Published in final edited form as:
Hum Genet. 2012 June ; 131(6): 823–842. doi:10.1007/s00439-012-1172-4.

The genetics of the opioid system and specific drug addictions

Orna Levran, **Vadim Yuferov**, and **Mary Jeanne Kreek**
Laboratory of the Biology of Addictive Diseases, The Rockefeller University, New York, NY 10065, USA

Abstract

Addiction to drugs is a chronic, relapsing brain disease that has major medical, social, and economic complications. It has been established that genetic factors contribute to the vulnerability to develop drug addiction and to the effectiveness of its treatment. Identification of these factors may increase our understanding of the disorders, help in the development of new treatments and advance personalized medicine. In this review we will describe the genetics of the major genes of the opioid system (opioid receptors and their endogenous ligands) in connection to addiction to opioids, cocaine, alcohol and methamphetamines. Particular emphasis is given to association and functional studies of specific variants. We will provide information on the sample populations and the size of each study, as well as a list of the variants implicated in association with addiction-related phenotypes, and with the effectiveness of pharmacotherapy for addiction.

Keywords

drug addiction; opioid peptides; opioid receptors; HPA axis; 118A>G

Introduction

Addiction to drugs is a chronic complex relapsing brain disease that causes major medical, social and economic problems and is caused by genetic, epigenetic, environmental, and drug-induced factors. The endogenous opioid system plays a key role in drug addiction, and mediates the analgesic and rewarding properties of drugs. The endogenous opioid family is a network of genes coding for neuropeptide ligands and their cell surface receptors. This system consists of four major subtypes of 7-transmembrane, G protein-coupled opioid receptors: mu, kappa, delta and receptor-like, encoded by distinct genes (*OPRM1, OPRK1, OPRD1,* and *OPRL1*), which are stimulated by endogenous opioid peptides: beta-endorphin, prodynorphin, enkephalin, and orphanin/nociceptin, encoded by *POMC, PDYN, PENK*, and *PNOC,* respectively, as well as exogenous opiates. The receptors' genes are highly conserved in their 7-transmembrane domain, but not in their amino and carboxyl termini, reflecting on their different ligand binding ability and signal transduction pathways (for figures see LaForge et al. 2000). The ligands' genes all share overall similar structure with a single intron in the coding region. The opioid system is presumed to have been formed by genome duplications early in vertebrate evolution (Cruz-Gordillo et al. 2010; Li et al. 1996). Each receptor gene also produces multiple mRNA isoforms through the use of alternative splicing, alternative promoters (*OPRM1, OPRK1*), alternative polyadenylation sites (*OPRK1*), or inclusion of non-coding exons.

Corresponding author: Orna Levran, Tel: (212) 327-8638, Fax: (212) 327-7023, levrano@rockefeller.edu.

Conflict of interest: The authors declare that they have no conflict of interest.

Several comprehensive reviews describe the role of the endogenous opioid family of genes in addiction and treatment responses (e.g. Kreek et al. 2005; Kreek et al. 2009; LaForge et al. 2000; Yuferov et al. 2010). In this review we will focus on the genetics of the opioid system that is relevant to addiction to opioids, cocaine, alcohol and methamphetamines, with particular emphasis given to genetic association studies and functional studies. Cannabis or tobacco dependence will not be discussed. We will also discuss the genetics of the opioid system in relation to specific addiction treatments (methadone, buprenorphine, naltrexone and nalmefene), as well as stress responsivity and the hypothalamic-pituitary-adrenal (HPA) axis.

Association studies

A vast number of studies have been reported the association of variants of the opioid system genes and drug addiction-related phenotypes, but the results are not always consistent. This inconsistency may be explained by several factors, including inconsistency in phenotyping, severity of diagnosis, small sample size, inadequate statistics, ethnic heterogeneity and population stratification, large phenotype range, and different diagnostic criteria. The majority of studies have used individual single nucleotide polymorphism (SNP) analysis, and several studies have used hypothesis-based multi-SNP arrays that are based on linkage disequilibrium (LD)-tagging SNPs and capture a substantial proportion of common genetic variation (e.g. Hodgkinson et al. 2008; Levran et al. 2008; Levran et al. 2009; Maher et al. 2011). In this article, we will define SNP as a variation in a single nucleotide of any allele frequency (see dbSNP). Linkage studies and genome-wide association studies are beyond the scope of this review. The studied populations include Asian (Japanese, Chinese, Taiwanese, and Indians) (As); European (E); European American (EA); African (including African Americans, AA); Native American (NA); and Hispanic (His). Some studies have mixed populations and only a few studies have applied methods to control for population stratification.

The studies included a range of phenotypes, including heroin addiction, opioid dependence (OD); heroin-induced subjective response; cocaine addiction/dependence (CD); alcohol dependence (AD), methamphetamine (MAP) dependence/psychosis (MD); amphetamine-induced euphoria; response to alcohol; adolescent alcohol misuse; antisocial drug dependence in adolescents; response to naltrexone (NTX) treatment; and personality traits. For review of association studies of MAP use disorders see (Bousman et al. 2009).

Different studies have used different criteria for defining specific addictions or different criteria for the definition of controls. For example, in our studies we have analyzed heroin addicts that have met the stringent criteria of entering into methadone maintenance treatment (MMT) (at least one year of multiple daily use), while other studies rely on DSM-IV criteria that may be less stringent. Several studies use the more general phenotypes that are based on the concept of common drug use disorders (DUD) liability (Vanyukov et al. 2003), including substance dependence (SD), substance use disorder (SUD), and illicit drug dependence.

To allow a comprehensive and critical examination of the data, and to assist with planning future studies, we have listed the various association studies, with information about the specific addiction or related phenotype, the numbers of cases (or families) and controls, the specific genes analyzed, and the populations studied (Table 1). In Table 2 we provide the list of all the SNPs (sorted by rs number) that were reported to be associated with drug addiction in at least one study. For each SNP the specific addiction and the specific population in which the association was found (indicated under the specific addiction) are indicated. The references listed are all the studies that analyzed the specific SNP including the one/s that

identified the association. In addition, we have listed all the SNPs that were analyzed and were not reported to be associated with drug addiction, along with the gene location and the relevant references (Supplement Table 1). In Supplement Table 2 we provide the allele frequencies of all the variants reported in this review in three HapMap populations: CEU (Utah residents with ancestry from northern and western Europe), YRI (Yoruba, Nigeria) and CHB (Han Chinese in Beijing, China).

The mu opioid receptor gene (*OPRM1*)

The G protein-coupled mu opioid receptor (encoded by the *OPRM1* gene) is the major site of action for endogenous opioids, opiate and opioid analgesic drugs, and exogenous opioid drugs such as methadone, heroin and morphine (Kreek 2005). The receptor mediates the action of non-opioid drugs of abuse (e.g. alcohol, nicotine) and the stress-responsive HPA axis. Receptor activation results in the opening of G protein-gated inwardly-rectifying K+ (GIRK) channels, inhibition of voltage-gated Ca^{2+} channels, and reduction of adenylyl cyclase-mediated cAMP production. Binding of beta-endorphin results in disinhibition of dopaminergic neurons and this dopamine influx has been associated with reward and reinforcement and is believed to contribute to the development of drug dependence.

The *OPRM1* gene is located at cytogenetic band 6q25.2. The major subtype contains 4 exons. A number of alternatively-spliced variants have been reported in rodents and humans. Two human receptor variants (encoded by splice variants) (hMOR-1X and hMOR-1O) were identified (Pan 2003). An alternatively-spliced exon with a specific promoter was identified -28 kb upstream of exon 1 (Xu et al. 2009). An alternatively-spliced exon with an alternative promoter was identified in rodents and humans (Shabalina et al. 2009). Notably, the genomic organization of the human *OPRM1* locus is highly similar to the mouse locus. However, alternative-splicing events display some substantial differences between human and mouse.

Only two SNPs out of the variants described in dbSNP in the *OPRM1* coding sequence (17C>T (Ala6Val) and 118A>G (Asp40Asn) in exon 1) are relatively common at least in one population (see sections below). Numerous SNPs have been described in the regulatory region, some of which are population-specific (Hoehe et al. 2000; Ono et al. 2009b), and several have been functionally characterized. Two promoter polymorphisms, -554G>A and -1320A>G, have been shown to affect transcription (Bayerer et al. 2007). SNPs -554G>A, in a STAT6 binding site, and SNP -995C>A, in a nuclear factor (NF)-kB binding site, decreased the amount of transcription factor binding and the transcriptional activity (Kraus et al. 2001; Kraus et al. 2003). SNP -1793T>A is located in an YY1 transcription binding site; SNP -1699insT is located in an AP-1 binding site (Hoehe et al. 2000). The Poly (ADP-ribose) polymerase-1 (PARP-1) was shown to preferentially bind to the -172T allele and positively regulate *OPRM1* gene expression (Ono et al. 2009a). Bioinformatics assessment suggests that C/EBP or CREB binds to the SNP -1748G>A region, OCT-1 binds to the SNP -1565T>C region and the SNP -1045A>G region, and GATA, MZF, and SP1 bind to the SNP -172G>T region (Ono et al. 2009b).

Functional evidence for a few coding variants was reported. The 118A>G SNP was the first variant that was shown to be functional by the combined groups of Kreek and Yu (Bond et al. 1998) (see section below). Three rare SNPs in highly evolutionary conserved amino acids 779G>A (Arg260His), 794G>A (Arg265His), and 802T>C (Ser268Pro) in the third intracellular loop of the receptor were shown to decrease receptor signaling activity (Befort et al. 2001; Wang et al. 2001). SNP 802T>C was also shown to lose Ca^{2+}/calmodulin-dependent protein kinase-induced receptor desensitization (Koch et al. 2000).

118A>G (Asn40Asp, rs1799971)

The most studied *OPRM1* variant is the non-synonymous (changing an amino acid) variant rs1799971 (118A>G, Asn40Asp) that was shown to remove a potential N-glycosylation site in the extracellular domain, to be more potent in beta-endorphin binding, and to reduce receptor signaling efficacy (Bond et al. 1998). The 118G allele is common in persons of European (15–30%) and Asian ancestry (40–50%), and has lower prevalence in African Americans (AA) (1-3%) (Deb et al. 2010; Gelernter et al. 1999). The variant 118G allele is not found in the African HapMap population (Yoruba, Nigeria), suggesting that it arose after the 'out-of-Africa' migration (Cavalli-Sforza and Feldman. 2003).

The functionality of this variant was subject to numerous studies (e.g. Befort et al. 2001; Bond et al. 1998; Deb et al. 2010; Filbey et al. 2008; Margas et al. 2007; Ray et al. 2011). The 118G variant was associated with lower cell-surface receptor binding site availability (Beyer et al. 2004; Kroslak et al. 2007), reduced mRNA levels *in vivo* and *in vitro* (Zhang et al. 2005), altered signal transduction (PKA and pERK), *in vitro* (Deb et al. 2010), and enhanced affinity for beta-endorphin (Bond et al. 1998). For more information and references, see a current review (Mague and Blendy 2010).

Recently, in a positron emission tomography (PET) study of 22 smokers and 20 controls, the 118G variant was associated with reduced receptor binding availability in the bilateral amygdala, left thalamus, and left anterior cingulate cortex (Ray et al. 2011). An fMRI study showed that the 118G allele is associated with increased cue-elicited activation of mesocorticolimbic structures and that this activation is extended by a priming dose of alcohol. This activity in the striatum was correlated with drinking behavior in individuals with the 118G allele (Filbey et al. 2008; Ramchandani et al. 2011). Taken together, some results may be interpreted as a loss-of-function while others may be interpreted as a gain-of-function of the 118G receptor. These results are not mutually exclusive and it is possible that the variant causes reduction in receptor numbers but also enhanced binding. It is also possible that some results reflect the action of another SNP that is in high LD with the 118G allele in some chromosomes (haplotypes) but not in others. The exact nature of the physiological changes has yet to be elucidated.

Association studies of 118A>G

A large number of association studies of this SNP across various phenotypes were reported (for a recent review see Mague and Blendy 2010). The 118G allele has been implicated in drug addiction, stress responsivity, and in treatment responses. Several association studies of 118A>G reported negative results, and meta-analyses revealed mixed results (Arias et al. 2006; Glatt et al. 2007). The118G allele was shown to be associated with opioid dependence (OD) and other substance dependencies in several studies in diverse populations. An association was observed between the 118G allele and opioid addiction in Swedish (Bart et al. 2004), Chinese (Szeto et al. 2001), EA (Drakenberg et al. 2006), and Indian patients (Deb et al. 2010; Kapur et al. 2007; Tan et al. 2003), whereas other studies did not detect such association (Franke et al. 2001; Glatt et al. 2007; Levran et al. 2008; Levran et al. 2009; Shi et al. 2002).

Several studies reported an association of the 118G allele with alcohol dependence (AD) in different populations (e.g. Bart et al. 2005; Deb et al. 2010; Kim et al. 2004; Nishizawa et al. 2006; Rommelspacher et al. 2001; Schinka et al. 2002), and with the development of alcohol use disorder diagnoses during adolescence in EA drinkers (Miranda et al. 2010). Carriers of the 118G allele were more sensitive to the euphoric effects of alcohol, more likely to abuse alcohol and had greater cue-induced alcohol craving during neutral condition, when compared to stressful imagery condition (Ray 2011; Ray and Hutchison 2004). Increased

dopaminergic sensitivity (assessed by using the apomorphine induced growth hormone secretion as indicator) was reported in abstinent alcoholic individuals who were 118G carriers (Smolka et al. 1999). Several studies did not find association with this variant (e.g. Bergen et al. 1997; Gscheidel et al. 2000; Loh el et al. 2004; Sander et al. 1998; Town et al. 1999).

The SNP 118A>G was also associated with social hedonic capacity (Troisi et al. 2011) and with MAP psychosis, having latency less than three years from first methamphetamine intake in Japanese subjects (Ide et al. 2004).

As the 118A>G SNP changes an amino acid, it has been generally assumed that it is the causative variant for the phenotypes associated with it. There is a possibility that other variants, which are in LD with 118A>G, contribute to these phenotypes. The mixed results for 118A>G may be explained in part by different and/or population-specific haplotype patterns. The 118G allele was shown to be represented by a specific haplotype that includes several SNPs from the 5′ flanking region of the gene in EA subjects, but appears in two haplotypes in the Asian HapMap population. The major haplotype is similar to the one found in EA subjects and the second one includes other SNP combinations (Levran et al. 2011).

Animal models of 118A>G

Two mouse models of 118A>G with the equivalent amino acid substitution have been developed using two different approaches. In one model, knock-in mice homozygous for the equivalent (112G) allele (Asn38Asp) exhibited reduced oprm1 mRNA and protein levels in multiple brain regions and sex-specific reductions in the rewarding properties of morphine (Mague et al. 2009). In the second model, two humanized mice lines were produced by introduction of human exon 1 with and without the variant 118G into the mouse gene. Mice bearing the 118GG genotype showed a greater peak of striatal dopamine response to an alcohol challenge (Ramchandani et al. 2011).

In rhesus macaques, SNP 77C>G (Pro26Arg) in the N-terminal appears to be functionally equivalent to the human 118A>G. Carriers of the 77G variant showed increased psychomotor stimulation in response to alcohol, increased frequency of alcohol consumption to intoxication, increase of alcohol preference following naltrexone treatment, altered stress reactivity, reduced cortisol response to maternal separation in infancy and to acute alcohol exposure later in life and attenuated cortisol levels during the maternal postpartum period (Barr et al. 2010; Barr et al. 2007; Miller et al. 2004; Schwandt et al. 2011; Vallender et al. 2010).

17C>T (Ala6Val, rs1799972)

The function of the 17C>T polymorphism in the extracellular space of the N-terminal is yet unknown. The frequency of the 17T allele varies significantly between populations. It is very rare in subjects of European descent, Hispanics, Middle Eastern subjects (Gelernter et al. 1999), and Asian subjects (dbSNP) (Tan et al. 2003; Xu et al. 2002) and common (15–20%) in subjects of African descent (Crowley et al. 2003; Gelernter et al. 1999; Luo et al. 2003). A relatively high allele frequency was also reported in Indian males from Delhi, India (Kapur et al. 2007).

No association was found with the17T allele and opioid dependence in an Indian sample (Kapur et al. 2007), nor in an AA sample (Crowley et al. 2003). A recent large study of HIV + and HIV- women identified association between the 17TT genotype and a quantitative measure (Kellogg et al. 2003)) for cocaine and alcohol use in AA (Crystal et al. 2010).

Other *OPRM1* SNPs

Several studies analyzed other SNPs in the *OPRM1* gene for association with addiction. An association with substance dependence (SD) (heroin, cocaine and alcohol) was shown with three promoter SNPs (-1793T>A, -1699insT and -2044C>A) (Hoehe et al. 2000; Luo et al. 2003). SNP rs1074287, located in the 5′ upstream region (-11.6 kb from exon 1) was found to be associated with heroin addiction in EA subjects (Nielsen et al. 2008).

Several SNPs in intron 1 were associated with drug addiction. In a study of 9 SNPs in Chinese subjects, heroin-induced positive response on first use was associated with SNPs rs534673 (originally called rs696522), rs1381376, and rs3778151 (Zhang et al. 2007). SNPs rs510769 and rs3778151 were found to be associated with heroin addiction in EA subjects, but not in AA subjects (Levran et al. 2008; Levran et al. 2009). SNP rs510769 was also associated with several effects of amphetamine (euphoria, stimulation and blood pressure) in healthy subjects of EA ancestry (Dlugos et al. 2011).

Haplotype analysis revealed that SNPs rs510769 and rs3778151 are part of a haplotype block that spans intron 1. Several SNPs at the -20 kb 5′ region (including SNP rs1074287) are in high LD with this haplotype block (Levran et al. 2011). Several lines of evidence suggest a special functionality to intron 1 (Choi et al. 2006; Shabalina et al. 2009). A potential functional SNP in intron 1 (rs563649) is shown to be located within a structurally conserved internal ribosome entry site (IRES) in the 5′ UTR of a novel exon 13 in an *OPRM1* isoform and to affect both mRNA levels and translation efficiency. This SNP was also associated with pain perception (Shabalina et al. 2009). A (CA) repeat in intron 1 was associated with substance dependence (alcohol, cocaine or opioid) in EAs, but not in AAs (Kranzler et al. 1998).

Two SNPs in the 3′ region near the gene (rs483481, rs2281617) showed association with drug use disorder diagnosis (Maher et al. 2011) and response to amphetamine use (euphoria, energy and blood pressure) in healthy EA subjects (Dlugos et al. 2011), respectively.

Several intronic SNPs were associated with response to alcohol in Native Americans (NA), which is correlated with less susceptibility to dependence (Ehlers et al. 2008). In a study of methamphetamine dependence/psychosis (Ide et al. 2004; Ide et al. 2006), 16 variants in the 5′ regulatory region and intron 1 were studied in Japanese subjects. Association was found with SNP rs2075572 (IVS2+691G>C).

No association with opioid dependence was found in two studies of AA and EA subjects analyzing SNPs -1793T>A, -1699insT, -1320A>G, 17C>T, 118A>G, as well as SNPs 540825 and 562859 (Crowley et al. 2003; Smith et al. 2005).

The kappa opioid receptor gene (*OPRK1*)

The kappa opioid receptors have widespread distribution in the central nervous system and play a role in a wide variety of physiological systems, including pain regulation, addiction to drugs of abuse, neuroendocrine regulation, cardiovascular function, respiration, temperature regulation, feeding behavior, and stress responsivity (e.g. Bruchas et al. 2010; Knoll and Carlezon 2010; Kreek et al. 2005). Kappa opioid receptors play an important role in modulation of opioid, cocaine and other rewarding stimuli, presumably through modulation of basal and drug-induced dopaminergic tone (Kreek et al. 2002). *Oprk1* knockout mice showed elevated basal dopamine release in the nucleus accumbens and enhanced cocaine-induced dopamine levels compared to wild-type mice, suggesting association with greater vulnerability to cocaine abuse (Chefer et al. 2005) (also see PDYN section below).

OPRK1 contains four exons and is located on chromosome 8q11.2 (Yuferov et al. 2004). Twenty-seven SNPs are described in the coding sequence, out of which twelve are rare non-synonymous SNPs that alter an amino acid in the protein. Four synonymous SNPs that do not modify an amino acid but may have other functions (rs1051660 (36G>T), rs702764, rs16918875 and rs7815824) are common in at least one population. An indel of net insertion of 830 bp (rs35566036) was described at the 5′ flanking region (-1986 bp) and was shown to reduce transcription in transient transfection assays, *in vitro* (Edenberg et al. 2008).

Four studies reported association of *OPRK1* SNPs with alcohol dependence (AD); a study of a Taiwanese sample reported no association for SNPs rs1051660 and rs702764 (843A>G) (Loh el et al. 2004); in a study of 13 SNPs in 219 EA COGA families, an association of several SNPs in intron 2 was reported (Xuei et al. 2006). A third study of seven SNPs (not including SNPs from intron 2) in EA subjects reported an association of three SNPs (rs1051660, rs6985606 and rs997917) with AD or cocaine dependence (CD), and a seven-SNP haplotype with AD (Zhang et al. 2008). An association of the 830 bp indel (rs35566036) was reported in the COGA sample (Edenberg et al. 2008).

Four studies reported association of *OPRK1* SNPs with OD. A study of eight SNPs in EA, AA and His subjects, reported association with the synonymous SNP rs1051660 (Yuferov et al. 2004). A study of an Italian sample replicated this finding (Gerra et al. 2007). A third study of 11 SNPs (not including SNP rs1051660) reported an association with the intronic SNP rs6473797 in EA subjects (Levran et al. 2008). No association with these 11 SNPs was detected in AA subjects (Levran et al. 2009).

The delta opioid receptor gene (*OPRD1*)

Delta opioid receptors bind enkephalin as its endogenous ligand. Delta opioid receptors have been implicated in the modulation of reward, addiction, affective state, pain perception, and analgesia. A blunted ability to form and/or retrieve drug-context associations was shown in *Oprd1*−/− mice (Le Merrer et al. 2011).

OPRD1 contains 3 exons and is located on chromosome 1p36. Nine polymorphisms were identified in the coding region (four non-synonymous, three synonymous and one insertion), out of which only one SNP (921T>C, rs2234918) is common in several ethnicities. SNP rs1042114 (80G>T, Phe27Cys) is common mainly in Europeans, and the synonymous SNP rs118175398 was described in Asians. In addition, two SNPs were described in the 3′ UTR, out of which SNP rs4654327 is common in several ethnicities.

The promoter SNP rs569356 is located ~2 Kb upstream to the transcription start site and is in high LD with SNP rs1042114 (80G>T, Phe27Cys). Functional characterization of SNP rs569356 (A>G) with luciferase reporter gene assay in HEK293 cells demonstrated that the G-allele can enhance *OPRD1* promoter activity under basal conditions. Electrophoretic mobility shift assay (EMSA) with human brain nuclear proteins showed enhanced DNA protein binding of the probe with the G-allele (Zhang et al. 2010).

The non-synonymous SNP rs1042114 (80G>T, Phe27Cys) changes the evolutionary conserved phenylalanine to cysteine in the extracellular N terminus. Interestingly, the reference 80G-allele is the minor allele and is absent in Asians, rare in Africans, and has a minor allele frequency (MAF) of 0.1, in Europeans. One of the possible explanations for this phenomenon may be selective advantage for the 80T-allele, but the biological mechanism underlying this potential advantage has yet to be identified. The minor 80G-allele has been found to be associated with OD in EA subjects (Zhang et al. 2008). These results were not found in a family-based association study of 18 SNPs with AD (219 EA families), a case control association study with “illicit drug dependence”, and in a small subsample with OD

(Xuei et al. 2007). This SNP was not included in the array used in our studies of heroin addiction (Levran et al. 2008; Levran et al. 2009). Functional studies revealed that the two variants (27Phe and 27Cys) have identical pharmacological properties, but differ in maturation efficiency, stability at the plasma membrane, and Ca^{2+} signaling regulation (Leskela et al. 2009; Tuusa and Petaja-Repo 2011).

The C-allele of the synonymous SNP rs2234918 (921T>C) in exon 3 was reported to be associated with heroin dependence in Germans (Mayer et al. 1997), but this result was not found in several other studies of this SNP in Germans (Franke et al. 1999), Han Chinese (Shi et al. 2002; Xu et al. 2002), EAs (Levran et al. 2008; Zhang et al. 2008), and AAs (Levran et al. 2009). No association of this SNP was found with AD in Taiwanese Han (Loh el et al. 2004) or with methamphetamine dependence/psychosis in Japanese (Kobayashi et al. 2006). A haplotype, which harbors the 80G-allele and the 921C-allele, was associated with OD, CD, and AD (Zhang et al. 2008).

In a study of 11 *OPRD1* SNPs, three common SNPs in intron 1 (rs2236861, rs2236857 and rs3766951) and a haplotype block (SNPs rs204055, rs2236857 and rs2298896) showed associations with heroin addiction in EAs (Levran et al. 2008). No associations of these SNPs and heroin addiction were found in AAs (Levran et al. 2009).

The opiate receptor-like 1 (nociceptin/orphanin FQ receptor) (*OPRL1*)

The opiate receptor-like 1 receptor for the neuropeptide nociceptin shows high homology to opioid receptors and plays an important role in inhibition of the rewarding effects of addictive drugs. The opiate receptor-like 1 receptor couples to inhibitory G proteins and negatively regulates the function of the mesolimbic dopaminergic system. Studies suggest that the endogenous nociceptin system has a role in mediating responses to alcohol (Murphy 2010). *Oprl1* knockout rats are more sensitive to the rewarding effect of morphine than wild-type controls (Rutten et al. 2011). *Oprl1* knockout mice displayed increased anxiety-related behavior (Gavioli et al. 2007) and nociceptin blocked the development of cocaine-induced locomotor sensitization in mice (Bebawy et al. 2010). In humans, reduction in PNOC mRNA (1.7-fold) in the hippocampus and OPRL1 mRNA (1.4-fold) in the central amygdala of postmortem brain of alcoholics, compared with controls, was reported (Kuzmin et al. 2009).

OPRL1 is located on chromosome 20q13 and has alternative splicing transcript variants that are controlled by alternate-promoter mechanism and contain 4 or 5 exons (Ito et al. 2000; Wick et al. 1995). The protein is encoded by three exons. Seventeen coding SNPs have been described, of which only the synonymous SNP rs2229205 is common in several populations.

The regulator of G protein signaling 19 protein (*RGS19/GAIP*) which has been shown to modulate signaling of the mu opioid receptor, is located immediately upstream of *OPRL1*, and is transcribed from the opposite strand. The two genes (*RGS19*, *OPRL1*) share their promoter (Ito et al. 2000; Xie et al. 2007). Two unique repeat polymorphisms were described in the promoter region but no significant effect on promoter activities was found (Ito et al. 2000).

Three association studies of *OPRL1* and drug addiction were reported. In the first study, 10 SNPs covering *OPRL1* (and *RGS19*) were analyzed and no association was found with alcohol addiction or illicit drug dependence. Two intronic SNPs in high LD (rs6512305 and rs6090043) were marginally associated with OD in a small subsample of 83 affected subjects (Xuei et al. 2008). In the second study, 15 SNPs were analyzed and one SNP (rs6010718) showed an association with AD (Huang et al. 2008). A haplotype of five tag SNPs TTTGC (rs6090043, rs6010718, rs7271530, rs2295448, and rs6089789) was

significantly more common in cases than in controls (Huang et al. 2008). In the third study of five SNPs in three ethnicities (EA, AA and His), association of two SNPs in the 5′ flanking region (rs6090041 and rs6090043) with vulnerability to develop heroin addiction was reported in EA only, and a haplotype was associated with heroin addiction in AA and EA (Briant et al. 2010). No association with heroin addiction was detected for six SNPs (including rs6512305, rs6090041 and rs6090043) in a larger cohort of EA and AA from our laboratory. A trend toward association was detected for SNP rs6090041 in EA (Levran et al. 2008; Levran et al. 2009).

The endogenous opioid neuropeptides

The endogenous opioid peptides acting at their cognate opioid receptors modulate the effects of many drugs of abuse. The endogenous opioid peptides, beta-endorphin, dynorphin, enkephalin, and orphanin/nociceptin, are derived from precursors encoded by proopiomelanocortin (*POMC*), prodynorphin (*PDYN*), proenkephalin (*PENK*), and nociceptin/orphanin FQ (*PNOC*), respectively (for figures see LaForge et al. 2000).

The proopiomelanocortin gene (*POMC*)

POMC is a polypeptide precursor protein with 241 amino acid residues. Ten different peptides can be derived from POMC through tissue-specific posttranslational processing, including adrenocorticotropin (ACTH) and beta-endorphin, which are principal components of the HPA axis. Studies in rodents have shown that stressors elevate *POMC* mRNA levels in the pituitary. POMC-derived peptides actively regulate drug-related behaviors (Kiefer et al. 2002; O'Malley et al. 2002). Beta-endorphin is a 31-amino acid peptide that is the major endogenous ligand of the mu opioid receptor and is found mainly in neurons of the hypothalamus and the pituitary gland (Dores and Baron et al. 2011).

The *POMC* gene is located on chromosome 2p23 and all the variants in the coding regions are rare. In one reported association study, seven SNPs were genotyped in a sample of alcoholic families (COGA) and association was found for intronic SNP rs934778 and general illicit drug dependence. Two intronic SNPs (rs934778 and rs1009388) were associated with opioid dependence in a small subsample of this cohort (Xuei et al. 2007). In a second association study of AD in European sample, nine SNPs were analyzed. Three SNPs were associated with AD, out of which SNP rs934778 was associated after Bonferroni correction. The T-A haplotype (rs934778 and rs3769671) was associated with AD in women only (Racz et al. 2008). A third association study of five SNPs with AD, CD or OD was reported in AA and EA (Zhang et al. 2009). The main finding is of SNP rs1866146 in the 3′ flanking region that was associated with OD or CD in AAs, and with AD, CD or OD in EAs. In addition, the intronic SNP rs6713532 was marginally associated with AD or CD in EAs, and SNP rs6719226 in the 5′ flanking region was associated with OD in AAs (Zhang et al. 2009). In another study, SNP rs1042571 in the 3′ UTR was associated with higher cortisol exposure and reduced negative feedback of the HPA axis, in a nonchallenged condition, in women (Rutters et al. 2011).

The prodynorphin gene (*PDYN*)

Prodynorphin is the precursor for the opioid peptides alpha- and beta-neoendorphins, dynorphin A and dynorphin B, which are endogenous ligands for the kappa opioid receptor. Dynorphin peptides decrease basal and drug-induced dopamine levels in several areas of the dopaminergic, nigrostriatal, and mesolimbic–mesocortical systems. Expression of the *PDYN* gene is increased by cocaine (for a recent review see Yuferov et al. 2010). *Pdyn* knockout mice showed increased explorative behavior in anxiety tests demonstrating the anxiogenic role of prodynorphin-derived peptides (Wittmann et al. 2009).

The *PDYN* gene contains four exons and is located at chromosome 20p13. Exons 1 and 2 encode the 5′ UTR, exon 3 encodes a signal peptide, and exon 4 encodes the dynorphin peptides. Nine SNPs were described in the coding sequence of which only one synonymous SNP in exon 4 (rs6045819) is not rare. Seven alternative transcripts with different 5′-ends were detected in brain tissue; some have novel initiation sites and some contain new exons (Nikoshkov et al. 2005; Telkov et al. 1998).

One of the first discovered and most studied *PDYN* polymorphisms is rs35286281 a variable number nucleotide repeat (VNTR) of 1-5 copies of 68-bp tandem which contains a putative AP-1 transcription complex binding site, located 1250 bp upstream of exon 1. SNP rs61761346 was identified at the ninth nucleotide of each repeat (Rockman et al. 2005; Rouault et al. 2011). *In vitro,* PDYN expression studies using various constructs, different cell lines, and different species reported opposite effects (Babbitt et al. 2010; Rouault et al. 2011; Zimprich et al. 2000).

Several association studies of *PDYN* SNPs and different addictions were reported. Nine out of the eighteen *PDYN* SNPs tested in the COGA cohort (including rs1997794) were associated with AD (Xuei et al. 2006). The results were supported by haplotype analysis. SNP rs1997794 was reported to show no association with alcoholism in a small European sample (Geijer et al. 1997). Three SNPs were analyzed in Chinese subjects for association with OD (Clarke et al. 2009). No association in the overall sample, but an interaction between sex and genotype distribution was detected for rs1997794, in females. Also, SNP rs1022563 was associated with OD in females, suggesting a gender-specific role of *PDYN.* Association between a haplotype (SNPs rs1022563, rs2235749 and rs910080) and OD was reported in Han Chinese (Wei et al. 2011). Several studies of SNP rs35286281 (the 68-bp VNTR) did not produce consistent results for association with OD, CD or MD in several ethnic groups (Chen et al. 2002; Dahl et al. 2005; Nomura et al. 2006; Ray et al. 2005; Wei et al. 2011; Williams et al. 2007). An association between three SNPs (rs910080, rs910079 and rs2235749) in the 3′ UTR, and the haplotype CCT, with both CD and CD/AD, was reported in EAs, but not in AAs (Yuferov et al. 2009). Allele-specific gene expression of *PDYN*, using SNP rs910079 as a reporter, in postmortem human brains, showed lower expression for the C-allele in the caudate and nucleus accumbens. Total *PDYN* expression was also lower in carriers of the CCT haplotype (Yuferov et al. 2009).

Three SNPs (rs1997794, rs6045819 and rs2235749) that showed association with AD, CD or OD form a CpG dinucleotide (methylation associated SNPs). Alterations in methylation of a specific allele through epigenetic mechanisms may affect transcription. An increase in methylation levels of the C- allele of the 3′ UTR SNP rs2235749 was reported in the dorsolateral prefrontal cortex in alcohol-dependent subjects (Taqi et al. 2011). A 63 kDa protein showed differential binding affinity for the risk T-allele, and the methylated and unmethylated C-allele in the brain. The T-allele of SNP rs1997794 resides within a noncanonical AP-1-binding element and was associated with lower PDYN expression in brain cortical areas. The C-allele was shown to abrogate AP-1 binding (Yuferov et al. 2009).

The proenkephalin gene (*PENK*)

Proenkephalin-derived peptides act on mu and delta opioid receptors to produce rewarding actions of substances of abuse in several brain regions, including the ventral tegmental area and nucleus accumbens. Specific inbred mouse strains (e.g. DBA/2J and SWR) are characterized by relative insensitivity to drug reward and reinforcement, compared to C57BL/6J. These differences were shown to parallel inter-strain differences in basal proenkephalin expression in the nucleus accumbens (Gieryk et al. 2010).

The *PENK* gene is located on chromosome 8q23. Forty-six coding SNPs have been reported, most of them are rare and some are population-specific. A $(CA)_n$ repeat (rs3219515) in the 5′ flanking region was reported to be associated with OD (Comings et al. 1999). Seven SNPs were genotyped in a sample of alcoholic families (COGA) and no association was detected with AD or general illicit drug dependence. Three SNPs (rs2609997 and rs1975285, in the 5′ flanking region, and the intronic rs1437277) provided evidence of association with opioid dependence in a small subsample (Xuei et al. 2007). In another study of a different $(CA)_n$ repeat (rs3138832) in the 3′ flanking region, a significant association of a specific allele $(CA)_{79}$ (based on PCR product described in Weber and May 1990), with heroin abuse was reported in a European sample. This allele was also associated with higher striatal PENK mRNA expression in the fetal postmortem human brain, but not adult brain (Nikoshkov et al. 2008). In another study of AD in two European cohorts, four SNPs were analyzed and two SNPs (rs12545109 and rs2576581) showed association in the German cohort but not in the Swedish cohort (Racz et al. 2008).

Nociceptin/orphanin FQ (*PNOC*)

Nociceptin is a 17-amino acid neuropeptide that binds *OPRL1.* The *PNOC* gene is located on chromosome 8p21. Ten rare coding SNPs were described and one non-synonymous SNP (rs76786693, Ala118Gly) is common in Asian populations. Only three association studies have been reported with *PNOC* SNPs. Fifteen *PNOC* SNPs were analyzed in the COGA cohort. Two SNPs (rs17058952, in the 5′ flanking region, and rs351779, in the 3′ flanking region) were associated with AD, and one SNP (rs4732636, in the 5′ flanking region) was associated with illicit drug dependence (Xuei et al. 2008). No associations were reported for seven SNPs studied in EAs and AAs (Levran et al. 2008; Levran et al. 2009). The only SNP that was common to these studies is rs351784.

Addiction treatment

Methadone, the long-term major treatment of opioid addiction, is a mu opioid receptor agonist and a weak N-methyl-D-aspartic acid (NMDA) receptor antagonist. Part of the large inter-individual variability in drug response may be accounted for by genetic factors. Successful methadone treatment for opiate dependence relies in part on dosage optimization. Several pharmacogenetics studies of methadone have been performed to date, but only a few have studied variants in the opioid system genes that are relevant to this review. No association was found between *OPRM1* 118A>G or *OPRD1* 921T>C and response to MMT and methadone dose in a study of 238 European patients (Crettol et al. 2008).

Buprenorphine has been an alternative treatment approved relative recently for opioid addiction. No association studies of the opioid system genes have been reported on the response to buprenorphine treatment (see below a study of the HPA axis reactivity after buprenorphine-maintained patients (Kakko et al. 2008).

The hypothalamic-pituitary-adrenal (HPA) axis

The HPA axis is a neuroendocrine system involved in stress response by regulating ACTH and cortisol secretion (Hernandez-Avila et al. 2003). Disruption of stress pathways is considered to be one of the causes of addictive disorders (Koob and Kreek 2007; Kreek and Koob 1998). The mu opioid system plays an important role in stress response by regulating the HPA axis. Studies have shown that the mu opioid receptor is involved in modulation of the HPA axis by tonic inhibition of corticotropin-releasing hormone (CRH, also called CRF) in the hypothalamus and POMC in the anterior pituitary. The PDYN/OPRK1 system may also modulate the HPA axis by activation. Naloxone, nalmefene or naltrexone challenge in healthy subjects caused transient increase in plasma levels of ACTH and cortisol by

disinhibition of the hypothalamic-pituitary part, indicating activation of the HPA axis (King et al. 2002; Schluger et al. 1998). HPA-axis stimulation plays an important role in the neurobiology of AD, CD and OD. Clinical studies and studies of animal models have shown that modest stimulation of the HPA axis is sought or desired by alcohol- and cocaine-dependent individuals. In contrast, opiate dependents find it aversive, since HPA axis activation is a characteristic of opioid withdrawal (e.g. Bond et al. 1998; Culpepper-Morgan and Kreek 1997; Koob and Kreek 2007; O'Malley et al. 2002). Long-term methadone maintenance treatment normalizes HPA axis activity in heroin addicts (Kreek 1973; Kreek et al. 1983).

Several studies report the effect of the *OPRM1* 118A>G polymorphism on the HPA axis. The 118G allele was associated with a robust cortisol response to naloxone blockade in subjects of predominantly European ancestry (Chong et al. 2006; Hernandez-Avila et al. 2003; Wand et al. 2002), but the effect was not found in Asians (Hernandez-Avila et al. 2007). It was also associated with blunted cortisol response to psychosocial stress (Chong et al. 2006) and with greater baseline concentrations of plasma cortisol in healthy subjects (Bart et al. 2006; Hernandez-Avila et al. 2007).

Metyrapone transiently blocks glucocorticoid production in the adrenal cortex. The 118G allele blunted the ACTH response to metyrapone in healthy subjects (Ducat et al. 2011). 118G carriers in buprenorphine maintenance treatment showed even greater attenuated response to metyrapone compared to 118A carriers, indicating more potent HPA axis suppression by buprenorphine in 118G carriers (Kakko et al. 2008).

Naltrexone and nalmefene

Two antagonists of opioid receptors are used for the treatment for AD: naltrexone (NTX) and nalmefene. Both antagonists reduce drinking and craving in alcoholic individuals in treatment and also in heavy drinkers. It is hypothesized that NTX works in part by occupying opioid receptors, preventing their binding by endogenous opioid peptides released upon alcohol intake, and in part by modest activation of the HPA axis (e.g. O'Brien et al. 2011; O'Malley et al. 2002). Activation of the HPA axis by the mechanism of disinhibition of the tonic mu opioid receptor inhibition is one of the pharmacological effects of NTX (Schluger et al. 1998). A substantial number of patients still do not respond to treatment, and family history of alcoholism was reported to be predictive of NTX response, suggesting the possibility that genetic factors may play a role in its effect (Rubio et al. 2005).

Several studies showed a positive effect of the *OPRM1* 118G allele on NTX treatment response (for review see Sturgess et al. 2011). Healthy subjects expressing the 118G-allele showed greater cortisol response to opioid receptor blockade by NTX and naloxone (Wand et al. 2002). Since alcoholics seek activation of the HPA axis, we predicted that alcoholics with the 118G allele would respond better to NTX treatment. This prediction has been supported by several studies showing that AD subjects with the 118G allele have better clinical response (Anton et al. 2008; Oroszi et al. 2009; Oslin et al. 2003; Ray and Hutchison 2007). However, these results were not supported by two other studies (Gelernter et al. 2007; Tidey et al. 2008). NTX was also shown to increase the urge for alcohol in 118G allele carriers (McGeary et al. 2006) and to decrease the positive subjective effect of alcohol (Setiawan et al. 2011).

Neurosteroids have been implicated as a factor that increases subjective effects of alcohol (Ray et al. 2010). Carriers of the 118G allele displayed increased neurosteroid levels after NTX treatment, suggesting that GABAergic neurosteroids may be a useful adjunctive

therapy for alcoholism in non-carriers of the 118G allele associated with therapeutic efficacy to NTX (Ray et al. 2010).

Similar studies in rhesus macaques showed that carriers of the 77G variant that is functionally equivalent to the human 118G (see animal models of 118A>G, above) were selectively sensitive to suppression of alcohol preference by NTX treatment (Barr et al. 2010), were more sensitive to the effects of NTX, and showed greater reductions in alcohol consumption at lower NTX doses (Vallender et al. 2010).

NTX also modulates amphetamine-induced effects and has a potential in the treatment of amphetamine dependence (Jayaram-Lindstrom et al. 2008a;b). No pharmacogenetics studies were reported for the effects of specific variants on NTX response in amphetamine-dependent subjects. No association was found between the *OPRM1* SNP 118A>G, the *OPRD1* SNPs rs2234918 (921T>C) and the intronic rs678849, and the *OPRK1* SNP rs963549 and outcome of nalmefene treatment for alcoholism (Arias et al. 2008).

Conclusions

In this article we reviewed the genetics of the endogenous opioid system genes, including association studies, which identified variants that may contribute to the vulnerability to develop specific drug addiction or common drug liability. We also discussed the genetics of the HPA axis and the pharmacogenetics of current treatment for addiction. Association studies in complex disorders such as addiction are challenging. Nevertheless, there is growing evidence for association and/or functionality of several SNPs in the opioid system genes that may have implications for understanding the addictive diseases and for improvements in treatment strategies and personalized medicine. More work is clearly needed to verify the role of variants suggested to be associated with addiction in small studies and for better understanding of their role in different populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by grants DA-P60-05130 and MH-79880 from the National Institutes of Health to MJK. We would like to thank Susan Russo for her help with manuscript preparation.

References

Anton RF, Oroszi G, O'Malley S, Couper D, Swift R, Pettinati H, Goldman D. An evaluation of mu-opioid receptor (OPRM1) as a predictor of naltrexone response in the treatment of alcohol dependence: results from the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) study. Arch Gen Psychiatry. 2008; 65:135–144. [PubMed: 18250251]

Arias A, Feinn R, Kranzler HR. Association of an Asn40Asp (A118G) polymorphism in the mu-opioid receptor gene with substance dependence: a meta-analysis. Drug Alcohol Depend. 2006; 83:262–268. [PubMed: 16387451]

Arias AJ, Armeli S, Gelernter J, Covault J, Kallio A, Karhuvaara S, Koivisto T, Makela R, Kranzler HR. Effects of opioid receptor gene variation on targeted nalmefene treatment in heavy drinkers. Alcohol Clin Exp Res. 2008; 32:1159–1166. [PubMed: 18537939]

Babbitt CC, Silverman JS, Haygood R, Reininga JM, Rockman MV, Wray GA. Multiple functional variants in cis modulate PDYN expression. Mol Biol Evol. 2010; 27:465–479. [PubMed: 19910384]

Barr CS, Chen SA, Schwandt ML, Lindell SG, Sun H, Suomi SJ, Heilig M. Suppression of alcohol preference by naltrexone in the rhesus macaque: a critical role of genetic variation at the micro-opioid receptor gene locus. Biol Psychiatry. 2010; 67:78–80. [PubMed: 19748082]

Barr CS, Schwandt M, Lindell SG, Chen SA, Goldman D, Suomi SJ, Higley JD, Heilig M. Association of a functional polymorphism in the mu-opioid receptor gene with alcohol response and consumption in male rhesus macaques. Arch Gen Psychiatry. 2007; 64:369–376. [PubMed: 17339526]

Bart G, Heilig M, LaForge KS, Pollak L, Leal SM, Ott J, Kreek MJ. Substantial attributable risk related to a functional mu-opioid receptor gene polymorphism in association with heroin addiction in central Sweden. Mol Psychiatry. 2004; 9:547–549. [PubMed: 15037869]

Bart G, Kreek MJ, Ott J, LaForge KS, Proudnikov D, Pollak L, Heilig M. Increased attributable risk related to a functional mu-opioid receptor gene polymorphism in association with alcohol dependence in central Sweden. Neuropsychopharmacology. 2005; 30:417–422. [PubMed: 15525999]

Bart G, LaForge KS, Borg L, Lilly C, Ho A, Kreek MJ. Altered levels of basal cortisol in healthy subjects with a 118G allele in exon 1 of the mu opioid receptor gene. Neuropsychopharmacology. 2006; 31:2313–2317. [PubMed: 16794569]

Bayerer B, Stamer U, Hoeft A, Stuber F. Genomic variations and transcriptional regulation of the human mu-opioid receptor gene. Eur J Pain. 2007; 11:421–427. [PubMed: 16843022]

Bebawy D, Marquez P, Samboul S, Parikh D, Hamid A, Lutfy K. Orphanin FQ/nociceptin not only blocks but also reverses behavioral adaptive changes induced by repeated cocaine in mice. Biol Psychiatry. 2010; 68:223–230. [PubMed: 20359694]

Befort K, Filliol D, Decaillot FM, Gaveriaux-Ruff C, Hoehe MR, Kieffer BL. A single nucleotide polymorphic mutation in the human mu-opioid receptor severely impairs receptor signaling. J Biol Chem. 2001; 276:3130–3137. [PubMed: 11067846]

Bergen AW, Kokoszka J, Peterson R, Long JC, Virkkunen M, Linnoila M, Goldman D. Mu opioid receptor gene variants: lack of association with alcohol dependence. Mol Psychiatry. 1997; 2:490–494. [PubMed: 9399694]

Beyer A, Koch T, Schroder H, Schulz S, Hollt V. Effect of the A118G polymorphism on binding affinity, potency and agonist-mediated endocytosis, desensitization, and resensitization of the human mu-opioid receptor. J Neurochem. 2004; 89:553–560. [PubMed: 15086512]

Bond C, LaForge KS, Tian M, Melia D, Zhang S, Borg L, Gong J, Schluger J, Strong JA, Leal SM, Tischfield JA, Kreek MJ, Yu L. Single-nucleotide polymorphism in the human mu opioid receptor gene alters beta-endorphin binding and activity: possible implications for opiate addiction. Proc Natl Acad Sci U S A. 1998; 95:9608–9613. [PubMed: 9689128]

Bousman CA, Glatt SJ, Everall IP, Tsuang MT. Genetic association studies of methamphetamine use disorders: a systematic review and synthesis. Am J Med Genet B Neuropsychiatr Genet. 2009; 150B:1025–1049. [PubMed: 19219857]

Briant JA, Nielsen DA, Proudnikov D, Londono D, Ho A, Ott J, Kreek MJ. Evidence for association of two variants of the nociceptin/orphanin FQ receptor gene OPRL1 with vulnerability to develop opiate addiction in Caucasians. Psychiatr Genet. 2010; 20:65–72. [PubMed: 20032820]

Bruchas MR, Land BB, Chavkin C. The dynorphin/kappa opioid system as a modulator of stress-induced and pro-addictive behaviors. Brain Res. 2010; 1314:44–55. [PubMed: 19716811]

Cavalli-Sforza LL, Feldman MW. The application of molecular genetic approaches to the study of human evolution. Nat Genet. 2003; (33 Suppl):266–275. [PubMed: 12610536]

Chefer VI, Czyzyk T, Bolan EA, Moron J, Pintar JE, Shippenberg TS. Endogenous kappa-opioid receptor systems regulate mesoaccumbal dopamine dynamics and vulnerability to cocaine. J Neurosci. 2005; 25:5029–5037. [PubMed: 15901784]

Chen AC, LaForge KS, Ho A, McHugh PF, Kellogg S, Bell K, Schluger RP, Leal SM, Kreek MJ. Potentially functional polymorphism in the promoter region of prodynorphin gene may be associated with protection against cocaine dependence or abuse. Am J Med Genet. 2002; 114:429–435. [PubMed: 11992566]

Choi HS, Kim CS, Hwang CK, Song KY, Wang W, Qiu Y, Law PY, Wei LN, Loh HH. The opioid ligand binding of human mu-opioid receptor is modulated by novel splice variants of the receptor. Biochem Biophys Res Commun. 2006; 343:1132–1140. [PubMed: 16580639]

Chong RY, Oswald L, Yang X, Uhart M, Lin PI, Wand GS. The mu-opioid receptor polymorphism A118G predicts cortisol responses to naloxone and stress. Neuropsychopharmacology. 2006; 31:204–211. [PubMed: 16123758]

Clarke TK, Krause K, Li T, Schumann G. An association of prodynorphin polymorphisms and opioid dependence in females in a Chinese population. Addict Biol. 2009; 14:366–370. [PubMed: 19298317]

Comings DE, Blake H, Dietz G, Gade-Andavolu R, Legro RS, Saucier G, Johnson P, Verde R, MacMurray JP. The proenkephalin gene (PENK) and opioid dependence. Neuroreport. 1999; 10:1133–1135. [PubMed: 10321497]

Crettol S, Besson J, Croquette-Krokar M, Hammig R, Gothuey I, Monnat M, Deglon JJ, Preisig M, Eap CB. Association of dopamine and opioid receptor genetic polymorphisms with response to methadone maintenance treatment. Prog Neuropsychopharmacol Biol Psychiatry. 2008; 32:1722–1727. [PubMed: 18687376]

Crowley JJ, Oslin DW, Patkar AA, Gottheil E, DeMaria PA Jr, O'Brien CP, Berrettini WH, Grice DE. A genetic association study of the mu opioid receptor and severe opioid dependence. Psychiatr Genet. 2003; 13:169–173. [PubMed: 12960749]

Cruz-Gordillo P, Fedrigo O, Wray GA, Babbitt CC. Extensive changes in the expression of the opioid genes between humans and chimpanzees. Brain Behav Evol. 2010; 76:154–162. [PubMed: 21079395]

Crystal HA, Hamon S, Randesi M, Cook J, Anastos K, Lazar J, Liu C, Pearce L, Golub E, Valcour V, Weber KM, Holman S, Ho A, Kreek MJ. A C17T polymorphism in the mu opiate receptor is associated with quantitative measures of drug use in African American women. Addict Biol. 2010 in press.

Culpepper-Morgan JA, Kreek MJ. Hypothalamic-pituitary-adrenal axis hypersensitivity to naloxone in opioid dependence: a case of naloxone-induced withdrawal. Metabolism. 1997; 46:130–134. [PubMed: 9030816]

Dahl JP, Weller AE, Kampman KM, Oslin DW, Lohoff FW, Ferraro TN, O'Brien CP, Berrettini WH. Confirmation of the association between a polymorphism in the promoter region of the prodynorphin gene and cocaine dependence. Am J Med Genet B Neuropsychiatr Genet. 2005; 139B:106–108. [PubMed: 16184603]

Deb I, Chakraborty J, Gangopadhyay PK, Choudhury SR, Das S. Single-nucleotide polymorphism (A118G) in exon 1 of OPRM1 gene causes alteration in downstream signaling by mu-opioid receptor and may contribute to the genetic risk for addiction. J Neurochem. 2010; 112:486–496. [PubMed: 19891732]

Dlugos AM, Hamidovic A, Hodgkinson C, Shen PH, Goldman D, Palmer AA, de Wit H. OPRM1 gene variants modulate amphetamine-induced euphoria in humans. Genes Brain Behav. 2011; 10:199–209. [PubMed: 21029375]

Dores RM, Baron AJ. Evolution of POMC: origin, phylogeny, posttranslational processing, and the melanocortins. Ann N Y Acad Sci. 2011; 1220:34–48. [PubMed: 21388402]

Drakenberg K, Nikoshkov A, Horvath MC, Fagergren P, Gharibyan A, Saarelainen K, Rahman S, Nylander I, Bakalkin G, Rajs J, Keller E, Hurd YL. Mu opioid receptor A118G polymorphism in association with striatal opioid neuropeptide gene expression in heroin abusers. Proc Natl Acad Sci U S A. 2006; 103:7883–7888. [PubMed: 16682632]

Ducat E, Ray B, Bart G, Umemura Y, Varon J, Ho A, Kreek MJ. Mu-opioid receptor A118G polymorphism in healthy volunteers affects hypothalamic-pituitary-adrenal axis adrenocorticotropic hormone stress response to metyrapone. Addict Biol. 2011 in press.

Edenberg HJ, Wang J, Tian H, Pochareddy S, Xuei X, Wetherill L, Goate A, Hinrichs T, Kuperman S, Nurnberger JI Jr, Schuckit M, Tischfield JA, Foroud T. A regulatory variation in OPRK1, the gene encoding the kappa-opioid receptor, is associated with alcohol dependence. Hum Mol Genet. 2008; 17:1783–1789. [PubMed: 18319328]

Ehlers CL, Lind PA, Wilhelmsen KC. Association between single nucleotide polymorphisms in the mu opioid receptor gene (OPRM1) and self-reported responses to alcohol in American Indians. BMC Med Genet. 2008; 9:35. [PubMed: 18433502]

Filbey FM, Ray L, Smolen A, Claus ED, Audette A, Hutchison KE. Differential neural response to alcohol priming and alcohol taste cues is associated with DRD4 VNTR and OPRM1 genotypes. Alcohol Clin Exp Res. 2008; 32:1113–1123. [PubMed: 18540916]

Franke P, Nothen MM, Wang T, Neidt H, Knapp M, Lichtermann D, Weiffenbach O, Mayer P, Hollt V, Propping P, Maier W. Human delta-opioid receptor gene and susceptibility to heroin and alcohol dependence. Am J Med Genet. 1999; 88:462–464. [PubMed: 10490698]

Franke P, Wang T, Nothen MM, Knapp M, Neidt H, Albrecht S, Jahnes E, Propping P, Maier W. Nonreplication of association between mu-opioid-receptor gene (OPRM1) A118G polymorphism and substance dependence. Am J Med Genet. 2001; 105:114–119. [PubMed: 11424981]

Gavioli EC, Rizzi A, Marzola G, Zucchini S, Regoli D, Calo G. Altered anxiety-related behavior in nociceptin/orphanin FQ receptor gene knockout mice. Peptides. 2007; 28:1229–1239. [PubMed: 17499882]

Geijer T, Jonsson E, Neiman J, Gyllander A, Sedvall G, Rydberg U, Terenius L. Prodynorphin allelic distribution in Scandinavian chronic alcoholics. Alcohol Clin Exp Res. 1997; 21:1333–1336. [PubMed: 9347097]

Gelernter J, Gueorguieva R, Kranzler HR, Zhang H, Cramer J, Rosenheck R, Krystal JH. Opioid receptor gene (OPRM1, OPRK1, and OPRD1) variants and response to naltrexone treatment for alcohol dependence: results from the VA Cooperative Study. Alcohol Clin Exp Res. 2007; 31:555–563. [PubMed: 17374034]

Gelernter J, Kranzler H, Cubells J. Genetics of two mu opioid receptor gene (OPRM1) exon I polymorphisms: population studies, and allele frequencies in alcohol- and drug- dependent subjects. Mol Psychiatry. 1999; 4:476–483. [PubMed: 10523821]

Gerra G, Leonardi C, Cortese E, D'Amore A, Lucchini A, Strepparola G, Serio G, Farina G, Magnelli F, Zaimovic A, Mancini A, Turci M, Manfredini M, Donnini C. Human kappa opioid receptor gene (OPRK1) polymorphism is associated with opiate addiction. Am J Med Genet B Neuropsychiatr Genet. 2007; 144:771–775. [PubMed: 17373729]

Gieryk A, Ziolkowska B, Solecki W, Kubik J, Przewlocki R. Forebrain PENK and PDYN gene expression levels in three inbred strains of mice and their relationship to genotype- dependent morphine reward sensitivity. Psychopharmacology (Berl). 2010; 208:291–300. [PubMed: 19997907]

Glatt SJ, Bousman C, Wang RS, Murthy KK, Rana BK, Lasky-Su JA, Zhu SC, Zhang R, Li J, Zhang B, Li J, Lyons MJ, Faraone SV, Tsuang MT. Evaluation of OPRM1 variants in heroin dependence by family-based association testing and meta-analysis. Drug Alcohol Depend. 2007; 90:159–165. [PubMed: 17416470]

Gscheidel N, Sander T, Wendel B, Heere P, Schmidt LG, Rommelspacher H, Hoehe MR, Samochowiec J. Five exon 1 variants of mu opioid receptor and vulnerability to alcohol dependence. Pol J Pharmacol. 2000; 52:27–31. [PubMed: 10949117]

Hernandez-Avila CA, Covault J, Wand G, Zhang H, Gelernter J, Kranzler HR. Population-specific effects of the Asn40Asp polymorphism at the mu-opioid receptor gene (OPRM1) on HPA-axis activation. Pharmacogenet Genomics. 2007; 17:1031–1038. [PubMed: 18004207]

Hernandez-Avila CA, Wand G, Luo X, Gelernter J, Kranzler HR. Association between the cortisol response to opioid blockade and the Asn40Asp polymorphism at the mu-opioid receptor locus (OPRM1). Am J Med Genet B Neuropsychiatr Genet. 2003; 118:60–65. [PubMed: 12627468]

Hodgkinson CA, Yuan Q, Xu K, Shen PH, Heinz E, Lobos EA, Binder EB, Cubells J, Ehlers CL, Gelernter J, Mann J, Riley B, Roy A, Tabakoff B, Todd RD, Zhou Z, Goldman D. Addictions biology: haplotype-based analysis for 130 candidate genes on a single array. Alcohol Alcohol. 2008; 43:505–515. [PubMed: 18477577]

Hoehe MR, Kopke K, Wendel B, Rohde K, Flachmeier C, Kidd KK, Berrettini WH, Church GM. Sequence variability and candidate gene analysis in complex disease: association of mu opioid receptor gene variation with substance dependence. Hum Mol Genet. 2000; 9:2895–2908. [PubMed: 11092766]

Huang J, Young B, Pletcher MT, Heilig M, Wahlestedt C. Association between the nociceptin receptor gene (OPRL1) single nucleotide polymorphisms and alcohol dependence. Addict Biol. 2008; 13:88–94. [PubMed: 18269382]

Ide S, Kobayashi H, Tanaka K, Ujike H, Sekine Y, Ozaki N, Inada T, Harano M, Komiyama T, Yamada M, Iyo M, Ikeda K, Sora I. Gene polymorphisms of the mu opioid receptor in methamphetamine abusers. Ann N Y Acad Sci. 2004; 1025:316–324. [PubMed: 15542732]

Ide S, Kobayashi H, Ujike H, Ozaki N, Sekine Y, Inada T, Harano M, Komiyama T, Yamada M, Iyo M, Iwata N, Tanaka K, Shen H, Iwahashi K, Itokawa M, Minami M, Satoh M, Ikeda K, Sora I. Linkage disequilibrium and association with methamphetamine dependence/psychosis of mu-opioid receptor gene polymorphisms. Pharmacogenomics J. 2006; 6:179–188. [PubMed: 16402083]

Ito E, Xie G, Maruyama K, Palmer PP. A core-promoter region functions bi-directionally for human opioid-receptor-like gene ORL1 and its 5′-adjacent gene GAIP. J Mol Biol. 2000; 304:259–270. [PubMed: 11090272]

Jayaram-Lindstrom N, Hammarberg A, Beck O, Franck J. Naltrexone for the treatment of amphetamine dependence: a randomized, placebo-controlled trial. Am J Psychiatry. 2008a; 165:1442–1448. [PubMed: 18765480]

Jayaram-Lindstrom N, Konstenius M, Eksborg S, Beck O, Hammarberg A, Franck J. Naltrexone attenuates the subjective effects of amphetamine in patients with amphetamine dependence. Neuropsychopharmacology. 2008b; 33:1856–1863. [PubMed: 17957221]

Kakko J, von Wachenfeldt J, Svanborg KD, Lidstrom J, Barr CS, Heilig M. Mood and neuroendocrine response to a chemical stressor, metyrapone, in buprenorphine-maintained heroin dependence. Biol Psychiatry. 2008; 63:172–177. [PubMed: 17850768]

Kapur S, Sharad S, Singh RA, Gupta AK. A118G polymorphism in mu opioid receptor gene (*OPRM1*): association with opiate addiction in subjects of Indian origin. J Integr Neurosci. 2007; 6:511–522. [PubMed: 18181266]

Kellogg SH, McHugh PF, Bell K, Schluger JH, Schluger RP, LaForge KS, Ho A, Kreek MJ. The Kreek-McHugh-Schluger-Kellogg scale: a new, rapid method for quantifying substance abuse and its possible applications. Drug Alcohol Depend. 2003; 69:137–150. [PubMed: 12609695]

Kiefer F, Jahn H, Schick M, Wiedemann K. Alcohol self-administration, craving and HPA-axis activity: an intriguing relationship. Psychopharmacology (Berl). 2002; 164:239–240. [PubMed: 12404089]

Kim SG, Kim CM, Kang DH, Kim YJ, Byun WT, Kim SY, Park JM, Kim MJ, Oslin DW. Association of functional opioid receptor genotypes with alcohol dependence in Koreans. Alcohol Clin Exp Res. 2004; 28:986–990. [PubMed: 15252283]

King AC, Schluger J, Gunduz M, Borg L, Perret G, Ho A, Kreek MJ. Hypothalamic-pituitary-adrenocortical (HPA) axis response and biotransformation of oral naltrexone: preliminary examination of relationship to family history of alcoholism. Neuropsychopharmacology. 2002; 26:778–788. [PubMed: 12007748]

Knoll AT, Carlezon WA Jr. Dynorphin, stress, and depression. Brain Res. 2010; 1314:56–73. [PubMed: 19782055]

Kobayashi H, Hata H, Ujike H, Harano M, Inada T, Komiyama T, Yamada M, Sekine Y, Iwata N, Iyo M, Ozaki N, Itokawa M, Naka M, Ide S, Ikeda K, Numachi Y, Sora I. Association analysis of delta-opioid receptor gene polymorphisms in methamphetamine dependence/psychosis. Am J Med Genet B Neuropsychiatr Genet. 2006; 141B:482–486. [PubMed: 16741914]

Koch T, Kroslak T, Averbeck M, Mayer P, Schroder H, Raulf E, Hollt V. Allelic variation S268P of the human mu-opioid receptor affects both desensitization and G protein coupling. Mol Pharmacol. 2000; 58:328–334. [PubMed: 10908300]

Koob G, Kreek MJ. Stress, dysregulation of drug reward pathways, and the transition to drug dependence. Am J Psychiatry. 2007; 164:1149–1159. [PubMed: 17671276]

Kranzler HR, Gelernter J, O'Malley S, Hernandez-Avila CA, Kaufman D. Association of alcohol or other drug dependence with alleles of the mu opioid receptor gene (OPRM1). Alcohol Clin Exp Res. 1998; 22:1359–1362. [PubMed: 9756053]

Kraus J, Borner C, Giannini E, Hickfang K, Braun H, Mayer P, Hoehe MR, Ambrosch A, Konig W, Hollt V. Regulation of mu-opioid receptor gene transcription by interleukin-4 and influence of an allelic variation within a STAT6 transcription factor binding site. J Biol Chem. 2001; 276:43901–43908. [PubMed: 11572871]

Kraus J, Borner C, Giannini E, Hollt V. The role of nuclear factor kappaB in tumor necrosis factor-regulated transcription of the human mu-opioid receptor gene. Mol Pharmacol. 2003; 64:876–884. [PubMed: 14500744]

Kreek MJ. Medical safety and side effects of methadone in tolerant individuals. JAMA. 1973; 223:665–668. [PubMed: 4739193]

Kreek MJ, Bart G, Lilly C, LaForge KS, Nielsen DA. Pharmacogenetics and human molecular genetics of opiate and cocaine addictions and their treatments. Pharmacol Rev. 2005; 57:1–26. [PubMed: 15734726]

Kreek MJ, Koob GF. Drug dependence: stress and dysregulation of brain reward pathways. Drug Alcohol Depend. 1998; 51:23–47. [PubMed: 9716928]

Kreek MJ, LaForge KS, Butelman E. Pharmacotherapy of addictions. Nat Rev Drug Discov. 2002; 1:710–726. [PubMed: 12209151]

Kreek MJ, Wardlaw SL, Hartman N, Raghunath J, Friedman J, Schneider B, Frantz AG. Circadian rhythms and levels of beta-endorphin, ACTH, and cortisol during chronic methadone maintenance treatment in humans. Life Sci. 1983; 33(1):409–411. [PubMed: 6319894]

Kreek MJ, Zhou Y, Butelman ER, Levran O. Opiate and cocaine addiction: from bench to clinic and back to the bench. Curr Opin Pharmacol. 2009; 9:74–80. [PubMed: 19155191]

Kroslak T, LaForge KS, Gianotti RJ, Ho A, Nielsen DA, Kreek MJ. The single nucleotide polymorphism A118G alters functional properties of the human mu opioid receptor. J Neurochem. 2007; 103:77–87. [PubMed: 17877633]

Kuzmin, A.; Bazov, I.; Sheedy, D.; Garrick, T.; Harper, C.; Bakalkin, G. Brain Res. 2009. Expression of pronociceptin and its receptor is downregulated in the brain of human alcoholics; p. S80-85.

LaForge KS, Yuferov V, Kreek MJ. Opioid receptor and peptide gene polymorphisms: potential implications for addictions. Eur J Pharmacol. 2000; 410:249–268. [PubMed: 11134674]

Le Merrer J, Plaza-Zabala A, Del Boca C, Matifas A, Maldonado R, Kieffer BL. Deletion of the delta opioid receptor gene impairs place conditioning but preserves morphine reinforcement. Biol Psychiatry. 2011; 69:700–703. [PubMed: 21168121]

Leskela TT, Markkanen PM, Alahuhta IA, Tuusa JT, Petaja-Repo UE. Phe27Cys polymorphism alters the maturation and subcellular localization of the human delta opioid receptor. Traffic. 2009; 10:116–129. [PubMed: 19000170]

Levran O, Awolesi O, Linzy S, Adelson M, Kreek MJ. Haplotype block structure of the genomic region of the mu opioid receptor gene. J Hum Genet. 2011; 56:147–155. [PubMed: 21160491]

Levran O, Londono D, O'Hara K, Nielsen DA, Peles E, Rotrosen J, Casadonte P, Linzy S, Randesi M, Ott J, Adelson M, Kreek MJ. Genetic susceptibility to heroin addiction: a candidate gene association study. Genes Brain Behav. 2008; 7:720–729. [PubMed: 18518925]

Levran O, Londono D, O'Hara K, Randesi M, Rotrosen J, Casadonte P, Linzy S, Ott J, Adelson M, Kreek MJ. Heroin addiction in African Americans: a hypothesis-driven association study. Genes Brain Behav. 2009; 8:531–540. [PubMed: 19500151]

Li X, Keith DE Jr, Evans CJ. Mu opioid receptor-like sequences are present throughout vertebrate evolution. J Mol Evol. 1996; 43:179–184. [PubMed: 8703083]

Loh el W, Fann CS, Chang YT, Chang CJ, Cheng AT. Endogenous opioid receptor genes and alcohol dependence among Taiwanese Han. Alcohol Clin Exp Res. 2004; 28:15–19. [PubMed: 14745298]

Luo X, Kranzler HR, Zhao H, Gelernter J. Haplotypes at the OPRM1 locus are associated with susceptibility to substance dependence in European-Americans. Am J Med Genet B Neuropsychiatr Genet. 2003; 120:97–108. [PubMed: 12815747]

Mague SD, Blendy JA. OPRM1 SNP (A118G): involvement in disease development, treatment response, and animal models. Drug Alcohol Depend. 2010; 108:172–182. [PubMed: 20074870]

Mague SD, Isiegas C, Huang P, Liu-Chen LY, Lerman C, Blendy JA. Mouse model of OPRM1 (A118G) polymorphism has sex-specific effects on drug-mediated behavior. Proc Natl Acad Sci U S A. 2009; 106:10847–10852. [PubMed: 19528658]

Maher BS, Vladimirov VI, Latendresse SJ, Thiselton DL, McNamee R, Kang M, Bigdeli TB, Chen X, Riley BP, Hettema JM, Chilcoat H, Heidbreder C, Muglia P, Murrelle EL, Dick DM, Aliev F, Agrawal A, Edenberg HJ, Kramer J, Nurnberger J, Tischfield JA, Devlin B, Ferrell RE, Kirillova GP, Tarter RE, Kendler KS, Vanyukov MM. The AVPR1A gene and substance use disorders: association, replication, and functional evidence. Biol Psychiatry. 2011; 70:519–527. [PubMed: 21514569]

Margas W, Zubkoff I, Schuler HG, Janicki PK, Ruiz-Velasco V. Modulation of Ca2+ channels by heterologously expressed wild-type and mutant human mu-opioid receptors (hMORs) containing the A118G single-nucleotide polymorphism. J Neurophysiol. 2007; 97:1058–1067. [PubMed: 17151221]

Mayer P, Rochlitz H, Rauch E, Rommelspacher H, Hasse HE, Schmidt S, Hollt V. Association between a delta opioid receptor gene polymorphism and heroin dependence in man. Neuroreport. 1997; 8:2547–2550. [PubMed: 9261824]

McGeary JE, Monti PM, Rohsenow DJ, Tidey J, Swift R, Miranda R Jr. Genetic moderators of naltrexone's effects on alcohol cue reactivity. Alcohol Clin Exp Res. 2006; 30:1288–1296. [PubMed: 16899031]

Miller GM, Bendor J, Tiefenbacher S, Yang H, Novak MA, Madras BK. A mu-opioid receptor single nucleotide polymorphism in rhesus monkey: association with stress response and aggression. Mol Psychiatry. 2004; 9:99–108. [PubMed: 14699447]

Miranda R, Ray L, Justus A, Meyerson LA, Knopik VS, McGeary J, Monti PM. Initial evidence of an association between OPRM1 and adolescent alcohol misuse. Alcohol Clin Exp Res. 2010; 34:112–122. [PubMed: 19860800]

Murphy NP. The nociceptin/orphanin FQ system as a target for treating alcoholism. CNS Neurol Disord Drug Targets. 2010; 9:87–93. [PubMed: 20201819]

Nielsen DA, Ji F, Yuferov V, Ho A, Chen A, Levran O, Ott J, Kreek MJ. Genotype patterns that contribute to increased risk for or protection from developing heroin addiction. Mol Psychiatry. 2008; 13:417–428. [PubMed: 18195715]

Nikoshkov A, Drakenberg K, Wang X, Horvath MC, Keller E, Hurd YL. Opioid neuropeptide genotypes in relation to heroin abuse: dopamine tone contributes to reversed mesolimbic proenkephalin expression. Proc Natl Acad Sci U S A. 2008; 105:786–791. [PubMed: 18184800]

Nikoshkov A, Hurd YL, Yakovleva T, Bazov I, Marinova Z, Cebers G, Pasikova N, Gharibyan A, Terenius L, Bakalkin G. Prodynorphin transcripts and proteins differentially expressed and regulated in the adult human brain. FASEB J. 2005; 19:1543–1545. [PubMed: 16014400]

Nishizawa D, Han W, Hasegawa J, Ishida T, Numata Y, Sato T, Kawai A, Ikeda K. Association of mu-opioid receptor gene polymorphism A118G with alcohol dependence in a Japanese population. Neuropsychobiology. 2006; 53:137–141. [PubMed: 16679777]

Nomura A, Ujike H, Tanaka Y, Otani K, Morita Y, Kishimoto M, Morio A, Harano M, Inada T, Yamada M, Komiyama T, Sekine Y, Iwata N, Sora I, Iyo M, Ozaki N, Kuroda S. Genetic variant of prodynorphin gene is risk factor for methamphetamine dependence. Neurosci Lett. 2006; 400:158–162. [PubMed: 16529859]

O'Brien CP, Gastfriend DR, Forman RF, Schweizer E, Pettinati HM. Long-term opioid blockade and hedonic response: preliminary data from two open-label extension studies with extended-release naltrexone. Am J Addict. 2011; 20:106–112. [PubMed: 21314752]

O'Malley SS, Krishnan-Sarin S, Farren C, Sinha R, Kreek MJ. Naltrexone decreases craving and alcohol self-administration in alcohol-dependent subjects and activates the hypothalamo-pituitary-adrenocortical axis. Psychopharmacology (Berl). 2002; 160:19–29. [PubMed: 11862370]

Ono T, Kaneda T, Muto A, Yoshida T. Positive transcriptional regulation of the human mu opioid receptor gene by poly(ADP-ribose) polymerase-1 and increase of its DNA binding affinity based on polymorphism of G-172->T. J Biol Chem. 2009a; 284:20175–20183. [PubMed: 19447888]

Ono T, Muto A, Kaneda T, Arita E, Yoshida T. Novel linkage disequilibrium of single nucleotide polymorphisms in the transcriptional regulatory region of mu-opioid receptor gene in Japanese population. Biol Pharm Bull. 2009b; 32:721–723. [PubMed: 19336912]

Oroszi G, Anton RF, O'Malley S, Swift R, Pettinati H, Couper D, Yuan Q, Goldman D. OPRM1 Asn40Asp predicts response to naltrexone treatment: a haplotype-based approach. Alcohol Clin Exp Res. 2009; 33:383–393. [PubMed: 19053977]

Oslin DW, Berrettini W, Kranzler HR, Pettinati H, Gelernter J, Volpicelli JR, O'Brien CP. A functional polymorphism of the mu-opioid receptor gene is associated with naltrexone response in alcohol-dependent patients. Neuropsychopharmacology. 2003; 28:1546–1552. [PubMed: 12813472]

Pan YX. Identification of alternatively spliced variants from opioid receptor genes. Methods Mol Med. 2003; 84:65–75. [PubMed: 12703318]

Racz I, Schurmann B, Karpushova A, Reuter M, Cichon S, Montag C, Furst R, Schutz C, Franke PE, Strohmaier J, Wienker TF, Terenius L, Osby U, Gunnar A, Maier W, Bilkei-Gorzo A, Nothen M, Zimmer A. The opioid peptides enkephalin and beta-endorphin in alcohol dependence. Biol Psychiatry. 2008; 64:989–997. [PubMed: 18589403]

Ramchandani VA, Umhau J, Pavon FJ, Ruiz-Velasco V, Margas W, Sun H, Damadzic R, Eskay R, Schoor M, Thorsell A, Schwandt ML, Sommer WH, George DT, Parsons LH, Herscovitch P, Hommer D, Heilig M. A genetic determinant of the striatal dopamine response to alcohol in men. Mol Psychiatry. 2011; 16:809–817. [PubMed: 20479755]

Ray LA. Stress-induced and cue-induced craving for alcohol in heavy drinkers: preliminary evidence of genetic moderation by the OPRM1 and CRH-BP genes. Alcohol Clin Exp Res. 2011; 35:166–174. [PubMed: 21039637]

Ray LA, Hutchison KE. A polymorphism of the mu-opioid receptor gene (OPRM1) and sensitivity to the effects of alcohol in humans. Alcohol Clin Exp Res. 2004; 28:1789–1795. [PubMed: 15608594]

Ray LA, Hutchison KE. Effects of naltrexone on alcohol sensitivity and genetic moderators of medication response: a double-blind placebo-controlled study. Arch Gen Psychiatry. 2007; 64:1069–1077. [PubMed: 17768272]

Ray LA, Hutchison KE, Ashenhurst JR, Morrow AL. Naltrexone selectively elevates GABAergic neuroactive steroid levels in heavy drinkers with the Asp40 allele of the OPRM1 gene: a pilot investigation. Alcohol Clin Exp Res. 2010; 34:1479–1487. [PubMed: 20528823]

Ray R, Doyle GA, Crowley JJ, Buono RJ, Oslin DW, Patkar AA, Mannelli P, DeMaria PA Jr, O'Brien CP, Berrettini WH. A functional prodynorphin promoter polymorphism and opioid dependence. Psychiatr Genet. 2005; 15:295–298. [PubMed: 16314761]

Ray R, Ruparel K, Newberg A, Wileyto EP, Loughead JW, Divgi C, Blendy JA, Logan J, Zubieta JK, Lerman C. Human mu opioid receptor (OPRM1 A118G) polymorphism is associated with brain mu-opioid receptor binding potential in smokers. Proc Natl Acad Sci U S A. 2011; 108:9268–9273. [PubMed: 21576462]

Rockman MV, Hahn MW, Soranzo N, Zimprich F, Goldstein DB, Wray GA. Ancient and recent positive selection transformed opioid cis-regulation in humans. PLoS Biol. 2005; 3:e387. [PubMed: 16274263]

Rommelspacher H, Smolka M, Schmidt LG, Samochowiec J, Hoehe MR. Genetic analysis of the mu-opioid receptor in alcohol-dependent individuals. Alcohol. 2001; 24:129–135. [PubMed: 11522434]

Rouault M, Nielsen DA, Ho A, Kreek MJ, Yuferov V. Cell-specific effects of variants of the 68-base pair tandem repeat on prodynorphin gene promoter activity. Addict Biol. 2011; 16:334–346. [PubMed: 20731629]

Rubio G, Ponce G, Rodriguez-Jimenez R, Jimenez-Arriero MA, Hoenicka J, Palomo T. Clinical predictors of response to naltrexone in alcoholic patients: who benefits most from treatment with naltrexone? Alcohol Alcohol. 2005; 40:227–233. [PubMed: 15797885]

Rutten K, De Vry J, Bruckmann W, Tzschentke TM. Pharmacological blockade or genetic knockout of the NOP receptor potentiates the rewarding effect of morphine in rats. Drug Alcohol Depend. 2011; 114:253–256. [PubMed: 21095077]

Rutters F, Nieuwenhuizen AG, Lemmens SG, Bouwman F, Mariman E, Westerterp-Plantenga MS. Associations between anthropometrical measurements, body composition, single-nucleotide

polymorphisms of the hypothalamus/pituitary/adrenal (HPA) axis and HPA axis functioning. Clin Endocrinol (Oxf). 2011; 74:679–686. [PubMed: 21521257]

Sander T, Gscheidel N, Wendel B, Samochowiec J, Smolka M, Rommelspacher H, Schmidt LG, Hoehe MR. Human mu-opioid receptor variation and alcohol dependence. Alcohol Clin Exp Res. 1998; 22:2108–2110. [PubMed: 9884158]

Schinka JA, Town T, Abdullah L, Crawford FC, Ordorica PI, Francis E, Hughes P, Graves AB, Mortimer JA, Mullan M. A functional polymorphism within the mu-opioid receptor gene and risk for abuse of alcohol and other substances. Mol Psychiatry. 2002; 7:224–228. [PubMed: 11840318]

Schluger JH, Ho A, Borg L, Porter M, Maniar S, Gunduz M, Perret G, King A, Kreek MJ. Nalmefene causes greater hypothalamic-pituitary-adrenal axis activation than naloxone in normal volunteers: implications for the treatment of alcoholism. Alcohol Clin Exp Res. 1998; 22:1430–1436. [PubMed: 9802524]

Schwandt ML, Lindell SG, Higley JD, Suomi SJ, Heilig M, Barr CS. OPRM1 gene variation influences hypothalamic-pituitary-adrenal axis function in response to a variety of stressors in rhesus macaques. Psychoneuroendocrinology. 2011 in press.

Setiawan E, Pihl RO, Cox SM, Gianoulakis C, Palmour RM, Benkelfat C, Leyton M. The effect of naltrexone on alcohol's stimulant properties and self-administration behavior in social drinkers: influence of gender and genotype. Alcohol Clin Exp Res. 2011; 35:1134–1141. [PubMed: 21410481]

Shabalina SA, Zaykin DV, Gris P, Ogurtsov AY, Gauthier J, Shibata K, Tchivileva IE, Belfer I, Mishra B, Kiselycznyk C, Wallace MR, Staud R, Spiridonov NA, Max MB, Goldman D, Fillingim RB, Maixner W, Diatchenko L. Expansion of the human mu-opioid receptor gene architecture: novel functional variants. Hum Mol Genet. 2009; 18:1037–1051. [PubMed: 19103668]

Shi J, Hui L, Xu Y, Wang F, Huang W, Hu G. Sequence variations in the mu-opioid receptor gene (OPRM1) associated with human addiction to heroin. Hum Mutat. 2002; 19:459–460. [PubMed: 11933204]

Smith RJ, Doyle GA, Han AM, Crowley JJ, Oslin DW, Patkar AA, Mannelli P, DeMaria PA Jr, O'Brien CP, Berrettini WH. Novel exonic mu-opioid receptor gene (OPRM1) polymorphisms not associated with opioid dependence. Am J Med Genet B Neuropsychiatr Genet. 2005; 133B:105–109. [PubMed: 15558714]

Smolka M, Sander T, Schmidt LG, Samochowiec J, Rommelspacher H, Gscheidel N, Wendel B, Hoehe MR. mu-opioid receptor variants and dopaminergic sensitivity in alcohol withdrawal. Psychoneuroendocrinology. 1999; 24:629–638. [PubMed: 10399772]

Sturgess JE, George TP, Kennedy JL, Heinz A, Muller DJ. Pharmacogenetics of alcohol, nicotine and drug addiction treatments. Addict Biol. 2011; 16:357–376. [PubMed: 21362114]

Szeto CY, Tang NL, Lee DT, Stadlin A. Association between mu opioid receptor gene polymorphisms and Chinese heroin addicts. Neuroreport. 2001; 12:1103–1106. [PubMed: 11338173]

Tan EC, Tan CH, Karupathivan U, Yap EP. Mu opioid receptor gene polymorphisms and heroin dependence in Asian populations. Neuroreport. 2003; 14:569–572. [PubMed: 12657887]

Taqi MM, Bazov I, Watanabe H, Nyberg F, Yakovleva T, Bakalkin G. Prodynorphin promoter SNP associated with alcohol dependence forms noncanonical AP-1 binding site that may influence gene expression in human brain. Brain Res. 2011; 1385:18–25. [PubMed: 21338584]

Telkov M, Geijer T, Terenius L. Human prodynorphin gene generates several tissue-specific transcripts. Brain Res. 1998; 804:284–295. [PubMed: 9757065]

Tidey JW, Monti PM, Rohsenow DJ, Gwaltney CJ, Miranda R Jr, McGeary JE, MacKillop J, Swift RM, Abrams DB, Shiffman S, Paty JA. Moderators of naltrexone's effects on drinking, urge, and alcohol effects in non-treatment-seeking heavy drinkers in the natural environment. Alcohol Clin Exp Res. 2008; 32:58–66. [PubMed: 18028530]

Town T, Abdullah L, Crawford F, Schinka J, Ordorica PI, Francis E, Hughes P, Duara R, Mullan M. Association of a functional mu-opioid receptor allele (+118A) with alcohol dependency. Am J Med Genet. 1999; 88:458–461. [PubMed: 10490697]

Troisi A, Frazzetto G, Carola V, Di Lorenzo G, Coviello M, D'Amato FR, Moles A, Siracusano A, Gross C. Social hedonic capacity is associated with the A118G polymorphism of the mu-opioid receptor gene (OPRM1) in adult healthy volunteers and psychiatric patients. Soc Neurosci. 2011; 6:88–97. [PubMed: 20486014]

Tuusa JT, Petaja-Repo UE. Phe27Cys polymorphism of the human delta opioid receptor predisposes cells to compromised calcium signaling. Mol Cell Biochem. 2011; 351:173–181. [PubMed: 21234650]

Vallender EJ, Ruedi-Bettschen D, Miller GM, Platt DM. A pharmacogenetic model of naltrexone-induced attenuation of alcohol consumption in rhesus monkeys. Drug Alcohol Depend. 2010; 109:252–256. [PubMed: 20153935]

Vanyukov MM, Tarter RE, Kirisci L, Kirillova GP, Maher BS, Clark DB. Liability to substance use disorders: 1. Common mechanisms and manifestations. Neurosci Biobehav Rev. 2003; 27:507–515. [PubMed: 14599432]

Wand GS, McCaul M, Yang X, Reynolds J, Gotjen D, Lee S, Ali A. The mu-opioid receptor gene polymorphism (A118G) alters HPA axis activation induced by opioid receptor blockade. Neuropsychopharmacology. 2002; 26:106–114. [PubMed: 11751037]

Wang D, Quillan JM, Winans K, Lucas JL, Sadee W. Single nucleotide polymorphisms in the human mu opioid receptor gene alter basal G protein coupling and calmodulin binding. J Biol Chem. 2001; 276:34624–34630. [PubMed: 11457836]

Weber JL, May PE. Dinucleotide repeat polymorphism at the PENK locus. Nucleic Acids Res. 1990; 18:2200.

Wei SG, Zhu YS, Lai JH, Xue HX, Chai ZQ, Li SB. Association between heroin dependence and prodynorphin gene polymorphisms. Brain Res Bull. 2011; 85:238–242. [PubMed: 21382455]

Wick MJ, Minnerath SR, Roy S, Ramakrishnan S, Loh HH. Expression of alternate forms of brain opioid ‘orphan’ receptor mRNA in activated human peripheral blood lymphocytes and lymphocytic cell lines. Brain Res Mol Brain Res. 1995; 32:342–347. [PubMed: 7500847]

Williams TJ, LaForge KS, Gordon D, Bart G, Kellogg S, Ott J, Kreek MJ. Prodynorphin gene promoter repeat associated with cocaine/alcohol codependence. Addict Biol. 2007; 12:496–502. [PubMed: 17559549]

Wittmann W, Schunk E, Rosskothen I, Gaburro S, Singewald N, Herzog H, Schwarzer C. Prodynorphin-derived peptides are critical modulators of anxiety and regulate neurochemistry and corticosterone. Neuropsychopharmacology. 2009; 34:775–785. [PubMed: 18800067]

Xie Z, Li Z, Guo L, Ye C, Li J, Yu X, Yang H, Wang Y, Chen C, Zhang D, Liu-Chen LY. Regulator of G protein signaling proteins differentially modulate signaling of mu and delta opioid receptors. Eur J Pharmacol. 2007; 565:45–53. [PubMed: 17433292]

Xu J, Xu M, Hurd YL, Pasternak GW, Pan YX. Isolation and characterization of new exon 11-associated N-terminal splice variants of the human mu opioid receptor gene. J Neurochem. 2009; 108:962–972. [PubMed: 19077058]

Xu K, Liu XH, Nagarajan S, Gu XY, Goldman D. Relationship of the delta-opioid receptor gene to heroin abuse in a large Chinese case/control sample. Am J Med Genet. 2002; 110:45–50. [PubMed: 12116270]

Xuei X, Dick D, Flury-Wetherill L, Tian HJ, Agrawal A, Bierut L, Goate A, Bucholz K, Schuckit M, Nurnberger J Jr, Tischfield J, Kuperman S, Porjesz B, Begleiter H, Foroud T, Edenberg HJ. Association of the kappa-opioid system with alcohol dependence. Mol Psychiatry. 2006; 11:1016–1024. [PubMed: 16924269]

Xuei X, Flury-Wetherill L, Almasy L, Bierut L, Tischfield J, Schuckit M, Nurnberger JI Jr, Foroud T, Edenberg HJ. Association analysis of genes encoding the nociceptin receptor (OPRL1) and its endogenous ligand (PNOC) with alcohol or illicit drug dependence. Addict Biol. 2008; 13:80–87. [PubMed: 17910740]

Xuei X, Flury-Wetherill L, Bierut L, Dick D, Nurnberger J Jr, Foroud T, Edenberg HJ. The opioid system in alcohol and drug dependence: Family-based association study. Am J Med Genet B Neuropsychiatr Genet. 2007; 144:877–884. [PubMed: 17503481]

Yuferov V, Fussell D, LaForge KS, Nielsen DA, Gordon D, Ho A, Leal SM, Ott J, Kreek MJ. Redefinition of the human kappa opioid receptor gene (OPRK1) structure and association of haplotypes with opiate addiction. Pharmacogenetics. 2004; 14:793–804. [PubMed: 15608558]

Yuferov V, Ji F, Nielsen DA, Levran O, Ho A, Morgello S, Shi R, Ott J, Kreek MJ. A functional haplotype implicated in vulnerability to develop cocaine dependence is associated with reduced PDYN expression in human brain. Neuropsychopharmacology. 2009; 34:1185–1197. [PubMed: 18923396]

Yuferov V, Levran O, Proudnikov D, Nielsen DA, Kreek MJ. Search for genetic markers and functional variants involved in the development of opiate and cocaine addiction and treatment. Ann N Y Acad Sci. 2010; 1187:184–207. [PubMed: 20201854]

Zhang D, Shao C, Shao M, Yan P, Wang Y, Liu Y, Liu W, Lin T, Xie Y, Zhao Y, Lu D, Li Y, Jin L. Effect of mu-opioid receptor gene polymorphisms on heroin-induced subjective responses in a Chinese population. Biol Psychiatry. 2007; 61:1244–1251. [PubMed: 17157823]

Zhang H, Gelernter J, Gruen JR, Kranzler HR, Herman AI, Simen AA. Functional impact of a single-nucleotide polymorphism in the OPRD1 promoter region. J Hum Genet. 2010; 55:278–284. [PubMed: 20300121]

Zhang H, Kranzler HR, Weiss RD, Luo X, Brady KT, Anton RF, Farrer LA, Gelernter J. Pro-opiomelanocortin gene variation related to alcohol or drug dependence: evidence and replications across family- and population-based studies. Biol Psychiatry. 2009; 66:128–136. [PubMed: 19217079]

Zhang H, Kranzler HR, Yang BZ, Luo X, Gelernter J. The OPRD1 and OPRK1 loci in alcohol or drug dependence: OPRD1 variation modulates substance dependence risk. Mol Psychiatry. 2008; 13:531–543. [PubMed: 17622222]

Zhang Y, Wang D, Johnson AD, Papp AC, Sadee W. Allelic expression imbalance of human mu opioid receptor (OPRM1) caused by variant A118G. J Biol Chem. 2005; 280:32618–32624. [PubMed: 16046395]

Zimprich A, Kraus J, Woltje M, Mayer P, Rauch E, Hollt V. An allelic variation in the human prodynorphin gene promoter alters stimulus-induced expression. J Neurochem. 2000; 74:472–477. [PubMed: 10646497]

Table 1

Association studies of drug addiction and related phenotype

Publication[1]	Population		Addiction						Controls		Genes							
			OD	CD	AD	AD (Fam)[2]	DD	MD			OPRM1	OPRK1	OPRD1	OPRL1	POMC	PDYN	PENK	PNOC
(Bart et al. 2004)	E	139						170										
(Bart et al. 2005)	E			389				170										
(Bergen et al. 1997)	EA			100														
	E			324														
	NA			367														
(Bousman et al. 2010)	EA						117	76										
(Briant et al. 2010)	EA	100						76										
	AA	59						44										
	His	94						29										
(Chen et al. 2002)	EA		18					43										
	AA		49					33										
	His		13					9										
(Clarke et al. 2009)	As	484						374										
(Comings et al. 1999)	EA	31				89		132										
(Crowley et al. 2003)	EA	124						100										
	AA	89						96										
(Dahl et al. 2005)	AA		167					88										
(Deb et al. 2009)	As	87		53				82										
(Dlugos et al. 2011)	EA							162[3]										
(Drakenberg et al. 2006)	EA	78						40										

Publication[1]	Population		Addiction						Controls		Genes							
			OD	CD	AD	AD (Fam)[2]	DD	MD			OPRM1	OPRK1	OPRD1	OPRL1	POMC	PDYN	PENK	PNOC
(Edenberg et al. 2008)	EA			215	219													
(Ehlers et al. 2008)	NA			251														
(Franke et al. 1999)	E	233						173										
(Franke et al. 2001)	E	287			111			365										
	E			221	75			365										
(Geijer et al. 1997)	E			70				55										
(Gelernter et al. 1999)	Mix[4]	79	202	100				116										
(Gerra et al. 2007)	E	106						70										
(Glatt et al. 2007)	As				473													
(Gscheidel et al. 2000)	E			327				340										
(Hoehe et al. 2000)	AA	33	125					51										
(Huang et al. 2008)	E			189				167										
(Ide et al. 2004)	As						138	213										
(Ide et al. 2006)	As						128	232										
(Kapur et al. 2007)	As	123						156										
(Kim et al. 2004)	As			112				140										
(Kobayashi et al. 2006)	As						170	260										
(Kranzler et al. 1998)	AA	11	70	39				34										
	EA	22	84	201				84										
(Levran et al. 2008)	EA	412						184										

Publication[1]	Population		Addiction						Controls		Genes							
			OD	CD	AD	AD (Fam)[2]	DD	MD			OPRM1	OPRK1	OPRD1	OPRL1	POMC	PDYN	PENK	PNOC
(Levran et al. 2009)	AA	202						167										
(Loh el et al. 2004)	As			158				149										
(Luo et al. 2003)	EA					318		179										
	AA					124		55										
(Maher et al. 2011)	EA					359		398										
(Mayer et al. 1997)	E	103						115										
(Nishizawa et al. 2006)	As			64				74										
(Nomura et al. 2006)	As						143	209										
(Racz et al. 2008)	E			247				247										
(Sander et al. 1998)	E			327				340										
(Schinka et al. 2002)	EA			179				297										
(Shi et al. 2002)	As	145						48										
(Smith et al. 2005)	AA	76						71										
	EA	94						57										
(Szeto et al. 2001)	As	200						97										
(Town et al. 1999)	EA			105				122										
(Wei et al. 2011)	As	304						300										
(Williams et al. 2007)	EA		26					53										
	AA		110					49										
	His		25					12										
(Xu et al. 2002)	As	450			219			304										

Publication[1]	Population		Addiction						Controls		Genes							
			OD	CD	AD	AD (Fam)[2]	DD	MD			OPRM1	OPRK1	OPRD1	OPRL1	POMC	PDYN	PENK	PNOC
(Xuei et al. 2006)	EA				219													
(Xuei et al. 2007)	EA	83			219	508		832										
(Xuei et al. 2008)	EA	83				508		832										
(Yuferov et al. 2004)	EA	65						64										
	AA	36						34										
	His	35						25										
(Yuferov et al. 2009)	EA		82					65										
	AA		204															
(Zhang et al. 2007)	As	336[5]																
(Zhang et al. 2006)	EA	91	171	318				338										
(Zhang et al. 2008)	EA	111	225	557				443										
(Zhang et al. 2009)	AA	455			319			199										
	EA	336			313			483										

[1]The list is sorted by alphabetical order of the first authors; DD; Illicit drug dependence (marijuana, cocaine, stimulant, sedative or opioid), substance dependence, or substance use disorder;

[2]COGA families with AD;

[3]subjective response to amphetamine;

[4]EA, AA, His;

[5]heroin-induced positive responses on first use. Abbreviation: As; Asian; E; European; EA; European Americans; AA; African Americans; His; Hispanics; NA; Native Americans.

Table 2

Opioid system gene variants reported to be associated with specific drug addictions

SNP	Location	Addictions						References[7]
		OD	CD	AD	DD	MD	Other	
OPRM1								
rs1799971	exon 1	As, E, EA		As, E, EA				(e.g. Bart et al. 2004; Bart et al. 2005. For full list see text)
rs1799972	exon 1						AA[1]	(Levran et al. 2008; Levran et al. 2009; Crawley et al. 2003; Crystal et al. 2011; Kapur et al. 2007; Xu et al. 2002; Glatt et al. 2007; Hoehe et al. 2000)
rs1461773	intron 1			AI				(Ehlers et al. 2008)
rs2075572	intron 2			AI		As		(Zhang et al. 2006; Ehlers et al. 2008; Ide et al. 2006; Zhang et al. 2007; Xuei et al. 2007; Hernandez-Avila et al. 2007; Bergen et al. 1997)
rs2281617	3′ region						EA[5]	(Levran et al. 2008; Levran et al. 2009; Dlugos et al. 2011)
rs3778148	intron 1			AI				(Ehlers et al. 2008)
rs3778151	intron 1	EA, As						(Levran et al. 2008; Levran et al. 2009; Zhang et al. 2007)
rs3823010	intron 1				EA			(Zhang et al. 2006)
rs483481	3′ region				EA			(Maher et al. 2011)
rs495491	intron 1			EA	EA			(Zhang et al. 2006; Xuei et al. 2007; Hernandez-Avila et al. 2007)
rs510769	intron 1						EA[2]	(Levran et al. 2008; Levran et al. 2009; Dlugos et al. 2011; Zhang et al. 2007; Xuei et al. 2007)
rs524731	intron 1			AI				(Zhang et al. 2006; Ehlers et al. 2008; Xuei et al. 2007)
rs534673	intron 1	As						(Zhang et al. 2007) originally called rs696522
rs548646	intron 3			AI				(Zhang et al. 2006; Ehlers et al. 2008; Xuei et al. 2007)
rs553202	intron 1			AI				(Ehlers et al. 2008)
rs648007	intron 3			AI				(Ehlers et al. 2008; Xuei et al. 2007)
rs648893	intron 3			EA				(Zhang et al. 2006; Ehlers et al. 2008; Xuei et al. 2007; Hernandez-Avila et al. 2007)
rs609148	intron 3			EA				(Zhang et al. 2006; Ide et al. 2006; Xuei et al. 2007; Hernandez-Avila et al. 2007)
rs681243	intron 3			AI				(Ehlers et al. 2008)
rs9479757	intron 2						As[3;4]	(Ide et al. 2006; Shi et al. 2002)
OPRK1								
rs1051660	exon 2	E, His						(Yuferov et al. 2004; Gerra et al. 2007; Xuei et al. 2006; Zhang et al. 2008; Loh el et al. 2004)
rs12548098	intron 2		EA					(Xuei et al. 2006)

Hum Genet. Author manuscript; available in PMC 2013 July 24.

SNP	Location	Addictions						References[7]
		OD	CD	AD	DD	MD	Other	
rs16918941	intron 2		EA					(Xuei et al. 2006)
rs35991105	5′ region			EA				(Edenberg et al. 2008)
rs6473797	intron 2	EA	EA					(Levran 2008; 2009; Xuei 2006)
rs6985606	intron 2		EA					(Xuei et al. 2006; Zhang et al. 2008)
rs997917	intron 2		EA					(Xuei et al. 2006; Zhang et al. 2008)
OPRD1								
rs1042114	exon 1	EA						(Zhang et al. 2008; Xuei et al. 2007; Xu et al. 2002)
rs204055	intron 1			EA				(Levran et al. 2008; Levran et al. 2009; Xuei 2007)
rs2234918	exon 3	E			EA			(Mayer et al. 1997; Franke et al. 1999; Xu et al. 2002; Loh el et al. 2004; Zhang et al. 2008; Levran et al. 2008; Levran et al. 2009; Kobayashi et al. 2006)
rs2236857	intron 1	EA						(Levran et al. 2008; Levran et al. 2009; Zhang et al. 2008; Xuei et al. 2007)
rs2236861	intron 1	EA						(Levran et al. 2008; Levran et al. 2009)
rs2298896	intron 1	EA						(Levran et al. 2008; Levran et al. 2009; Zhang et al. 2008)
rs3766951	intron 1	EA						(Levran et al. 2008; Levran et al. 2009)
OPRL1								
rs6010718	intron 1			E				(Huang et al. 2008)
rs6090041	intron 1	EA,AA						(Briant et al. 2010; Levran et al. 2008; Levran et al. 2009; Xuei et al. 2008)
rs6090043	intron 1	EA,AA						(Xuei et al. 2008; Briant et al. 2010; Levran et al. 2008; Levran et al. 2009)
rs6512305	intron 1	EA						(Xuei et al. 2008; Levran et al. 2008; Levran et al. 2009)
POMC								
rs1009388	intron 1	EA						(Xuei et al. 2007)
rs1042571	3′ UTR	EA						(Rutters et al. 2011; Xuei et al. 2007)
rs12473543	intron 2	EA						(Xuei et al. 2007)
rs1866146	3′ region	EA, AA	EA, AA	EA				(Zhang et al. 2009)
rs3769671	Intron 1			E				(Racz et al. 2008; Levran et al. 2008; Levran et al. 2009; Zhang et al. 2009)
rs6713532	Intron 3		EA	EA				(Zhang et al. 2009; Levran 2008; 2009; Xuei 2007)
rs6719226	5′ region	AA						(Zhang et al. 2009; Levran et al. 2008; Levran et al. 2009)
rs934778	Intron 1	EA		EA				(Xuei et al. 2007)
PDYN								

Hum Genet. Author manuscript; available in PMC 2013 July 24.

SNP	Location	Addictions						References[7]
		OD	CD	AD	DD	MD	Other	
rs1022563	3′ region	As						(Clarke et al. 2009; Wei et al. 2011)
rs10485703	3′ UTR		EA	EA				(Levran et al. 2008; Levran et al. 2009; Xuei et al. 2006; Yuferov et al. 2009)
rs10854244	5′ region			EA				(Xuei et al. 2006)
rs1997794	5′ region	As		EA				(Levran et al. 2008; Levran et al. 2009; Xuei et al. 2006; Geijer et al. 1997; Clarke et al. 2009; Yuferov et al. 2009)
rs2235749	3′ UTR	As	EA	EA				(Taqi et al. 2011; Wei et al. 2011; Yuferov et al. 2009; Xuei et al. 2006)
rs35286281	5′ region		AA, His			As		(Wei et al. 2011; Chen et al. 2002; Dahl et al. 2005; Williams et al. 2007; Nomura et al. 2006)
rs6035222	intron 3			EA				(Levran et al. 2008; Levran et al. 2009; Xuei et al. 2006)
rs6045784	3′ region			EA				(Xuei et al. 2006)
rs6045819	exon 4		EA	EA				(Xuei et al. 2006; Yuferov et al. 2009)
rs6045868	intron 2			EA				(Xuei et al. 2006)
rs910079	3′ UTR	As	EA	EA				(Yuferov et al. 2009; Wei et al. 2011)
rs910080	3′ UTR		EA	EA				(Xuei et al. 2006; Yuferov et al. 2009)
PENK								
rs12545109	3′ region			E				(Racz et al. 2008)
rs1437277	intron 3	EA						(Xuei et al. 2007; Levran et al. 2008; Levran et al. 2009)
rs1975285	intron 2	EA						(Xuei et al. 2007; Levran et al. 2008; Levran et al. 2009)
rs2576581	5′ region			E				(Racz et al. 2008)
rs3138832	3′ region						E[6]	(Nikoshkov et al. 2008)
rs3219515	5′ region	EA						(Comings et al. 1999)
PNOC								
rs17058952	5′ region			EA				(Xuei et al. 2008)
rs351779	3′ region			EA				(Xuei et al. 2008)
rs4732636	5′ region				EA			(Xuei et al. 2008)

The SNPs are sorted by rs number for each gene.

Abbreviations: OD; opioid dependence; CD; cocaine dependence; AD; alcohol dependence; MD; amphetamine dependence; As; Asian; E; European; EA; European Americans; AA; African Americans; His; Hispanics; NA; Native Americans. Other:

[1] quantitative measure for cocaine and alcohol use;

[2] Response to amphetamine;

[3] MAP psychosis;

[4] Heroin intake dose;

[5] Euphoria; energy and stimulation after amphetamine use;

[6] heroin abuse.

[7] The references listed are all the studies that analyzed the specific SNP, including the one/s that identified the association in the specific population indicated in the specific addiction column.