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Genetics of Opioid Dependence: A Review of the Genetic Contribution to Opioid Dependence

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Abstract: This narrative review aims to provide an overview of the impact of opioid dependence and the contribution of genetics to opioid dependence. Epidemiological data demonstrate that opioid dependence is a global trend with far-reaching effects on the social, economic, and health care systems. A review of classical genetic studies of opioid use suggests significant heritability of drug use behavior, however the evidence from molecular genetic studies is inconclusive. Nonetheless, certain genetic variants are important to consider given their role in the pathophysiology of addictive behavior. We undertook a literature review to identify the current state of knowledge regarding the role of genes in opioid dependence. Determining the association of genetic markers could change the current understanding of the various factors contributing to opioid dependence and therefore may improve recognition of individuals at risk for the disorder and prevention and treatment strategies.

Keywords: Dependence, genes, opioid, opioid addiction, opioid receptors, SNP.

1. INTRODUCTION

There has been a steady rise in both prescription and non-prescription opioid use over the last decade that has resulted in rampant substance abuse among adult populations [1, 2]. Opioids belong to a class of highly addictive narcotics used for pain management, and their abuse often leads to the development of tolerance, dependence, and overdose. Methadone, codeine, hydrocodone (Vicodin, Lortab), oxycodone, propoxyphene (Darvon), fentanyl (Duragesic, Actiq, Oralet), tramadol (Ultram), hydromorphone (Dilaudid), morphine (MS-Contin and others), and levorphanol (Levo-Dromoran) are among the most commonly prescribed opioids [1, 2]. They are used for pain management in a number of acute and chronic medical conditions including chronic non-cancer pain [3], post-surgical care [4, 5], and musculoskeletal pain [6]. In addition, they are also prescribed for non-pain conditions such as multiple sclerosis [7, 8]. *Opiates* are naturally derived substances that have a physiological effect on humans, the class of *opioids* specifically refers to natural, semi-synthetic, and synthetic chemicals which confer anti-nociception effects by acting at opioid receptors in the central nervous system [9].

This paper aims to provide a review of the existing research on human genetic studies of opioid dependence, focusing on the most prominent genes reported in the literature. Twin and candidate gene studies will be the target of this review A brief description of the epidemiology and biological mechanisms will serve as background information that is central to the focus of the paper. Next, we will discuss the behavioural and psychological characteristics associated with opioid dependence in light of human genetic studies reviewed here.

2. MECHANISMS OF OPIOID FUNCTION AND DEPENDENCE POTENTIAL

Opioids are characterized by their ability to bind to opioid receptors *mu* (μ), *kappa* (κ), and *delta* (δ) and alter neural signal transmission [10, 11]. Opioid receptors are found in both the central nervous and peripheral nervous tissues [12]. They are distributed throughout the brain in varying concentrations depending on their classification, however all receptors are found to be highly abundant in the amygdala, the nucleus accumbens (NAc), and the caudate putamen (CP) [13]. These areas, as well as the ventral tegmental area (VTA), contain gamma-aminobutyric acid (GABA)-ergic interneurons that compose the complex neural circuitry involved in opioid dependence [14, 15]. Opioid receptors also differ in their binding affinities to specific ligands to induce varying degrees of analgesic effect and anti-nociception, in addition to other physiological effects [10, 12]. Endogenous opioid peptides, including enkephalins, β-endorphins, endomorphins and dynorphins, are mediated

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by their binding to opioid receptors [12, 16], and therefore play a role in modulating mood and regulating stress responses [11, 17, 18].

Dopamine, which is the primary neurotransmitter responsible for eliciting feelings of euphoria and pleasure, is the main component of the mechanism of dependence [15]. It works in conjunction with the opioid peptides and receptors to stimulate the dopaminergic pathway that is required for dopamine transmission [15]. The release of GABA, an inhibitory neurotransmitter also identified in this pathway, is decreased when opioid agonists bind to presynaptic *mu*-opioid receptors of (GABA)-ergic interneurons [17, 19]. The inhibition of GABA-ergic neurons *via* activation of the *mu*-opioid receptor allows dopaminergic neurons to release more dopamine into the reward pathway, creating a positive reinforcement of pleasurable feelings [15, 19].

3. EPIDEMIOLOGY OF OPIOID USE AND DEPENDENCE

Although opioids are commonly prescribed for pain, their addictive properties also make them liable for abuse. Opioid dependence and addiction are interchangeable terms, however the Diagnostic and Statistical Manual of Mental Disorders version IV (DSM IV) has adopted 'dependence' as the official term. Currently, the DSM IV is being revised to differentiate between the two aspects of substance dependence: the physiological changes in the brain that confer tolerance and the drug-seeking behaviors. The international review committee has proposed the non-pejorative, unambiguous term 'substance use disorder' to describe dependence behaviour and the associated neurobiological changes [20]. Throughout this paper, the terms 'opioid dependence' and 'substance use disorders' will be used to refer to dependence as defined by the DSM IV criteria.

Substance use disorders are complex conditions that are present in varying degrees between individuals [20]. A person that is diagnosed with substance dependence often exhibits a set of specific cognitive, behavioural, and psychological symptoms such as an increase in dosage, duration of use, and efforts to obtain substances [20]. Opioid dependence is also characterized by tolerance and compulsive use despite harmful consequences that eventually lead to severe withdrawal symptoms and life-threatening complications [21].

In 2006, the European Union concluded that there are between one to two million illicit drug users in Europe, of which an average of 1 million are parenteral drug users who used opioids as their principal drug [2]. According to a 2010 report by the European Monitoring Centre for Drugs and Drug Addiction, in 2008 there were an estimated 1.35 million dependent opioid users in the EU and Norway, equivalent to about 3.9-4.4 cases per 1000 people aged 15-64. with the highest prevalence of problem opioid use recorded in Ireland, Malta, Italy, and Luxembourg [22]. By comparison, Russia had a much larger population of opioid users (approximately 1.7 million) in 2009, equal to 16 cases of problem opioid use per 1000 people [22]. In addition, the Russian Federal Drug Control Service has concluded that nearly 10,000 deaths can be associated with heroin overdose each year in Russia [22]. Ukraine's situation is similar to Russia's with 10 to 13 cases per 1000 of problem opioid use [22].

Several small studies conducted in North America report different findings regarding the addiction profile. The majority of users are typically male (82%) and over half were between the ages of 31 and 40 (55%) [23]. The literature also reports an equal, if not greater, number of women than men abusing prescription opioids, which may be attributed to greater likelihood of reporting opioid dependence in women compared to men [24].

In addition to categorizing opioid users with regards to their demographics, there are emerging trends regarding the types and sources of opioid drugs. A Canadian multisite cohort study, OPICAN, investigated opioid use patterns of untreated opioid users in 6 major Canadian cities (Vancouver, Montreal, Toronto, Edmonton, Fredericton and Quebec cities) [2]. The most commonly used opioids in these Canadian cities were heroin, codeine (Tylenol 3 or 4), street methadone, hydromorphone, and oxycodone (Percodan, OxyContin) [25]. The non-medical use of prescription opioids, including meperidine, morphine, and oxycodone, were common in Toronto and Edmonton yet only comprised a small minority of opioid use in the other locations [1], which can be explained by differences in users' preferences or the availability of these drugs in the various regions.

The non-medical use of prescription opioids has been a global trend recognized by the International Narcotics Control Board (INCB). The abuse of prescription opioids is predicted to exceed illicit drug abuse and the dangers associated with the rise of prescription opioids are reflected in the associated increase in opioid-related deaths [4]. In a report released by the Institute for Clinical Evaluative Sciences (ICES), every additional opioid prescription dispensed per the Ontario Public Drug Programs (OPDP) correlated to an increase in the annual opioid-related mortality rate by 0.54 per 100 000 residents ($p<0.0001$) [26]. Studies report that 5-23 % of all opioid prescriptions are used non-medically [27], with 13.3% of Americans (equivalent to 33 million people) reported having used analgesics non-medically in their lifetime [28].

With regards to employment, the average employee takes 0.83 days off from work per month, the 2007 National Survey on Drug Use and Health (NSDUH) reported that individuals who abuse opioids are absent for more than 2.2 days of work monthly [28]. Opioid abusers cost the American health care system 8.7 times more than non-abusers ($15,884 versus $1,830 annually), and this cost increases after accounting for comorbidities such as depression and HIV [29].

4. MECHANISMS OF OPIOID DEPENDENCE

Addictive drugs primarily act on the neural circuits in the brain that are responsible for activating motivated adaptive behaviours [14, 30]. One important biological pathway is the mesolimbic dopamine system, or the reward pathway, which branches from the dopaminergic neurons of the VTA to the prefrontal cortex (PFC), amygdala, and the NAc [14, 30].

Natural reward pathways in the brain serve to perpetuate evolutionarily beneficial actions such as seeking food or avoiding psychological discomfort, which are referred to as motivated adaptive behaviours [14]. With regards to dependence, the prefrontal cortex is the main regulator of motivation and thus it determines the motivational value and intensity of behavior [31, 32]. When a beneficial stimulus is detected, the limbic system is capable of processing this information and producing a rewarding sensation that allows the organism to learn the adaptive value of the specified behaviour [15]. Individuals that are struggling with drug dependence display dependence-related behaviours that can be attributed to the dysregulation of prefrontal cortical activity. The transition from voluntary to habitual (and eventually compulsive) opioid use is hypothesized to represent a shift from prefrontal cortical to dorsal striatal control of dopamine pathways associated with the maintenance of drug-seeking and drug-taking behavior, which is manifested into an ultimate loss of control over the addictive behaviour [33].

Behavioural sensitization, which is described as a progressively enhanced responsiveness to the administration of opioid agonists, is hypothesized to also be involved in the pathophysiology of dependence [34]. The enhanced dopamine transmission initiates the positive reward aspect of dependence by triggering a shift from a dopamine-based system to a glutamate-based one in the mesolimbic pathway, which causes characteristics such as impaired decision making and impulsivity to emerge [35]. The transition from drug abuse to dependence is also associated with changes in neuroplasticity that guide the learning of conditioned responses, eventually leading to withdrawal symptoms and drug-seeking behaviours [14, 34, 36].

Studies have shown that the efficacy of opioid pain treatment varies between individuals, and opioids may also confer a range of adverse side effects such as nausea, depression, vomiting, and dependence based on inter-individual variability [9, 37]. The likelihood of developing a substance use disorder is influenced by both extrinsic and intrinsic variables, which will be reviewed in the following section.

5. EXTERNAL RISK FACTORS OR EXTRINSIC VARIABLES

Many factors have been associated with an increased risk of developing opioid dependence, however the extent of their contribution varies among individuals. When determining risk factors, it is important to note that causality is not always established in reported studies and therefore the findings should be interpreted with caution [38]. In addition, there is a distinction to be made between risk factors that contribute to substance use versus substance dependence or abuse [38, 39].

In addition to the risk factors themselves, the quantity of risk factors to which for example, youth are exposed to, has been directly correlated with the development of substance dependence [40]. A few longitudinal and cross-sectional studies have been conducted in this field, however large studies are not very prominent. Findings show that specific risk factors for adolescents include early antisocial behaviour, depression, anxiety, academic failure, socioeconomic status, delinquency, physical/sexual abuse [41, 42], hyperactivity [40] and family history of substance dependence [42]. In addition, levels of religious involvement, earlier age at first use, psychiatric history, or poor academic performance are likely to increase the frequency of substance use [39].

Adolescent substance use increases the risk of experiencing greater dependence severity and morbidity across both male and female groups [43]. According to the 2008 National Survey on Drug Use and Health conducted in the United States, 9.3% of youths aged 12 to 17 were currently using some sort of illicit drug (not including marijuana, hallucinogens, or inhalants) in the past month [44]. Earlier onset of substance use may confer neurobiological complications on the rapidly developing brain, and further research is needed to determine the effects of early opioid use on the likelihood of later use in life [8, 43].

6. INTERNAL PREPAREDNESS OR INTRINSIC VARIABLES

In addition to being influenced by societal conditions or familial background, there are also intrinsic biological and behavioural determinants that may increase a person's likelihood of developing substance use disorders. Variations in biological pathways and certain genetic polymorphisms have been associated with the onset of dependence [38]. Psychological characteristics such as reward or sensation seeking, decision-making, behavioural disinhibition, and impulsivity are also significant intrinsic contributors to dependence [38-40, 45].

Reward deficiency is reported to be an important factor involved in dependence behaviour and has been found to linked to lower expression of dopamine D2 receptors, resulting in a decrease in the number of physiological enforcers that are responsible for activating the reward pathway [46]. This reduction in activation circuits is hypothesized to predispose an individual to drug use as a means of compensating for the lack of reward [46]. Low dopamine receptor concentrations have been associated with impulsivity, as demonstrated by findings of escalated self-administration of cocaine in rat models [33]. This relationship highlights an important increase in the vulnerability to compulsive drug intake in humans leading to dependence, which stems from being in a reward-deficient state [33]. Sensation-seeking is another characteristic often associated with acquiring self-administration after initial exposure to a drug [33]. Deficient self-regulation mechanisms and difficulty controlling one's desires is often characterized as impulsivity, which has been hypothesized to contribute to the onset of substance use disorders [47, 48].

Therefore, it would be beneficial to monitor and assess behavioural patterns in order to identify individuals with a greater likelihood of misusing prescription opioids. Fortunately, several tools are currently available to assess such risks, including the Opioid Risk Tool (ORT), the Structured Clinical Interview for DSM-IV (SCID), and the Current Opioid Misuse Measure (COMM) [49]. A high rating according to the ORT was strongly correlated with an

increase in the risk of future substance abuse, whereas a high score on the COMM only weakly predicted future aberrant drug-use behaviours [49, 50]. Some of the behaviours that indicate an increased risk of substance dependence include taking prescription painkillers more frequently, using such medications to assist with sleep, hoarding unused medication, and requesting frequent refills on painkiller prescriptions [50].

7. GENETIC SUSCEPTIBILITY TO OPIOID DEPENDENCE

7.1. Family and Twin Studies

Family, twin, and adoption studies have consistently reported that genetic factors contribute to dependence behaviour and relapse after treatment through interactions with environmental factors [51-54]. Studies of probands with substance related disorders and their family members have reported significant associations between various drug groups and their genetic and environmental determinants of dependence [55]. These studies have provided the evidence to determine the extent of genetic contribution to dependence through estimation of heritability factor (h^2) [54, 55]. The heritability is characterized by three types of factors: genetic factors (A), shared family environmental factors (C), and random or unique environmental factors (E) [56, 57].

Tsuang *et al*. [57] conducted a twin study including 3372 male twin pairs from the Vietnam Era Twin (VET) Registry, 1874 of which were monozygotic (MZ) and 1498 of which were dizygotic (DZ), and found that DSM-III-R characterized drug dependence was apparent in 9.5% of the studied population. This study also investigated the co-occurrence of the abuse of drugs belonging to different categories (i.e. marijuana, stimulants, sedatives, heroin, and psychedelics) within an individual as well as their co-twin in order to determine how genetic and environmental factors contributed to concurrent drug abuse behaviour [57]. Using the common vulnerability model, 31% of the variance in drug abuse behaviour was attributed to additive genetic effects (A), while 25% and 44% were attributed to family (C) and non-family (E) environmental factors, respectively [57]. Single independent models of drug abuse patterns show that marijuana abuse was the only category to be influenced by family environmental factors, and heroin abuse had the largest contribution from specific genetic factors that were unshared with other drugs [57].

Using the same study population, the Harvard Twin Study of Substance Abuse that was conducted by Tsuang *et al* aimed to determine the genetic, and environmental factors that contribute to the heritability of various classes of drugs [53]. Genetic influences (A) contributed 34% of the total variance across all drugs overall, with significant proportions of variance accounted for by additive genetic influences in marijuana (0.33), opiate (0.43), and stimulant abuse (0.44) ($P<0.05$) [53]. Taken together, these results suggest a moderate genetic contribution to opioid abuse and dependence.

The same research team investigated the genetic and environmental influences on transitions in drug use patterns that varied from experimental to occasional, regular and eventually abuse or dependence [39]. Patterns across heroin use showed that heritability estimates are about 0.50 (95% CI: 0.00-0.56) for the transition from experimental to occasional use, and about 0.01 (95% CI: 0.00-0.31) for the transition from occasional to regular use [39]. In contrast, specific environmental influences showed significant contributions to the same transitions: 0.50 (95% CI: 0.32-0.38) from experimental to occasional use of heroin, and 0.99 (95% CI: 0.62-0.99) for occasional to regular use [39].

The familial aggregation of substance use disorders was investigated in families of probands with opioid, cocaine, cannabis, and alcohol abuse, and a direct association was found between drug disorders in probands and similar disorders affecting their relatives [55]. Relatives of probands with opioid use disorders were ten times more likely to have opioid related disorders (adjusted odds ratio (OR) 10.2, 95% CI: 3.2-32.6) [55]. In addition the risk for relatives was also higher for other substance use disorders when the proband is using such substances including cannabis (adjusted OR 5.8, 95% CI: 2.6-12.9), and cocaine (OR 4.4, 95% CI: 1.5-13.2) providing evidence for genetic susceptibility to substance use disorders [55].

7.2. Candidate Gene Studies

A. Dopamine Receptors

Dopamine, a neurotransmitter widely distributed throughout the central nervous system (CNS), is responsible for regulating movement, cognition, and pleasure by activating specific dopamine receptors [46]. There are two different types of dopamine receptors: the D1 and the D2 family. D1 and D5 receptors of the D1 family are located primarily in the amygdala, nucleus accumbens (NAc), substantia nigra, hypothalamus, and thalamus. D2, D3, and D4 receptors of the D2 family are more sparingly expressed in the hypothalamus and the nuclei of the thalamus [58]. A profile of the function and involvement of receptors is provided in Table **1**. Evidence suggests that dopamine release and dopaminergic receptor expression in the mesolimbic dopamine system is associated with traits of addictive behaviour such as impulsivity, novelty-seeking, and reward deficiency syndrome [33, 46]. As a result, the dopamine receptor genes have become prime candidates for the study of genetic polymorphisms and their effects on opioid dependence vulnerability [46, 47, 59-61].

i. DRD2

The D2 dopamine receptor is coded by the *DRD2* gene located on chromosome 11q23 [62]. Polymorphisms in *DRD2* have been associated with increased heroin use and vulnerability to addiction [47, 63]. A specific polymorphism at the *Taq*I RFLP (restriction fragment length polymorphism) site (rs1800497) involving a base pair substitution of C (A_2) for its minor allele T (A_1, minor allele frequency (MAF) = 0.01) has been investigated in subjects with opioid dependence [64]. This SNP was previously believed to be located on DRD2 but has since then been confirmed to be on the *ANKK1* (ankyrin repeat and kinase domain containing 1) gene, just downstream of DRD2. The close relative distance

Table 1. A summary of select genes commonly investigated in opioid addiction.

Gene	Category	Product	Product Profile	Effect on Opioid Addiction
DRD2	Dopamine receptor	D2 dopamine receptor	Inhibits adenylyl cyclase through inhibitory G-proteins	*DRD2* rs1800497 allele is higher in subjects with opioid addiction than controls, and it is predictive of successful methadone treatment outcomes[1].
DRD3	Dopamine receptor	D3 dopamine receptor	Inhibits adenylyl cyclase through inhibitory G-proteins	*DRD3 Bal*I allele is associated with higher sensation seeking, a risk factor for developing opioid addiction[2].
DRD4	Dopamine receptor	D4 dopamine receptor	Inhibits adenylyl cyclase, thereby reducing intracellular cAMP concentration	*DRD4* exon III long repeat alleles, specifically the 7-repeat variants, are more prevalent in opioid-dependent populations and associated with novelty seeking traits[3].
OPRM1	Opioid receptors	μ opioid receptor	Binds endogenous β-endorphins & enkephalins with highest affinity; binds dynorphins with lowest affinity[4, 5]	The rs1799971 G allele may confer protective effects in Hispanics, whereas it is associated with opioid-dependence in an Indian population. The rs1799972 T allele is less consistent across ethnic groups and is not definitively linked to opioid-dependence[6].
OPRD1	Opioid receptors	δ opioid receptor	Enkephalins as endogenous ligands; involved in producing analgesic and antidepressant effects[7] through cross talk with the μ opioid receptor	*The OPRDI* exon III rs2234918 variant is dubiously linked to dependence in a German population, whereas the rs1042114 variant is associated with opioid dependence in European Americans. The GCAACT haplotype, which includes both rs1042114 and rs2234918, is more frequent in opioid dependent cases than controls[8].
OPRK1	Opioid receptors	κ opioid receptor	Binds opioid peptide dynoprhin as primary endogenous ligand; also binds alkaloids and synthetic ligands	The *OPRKI* G36T SNP is slightly higher in opioid dependent subjects in Caucasians, and there are two haplotypes (AGCTCGTC, GGCGTGCC) which are significantly associated with opioid addiction in Hispanics[9].
BDNF	Neurotropic factors (NF)	Brain-derived NF	Binds to TrkB and p75 LNGFR receptors; also mediates neurotransmitter receptor activity	The G196A G allele is associated with heroin dependence and an earlier age of onset of substance abuse in Han Chinese men[10].
NRXN3	Neurotropic factors (NF)	Neurexin-3	Cell adhesion molecule involved in synaptic plasticity	No direct connection to opioid addiction, however one SNP (rs11624704) was associated with higher impulsivity in men[11].
NGFB	Neurotropic factors (NF)	Nerve growth factor, β subunit	Binds to TrkA and p75 LNGFR; involved in survival and maintenance of neurons	Carriers of the A allele of SNP rs2239622 are associated with lower daily methadone doses during methadone treatment[12].

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can explain how rs1800497 was able to exert its effects on the DRD2 receptor gene [65].

Hou *et al.* [64] investigated the association between the rs1800497polymorphism and heroin dependence. They recruited 530 Han Chinese heroin-addicted individuals from a Methadone Maintenance Treatment (MMT) Program and evaluated their allele and genotype frequencies at the A_1 allele [64]. Compared to the allele frequencies in 500 control subjects, the frequency of the A_1 allele was significantly higher in MMT patients (P=0.02) and the patients carrying at least one copy of the A_1 allele demonstrated mean daily heroin consumption twice as high as patients without the A_1 allele (P=0.003) [64]. This study provides evidence for an association between rs1800497 A_1 variant and higher mean daily heroin consumption.

In another study by Lawford *et al.* [63], the frequency of the rs1800497 A_1 allele in 95 Caucasian opioid-dependent patients was 19.0% compared to 4.6% in controls who had no history of alcohol or drug abuse (P=0.009). A follow up after one-year on an MMT program showed the A_1 allele frequency to be 9.3% in the group with successful methadone treatment outcomes, and 22.7% in the poor treatment group (χ^2=20.3, P<0.0001) [63]. It was concluded that less successful outcomes of MMT are associated with the A_1 variant [63].

ii. DRD3

The D3 dopamine receptors are coded by the *DRD3* gene, which is found on chromosome 3q13.3 [66], and are densely located in the limbic subcortical regions of the brain, specifically the NAc, thalamus, hypothalamus, and the cerebellum [58]. They are also distributed throughout the ventral striatal complex, which plays a role in the reward and gratification processes of addictive behavior [58]. Experimental evidence shows that repeated administration of opioids, psychostimulants, and L-dopa, a dopaminergic agonist precursor, induces the expression of D3 receptors in the dorsal striatum in animal models, thereby providing support for the involvement of these receptors in the behavioural sensitization of drug dependence [58, 67]. Post-mortem studies reported an elevated level of D3 receptors in the ventral striatum of cocaine fatalities, leading to the consideration of the *DRD3* gene as a candidate for susceptibility to drug dependence [67].

Duaux *et al*. [67] studied the *Bal*I polymorphism in the *DRD3* gene using a French Caucasian male population, where 54 opioid dependent patients and 70 control subjects were investigated [67]. While there were no significant genotype differences between the groups, patients had a higher sensation-seeking score on the Zuckerman scale (26 ± 5) than controls (17 ± 6), (P=0.001) [67]. In addition, patients with a sensation-seeking score above 24 were more likely to be homozygous for either *Bal*I allele than patients with a score below 24 (χ^2 = 6.53, d.f. = 1, P = 0.038) or controls (χ^2 = 4.48, d.f. = 1, P = 0.034) [67]. Sensation-seeking is considered a vulnerability factor for developing drug abuse behaviour, but the results are inconclusive and should be confirmed in larger samples.

iii. DRD4

The dopamine D4 receptor is encoded by the *DRD4* gene located on chromosome 11p15.5 [66]. The exon III region of the *DRD4* gene contains a variable number of tandem repeats (VNTR) polymorphism, which are nucleotide sequences that repeat themselves a certain number of times [64, 68]. The function of long-repeat allelic variants (> 4 repeats) and short-repeat alleles has been identified in disorders such as ADHD and Parkinson's disease. Presence of VNTR SNPs in ADHD has been shown to influence brain activation patterns of temporal processing and overall executive functioning [69]. In the case of substance use, the exon III VNTR polymorphism has been studied in association with addictive disorders, as hypothesized by Chien *et al.* [68]. After studying a sample of heroin-addicted Chinese men, Chien *et al*. reported a higher frequency of the long-repeat alleles in cases compared to controls, providing evidence for an association with heroin dependence [68]. A study of *DRD4* exon III VNTR polymorphisms in Israeli subjects found that the 4 and 7 repeats of exon III account for 90% of the alleles in an Israeli population, and the subjects possessing the 7-repeat allele demonstrated significantly higher levels of novelty seeking compared to subjects without this allele (F = 6.34, P = 0.013) [61]. Further studies of this gene as a risk factor for opioid dependence are therefore needed.

Kotler *et al*. [60] investigated the association between novelty seeking and long repeat alleles of *DRD4* and found a significantly increased number of the 7-repeat allele in 141 male opioid dependent subjects (29.1%) compared to 110 male controls (11.8%), (χ^2 = 10.9, d.f. = 1, P = 0.00096). To account for ethnic variations, which may confound the findings of a population's allele frequencies, the frequency of the 7-repeat allele was compared within the two ethnic groups that were studied. There was an increased number of long alleles within the opioid-dependent Israeli Arab cohort (χ^2 = 5.05, d.f. = 1, P = 0.024) and the Sephardic Jewish opioid-dependent cohort (χ^2 = 5.01, d.f. = 1, P = 0.023), without any significant differences noted between the two demographic populations [60].

Similar findings were reported in a case-control study of Han Chinese subjects including 121 heroin-dependent subjects and 154 controls [70]. There was an excess of longer (5-7 repeats) alleles in the cases (P = 0.023; OR: 2.30, 95% CI: 1.07-4.93) with the 7-repeat allele appearing exclusively in heroin dependent subjects [70]. Altogether, the findings of these studies provide strong evidence to support the hypothesis that the long repeat alleles of the *DRD4* exon III are associated with a higher vulnerability to opioid dependence.

B. Opioid Receptors

The μ, κ, and δ opioid receptors belong to the class of G-protein coupled receptors that are associated with inhibitory G-proteins and dopaminergic neurons to produce the physiological effects of opioids [37, 71].

i. OPRM1

The opioid receptor μ 1 *(OPRM1)* gene, located on chromosome 6q24-q25 [72], is responsible for encoding the

μ opioid receptor, which has been implicated in respiration, gastrointestinal motility, physical dependence, euphoria, and analgesia [66]. In-depth study of this gene has identified several single nucleotide polymorphisms (SNPs) that are associated with opioid dependence and with ethnic variation in opioid dependence [72].

In a study by Bond *et al.* [73], the investigators concluded that the most prevalent SNPs in the *OPRM1* gene occurred at A118G (rs1799971) and C17T (rs1799972); other SNPs were located at A24G, G779A, and G942A [73]. There were significant differences between the observed allelic frequencies of African-American, Caucasian, and Hispanic ethnic groups for both rs1799971 and rs1799972 alleles (χ^2=7.15 (P=0.028) and χ^2=26.0 (P<0.0001) respectively) [73]. Bond's study found no significant differences in rs1799971 allelic frequency between opioid-dependent and non-dependent subjects with all ethnic groups combined [χ^2=1.81 (P=0.159)], however in subgroup analyses by ethnicity, the rs1799971 minor allele (G) frequency was significantly higher in non-opioid dependent Hispanic subjects (χ^2 = 8.22, d.f. = 1, P = 0.0041) [73]. On the other hand, the rs1799972 minor allele (T) frequency was higher in subjects with opioid dependence (χ^2 = 3.70, d.f. = 1, P = 0.054) [73]. Different patterns are observed in a group of American, Finish, and Native American subjects where the minor allele frequency of the rs1799971 SNP was 10.5-16.3% without any significant detection of the rs1799972 polymorphism [73]. A study by Bart *et al* (2004) also confirmed this association in a Swedish population of 139 opiate-dependent subjects and 170 controls, demonstrating higher frequencies of the minor allele in opiate-dependent users (χ^2 = 10.27, d.f. = 1, p = 0.0014) [74]. These results support significant allelic variations between different ethnic groups that need to be accounted for when investigating the opioid receptor and other genes associated with opioid dependence.

In contrast to Bond *et al*'s study which did not detect the rs1799972 SNP in a Caucasian population [73], a prospective study of 282 opioid-dependent subjects of Indian origin found the minor allele frequencies of the rs1799971 and rs1799972 polymorphisms to be 31% and 17% respectively [72]. This study by Kapur *et al* [72] found an increased frequency of the rs1799971 variant in subjects with opioid dependence compared to controls (χ^2 = 32.495, P < 0.0001; OR: 3.50; CI (95%) = 2.21-5.56), and there was no significant difference between the two groups with respect to the rs1799972 SNP (χ^2 = 0.18, P < 0.67; OR: 0.79; CI (95%) = 0.35–1.79). A haplotype analysis found no association between the rs1799971 and rs1799972 SNPs and opioid dependence, therefore only the rs1799971 minor allele variant was associated with opioid dependence in the sample of Indian subjects [72]. The contrasting association of the rs1799971 SNP with opioid dependence in various ethnic groups is an important factor to consider in genetic association studies of multiethnic cohorts.

In response to evidence of an association between the rs1799971 SNP and opioid dependence, studies attempted to investigate the potential functional effects of the rs1799971 variant on cellular activity and binding affinity. Such functions were tested in cells expressing the most common μ receptor and the rs1799971 variant [73]. Bond *et al* [73] found that the rs1799971 receptor variant showed similar binding affinities to small endogenous opioid peptide agonists and exogenous agonists, suggesting that the rs1799971 SNP does not significantly alter the binding properties of the μ receptor [73]. However, the reaction between the rs1799971 receptor and human β-endorphin displayed a high binding affinity, which was represented by an association constant ratio of 3.46 ± 0.31 [73]. Bond *et al* [73] confirmed this association by measuring the potency of β-endorphin as an rs1799971 agonist and found that it was able to induce a greater response at a lower concentration when compared to the common μ receptor. Using different methods, a study by Kroslak *et al* [71] found no changes in β-endorphin signaling at the rs1799971 μ receptor, and also determined that the binding affinities for exogenous agonists (morphine, methadone, and DAMGO) were not different. The potential variation in β-endorphin's binding capacity in these two studies [71, 73] may be attributable to the distinct methodologies that were used, however the overall findings imply that the altered binding affinity and pathway activation of the rs1799971 μ opioid receptor may impact a subject's vulnerability to opioid dependence due to the involvement of β-endorphin in limbic signaling [75] and the stress response pathway [73]. This conclusion is supportive of the role that the rs1799971 SNP has in the pathophysiology of opioid dependence.

ii. OPRD1

The gene that codes for the δ opioid receptor, opioid receptor delta 1 *(OPRD1*), is located on chromosome 1p34 [66]. Several studies have linked the association between variations in allelic frequencies of SNPs on the *OPRD1* gene and opioid addiction. Mayer *et al* [76] studied a population of 103 German Caucasian individuals with heroin addiction and 115 control subjects, and reported the involvement of the C921T (rs2234918) SNP in exon 3 of the *OPRD1* gene [76]. Compared to control subjects, both the frequency of the C-allele and C/C homozygote genotype were increased in heroin users (relative risk (RR) = 4.42, CI (95%) = 1.82-10.75) however the T to C transition did not directly alter the primary amino acid sequence, therefore it was unlikely that this polymorphism altered the functioning of the δ opioid receptor [76].

In an association and family study, Franke *et al.* [77] failed to find an association between the silent rs2234918 mutation and heroin or alcohol dependence. This study included 233 heroin-dependent subjects, 262 alcohol dependent subjects, and 173 controls, all of German origin, as well as the biological parents of 90 heroin dependent subjects and 72 alcohol dependent subjects [77]. Despite the similar ethnic background of the samples selected for these studies [76, 77], the allele and genotype frequencies of individuals with heroin and alcohol dependence compared to controls were not found to be statistically significant [77]. In addition, there was no preferential transmission of alleles in families of subjects with heroin or alcohol dependence [77].

A larger study by Zhang *et al.* [12] examined 1063 European Americans, including 620 cases diagnosed with alcohol, cocaine, and opioid dependence, and 443 control

subjects without any substance use disorders [12]. The only SNP that survived multiple testing was the G80T (rs1042114) variant in exon 1 of the *OPRD1* gene, which showed significantly increased frequency of the minor G allele in opioid dependent subjects (21.0%) compared to controls (13.2%, P=0.005), and a higher frequency of the rs1042114 heterozygote in opioid dependent cases (32.4%) compared to controls (24.2%, P=0.008) [12]. Haplotype analysis showed an association between six *OPRD1* SNPs that contained the GCAACT sequence (including rs1042114 and rs2234918) and greater risk of opioid dependence (χ^2 = 20.68, d.f. = 1, P < 0.001) [12].

iii. OPRK1

The opioid receptor kappa 1 (*OPRK1*) gene, located on chromosome 8q11.2 [78], codes for the κ opioid receptor and has been implicated in the regulation of stress responses, as well as counteracting the euphoric sensations produced by μ opioid receptor agonists [59]. Activation of the κ receptor by endogenous ligand dynorphin A has been found to decrease the dopamine release in the striatum [79], however there is inconclusive evidence to support an association of *OPRK1* SNPs with opioid dependence and the results varied greatly with different ethnic populations.

In a study of Western Europeans, Gerra *et al.* [59] genotyped 106 heroin-dependent subjects and 70 healthy controls for a silent mutation on the *OPRK1* gene. At the rs1051660 SNP, there was a significantly higher frequency of the G allele among controls compared to cases, and the T allele was present in higher frequencies among heroin-dependent subjects (Fisher's exact = 0.044, Pearson $\chi 2$ = 4.2734, P = 0.039) [59]. Yuferov *et al.* [80] examined 12 SNPs in the *OPRK1* gene in African American, Caucasian, Hispanic, Asian-American, and mixed ethnic groups and reported that the rs1051660 SNP displayed slightly higher frequencies in all of the subjects with opioid dependence combined (P=0.016). In the Hispanic group, haplotype analysis revealed two combinations of *OPRK1* SNPs that were significantly associated with opioid dependence (AGCTCGTC and GGCGTGCC haplotypes) [80].

There is limited evidence that individual *OPRK1* SNPs are associated with substance dependence; instead, many experiments measure linkage disequilibrium to consider SNPs in the larger context of how those SNPs may be linked in haplotype blocks. Although Zhang's study found no significant differences in *OPRK1* allele or genotype frequencies for individual SNPs, one specific *OPRK1* haplotype, GGCTTCT, was significantly associated with alcohol dependence in European Americans [12]. While other findings may suggest that genetic variants in *OPRK1* may be associated with alcohol dependence rather than opioid dependence [81].

C. Neurotrophic Factors

Neurotrophins are a family of regulatory proteins that are necessary for the growth, survival, and differentiation of neurons in the central and peripheral nervous systems [82]. In addition, they modulate neuronal transmission, synaptogenesis, and play a role in modulating the plasticity of neurons [82-84]. The neurotrophin family includes brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and neurexins (NRXN) 3-7, which are involved in the development of neural networks as well as higher level processes such as learning, memory, and behavior [85]. The role of neurotophins in substance dependence disorders can be speculated to be a result of deregulated synaptic plasticity or differential binding affinities of these neurotrophins to their associated receptors [85].

i. BDNF

BDNF is encoded by the *BDNF* gene, which is located on chromosome 11p14 [84], and has been associated with opioid dependence [86]. As a regulator of many cellular signaling pathways, BDNF is hypothesized to play a role in the transition from drug use to dependence, specifically the reward pathway that is apparent in addiction [82]. A study by Guillin *et al* [34] showed that increased concentrations of BDNF in the ventral tegmental area (VTA) induced an over-expression of the D3 receptor, creating a reward state similar to that of opioids.

In addition, studies involving *BDNF* gene deletions have shown that decreased hippocampal BDNF may be associated with cognitive defects and a loss of aversive memory that is found in depression and anxiety-related disorders [87]. A dinucleotide repeat sequence on the main coding region of the *BDNF* gene has also been associated with vulnerability to drug abuse [86].

Similar to opioid receptor genes, the *BDNF* gene also contains several SNPs that have been linked to nicotine or alcohol abuse [86]. Itoh *et al.* [88] conducted a study to determine the personality traits associated with the G196A SNP (rs6265) of the *BDNF* gene. The Temperament and Character Inventory personality test was administered to a Japanese sample of 95 females and 56 males, and the results revealed significant differences among the personality traits of the three genotype groups in females (df=2.93, f=5.33, P=0.006) [88]. Females homozygous for valine (Val) scored significantly higher in reward dependence (P=0.013) and extraversion (P=0.022), both of which are negatively correlated with depression [88]. The findings suggest that female carriers of the methionine (Met) allele may be more likely to develop mood disorders such as depression [88].

Several studies have examined the relationship between heroin dependence and BDNF function and rs6265 SNP in the *BDNF* gene that codes for a valine (Val) to methionine (Met) substitution in the protein's pro-domain [89-91]. These studies reported impaired depolarization-dependent secretion of BDNF in neuronal cells [90]. It was also observed that valine carriers had a higher level of central BDNF and experienced more intense euphoric effects than methionine carriers [90]. In a study by Cheng *et al.* [91] that investigated methamphetamine and heroin-dependent Chinese men, the genotype distribution was significantly different in the methamphetamine (P=0.046) and heroin-dependent groups (P=0.045) compared to the control group. The *BDNF* rs6265 SNP also had an effect on the age of onset of substance abuse in 160 heroin-dependent cases, with the mean age of onset of 20.8 ± 5.1 years for subjects with a heterozygous genotype, which is significantly lower than both homozygous groups (21.2 ± 8.1 and 23.8 ± 7.5 for the Met/Met and Val/Val homozygous groups, respectively) (p = 0.048) [91].

Another investigation of the association between *BDNF* rs6265 SNP and heroin dependence in a population of 487 Han Chinese, showed a significantly higher frequency of G alleles in heroin-dependent subjects than controls (χ^2=10.150, P=0.001, OR=1.339, 95% CI=1.119–1.602) [89]. Taken together, these results support the hypothesis that the rs6265 SNP in the *BDNF* gene may influence a variety of psychological and behavioural traits including depression, euphoria, age of onset of substance abuse, and heroin dependence.

ii. NRXN3

Neurexins (NRXNs) are presynaptic transmembrane proteins that primarily act as cell adhesion molecules, but are also known to play a role in neuronal synapse function and development [92]. They are hypothesized to mediate impulsivity and therefore may be implicated in genetic vulnerability for opioid dependence [92]. In a genome-wide study, Lachman *et al.* [93] found an association between opioid dependence and a wide region of chromosome 14q (exclusive to the Puerto Rican subpopulation) where the NRXN3 gene is located. Similarly, Stoltenberg *et al* [92] assessed six SNPs in the *NRXN3* gene for associations between substance use problems, impulsivity, and these genetic polymorphisms. Using self-report questionnaires to assess impulsivity and health-risk behaviours [92], Stoltenberg *et al* reported that one SNP (rs11624704) was associated with impulsivity in men but not women, and that higher impulsivity is more common with regular tobacco and alcohol use [92]. Although the study did not find significant results with regards to opioid dependence, impulsivity may be indirectly linked to substance use disorders including opioid dependence and further research may elucidate a direct association between *NRXN3* SNPs and opioid dependence.

iii. NGFB

Nerve growth factor (NGF), located on chromosome 1p13.1 [85], is a member of the neurotrophin family and it consists of three subunits: alpha, beta, and gamma [94]. The beta subunit (NGFB), which is hypothesized to be the only subunit responsible for the biological activity of NGF, modulates the development and signaling of the nervous system *via* a testosterone-regulated process [94].

A study by Levran *et al.* [85] analyzed 15 SNPs in the *NGFB* gene and their association with treatment with methadone. The study reported that the average daily methadone doses were significantly lower in subjects homozygous for the A allele of SNP rs2239622 (81.7 mg) than heterozygous or non-carrier subjects (153 and 140 mg, respectively) [85]. Therefore this study provides an evidence for an association between *NGFB* and methadone dose.

8. SUMMARY

We sought to provide an overview of opioid dependence including epidemiology and genetic susceptibility and we summarized the evidence for genes most commonly associated with opioid dependence. These genes related to dopamine and opioid receptors, and neurotrophic factors (Table **1**). The majority of the studies reviewed were retrospective, case-control studies that compared genotype and allele frequencies between cases of opioid dependence and controls. These studies often excluded individuals with any major psychiatric disorders (Axis 1 disorders) and polysubstance use, and a significant portion of study participants were of European ethnicity. Other common ethnic groups included in previous studies were Han Chinese, Hispanics, Israelis, and African Americans with significant ethnic variations in the association between genetic variants and opioid dependence were reported. Most of the studies reviewed were of modest sample size and limited power to detect multiple genetic variants. Few larger studies included Zhang *et al.*'s study, which examined 1063 European American individuals with 620 cases of substance dependence [12], and Hou *et al.*'s study of 1030 Han Chinese males with 500 cases of opioid dependence [64]. The results from both of these studies suggested a significant association between specific SNPs and opioid dependence in two ethnic groups, however further large studies are needed to clarify the role of these common SNPs in opioid dependence. Nonetheless, the reviewed studies provide significant evidence for the genetic contribution to addiction disorders, and detailed investigations into the effects of these genes on the pathophysiology and metabolism of opioids will provide further clues into the etiology of such disorders. Ultimately, such information could aid in the identification of individuals at risk of developing opioid dependence and better treatment for individuals already affected with the disease.

We have observed a consistent contribution of variation within the *DRD2, OPRM1, OPRD1,* and *BDNF* genes towards the development of opioid dependence, where these particular genes encode receptors and signaling molecules which play important roles in the pathophysiology of substance use disorders. Despite the strong genetic susceptibility to opioid dependence, environmental factors play an important role in this disorder in keeping with many common disorders of multifactorial etiology. Therefore studies investigating the interactions between genes and the environment will add further to our understanding of opioid and other substances use disorders.

9. CONCLUSIONS

Opioid abuse and dependence disorders are widespread, chronic, multifactorial conditions that have detrimental effects on both the individual and society. Patients with opioid dependence require multi-level intervention strategies to address the biological, social and psychological elements of this disorder. Understanding the basic mechanisms behind such complex and multifactorial disorders will help identify management strategies in order to effectively prevent and treat cases of opioid related disorders. We have provided an overview of the genetic background of this disorder with few examples of common genes associated with addictive traits and disorders. We propose that there is a need for further large-scale studies that will help understand the biological mechanisms behind opioid addiction.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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