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A review of opioid addiction genetics

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Opioid use disorder (OUD) affects millions of people worldwide and the risk of developing the disorder has a significant genetic component according to twin and family studies. Identification of the genetic variants underlying this inherited risk has focused on two different methods: candidate gene studies and genome-wide association studies (GWAS). The most studied candidate genes have included the mu-opioid receptor (*OPRM1*), the delta-opioid receptor (*OPRD1*), the dopamine D2 receptor (*DRD2*), and brain-derived neurotrophic factor (*BDNF*). Variants in these genes have been associated with relatively small, but reproducible, effects on OUD risk. More recently, GWAS have identified potential associations with variants in *KCNG2*, *KCNC1*, *CNIH3*, *APBB2*, and *RGMA*. In total the genetic associations identified so far explain only a small portion of OUD risk. GWAS of OUD is still in the early stages when compared to studies of other psychiatric disorders, such as schizophrenia, which have found many relevant variants with small effect sizes only after large meta-analyses. Substantial increases in cohort sizes will likely be necessary in the OUD field to achieve similar results. In addition, it will be important for future studies of OUD to incorporate rare variants, epigenetics, and gene × environment interactions into models in order to better explain the observed heritability.

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Opioid use disorder (OUD) is a global epidemic and opioid-related overdose deaths have risen dramatically in recent years. There is clear genetic contribution to OUD risk, with heritability estimates of 23–54% based on twin and family studies [1,2]. Understanding the specific genes and variants involved can provide a better understanding of the biology of addiction and help identify individuals at the highest risk. This short review will cover the most well studied variants from candidate gene studies, as well as current genome-wide association study (GWAS) findings.

Opioid receptor genes

The mu-opioid receptor (MOR) is encoded by the *OPRM1* gene. Activation of MOR signaling by endogenous peptides (e.g. beta-endorphin), opioid analgesics, or illicit drugs results in downstream dopamine release in ventral striatum and medial prefrontal cortex and rewarding effects. *OPRM1* polymorphisms that affect MOR function or expression could alter this reward pathway and are therefore strong candidates for affecting OUD risk. There are two common variants in exon 1 of *OPRM1* that alter the MOR amino acid sequence: rs1799972, which is found predominantly in individuals of African descent, and rs1799971 (aka A118G), which is common in all non-African populations. Although there is a wealth of evidence indicating that rs1799971 genotype affects MOR function [3–6], case–control studies of this variant in OUD have produced equivocal results. Many of these studies have found no effect of the variant across multiple populations of African, Asian, or European ancestry [7–12], though some significant associations have been noted [3,13–15]. A meta-analysis from 2009 found no association between rs1799971 and OUD, but noted substantial variability between cohorts that could be the result of methodological differences or genetic background [16].

One underlying issue might be lack of statistical power in individual studies, if rs1799971 has a relatively small effect size. Schwantes-An *et al.* meta-analyzed rs1799971 genotype in the context of substance dependence (nicotine, alcohol, cannabis, cocaine, and/or opioid) in a large population of European descent (case $n = 9064$, control $n = 7844$) [17•]. They found a small (odds ratio (OR) = 0.90), but significant, effect of genotype on substance dependence risk. In analyses of the individual substances, rs1799971 was found to have similar effect sizes regardless of drug. However, none of these associations were significant due to the reduced sample size (opioid dependence: case $n = 2139$, control $n = 5168$; OR = 0.84).

Variants that do not alter the amino acid sequence can also be relevant to gene function, possibly by affecting gene expression. Hancock *et al.* identified 16 polymorphisms within *OPRM1* that were associated with the expression levels of *OPRM1* transcript in the prefrontal cortex [18]. One variant, rs3778150, was significantly associated with opioid dependence in a mixed population of African-Americans and European-Americans (case $n = 2004$,

control $n = 8753$). The effect of rs3778150 was replicated in an independent population of European descent (case $n = 1976$, control $n = 3144$), whereas the effect was the same direction but not significant in a much smaller African-American replication sample (case $n = 307$, control $n = 545$). The study also described an interaction between rs3778150 and rs1799971; rs1799971 was only associated with opioid dependence in the presence of the C allele of rs3778150. These results suggest a possibility that disparate findings for rs1799971 across different populations may be partially due to differences in relevant genetic background (Table 1).

The *OPRD1* gene encodes the delta-opioid receptor (DOR). DOR is not the primary target of any commonly abused opioids; however, the receptor is involved in reward pathways [19], and evidence suggests it regulates factors with clear connections to substance use, such as mood and contextual learning [20,21]. Levran *et al.* performed a candidate gene analysis in heroin-dependent subjects of European descent (case $n = 412$, control $n = 184$) [7], and nominally significant associations were observed for three variants in *OPRD1*: rs2236861, rs2236857, and rs3766951. In a larger Australian cohort (case $n = 1459$, control $n = 1495$), rs2236857 and rs3766951 were significantly associated with opioid dependence [22], while rs2236861 remained nominally significant. A European study (case $n = 142$, control $n = 142$) did find a significant association between rs2236861 and opioid dependence [23]. In contrast, Randesi *et al.* found rs2236861 to be significant associated only with non-dependent opioid use (case $n = 163$, control $n = 153$) but not opioid dependence (case $n = 281$) in a Dutch population [24], with no effect observed for either rs2236857 or rs3766951. The variation between European and Australian subjects or simply sample size might explain the divergent results in *OPRD1*. In total, the literature supports an effect of *OPRD1* intron 1 genotype on opioid abuse or dependence risk; however, the identity of the causative single nucleotide polymorphism (SNP) and the specific nature of the effect still require additional research (Table 1).

Other candidate genes

Dopamine release and post-synaptic receptor activation underlies the rewarding effects of opioids. *DRD2* encodes the dopamine D2 receptor and is located <10 kb downstream of *ANKK1*, a gene encoding a serine/threonine protein kinase. The DRD2/ANKK1 locus contains two commonly studied polymorphisms: rs1800497 (aka Taq1A), a missense variant in exon 8 of *ANKK1*, and rs1079597 (aka Taq1B), located in intron 1 of *DRD2*. Rs1800497 and rs1079597 are in relatively high linkage disequilibrium ($r^2 = 0.5–1.0$) in almost all non-African populations, meaning the two variants are inherited together more often than would be expected by chance in those ethnic groups [25]. Both variants have been associated with opioid dependence in Han Chinese [26–28], with one study noting that the effect was largest in subjects who developed opioid dependence later in life [26]. Significant associations for rs1800497 and rs1079597 have also been found in Europeans (case $n = 303$, control $n = 555$) [29]. Meta-analyses from 2015 (case $n = 3423$, control $n = 3096$) and 2018 (case $n = 4529$, control $n = 4168$) both found a small effect of rs1800497 on OUD risk, further supporting the relevance of this variant in at least Asian and European populations [30,31]. Other variants and haplotypes (i.e. multiple variants on a single chromosome that are inherited together) across the DRD2/ANKK1 locus have also been implicated in OUD; however, most of these findings have yet to be replicated [26,27,30] (Table 1).

The brain-derived neurotrophic factor gene (*BDNF*) encodes a factor involved in neuronal growth and differentiation and contains a SNP in exon 2 that alters the amino acid sequence (rs6265, aka Val66Met). The most convincing results for this variant come from Asian populations, who have a minor allele frequency of 49% [25]. In Han Chinese individuals, the C allele of rs6265 was

Table 1

Selected findings from candidate gene studies of opioid use disorder

Gene symbol	Gene name	Variants	Findings	References
OPRM1	Mu-Opioid Receptor	rs1799971	Possible small effect on OUD risk in individuals of European descent	[17•]
		rs3778150	Associated with OUD in European-Americans and African-Americans. Expression QTL for *OPRM1* in prefrontal cortex	[18]
OPRD1	Delta-Opioid Receptor	rs2236857 rs2236861 rs3766951	Associated with OUD in individuals of European descent	[7,22,23]
DRD2	Dopamine Receptor D2	rs1800497 rs1079597	Associated with OUD in individuals of Asian or European descent	[26–31]
BDNF	Brain-Derived Neurotrophic Factor	rs6265	Associated with OUD in individuals of Asian descent. Possible association with age of onset	[32–35]

QTL, quantitative train locus; OUD, opioid use disorder.