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Clinical Relevance of μ -Opioid Receptor A118G Polymorphism in Demographically Variant Populations

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Abstract

Use of opioids is essential in providing a broad and effective analgesic effect. Opioid dosing has to be monitored and controlled in order to manage pain and the corresponding side effects due to opioid treatment. A very common single nucleotide polymorphism (SNP) associated with the μ opioid receptor is A118G. A118G, located on exon 1 of the μ -opioid receptor gene (OPRM1), may alter how patients respond to opioid treatment. This polymorphism results in an exchange of adenine for guanine, which in turn leads to substitution of asparagine for the aspartic acid. In order to understand how individuals with the G allele differ from the wild type A118A, it is important to review the response to opioid treatment, as well as to understand the reactions of the opioidergic system to this SNP. Studies show that individuals with the G allele tend to react differently to opioid treatment compared to wild type A118A. Their μ -opioid receptors have decreased sensitivity to opioids, which in turn leads to decreased analgesic effect. People with the G allele may be more predisposed to heroin addiction, drug overdosing, as well as development of breast cancer.

Keywords: Opioid; Receptor; Polymorphism; A118G; Personalized Medicine; Drug Efficacy

Abbreviations

SNP: Single Nucleotide Polymorphism; VNTR: Variable Number Tandem Repeats; ORL1: Opioid Receptor Like-1; GPCR: G-Protein Coupled Receptor; MA: Migraine with Aura; PCEA: Patient Controlled Epidural Analgesia; MIRD: Morphine-Induced Respiratory Depression; PONV: Postoperative Nausea and Vomiting; ESCC: Esophageal Squamous Cell Carcinoma; MOR: μ -Opioid Receptor; LLC: Lewis Lung Carcinoma; NSCLC: Non-Small Cell Lung Cancer

Introduction

Variability in drug efficacy is a significant challenge in clinical medicine as well as in pharmaceutical development. Genetic polymorphisms are fundamental to differential drug efficacy [1,2]. The convergence of the fields of genomics and pharmacology in recent years has contributed greatly to our knowledge of how genetic variability may impact therapeutic response and has given rise to the field of pharmacogenomics [3].

The molecular basis for the differential response to therapeutic intervention is found in the different forms of genetic variants. There are several types of genetic variants such as single nucleotide polymorphisms (SNPs) that are point mutations in a DNA sequence, variable number of tandem repeats (VNTR) that are short repeat units and include the micro- and mini-satellites, insertions, deletions, and chromosomal aberrations [4].

Pain therapy pharmacogenomics is segmented broadly into two components. In the first component, genetic information used to examine the impact of genetic variability on factors modulating pain and its intensity is referred to as functional pain genomics [5]. Functional pain genomics focuses on how a group of genes work in concert to regulate response to pain [4,5]. The second component of pain pharmacogenomics is focused on characterization of the genetic variations that contribute to an individual's response to drugs used in pain management. It is pharmacogenomics of pain management that represents the most common segment of pain genomics [5].

Recently, an increased effort on pain management has resulted in a multifold increase in the sale of prescription opioids in the United States [6-9]. When it comes to treating severe pain, opioids have been very effective in providing an analgesic effect [10]. Opioids, derived either from naturally occurring opiates or synthesized in the lab, can achieve analgesia by activating opioid receptors [11]. Opioid receptors are part of the central nervous system and they affect emotion and the reward circuits in the brain. There are four identified opioid receptors: mu (μ), delta (δ), kappa (κ) and opioid receptor like-1 (ORL1) [11,12]. These receptors are G-protein Coupled Receptors (GPCR's) and work by activating inhibitory G-proteins [11]. Opioids are mainly prescribed to reduce pain intensity; however, opioids often produce side effects such as: nausea, vomiting, constipation, sedation, urinary retention, meiosis, and respiratory depression [11,13,14]. Appropriate dosing is necessary to provide a desirable therapeutic effect. Under-dosing can cause poor pain control, while over-dosing can exacerbate the toxicity and increase the severity of side effects [11]. Opioid receptors are also responsible for causing euphoria through activation of the central dopamine reward pathway [15-17]. When opioids are used chronically, or misused for recreational purposes, patients may develop tolerance which will then require higher doses, and may eventually lead to physical and emotional dependence to opiates [18].

Out of the four identified opioid receptors, μ -opioid receptor is the main target in therapeutic treatment, because endogenous opioid peptides exhibit their analgesic effect primarily on μ -opioid receptors [19]. Each patient responds differently to the opioid treatment and may require dose adjustments. This can be due to various factors, such as previous exposure to the opioid treatment, pain tolerability, age, emotional state and environmental factors. However, it has been widely investigated that genetic factors may also play a key role [15]. Single nucleotide polymorphisms (SNPs) are genetic variations that occur as frequently as every 1200 base pairs in the human genome. SNPs differ from one another through the location of the nucleotide alteration [15,20]. A very common SNP found in the μ -opioid receptor gene (OPRM1) is located at position 118 of exon 1 [3,21,22]. This polymorphism exchanges an adenine to a guanine which in turn results in an asparagine substitution for the aspartic acid [15,23,24]. The A118A genotype responds differently to opioid treatment compared to the A118G and the G118G variant types [25]. Presence of the G allele causes a different response to the opioid therapy that may also include altered side effects. It may also affect the response to analgesia, and cause an increased propensity for substance abuse [26-28] and promote cancer development [21,29]. To maximize the efficacy, and minimize side effects, the patient population may be screened for the presence of the G allele through genetic testing.

A118G and Pain

The endogenous opioidergic system is involved in multiple functions within the body. These functions are associated with a variety of responses such as analgesia, pain threshold, etc [5,30]. Several studies have validated the variability in patient's sensitivity to pain and or response to the analgesic effects. For example, most patients respond well to the analgesia associated with morphine, however, some patients may experience inadequate analgesia despite increasing doses of morphine [31-33].

Migraine is a chronic neurovascular disorder, which involves cranial blood vessels, the trigeminal innervations of the vessels and the reflex connection of the trigeminal system [34,35]. With migraine disorder being so complex, Menon., *et al.* 2012, reported the possible link between migraine with aura and G carrier females [5,35]. Further studies, however, are required to fully understand the relationship between the G allele and migraine head pain. Higher pain score in G allele population is not only limited to migraine but is also related to other physiological outcomes. Studies have demonstrated that A118G genotype had an association with 24-h postoperative analgesic requirements, although there was no correlation between A118G and NRS pain scores [36,37]. Additionally, the patients demonstrate variable sensitivity to the amount of opioid analgesics, used to manage postoperative pain, even following a similar surgery [38].

Interestingly, the findings on influence of A118G genotype and opioid analgesia on labor pain do not corroborate with the finding on the pain experienced in other clinical settings [39,40]. Furthermore, it has been demonstrated that allelic frequency of G118 varies according to ethnicity. For example, Asian populations such as Chinese and Indian show evidence of increased frequency of G118 [40]. Hence, ethnic composition, sex differences, and the hormonal changes associated with labor may account for the inconsistency of the findings.

A118G and Respiratory Depression

Respiratory depression is most frequently observed as a side effect of morphine treatments. If left unresolved, respiratory depression can be fatal because of cerebral hypoxia [13,18]. Due to respiratory complications, patients may not receive necessary opioid treatment and suffer from pain. Morphine is widely used for analgesia in perioperative cases of all age groups [41-43]. A prospective, genotype-blinded, clinical observational cohort study was performed between 2008 and 2013 with adolescents 10 - 18 years old undergoing spine fusions. The participants were Caucasian, African American, or of another race. Researchers wanted to determine if the OPRM1 variant A118G elicits an effect on the susceptibility to the morphine-induced respiratory depression (MIRD). Results from this study showed that most of the participants who experienced MIRD were homozygous for the A allele. There is a possible correlation between pain intensity and presence of G allele. Hence, adolescents who were G allele positive had less respiratory depression and less analgesic affect due to decreased sensitivity to morphine [41-43]. The overall frequency of the A118G allele is around 10.5%, however, this frequency is significantly decreased in African-Americans and is increased in Caucasians and Hispanics. Although not statistically significant, the study found that Caucasians have an increased risk of MIRD compared to African-Americans. However, African-Americans had a higher postoperative pain score compared to Caucasians and other races [43]. These differences are very important to consider when treating patients with acute postoperative pain.

A118G and PONV

Postoperative nausea and vomiting (PONV) are discomforting side effects that can lead to additional distress in patients as well as contribute to additional healthcare costs [44-46]. Treatment with opioid agents such as fentanyl can intensify PONV in patients undergoing general anesthesia. Fentanyl is a high efficacy μ -opioid receptor agonist which is used in postoperative analgesia. A study, to test if a genetic variation in the OPRM1 A118G allele was associated with PONV induced by fentanyl in Chinese women ages 20 - 50 years old who underwent gynecological surgery was performed at the Department of Anesthesiology, first Affiliated Hospital, Zhengzhou University. This cohort underwent abdominal hysterectomies and myomectomies performed under general anesthesia. It was observed that the OPRM1 A118G genotype had no clinical or statistical significance on fentanyl induced PONV in Chinese women in postoperative analgesia treatment [47]. This may be because this specific polymorphism is not the only factor that alters vomiting in the presence of fentanyl. For example, receptors such as serotonin type 3 receptors and dopamine type 2 receptors also affect PONV. Thus, in cases of PONV, the activity of other receptors may override or subdue the effects associated with the A118G genotype.

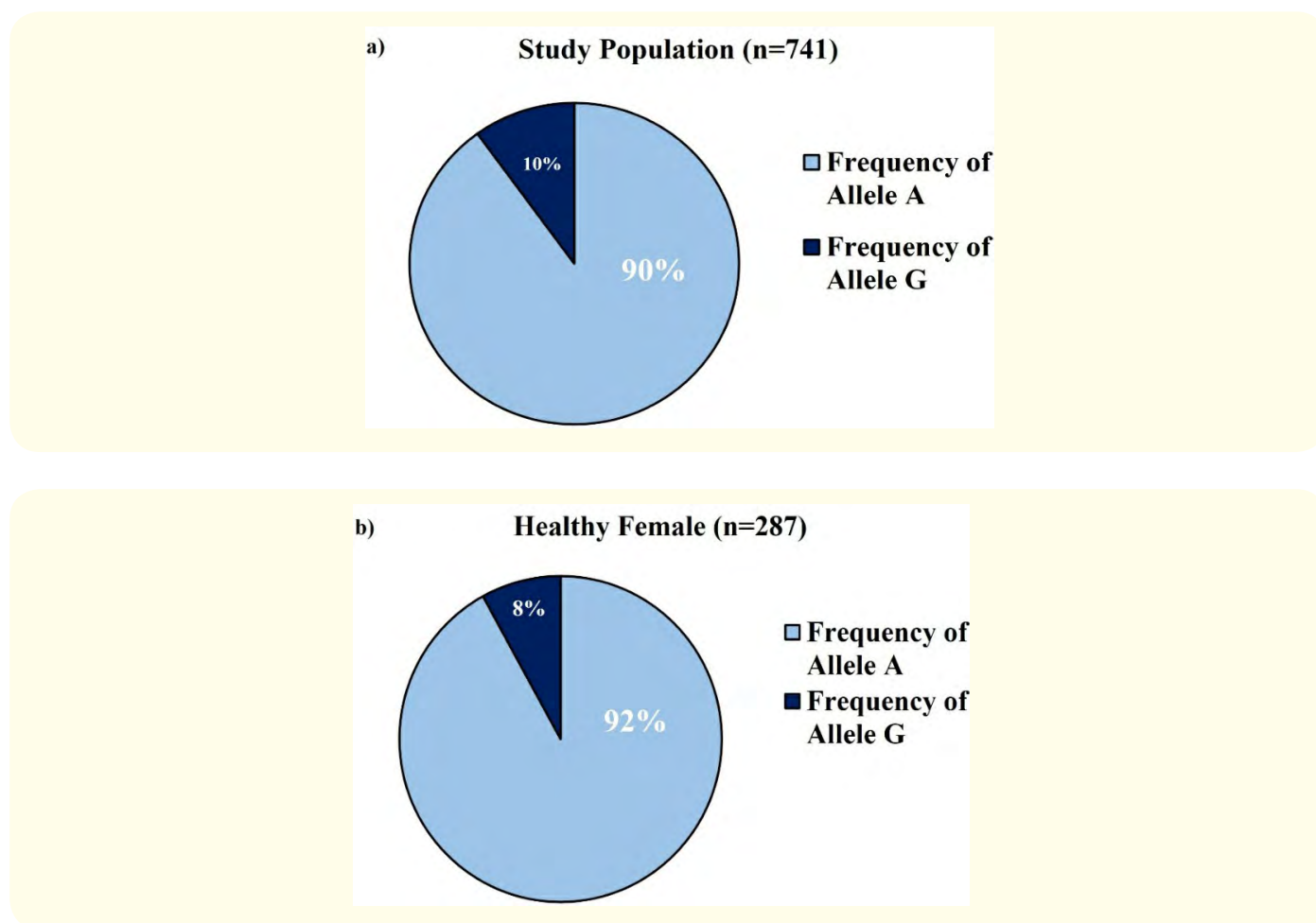
A118G: Heroin Addiction and Drug Overdose

Heroin dependence is a very serious and concerning issue. In addition to being addictive, heroin is a significant problem because most of the time drug is being administered intravenously which can easily lead to an overdose as well as spread of communicable diseases [14]. The A118G SNP has been characterized for its linkage to heroin addiction and investigated in relation to drug and alcohol addiction [48]. Heroin functions by binding to the μ -opioid receptor creating a euphoric effect. A postmortem investigational study performed on two investigational groups; control and heroin addicts. Subjects' brains were examined and compared for evidence of neuronal disturbances and the OPRM1 A118G genotype. All the subjects were of Caucasian origin and the majority of them were of Swedish nationality. Results showed that the heroin group had a higher A118G genotype frequency compared to the control. This study also demonstrated that subjects with a G allele had reduced proenkephalin and prodynorphin mRNA expression. Prodynorphin and proenkephalin systems tend to be downregulated in individuals with a history of heroin use. These individuals also show evidence of decreased opioid neuropeptide transcription and increased dynorphin and enkaphalin peptide concentrations, which can be attributed to Heroin use [14]. Thus, changes in neuropeptide systems may increase the risk of opiate abuse in 118G individuals.

Medication overdose is a life-threatening event that can lead to serious health complications that are potentially fatal. A prospective cohort pilot study was performed on patients admitted to an emergency department (ED) with an acute drug overdose [49]. The rationale for the study was to determine if a correlation exists between G allele genotype and the severity of drug overdose. The investigation was done over a 12-month period and included individuals 18 years and older. Based on medical records of the participants, overdose was mostly associated with opioids from 5 drug classes; opioids, sympathomimetics, benzodiazepines, antipsychotics, and antidepressants. It was also shown that G allele carriers have a 2.5-fold increased propensity for cardiac or respiratory arrest due to drug overdose [32,50-52]. This suggests that the presence of the G allele is potentially correlated with drug overdose in patients

A118G and Breast Cancer Development

In recent years, OPRM1 A118G has been studied not only in association with alcohol/drug dependence and side effects but also in association with increased risk of cancer development. Breast cancer accounts for about 25% of all cancers in women [52-54]. A study with a population from Poland, comprised of healthy controls and histopathologically confirmed breast cancer patients, was performed to explore a possible A118G genotypic relationship with breast cancer. The study included both males and females. Results showed that there was a significant association between G allele and increased breast cancer incidence (Figure 1). A possible explanation is that the endogenous opioid system is involved in the body's homeostasis, and if downregulated it may cause metabolic disturbances [4,38,52,55]. This warrants a more extensive study to investigate the correlation between the G allele and its potential predisposition to cancer progression.



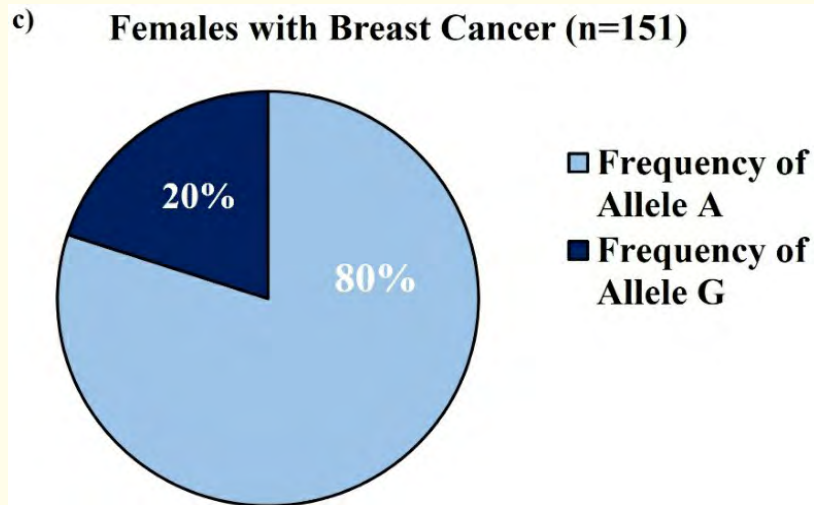


Figure 1: G allele frequency in breast cancer patients [14].

A case-control study sought to investigate the link between the μ -opioid receptor gene and breast cancer survival. African American and European American women who were diagnosed with breast cancer between 1993 and 2001 were recruited for the study. Patient information including a blood sample, menopausal status, ethnicity, estrogen receptor status, and tumor stage at diagnosis were obtained. A118G was found to be significantly associated with breast cancer mortality. Women who were at a more advanced stage (III-IV) were less likely to have one or more copies of the G allele than women in the beginning stages (I-II). Thus, having at least one G allele was associated with having a less advanced stage at diagnosis. This relationship was only significant in European American women [56]. The study also found that the G allele is less prevalent in African American women than in European American women. Consequently, if the G allele aids in breast cancer survival then this ethnic disparity at A118G may account for the reduced breast cancer survival in African Americans.

Conclusion

Since opioids are often the drug of choice for pain control, it is crucial to understand the relationship of SNP mutations on the treatment. It is also important to understand the effect of the opioidergic system on metabolism. Based on the studies that were previously discussed, a few suggestions can be made regarding the differences between the wild type A118A genotype and carriers of the G allele (Figure 2). Caucasian women that have migraine with aura can potentially experience higher pain compared to wild type AA carriers [5,35]. Another important observation that can be made is that individuals with G alleles have a decreased sensitivity to morphine, which leads to decreased respiratory depression and analgesic effect [41-43]. A correlation between heroin addiction and G allele carriers have been established; G allele carriers' prodynorphin mRNA and proenkephalin mRNA levels tend to be decreased in putamen and nucleus accumbens in the brain which may result in loss of sensitivity to opioid analgesia and increase in heroin abuse [14]. In addition, drug overdose, particularly by opioids tends to be more intensified by G allele carriers that are expressed in cardiac and respiratory arrest [32,50-52]. On the other hand, a study performed in China has shown that Chinese women who underwent gynecological surgeries when treated with fentanyl had no difference with respect to PONV between A118A genotype and G allele carriers. This is possibly because many other types of receptors are involved in PONV [47]. One of the intriguing studies that touched upon the A118G SNP, is its correlation to cancer. Women with the G allele may experience a higher chance of developing breast cancer due to lack of balance in body's homeostasis because of the changes in endogenous opioid system [55].

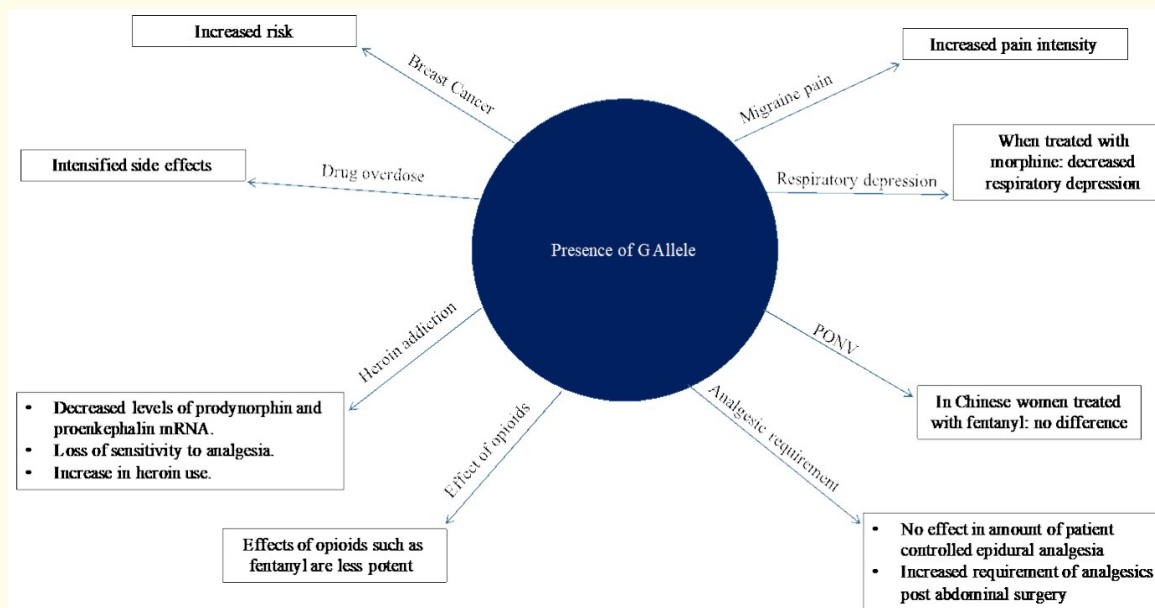


Figure 2: Significance of G allele presence.

Pain can cause tremendous distress and thus it is important to know how to properly treat patients with a G allele on the 118 exon for optimal treatment. If individuals can be identified beforehand who are more susceptible to drug addiction, overdose and cancer development, it can greatly improve the quality of life.

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Conflict of Interest

Authors declare that there is no conflict of interest to reveal.

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