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<td>Authors(s)</td>
<td>Martin, Mariss; Klismas, Jan; Dunne, Colum; Meagher, David; O'Connor, William T.; O'Dwyer, Patrick; Smyth, Bobby P.; Cullen, Walter</td>
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Genetic pre-determinants of concurrent alcohol and opioid dependence:  
A critical review

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All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.
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Abstract

Concurrent alcohol dependence poses a significant burden to health and wellbeing of people with established opioid dependence. Although previous research indicates that both genetic and environmental risk factors contribute to the development of drug or alcohol dependence, the role of genetic determinants in development of concurrent alcohol and opioid dependence has not been scrutinised.

To search for genetic pre-determinants of concurrent alcohol and opioid dependence, electronic literature searches were completed using MEDLINE (PubMed) and EBSCO (Academic Search Complete) databases. Reference lists of included studies were also searched. In this discussion paper, we provide an overview of the genes (n=33) which are associated with the opioid, serotonergic, dopaminergic, GABA-ergic, cannabinoid, and metabolic systems for each dependency (i.e., alcohol or opioid) separately.

The current evidence base is inconclusive regarding an exclusively genetic pre-determinant of concurrent alcohol and opioid dependence. Further search strategies and original research are needed to determine the genetic basis for concurrent alcohol and opioid dependency.

Key words: Alcohol, Opioids, Substance-related disorders, Comorbidity, Genetic predisposition
Introduction

Problem opioid use is highly prevalent in Europe, including high rates in Ireland of seven per 1000 (1). Opioids are responsible for the highest rate of drug-related morbidity and mortality, contributing to greater than 77% of drug induced fatalities in Europe (1). Concurrent alcohol dependence poses a significant burden to the health care of people with established opioid dependence (2). Its negative impacts on addiction treatment include behaviours leading to clinical management difficulties, *e.g.*, illicit drug use or non-adherence with clinicians’ advice and early drop out (3).

Multiple studies have confirmed that both gene-gene and gene-environment interactions contribute to the development of drug dependence or alcohol dependence alone (4). Alcohol dependence has been associated with polymorphisms in genes coding for opioid receptors, serotonin receptors, GABA-ergic receptors, nicotinic and muscarinic acetylcholine receptors, CREB genes involved in familial predisposition to alcohol (cyclic AMP responsive element binding protein), and alcohol dehydrogenase (5). Opioid dependence has been associated with opioid system genes, particularly the mu-opioid receptor gene PKNOX2, as well as the dopaminergic system (6). Genome-wide association studies of multiple addictions have discussed potential vulnerability genes, more specifically cell adhesion genes that control the formation, stabilization, enhancement, and elimination of contacts between brain cells (7). A previous review has discussed several genes associated with multiple addictions; however, the contribution of genes to concurrent alcohol and opioid dependence has been neglected to date (4).

Clinical experience suggests that alcohol and opioid dependence may have common genetic aetiological origin. For example, Naltrexone (an opiate antagonist) is useful in the treatment of alcohol dependence (8). Most psychotropic substances (apart from benzodiazepines) have
been shown to directly or indirectly increase dopaminergic activity in the "reward pathway" (Nucleus Accumbans - Ventral Tegmental Area - pre frontal cortex) (1). Alcohol and opiates both stimulate the mu-opioid receptor on the GABA neuron thereby inhibiting its activity in GABA. This, in turn, reduces the inhibitory effect of GABA on the dopaminergic system in nucleus accumbans and the pre frontal cortex. Studies have found elevations of mu-opioid receptors in people with alcohol dependence (9). Higher observed rates of alcohol dependence in parents of adults with heroin dependence raise the possibility of a common risk factor. Another clinical reality is that early onset drinking may be associated with subsequent heroin dependence. Alcohol dependence in this cohort tends to become evident only after entry into opioid substitution treatment, following cessation or dramatic reduction in heroin use (10). Taken together, clinical evidence suggests the possibility of a common genetic link between opioid and alcohol dependence but the nature of that link remains unclear.

The aim of the present study was to critically review genetic pre-determinants of concurrent alcohol and opioid dependence through an electronic search of the relevant literature. Electronic searches were completed using MEDLINE (PubMed) and EBSCO (Academic Search Complete) databases.
Discussion

Twenty included studies examined the role of 33 genes in alcohol or opioid dependence. They were associated with the opioid, cholinergic, serotonergic, dopaminergic, GABA-ergic, cannabinoid, and metabolic systems. The identified genes classified by their system and function are presented in Table 1. <instruction for editors: insert Table 1 here>

**Opioid system**

Seven studies investigated the role of genes in the opioid system (11-18). Genes encoding all three types of opioid receptors were studied with variable results. Kumar et al., (2012) and Deb et al., (2010) concluded that the A118G polymorphism of OPRM1 (mu-opioid receptor gene) was associated with alcohol and opioid addiction in males in Eastern India (16, 17). Kumar et al., (2012) found that people with alcohol dependence and heroin dependence were 1.7 times and 1.9 times more likely, respectively, than control subjects to have the A11G polymorphism (16). Deb et al., (2010) found that subjects with alcohol dependence and opioid dependence were more likely than control to have the A11G polymorphism (17).

However, a study conducted in Germany by Franke et al., (2001) found no difference in the frequency of the A118G polymorphism between heroin or alcohol dependent subjects and controls (15). In addition to the A118G single nucleotide polymorphism (SNP), Luo et al., (2003) found that the allele -2442A of OPRM1 was associated with concurrent alcohol and opioid dependence in European Americans, but not in African Americans (13).

Zhang et al., (2008) conducted the only apparent study to associate the delta opioid receptor gene (OPRD1) with alcohol and opioid addiction. They found that the GCAACT haplotype containing G80T G-allele and C921T C-allele was associated with an increased risk of alcohol dependence (OR= 6.43) and opioid addiction (OR= 50.57) (11). Franke et al., (1999)
studied the silent T to C substitution at position 921 and found no association between this polymorphism and alcohol or opioid addiction (14). Similarly, Xuei et al., (2007) used a family-based association to investigate the opioid system in alcohol and drug dependence by analyzing the genes encoding the micro- and delta-opioid receptors and their peptide ligands. They found no significant associations of the OPRM1, OPRD1, PENK and POMC genes with alcohol or illicit drug dependence (18). In summary, the results of opioid receptors are variable with OPRM1 being most promising.

**Dopaminergic system**

A study by Yang et al., (2008) analysed the cluster of genes functionally associated with the dopaminergic system on chromosome 11q23. These genes included DRD2, TTC12, ANKK1, and NCAM1. They concluded that variants in TTC12 exon 3, NCAM1 exon 12, and the two 3’-ends of ANKK1 and DRD2 co-regulate risk for concurrent alcohol dependence and drug dependence (19). This co-regulation may play a role in concurrent dependencies, but we found only one study with such result.

**Alcohol dehydrogenase (ADH)**

A total of seven ADH genes (ADH1A, ADH1B, ADH1C, ADH4, ADH5, ADH6, and ADH7) were analysed in two separate studies (20, 21). It is important to note that this was a recessive association. Two ADH4 single nucleotide polymorphisms (SNPs) (rs1042363 and rs1800759) showed Hardy-Weinberg disequilibrium in Americans of European origin but not in controls (20). Two SNPs were more likely to be associated with concurrent drug and alcohol dependence in European Americans (ADH5 rs1154400, ADH7 rs1573496), compared to drug dependence alone (21). One SNP was associated with concurrent drug and alcohol dependence in African Americans (ADH1C rs1693482) and one SNP was associated with concurrent drug and alcohol dependence in both populations (ADH1B rs1229984) (21). It seems that the ADH genes function in concurrent dependencies is population-specific.
**Cholinergic**

Genes for both muscarinic and nicotinic cholinergic receptors play a significant role in concurrent alcohol and opioid dependence (22, 23). Dick et al., (2007) found 11 SNPs of muscarinic acetylcholine receptor gene (CHRM2) to be significant for individuals with alcohol dependence and concurrent drug dependence. These SNPs were not found to be associated with alcohol dependence alone (22). Sherva et al., (2010) investigated the role of the nicotinic gene cluster on chromosome 15q25.1 in case-control and family-based association studies. They found that multiple SNPs were associated with substance dependence, but only one SNP (rs16969968) was associated with both alcohol dependence and opioid dependence (23).

**Serotonergic**

Two studies have examined the role of the serotonergic system (24, 25) focusing on the 5HT transporter gene, SLC 6A4. Saiz et al., (2009) found no significant differences in the genotypic frequencies of the 5-HTTLPR and STin2 VNTR polymorphisms of SLC 6A4 between subjects with heroin addiction, alcohol addiction, or controls. This study also did not find an association between HTR2A A-1438G polymorphism and alcohol or opioid addiction (25). Enoch et al., (2011) found that low 5-HTTLPR activity and the HTR2B Ser 129 allele were more common in men with concurrent alcohol and drug dependence compared to controls. Together, they had an additive effect. The study also found no association between HTR3A haplotype and alcohol or drug dependence (24). Serotonergic system appears to be less important for concurrent dependencies.

**GABA-ergic**

Three studies investigated the role of GABA-receptor genes in substance dependence (26-28). A fuzzy clustering analysis performed by Yang et al., (2012) on 1758 individuals in
families with two siblings with alcohol, opioid, or cocaine dependence showed a significant linkage signal in chromosome 4 in European Americans. The location of the linkage peak corresponds with \textit{GABRA4}, \textit{GABRB1}, and \textit{CLOCK}. A second suggestive linkage peak was also found on chromosome 21. In African Americans, suggestive linkage peaks were found on chromosomes 10, 3, and 9. No linkage peaks were found on chromosome 4 in African Americans (26).

A family based association study conducted by Agrawal \textit{et al.}, (2006) found an association between five \textit{GABRA2} SNPs and concurrent alcohol and drug dependence. No association was found with any other GABAA receptor genes (\textit{GABRA2}, \textit{GABRA4}, \textit{GABRB1}, \textit{GBRG2}) (27). On the whole, some GABA-ergic genes can be relevant for concurrent dependencies, but no GABAA receptor genes.

\textit{IL-B}

A case control study from Australia found that \textit{IL-1B} -511C and -31T alleles were more frequent in both opioid- and alcohol-dependent patients compared with controls (29). While the higher frequency of these alleles in both dependencies may suggest a link with concurrent dependencies, only one study showed such results.

\textit{Nociception}

Xuei \textit{et al.}, (2008) conducted a study on the role of the nociception receptor gene (\textit{OPRL1}) and its ligand (\textit{PNOC}) on substance dependence in European Americans. SNPs in \textit{PNOC} showed marginal association with alcohol dependence rs17058952 (p=0.05). Two adjacent SNPs in intron 1 of \textit{OPRL1} were marginally associated with opioid dependence (rs6512305 (p=0.05), and rs6090043 (p=0.05)). However, neither gene showed association with both alcohol and opioid dependence (12).
Cannabinoid

A study conducted by Zuo et al., (2007) found that for European Americans, the risk for developing substance dependence significantly increased with the number of “G” alleles at rs6454674 in the cannabinoid receptor gene (CNR1). Interaction between rs6454674 and rs806368 had a significant risk factor for alcohol dependence, drug dependence cocaine and/or alcohol dependence, and concurrent alcohol and drug dependence (30).

Future research

Some evidence suggests that muscarinic acetylcholine receptor gene (CHRM2) may be implicated in concurrent alcohol and opioid dependence; similarly, dopaminergic mechanisms are very likely to be relevant to both dependencies. Like most conditions, none of those genes can be identified as their sole genetic pre-determinant. The impact of genes on concurrent dependence results at least in part from the combined effects of multiple genes (4).

Many other addictions also commonly coexist with opioid dependence, e.g. cannabis, benzodiazepines, or tobacco (4). Current neurobiological theories of addiction suggest that people with hypo-activity of dopamine system may be more vulnerable to developing all addictions (4). Also, current theory on mechanism of addiction centres on impairment of ability of pre-frontal cortex to inhibit hedonic activity, i.e. past drug use damages the brain’s ‘braking’ system, making it harder to resist impulse to use again in future (9). Therefore, if one has a genetically caused dopaminergic hypo-activity or a prefrontal cortex more prone (genetically) to damage by past addiction to other substance, one may be more likely to develop any other addiction. Hence, if there are genes that are associated with increased risk of alcohol dependence in people who are dependent on opioids, some of these genes may cause a specific increase in risk of alcohol dependence, while others may just cause a general increase in all other addictions, including alcohol.
Multiple studies confirmed that both gene-gene and gene-environment interactions contribute to the development of drug dependence or alcohol dependence (4). This is consistent with the notion that no condition should be studied in isolation. Gene expression is as important as gene-environment interaction and individual upbringing or personality, all of which influence dependence. Therefore, a systematic review on the relationships between genes and environment (including social and/or psychological sequel) is needed to provide context necessary for identification of genetic predeterminants of a concurrent dependence.

Many studies were conducted by the same group of researchers; they studied cohorts of European-Americans and African-American sub-populations (11, 13, 19, 23, 30). None of those studies were performed in Ireland or the United Kingdom. This omission provides an opportunity for further exploration in these countries. Ireland is located on the Western edge of Europe and may have a different gene pool compared to the rest of Europe. Additionally, Ireland has the third highest per capita alcohol consumption in Europe as well as the highest rate of binge drinking (1). Moreover, such observation underscores the need to carefully identify the ethnic origins of each sub-population, as the prevalence of a given polymorphism can vary across populations. For example, the prevalence of the A118G variant of the mu opioid receptor gene varies from 2-49% among different ethnic groups (31). Asian ‘glow’ is yet another, well recognised example of how ethnicity can impact upon genetic expression that is relevant to alcohol use. These polymorphisms may account for the varying results among European, African American or Asian studies.

It is also likely that the genes responsible for addictive disorders are present in a much greater percentage of the population than the phenotype due to a limited availability of illicit substances such as opioids. For future case control studies we suggest that the control groups should consist of people with opioid dependencies who were non-dependent alcohol drinkers. From a clinical perspective, the issue of dual dependence tends to be a concern in one direction only. Treatment providers don't encounter substantial numbers of people with
alcohol dependence going on to become opioid dependent. Only a minority of patients treated for alcohol dependence ever use illicit opioids. One could speculate that while they may have high risk gene for development of opioid dependence this risk never becomes manifest in the absence of use of that class of drugs. However, almost everyone who is opioid dependent will have had exposure to alcohol use. Hence, if they had a risky gene, it would be quite likely to manifest itself.

Finally, we suggest that examining the genetic pre-determinants feature prominently in future research endeavours among problem drug users, especially in geographical regions with a high prevalence of concurrent alcohol and opioid dependency.
Conclusion

On the basis of the electronic search of relevant literature, the current evidence base is inconclusive regarding an exclusively genetic pre-determinant of concurrent alcohol and opioid dependence. A systematic review of literature is needed; however, our findings do have some immediate implications for study design. Trials should use precise and consistent criteria for selection of subjects with dual drug dependence. Future case control studies should have control groups that consist of people with opioid dependencies who are non-dependent problem alcohol users. Future investigations of the genetic pre-determinants of these concurrent problems should focus on high-risk populations and regions.
Acknowledgement

The idea was conceived by MM and WC, the literature was searched and collated by MM, with the guidance of JK, WC. The manuscript was drafted by MM and JK with feedback from co-authors, according to their thematic expertise in the genetic studies and genetics (CD), neurobiology of addiction (WOC), clinical understanding of addiction (BPS, DM), and general practice (WC, POD). All authors reviewed and approved this manuscript. We thank Ellie Juarez, Spencer Watson, Lillian Welch, Sean McBurney and Rachel Dresbeck from the Vollum Writing Class at OHSU (Summer 2013), for proof reading drafts of this manuscript.
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Table 1 Summary of genes, included studies and their characteristics

Genes identified as having a potential role in concurrent alcohol and opioid dependence.

<table>
<thead>
<tr>
<th>Genes</th>
<th>Function</th>
<th>System</th>
<th>Study characteristics</th>
<th>Type(s) of study</th>
<th>Sample Size</th>
<th>Setting/ Participants</th>
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