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Genetic Predispositions to Opioid Addiction, Legislative Action and Implications to Pharmacy Practice

Adam N. Trimble
Ohio Northern University

David N. Jones
Ohio Northern University

Courtney L. Salvino
Ohio Northern University

Michael M. Milks
Ohio Northern University

David Kisor
Ohio Northern University

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There are hundreds of different studies that have tried to link genetics and predispositions to addiction.
Abstract

Prescription pain-relievers can be powerfully effective agents in the treatment of moderate to severe pain; however, these drugs are also strongly associated with drug abuse and addiction. In the brain, opioid analgesics bind to various receptors in the mesocorticolimbic dopaminergic pathways, which play a role in reward. Several specific single nucleotide polymorphisms (SNPs) have been identified as potential genetic factors that increase an individual's risk for addiction; however, confounding studies and lack of large trials prohibit definitive conclusions from being drawn. As a result of genetic testing, federal and state laws have been enacted to protect individuals from discriminations. As more definitive evidence becomes apparent, a large impact on pharmacy practice is expected.

Introduction

Prescription pain-relievers are essential pharmacologic tools in the treatment of moderate to severe pain; however, due to their euphoric potential, these drugs are strongly associated with misuse, which can lead to abusive behaviors. Over time, there has been a dramatic increase in the use and abuse of opioid analgesics. As physicians have resorted to treating chronic pain with more powerful analgesics, an exponential growth in the domestic sale of opioids has been observed. Currently, many researchers are studying variations in DNA that increase a person's risk for developing opioid addiction. Theoretically, by understanding those mutations in the genome responsible for an increased risk for addiction, physicians will be able to make more appropriate decisions when prescribing a drug and dosage regimen to treat chronic pain while minimizing the risk of addiction. When considering pharmacogenomic-based dosing regimens, it is important to consider environmental and psychosocial risk factors as well. In response to genetic testing to identify disease-related causation and predisposition, a growing number of federal and state laws have been enacted to protect patients from insurance and employment discrimination that might exclude or otherwise penalize patients on the basis of their specific genetic profiles.

Pathology of Opioid Dependence

Opioids, such as heroin, oxycodone and morphine-like substances, exert their action by binding to a number of receptors throughout the body. The most common receptors include the μ, δ, and κ opioid receptors. Though they are located throughout the central nervous system (CNS), there is a high concentration of these receptors in the nucleus accumbens (NAc), ventral tegmental area (VTA), locus ceruleus (LC), and prefrontal cortex (PFC). These individual brain components are incorporated in the mesocorticolimbic dopaminergic pathway, which plays an important role in reward, laughter, pleasure, fear and addiction.

According to Goodman & Gilman's, the mesocorticolimbic dopaminergic pathway originates in the VTA and projects into the NAc and forebrain. Dopamine released from the VTA binds to post-synaptic dopamine (D2) receptors in the NAc on GABAergic neurons, producing an inhibitory response. The stimuli that cause the release of dopamine to the NAc, thereby allowing the catecholamine neurotransmitter to occupy the D2-like receptors, presumably elicits a positive reward and causes the user to experience a euphoric "high." This high is experienced through stimulation by natural endogenous substances or exogenous substances, like heroin or morphine. One way to activate this reward center is via the opioid receptors. It is hypothesized that the receptors increase the amount of dopamine stimulating the receptors in the NAc and/or directly stimulating the NAc, resulting in a "high" (Figure 1).

Drug addiction is a complex disease that is difficult to treat due to the multifaceted interaction of environmental, social, psychological and genetic factors. Currently, pharmacogenomics is being utilized to examine patient populations’ DNA and SNPs, which
have been associated with an increased risk for an individual to develop addiction. More specifically, research efforts are being concentrated into identifying SNPs in genes that code for the µ-opioid receptor and its associated signal transduction mechanisms.

SNPs in Genetic Code

Researchers are exploring potential genetic predispositions to drug addiction. A genetic predisposition to addiction does not mean an individual will inescapably become addicted to a medication. Genetic variations in DNA may, however, predispose the individual to addiction, increasing their relative risk. Relative risk is defined as the measure of risk of an event in one group compared to the same event in another group. For example, people who are not genetically predisposed to addiction can still become addicted. Likewise, people who are genetically predisposed will not necessarily become addicted. Current research has discovered SNPs associated with the mesocorticolimbic pathway and evidence suggests that some of these SNPs may be linked to opioid addiction.

A118G

One of the more widely studied SNPs thought to be involved in opioid addiction is known as rs1799971. This SNP is also referred to as A118G located on exon 1 of the gene OPRM1 (Opioid Receptor µ 1), which can be found on chromosome 6. OPRM1 codes for the µ opioid receptor, which is responsible for binding endogenous and exogenous ligands. Binding of these agonist ligands results in the activation of the mesocorticolimbic pathway to produce sensations of pleasure in the brain. This SNP results in a non-synonymous substitution of asparagine for aspartic acid on the µ-opioid receptor, resulting in altered function (Figure 2). With this particular SNP individuals will be either homozygous AA, homozygous GG or heterozygous AG. In most populations the AA is the wild type, or the most frequently seen genotype. Studies investigating this SNP have yielded variable results, making it difficult to determine the precise impact on drug addiction.

In an early study, the A118G SNP changed the sensitivity to the endogenous agonist, β-endorphin. The study included 113 former heroin addicts who were undergoing treatment with methadone and 39 control subjects who had no history of drug or alcohol abuse. This study compared the frequencies of the A118G polymorphism between the two groups and found no significant increase in the occurrence of the A118G SNP within the heroin addiction group. Although there was no relationship between the frequency of A118G occurrence and addiction, the researchers did find the SNP was associated with a threefold increase in binding affinity to β-endorphin. The SNP resulted in physiological changes in the brain, leading researchers to think that SNPs along with other factors could potentially increase a patient’s risk of addiction.

Another study looked at the A118G polymorphism and its association with opioid addiction, specifically to heroin. The study examined postmortem individuals. Sixty-five patients were divided into two groups; 26 non-heroin users in a control group and 39 heroin addicts. Researchers found a greater frequency of the heterozygous AG genotype in the heroin-addicted individuals (25.6 percent) compared to the control group (3.8 percent). This data provided a $X^2=6.153$ and $p=0.013$, which showed a significant difference between the two groups in the prevalence of the AG genotype. The same study was then preformed with 53 new subjects, splitting subjects into a control group (n=14) and a heroin addiction group (n=39). The second study also revealed a higher frequency of AG genotype in the heroin addiction group which provided a $X^2=4.741$ and $p=0.03$. This study also analyzed the postmortem brains of these subjects. In individuals with the AG genotype, researchers found an altered expression of the µ-opioid receptor and molecular differences that could potentially provide a mechanism for opioid addiction. This suggests that A118G could play a role in addiction. Due to the confounding results, a clear conclusion cannot be drawn.

In 2012, researchers uncovered a link between the A118G polymorphism and heroin addiction. The first study compared 130 heroin addicts to 200 non-addicted subjects in an Indian population. The frequencies of the AA, GG and AG genotypes in the addicts were 54 percent, 41 percent and 5 percent, and in the control group, the frequencies were 68.5 percent, 27.5 percent and 4 percent. The second study showed a greater frequency of the AG genotype in the heroin addiction group which provided a $X^2=4.741$ and $p=0.03$. This study also analyzed the postmortem brains of these subjects. In individuals with the AG genotype, researchers found an altered expression of the µ-opioid receptor and molecular differences that could potentially provide a mechanism for opioid addiction. This suggests that A118G could play a role in addiction. Due to the confounding results, a clear conclusion cannot be drawn.
and 4 percent. These genotype frequencies demonstrated a significant difference between the two groups as demonstrated by a $X^2=7.268$ and $p=0.0264$. Overall, it was shown the G allele was significantly more prevalent in the heroin addiction group as evidenced by an odds ratio (OR)=1.609 (1.102-2.348). As with the previous study, the AG genotype had the highest frequency in the addiction group and was associated with the greatest risk for addiction as demonstrated through the OR=1.886 (1.173-3.032) compared to the wild type AA genotype.7

Based on the three studies previously mentioned, it appears that the A118G may be implicated in opioid addiction, specifically if the individual is heterozygous AG. Drakenberg et al. and Deepak et al. also found an increased association between the A118G SNP and opioid addiction.6,7 Furthermore, there is evidence of physiologic changes that are associated with these SNPs.6,7 The A118G SNP could potentially be involved in opioid addiction, but more research is required. New SNPs are being discovered each day, and as a result some of the newer discoveries may provide a greater link to addiction than A118G.

**CREBBP**

One recent study provides evidence that a SNP in the cAMP response element binding protein (CREB) may be implicated in opioid addiction. Researchers identified SNP rs3025684, coding for CREB binding protein (CREBBP) intron 21 on chromosome 16. The study compared 131 heroin addicts with 150 individuals in India who had no history of alcohol or drug abuse to act as a control group.8 With respect to this SNP, individuals possess either the homozygous GG, homozygous AA, or the heterozygous AG. The most common allele found was the G allele, with the A allele being less common. The dominant genotype identified within both study groups was homozygous GG, which is generally the most common among most populations.9 The frequencies were given for the GG, AA and AG genotypes for the opioid dependent group (74 percent, 3 percent, and 23 percent) and the control group (93.3 percent, 1.3 percent and 5.3 percent), respectively. The study showed significant differences ($X^2=20.28$, $p<0.0001$) in the subjects’ genotypes between the control and the opioid addicts. There was an association between the A allele and opioid addiction. When comparing the opioid addicted group to the control group for the presence of the A allele, there was an OR= 4.11 (2.09-8.05). The AG genotype appeared to have the greatest distribution in the opioid dependent groups compared to the control group, giving an odds ratio of 5.32 (2.32-12.10). This study concluded that this SNP in CREB might be implicated in the development of opioid addiction. The effect on activity of the intron region in DNA is not completely understood. The researchers did conclude, however, that individuals with the rs3025684 SNP might potentially be at a higher risk for developing addiction.8

There are hundreds of different studies that have tried to link genetics and predispositions to addiction. Researchers have not yet been able to definitively link the two at this point due to a lack of conclusive evidence available from these studies. In addition, there is even less evidence available to mechanistically explain how these SNPs could predispose an individual to addiction. Individual SNPs may predispose an individual to addiction, but like many other diseases there are many other factors that play a role. One aspect that weakened many of the studies reviewed was the design – while evidence is promising that certain SNPs may play a role in addiction, a lack of large studies that incorporate greater sample sizes and multiple ethnic groups limited the implications of the study results.

If a SNP is identified in a gene, which is linked to an increased risk of developing addiction, individuals may be concerned about the implications. Current studies suggest certain SNPs may cause a higher relative risk, but because most study designs have multiple limitations, definitive conclusions cannot be drawn. While most studies concluded that multiple SNPs might contribute to the overall genetic relative risk to developing addiction, this issue has yet to be studied in clinical trials. Similarly, most studies did not incorporate environmental and psychosocial factors into their study design, which are additional, major contributors to drug addiction. For individuals still concerned about negative implications, federal and state laws are already in place to protect against discrimination in employment and insurance ratings.

**Federal and State Law**

The Genetic Information Nondiscrimination Act (GINA) of 2008 was signed into Law by President Bush on May 21, 2008.10 The law took effect on November 21, 2009.11 GINA has two major components; Title 1 of the law deals with issues pertaining to health insurance, and the second title addresses employment issues.11 GINA protects the genetic information of not only individuals, but extends protection to family members of the individual, and covers any information pertaining to the manifestation of disease for
both the individual and family. This includes information obtained during participation in clinical research. Genetic information protection includes any analysis of DNA, RNA, chromosomes, proteins or metabolites that are used to detect genotypes, mutations, SNPs or chromosomal changes. Testing for proteins or metabolites that do not detect genotypes, mutations or chromosomal changes are not protected under this act.\textsuperscript{11}

Title 2 states that employers may not use genetic information to make decisions about hiring, firing, compensation, terms, conditions or privileges of employment. Moreover, genetic information may not be used to limit, segregate or classify the employee in any way that would deprive the employee of opportunities that he/she may have had otherwise. Title 2 also puts limitations on how an employer may obtain information. Employers cannot request, require or purchase genetic information, with several exceptions. Examples of these exceptions include: written consent of the employee, government-required genetic monitoring or a job with the potential for DNA contamination (forensic lab technician), etc. The regulations established by Title 2 apply to training programs as well as to labor organizations. Genetic information held by any of these organizations is to be handled much like protected personal medical information. It is legal for an employer to require a test to see if an employee has drugs in their body, but it is illegal to require testing of employees to determine their predispositions to addiction. It is not to be released, like medical information, with several exceptions, including court order or written approval of the employee. GINA also outlines the formation of a committee to review the law and make recommendations for updates and changes after six years. This committee will consist of eight members, appointed by various government officials.

Title 1 covers health insurance rules and regulations. Much like Title 2, GINA prevents a group health plan from requiring an individual or family member to undergo genetic testing. The plan can, however, request a patient go under genetic testing for research as long as it is clearly stated that compliance is strictly voluntary. The insurer may not request, require or purchase genetic information for underwriting purposes or prior to an individual’s enrollment in a plan. Information that is obtained “by accident” is, of course, not in violation of GINA. Genetic information cannot be treated as typical, routine health information such as height, weight, age or medical conditions. Genetic information that is legally obtained cannot be used to deny an individual coverage, impose exclusions for “pre-existing conditions” or require an individual to pay a higher premium. The patient must display the phenotype of the disease to impose such penalties. “GINA also amends Title XVIII of the Social Security Act to prohibit the use of genetic information to form discriminatory policies for medical supplies.” Definitions of genetic information, genetic tests and services are the same as those outlined in Title 2. Family is defined as a dependent or relative out to fourth degree.\textsuperscript{12}

The Secretary of Labor is authorized by GINA to impose a penalty to health insurers in the group market that violate the law, or to issue a waiver if it is determined that the failure was reasonable and not due to negligence. The bill further extends these rules and regulations to protect individuals buying private health insurance. The Secretary of Health and Human Services retains the right to discipline any health insurer in the individual market.\textsuperscript{12}

According to the National Conference of State Legislatures, each state has its own laws concerning genetic testing in addition to GINA. Most states give their own definition of genetic testing, genetic information, and have their own disclosure policies. There is a high degree of variability among state legislation regarding protection of genetic information; for example, some states extend GINA protection to disability insurance, while others do not regulate genetic information as it pertains to life, long-term care and disability insurances. Research in pharmacogenomics is advancing quickly; as our understanding of genetics continues to progress, the laws enacted to protect genetic information must follow.

**Implications to Pharmacy Practice**

Hypothetically, what if a discovery were made that indicated a certain genotype of a given SNP was clearly related to an increased likelihood of becoming addicted? Would that change how physicians prescribe narcotics to patients? What would happen if a physician prescribed a narcotic to a patient who was predisposed to addiction, and both the pharmacist and physician had the genetic information on hand, but failed to recognize the predisposition? What if that patient becomes addicted and the doctor or the pharmacist is held liable? These points address many concerns of how misuse of genetic information could occur.

Ultimately, what does the search for a genetic link or predisposition to addiction mean for the practice of pharmacy? As more concrete relationships are established, opioid prescribing patterns may change. With regards to narcotics, pharmacists may have the ability to check gene-drug interactions if an associated predisposition to addiction can be identified. The pharmacist could be responsible for identifying high-risk individuals and consulting with the physician about changing pain management regimens in order
to avoid the potential of addiction in those patients considered high risk. The obvious benefit is our ability to prevent patients from receiving a medication if they have been identified as being at an increased risk of becoming addicted, but this may result in patients being unable to receive adequate analgesia or perhaps require some other alteration in treatment protocols.

As is the case with any genetic information, misuse and abuse are major public concerns. Could information about addiction be used to prevent you from obtaining a job in the medical profession? Some would argue it makes sense to keep those who are predisposed to drug abuse away from drugs. GINA clearly states that employers cannot use this information, but what about schools? Will medical professions screen applicants and reject entry into professional programs based upon genetic predispositions for addiction?

The law involving pharmacogenomics relative to patient care is very limited. The laws that are in place primarily protect individuals from discrimination from insurance and employment opportunities. The primary law concerning the practice of pharmacogenomics in the pharmacy setting is the Omnibus Reconciliation Act of 1990 (OBRA 90). According to this law, pharmacists must maintain proper patient records, perform prospective drug use reviews (Pro-DUR) and counsel patients. However, OBRA 90 does not specifically address patients' genetic information. Much like Social Security Act and the Health Insurance and Portability and Accountability Act (HIPPA) were amended in GINA, the genetic information component of health care needs to be addressed and amended in OBRA 90.

**Conclusion**

As technology and understanding of the human genome continue to advance, the role of genetics will become more evident. The identification of SNPs, predisposing a person to addiction, may be revealed. It is important to understand the basic science of drug addiction, and how genetic variants may drastically impact pharmacokinetic and pharmacodynamic processes, leading to altered responses. This is the fundamental idea in attempting to identify any genetic predispositions to drug addiction. Laws have been enacted to protect the individuals from the misuse of their genetic information. Advances in the field of pharmacogenomics will require adaption by both the judicial system and medical professionals.

**References**