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Glossary

Single nucleotide polymorphism (SNP): A single nucleotide variation in a genetic sequence, meaning that the purine or pyrimidine base of that nucleotide has been replaced by another purine or pyrimidine base, that occurs at a significant frequency in the population.[1]

Polymorphism: The existence of many different DNA sequences at a locus, a specific location on a chromosome, within the population.[2]

Allele: One member of a pair, or of a series, of genes on a specific locus that controls the same trait.[3]

DRD2 and DRD3 genetic codes: DNA that codes for dopamine receptors D2 and D3.[4]

Heterozygous deletion genotype: The individual has one normal allele and has one allele with a deletion of one or more base pairs.

Heterozygous A1/A2 genotype: The individual is heterozygous meaning that they express two different alleles of a gene.

Homozygotes of an allele: The individual expresses two of the same allele of a gene.

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Abstract

Pharmacogenomics is a growing area of pharmacy that has the potential to improve individualization of medication choices, dosing and predictability of side effects. Clozapine and risperidone are atypical antipsychotics whose metabolism, efficacy and side effects are influenced by single nucleotide polymorphisms (SNPs) in a patient's genetic makeup. It has been shown that a polymorphism in the D_3 dopamine receptor is associated with an increased risk in developing tardive dyskinesia as an adverse event while taking risperidone. Also, there is evidence that a patient with a homogenous C genotype in the gene coding for the 5-HT_{2C} receptor has a higher risk of weight gain from taking clozapine than a patient with a heterogeneous T genotype of that same gene. There are many other SNPs that have been, or are currently being, investigated with regards to the efficacy and side effects of clozapine and risperidone. However, more studies with longer durations and larger sample sizes are needed to determine the actual clinical significance of these genetic variants. In the future, pharmacists have the opportunity to become leaders in the area of pharmacogenomics to help apply this information to optimize patient outcomes and minimize adverse events.

Introduction

Patient responses to medications, particularly antipsychotics, can be extremely variable. This variability partially can be attributed to the genetic differences between patients. The study of these genetic differences and responses to medications is known as pharmacogenomics. The goal of pharmacogenomics is to allow for patient specific medication therapy through the application of genetic information related to drug absorption, distribution, metabolism and excretion, as well as drug response. SNPs may be utilized as biomarkers to determine drug metabolism and response. A thorough understanding of the consequences of discrete changes in an individual's DNA allows for evaluation of the efficacy and potential toxicity of antipsychotic medications.

Mental health medications, or antipsychotics, are used to treat the symptoms of a variety of conditions including schizophrenia, depression, bipolar disorder, anxiety disorders, and attention deficit-hyperactivity disorder (ADHD). Some of these medications have been available since the mid -1950s, and are classified as conventional, typical or first generation (FGA) antipsychotics. In the 1990s, new antipsychotic medications were developed. These new medications are classified as "atypical" antipsychotics or second generation antipsychotics (SGA).[1]

Clozapine and Risperidone

Clozapine is an SGA used to treat the symptoms of schizophrenia in patients who do not respond to other medications or who are suicidal.[2] It is commercially available in tablet form as well as an oral disintegrating tablet (ODT) both of which are available in multiple strengths.

Clozapine may cause adverse events including weight gain[4], drowsiness, dizziness, restlessness and headache, among others. It also has anticholinergic properties. Serious adverse events include uncontrollable shaking of the extremities, seizures, fainting, confusion, severe muscle stiffness, changes in behavior, fever and flu-like symptoms.[2] Clozapine also has five black box warnings concerning the potential for agranulocytosis, seizures, myocarditis, orthostatic hypotension and increased risk of death.[3]

Risperidone, also an SGA, is indicated for the treatment of schizophrenia in adults and adolescents, as well as the treatment of acute bipolar disorder in adults, children and adolescents. Risperidone is available as a tablet, an ODT and an oral solution. Risperidone contains a black box warning for increased incidence of cerebrovascular adverse events and mortality in elderly dementia patients. Other serious adverse events include tardive dyskinesia (TD), extrapyramidal symptoms (EPS) and weight gain.[5]

Clozapine and risperidone are dibenzodiazepine antipsychotics. Clozapine blocks the serotonin ($5HT_2$), alpha-adrenergic, histamine H_1 and cholinergic receptors. It also acts as a weak antagonist to the D_1, D_2, D_3 and D_5 dopamine receptor subtypes, however it shows high binding affinity for D_4 dopamine receptors.[3] Likewise, risperidone is a strong antagonist of the serotonin 5-HT_2 receptors, the dopamine D_2 and D_3 receptors, and the alpha-1 adrenergic receptors.[6] It has been noted that CYP2D6 is primarily responsible for metabolizing risperidone.[4]

The Effects of Genetic Variation on Clozapine Treatment

Clozapine binds with the highest affinity to the D_4 dopamine receptor. It has been hypothesized that the D_4 dopamine receptor genotype has a role in determining the effect of clozapine. The D_4 dopamine receptor (DRD_4) gene codes for the D_4 dopamine receptor. This gene is being studied because it is hypothesized that the longer the length of the repeat of the DRD_4 allele, the lower the binding affinity will be for clozapine. Several studies have been performed regarding this gene, and all studies yielded conflicting results. With more information on this particular gene and its coding, health care professionals will be able to determine if clozapine is an appropriate treatment for a patient based on how many repeats of a patient's particular allele are present.[4]

Clozapine is metabolized by CYP1A2, CYP2D6 and CYP3A4 enzymes. Various drugs can inhibit the function of these enzymes causing an increase in the plasma concentration of clozapine. If inhibitors of the aforementioned enzymes are given along with clozapine, a reduction in the clozapine dose would be necessary in order to avoid adverse events due to increased plasma clozapine levels. Conversely, there are several drugs which act as inducers of the CYP1A2, CYP2D6 and CYP3A4 enzymes. If a patient is using any of these inducers, the dose of clozapine may need to be increased in order to achieve therapeutic concentrations. Genes code for the expression of these CYP enzymes, and individuals can express different amounts of CYP enzymes depending on each individual's genetic code. For instance, an individual can either be heterozygous or homozygous for a specific CYP enzyme. Therefore, if the homozygous individual is taking a CYP3A4 inducer along with clozapine, that person is more likely to experience a higher clearance of clozapine than the heterozygous patient. The homozygous person would require an even greater dose of clozapine in order for the drug to have any therapeutic benefits. Therefore, by analyzing an individual's genetic code, health care professionals can adjust the dose of clozapine to achieve therapeutic plasma levels and avoid toxicity.[4,6,7]

Clozapine is said to antagonize 5-HT_{2A}, 5-HT_{2C}, and 5-HT_6 receptors. Therefore, genes that encode these receptors may play a significant role in predicting clozapine response. An amino acid change has been identified as a result of the SNP rs6313 (T102C). This variant 5-HT_{2A} receptor protein shows an association with poor response to clozapine; this association was confirmed through meta-analysis of several studies.[4,8]

Clozapine can cause significant weight gain as an adverse event. Several studies analyzing the relationship between the SNP rs3813929 (C-759T) of the 5-HT_{2C} receptor and weight gain have been conducted. A review of 10 studies showed that the C allele, specifically a homogenous C genotype, was associated with more weight gain than the T allele, specifically a heterogeneous T genotype. A meta-analysis of eight studies showed that the T allele is protective against antipsychotic therapy weight gain, and the C allele was found to be related to a two-fold increased risk for weight gain. The C allele is more common than the T allele, suggesting that genetic testing of a patient can indicate the potential for significant weight gain as an adverse event of clozapine therapy.[4]

The Effects of Genetic Variation on Risperidone Treatment

The most commonly investigated SNPs are found in the D_2 dopamine receptors and D_3 dopamine receptor genetic codes. The SNP rs1799732 (-141C Ins/Del) of the D_2 dopamine receptor, which results in an altered amino acid sequence of the receptor protein, has had significant associations with negative response symptoms and adverse events such as TD. A 2002 study, which also investigated the SNP rs1800497 Taq1A, determined a significant improvement (40 percent) in the response to risperidone in patients with both a heterozygous deletion genotype and a heterozygous A1/A2 genotype, however the results of this study were limited due to a small sample population.[9] A similar study, with a larger sample population, conducted in 2011 detected an improvement in the Brief Psychiatric Rating Scale (BPRS) and positive symptoms in patients that were receiving treatment and who were heterozygous deletion carriers.[10] Positive symptoms include delusions, disorganized behavior and hallucinations, or overall "an excess or distortion of normal function."[11] Evaluation of the -141 Ins/Del SNP has not been able to confirm association with a higher risk of developing TD. Although the relationship is still not clearly defined, there does appear to be an association between the SNP present at the -141 Ins/Del for the D_2 dopamine receptor and responsiveness to treatment with risperidone.

Risperidone is also an antagonist of the D_3 dopamine receptor. The SNP rs6280 causes a substitution in the amino acid sequence of serine (T allele) for glycine (C allele) in the D_3 receptor. A 2005 study found that heterozygous individuals for the C allele improved social functioning through lower negative symptoms scores on the Positive and Negative Syndrome Scale (PANSS) and a decrease in the Nurses' Observation Scale for Inpatients Evaluation (NOSIE) while taking risperidone.[12] Negative symptoms often occur before positive symptoms and are characterized by a decline in normal function, such as social withdrawal and a loss of interest or emotion.[11] Homozygous individuals for the T allele displayed a less receptive response in the same tests. A second study investigating the heterozygous genotype (C/T) yielded similar results. Patients were classified as responders or non-responders to risperidone, and the C allele was more frequently present in responders.[13] However, these results did not reach statistical significance. This study also evaluated the effect of the SNP rs6313 (T102C), which causes an amino acid change to a gene that codes the $5HT_{2A}$ serotonin recep-

tors. Patients classified as responders expressed a significantly higher proportion of C alleles than nonresponders.[13] It can therefore be inferred that risperidone treatment may not be an efficacious choice for patients of the T/T genotype.

Polymorphisms of D_3 dopamine receptors have also been studied for their association with adverse effects in patients receiving risperidone treatment. The $Ser^9 \rightarrow Gly$ amino acid change was shown to have an association with the risk of developing TD. Patients, especially females, who had at least one C allele were significantly more likely to develop limb TD.[14] A 2009 study found an association between the SNP rs167771, which expresses either allele A or allele G on the D_3 dopamine receptor (DRD_3) gene and EPS. Patients who possessed the G allele had a higher risk of an occurrence of EPS.[7] This study has not been repeated but was conducted on a large sample size of patients making the clinical association more relevant.

Pharmacy Implications

Pharmacists can take a lead role in applying pharmacogenomics by judicious use of appropriate genotyping. With genetic (SNP) information, pharmacists will be able to determine if a patient is likely to tolerate an antipsychotic, if a patient will have significant side effects and what range of dose a patient will require for therapeutic efficacy. Pharmacists can utilize the new tool that is pharmacogenetic testing to aid in selecting the appropriate medication for a given patient to maximize therapeutic outcomes while minimizing adverse events.

Conclusion

The current research demonstrates significant associations between SNPs and antipsychotic drug responses/effects, but much of the data is preliminary. All of these SNPs need to be reevaluated in studies with larger sample sizes over longer periods of time. Additionally, more variables need to be included for study in order to determine the true clinical significance of these SNPs. Single nucleotide polymorphisms of the D_2 receptors, D_3 receptors, D_4 receptors, and serotonin receptors have been associated with the efficacy of clozapine and risperidone. Cytochrome P450 SNPs have been investigated for association with TD as well as a way to predict proper dosing for patients. Both clozapine and risperidone, along with other antipsychotic medications, contain FDA black box warnings. These demonstrate the significant risk of adverse events associated with antipsychotic medication therapy. Through additional research of SNPs and their relationship to antipsychotic medications, genetic testing of patients could help determine the efficacy and the likelihood of adverse events of a potential medication therapy before it is prescribed for use.

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Table 1. Significant SNPs and Patient Response to Therapy

Drug	SNP	Genomic Modification	Effect of Modification on Patient Response to Therapy	Strength of Evidence
Clozapine	rs6313	Amino acid change that causes a variation in the $5HT_{2A}$	Poor clozapine response	Confirmed through meta-analysis
Clozapine	rs3813929	Amino acid change that causes a variation in the $5HT_{2C}$	CC genotype was shown to have a two-fold increase risk for weight gain	Confirmed through meta-analysis
Risperidone	rs1799732	Amino acid change in D_2 dopamine receptor	Increased negative symptoms for the deletion genotype	Association through multiple studies. More research needed.
Risperidone	rs6313	Amino acid change that causes a variation in the $5HT_{2A}$	TT genotype less responsive to risperidone treatment	Statistically significant in two studies

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