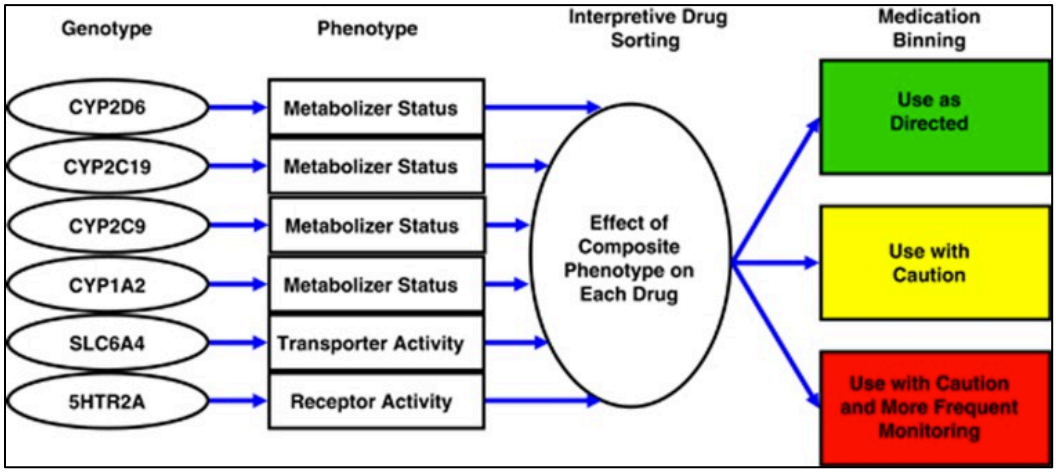
Data about variations in TPH2, the rate-limiting enzyme in serotonin biosynthesis, appear to be more consistent in indicating major depression and suicidal behavior[8]. Studies have indicated that there is a 55% reduction of serotonin levels in individuals with the pro447, as opposed to the arg447, variant[16]. Moreover, poor treatment response to SSRIs was linked to arg441his, a non-synonymous coding SNP that results in 80% loss of function of *TPH2*[8,16]. Still, there are certain cohorts in which there appears to be no correlation between SNPs in either of the genes encoding TPH and treatment response, therefore its pharmacodynamic utility remains to be confirmed[10].

Finally, brain derived neurotropic factor (BDNF) is of interest to many because BDNF signaling appears to mediate the behavioral effects generated by antidepressant drugs[11]. The hypothesis that neurotropic factors may be involved in the resolution of depression was derived from the observation that antidepressants can cause an increased expression of neurotropic factors that can reduce hippocampus atrophy following stress.[11] The rs6265 variant (Val66Met) has been proposed to affect intracellular trafficking and activity-dependent secretion of serotonin[7]. While

some studies have shown that the BDNF levels did not increase in the Met/Met genotype in response to fluoxetine treatment, other studies show more favorable outcomes with these allele carriers[7]. Still, other findings indicated that there is no influence or that Val/Val allele carriers show a better response[7]. Once again, the considerable heterogeneity reflects the different effects of different antidepressants and the divergent responses between ethnic populations, and suggests that more research is needed to resolve these contradictory findings.

Putting it into Practice

Though there is still a lack of consensus about if, and how, these allelic variants predict response to depression, some have already begun to look toward how these findings can be applied to clinical practice. A psychopharmacogenomic algorithm has been designed to calculate how a patient will generally respond to a drug based on the variations of his or her genome[4]. The algorithm, now known as GeneSight, is a genotype interpretive report developed by AssureRx Health, Inc. as a way to use personalized medicine to individualize antidepressant usage[4]. In the report, a composite phenotype response is determined for every drug based on the patients' genotypes for a specified set of genes[4]. The predicted phenotype then directs the antidepressant to be categorized into one of three bins regarding recommended use: "use as directed," "use with caution," or "use with caution and more frequent monitoring" (pictured below)[12].



The benefit of this pharmacogenomic testing tool was first evaluated in a non-randomized cohort study conducted at a non-profit outpatient behavioral health clinic in St. Paul, Minnesota[4]. It compared 22 depressed patients treated without knowing their genotyping results of the report to 22 subjects who were given the results for 5 informative genes (*CYP2C9* was not initially included) at the begging of the 8-week treatment period[4]. Using QIDS-C16 and HAM-D17 ratings of depression collected throughout the trial, the authors reported a 7.2% reduction in QIDS-C16 score and 18.2% reduction in HAM-D17 rating for the unguided group compared to a 31.2% and 30.8% reduction for those depression measures in the guided group ($p=0.002$, $p=0.004$)[4]. Despite the possibility of a placebo effect that may result from knowing the anticipated response to a drug, this pilot study seems to suggest that pharmacogenomic testing can lead to better treatment outcomes in a outpatient clinical setting.

An interesting continuation of this study has indicated that pharmacogenomic testing for patients with unremitting depressive disorder, may lead to decreased healthcare utilization[12]. The study subjects consisted of current major depressive patients receiving health care services from Union Health Services in Chicago, who had all been prescribed one of 26 common antidepressant or antipsychotic medications[12]. DNA samples were analyzed for variations for 50 alleles in six genes: *CYP2D6*, *CYP2C19*, *CYP2C9*, *CYP1A2*, *5HTR2A* and *SLC6A4*[12]. Then, retrospectively applying the GeneSight report, they determined that patients the recommendations for the medication(s) that the patient had been taking for the previous year[12]. They found that the patients whose current medication was recommended to be "used with caution and more frequent monitoring" based on their genotype had the highest number of healthcare visits, medical absence days and disability claims during the previous year[12]. From this the authors concluded that prospective application of this pharmacogenomics test to guide the selection of antidepressant

therapy may reduce the number of patients taking "red bin" drugs and, thereby, lower health care costs by decreasing the need for healthcare utilization due to adverse effects[12]. Though this study is limited by its small sample size, retrospective nature and potential author bias, the results highlight the power of a pharmacogenomics tool in clinical practice.

Conclusion

Felix Frueh explained the basic goal of pharmacogenomics as the aim "to give the right dose of the right drug for the right indication for the right patient at the right time."[14] Because depression has such a complex phenotype, however, consistent identification of population wide allelic associations that will help to individualize treatment in the way Frueh describes remains an elusive goal. Though this paper was only able to review some of the most promising polymorphic associations, research is ongoing with regard to numerous other genes including COMT, MAOA as well as several related to norepinephrine, dopamine, and the HPA axis[3,9]. As the phenotypic variation poses an enormous challenge in quantifying responses to antidepressants, functional imaging studies may prove to be a useful tool in comparing treatment outcomes[7]. Furthermore, larger sample sizes from more diverse ethnic populations will be needed before definitive conclusions can be drawn. Future research also should seek to clarify epigenetic signatures and copy number variations that may give insight into the potential response to a given drug. Finally, there is significant hesitation to implement pharmacogenomics tests as a tool for clinical treatment. Thus, more studies on the efficacy and cost-effectiveness of such methods will be important to advance the utilization of pharmacogenomics by doctors and healthcare facilities. In all, though there have been major strides in identifying genomic variations that may predict treatment response, there is still a long way to go before pharmacogenomics can help resolve the problem of treatment resistant depression and ease the global disease burden.

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