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A Review of Opioid Addiction Genetics

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Abstract

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.

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.

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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- 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.

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.

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 <10kb 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].

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 significantly associated with increased risk of opioid dependence in two independent samples from central China (case n = 487, control n = 492) and Taiwan (case n = 200, control n = 122) [32, 33]. A meta-analysis found that the C/C genotype was more common in heroin-dependent Asian subjects than in healthy controls (case n = 1172, control n = 1211) [34]. Genotype at rs6265 may also predict the age of onset of OUD, although conflicting results have been observed [32, 33, 35].

Genome-Wide Association Studies

The previously mentioned candidate gene studies are hypothesis-driven and therefore only analyze genes with known connections to the phenotype of interest. This inherent bias can result in many relevant genes being overlooked. An unbiased method for identifying genetic variants associated with a phenotype is the genome-wide association study (GWAS), in which statistical analyses are performed on a large number of polymorphisms across the entire genome. One of the first GWAS of OUD compared the frequencies of 10,000 SNPs between 104 heroin dependent patients of European descent and 101 controls [36]. No significant associations were found after multiple testing correction, most likely due to the small cohort size and lack of statistical power. The same group published a larger study containing an analysis of 100,000 variants in 325 methadone-maintained heroin addicts and 250 controls [37]. This newer study included subjects of both African (case n = 125, control n = 100) and European (case n = 200, control n = 150) ancestry. A single intergenic variant (rs10494334) was significant in the patients of European descent after multiple testing correction ($p = 0.035$), whereas no SNPs were significant in African-Americans. Another relatively small GWAS of Han Chinese patients diagnosed with heroin dependence (case n = 370, control n = 134) did not identify any variants reaching genome-wide significance ($p < 5 \times 10^{-8}$) [38].

The first large scale GWAS of OUD was published in 2013 [39*]. The authors analyzed a total of 5432 African-Americans and 6877 European-Americans across multiple sub-groups, allowing the overall cohort to serve as a discovery sample and two replication samples for the most significant findings. Meta-analyses were also performed in the entire cohort. Analyses were performed using either Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) symptom counts for opioid dependence or case-control status. For the symptom count variable, rs62103177 in *KCNG2* was genome-wide significant in the final meta-analysis ($p = 3.6 \times 10^{-10}$). Additional variants in *KCNC1* (rs60349741) and *APBB2* (rs114070671) reached genome-wide significance in the combined analysis of the discovery and first replication sample, but were only nominally significant in the meta-analysis of the full cohort.

Case-control studies of OUD often have a significant caveat: a person cannot become opioid dependent if they are never exposed to opioids. In many case-control studies, controls are defined based solely on the DSM definition. Some controls may therefore have significant genetic risk for OUD but never develop the disorder due to lack of drug exposure. To mitigate this issue, Gelernter et al. analyzed only opioid-exposed individuals in the case-control GWAS. No significant findings were found. However, a subsequent study by Cheng et al. analyzed only opioid-exposed European-Americans in a larger cohort that included samples from the previous GWAS [40*]. When comparing 1290 subjects with opioid dependence to 1768 opioid-exposed controls, a SNP ~110kb downstream of *RGMA* was found to be significantly associated with dependence (rs12442183, $p = 1.3 \times 10^{-8}$). Analysis of microarray data from the frontal cortex suggested that rs12442183 was an expression quantitative trait locus (eQTL) for the *RGMA* gene [40*]. The previously identified hits in *KCNG2, KCNC1* and *APBB2* associated with symptom count were not identified in this

study, despite the overlapping sample sets, supporting the idea that limiting controls to only opioid-exposed individuals significantly changes GWAS results [40*].

Nelson et al. also performed a GWAS focused exclusively on opioid-exposed individuals, comparing daily injection opioid users in an Australian cohort to individuals who abused opioids but never injected daily (case n =1167, control n = 161) [41*]. A variant in *CNIH3* (Cornichon Family AMPA Receptor Auxiliary Protein 3) reached genome-wide significance (rs1436175, $p = 2.72 \times 10^{-8}$). Other polymorphisms in the gene were also nominally significant, further suggesting that a true association signal might be coming from this locus. Meta-analysis of these *CNIH3* variants in the discovery cohort and two independent populations resulted in five variants reaching genome-wide significance (rs10799590, rs12130499, rs298733, rs1436171, and rs1369846).

Common SNPs do not explain all of the heritability of many human phenotypes. Other genetic polymorphisms, such as rare variants or copy number variations (CNVs), likely account for some of this "missing heritability". GWAS of CNVs in OUD found three variants to be associated with opioid dependence in a meta-analysis of African-American (case n = 547, control n = 2944) and European-American (case n = 1054, control n = 607) samples [42*]. The findings included intergenic deletions on 18q12.3 and Xq28, and a duplication on 1q21.3 encompassing the *LCE3B* and *LCE3C* genes.

The GWAS results for OUD thus far have revealed a small number of significant loci that have not been replicated across the different studies. The lack of consistency may be driven by the relatively small sample sizes, particularly if OUD is highly polygenic and many variants have small effect sizes, as has been observed in other psychiatric disorders like schizophrenia [43], Genetic or environmental variation between the study populations, even genetically similar ones such as Americans and Australians of European descent, might also explain the variable results.

Discussion

While there are a handful of replicated genetic associations with OUD, these variants do not account for the majority of the heritability observed for the disorder. Candidate gene studies also suffer from an inherent bias problem, since they only analyze genes with known or suspected connections to the phenotype of interest. Unbiased approaches like GWAS are essential for identifying truly novel associations and the current published GWAS have indeed succeeded in providing new genes of interest. However, these types of analyses are hampered by relevant small sample sizes, in conjunction with significant multiple testing correction. Results from GWAS of other psychiatric disorders (e.g. schizophrenia, alcoholism, etc.) have indicated high levels of polygenicity, with many relevant variants carrying small effect sizes. The statistical power to identify these variants requires large cohorts that are not currently available in the OUD field. Maximizing the potential of GWAS in OUD research will necessitate organized sample collection and meta-analyses of existing data sets. An additional lesson from other disorders is the "missing heritability" problem in which even appropriately powered GWAS are unable to explain all of the calculated heritability of the phenotype. The OUD field will eventually need to move outside of

common variants and explore other relevant sources of variation, including rare variants, gene × environment effects, gene-gene interactions, and epigenetics.

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Highlights:

- Opioid use disorder risk has a large heritable component (23-54%)
- The *OPRM1* variant rs1799971 (aka A118G) as a small effect on risk for OUD and general substance use
- Variants in intron 1 of OPRD1 are associated with OUD risk in people of European descent
- Genome-wide association studies have identified associations between OUD and variants in *KCNG2, KCNC1, CNIH3, APBB2*, and *RGMA*

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- 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]

QL, quantitative train locus; OUD, opioid use disorder

Table 2:

Significant variants from genome-wide association studies of opioid use disorder

Gene Symbol	Gene Name	Variant	Ethnicity	Opioid-Exposed Controls	References
Intergenic	-	rs10494334	European-American	No	[38]
APBB2	Amyloid Beta Precursor Protein Binding Family B Member 2	rs114070671	Mixed (African-American, European-American)	No	[39]
KCNG2	Potassium Voltage-Gated Channel Modifier Subfamily G Member 2	rs62103177	Mixed (African-American, European-American)	No	[39]
KCNC1	Potassium Voltage-Gated Channel Subfamily C Member 1	rs60349741	Mixed (African-American, European-American)	No	[39]
CNIH3	Cornichon Family AMPA Receptor Auxiliary Protein 3	rs1436175	European-Australian	Yes	[41]
RGMA	Repulsive Guidance Molecule Family Member A	rs12442183	European-American	Yes	[40]