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Genetic pre-determinants of concurrent alcohol and opioid dependence: A critical review

M Martin[1], J Klimas[1,2], C Dunne[1], D Meagher[1], WT O'Connor[1,5], P O'Dwyer[1], BP Smyth[3,4], W Cullen[1]

[1]Graduate Entry Medical School, Faculty of Education and Health Sciences, University of Limerick, Limerick, Ireland
[2]School of Medicine and Medical Science, University College Dublin, Dublin, Ireland
[3]Department of Public Health and Primary care, Trinity College Dublin, Ireland
[4]Addiction Services, Health Service Executive, Dublin, Ireland
[5]Flinders University School of Medicine, Bedford Park, SA 5042, Australia

Corresponding authors:

W Cullen, J Klimas

Emails:

M Martin: 09001041@studentmail.ul.ie
J Klimas: jan.klimas@ucd.ie
C Dunne: colum.dunne@ul.ie
D Meagher: david.meagher@ul.ie
WT O'Connor: william.oconnor@ul.ie
P O'Dwyer: patrickodwyer@eircom.net
BP Smyth: bobby.smyth@ul.ie
W Cullen: walter.cullen@ul.ie

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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 OPRMI 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). Serotogenic 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 *GABRA4*, *GABRB1*, and *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 *et al.*, (2006) found an association between five *GABRA2* SNPs and concurrent alcohol and drug dependence.. No association was found with any other GABAA receptor genes (*GABRA2*, *GABRA4*, *GABRB1*, *GBRG2*) (27). On the whole, some GABA-ergic genes can be relevant for concurrent dependencies, but no GABAA receptor genes.

IL-B

A case control study from Australia found that *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.

Nociception

Xuei *et al.*, (2008) conducted a study on the role of the nociception receptor gene (*OPRL1*) and its ligand (*PNOC*) on substance dependence in European Americans. SNPs in *PNOC* showed marginal association with alcohol dependence rs17058952 (p=0.05). Two adjacent SNPs in intron 1 of *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.

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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.

Genes	**Function**	**System**	**Study characteristics**			
			Type(s) of study	*Sample Size*	*Setting/ Participants*	*Author*
GABRA2 *GABRA4* *GABRB1* *GBRG2*	Receptor Receptor Receptor Receptor	GABA-ergic GABA-ergic GABA-ergic GABA-ergic	Family based association	2286	European and African Americans	Agrawal, *et al.*, 2006
OPRM1	Receptor	Opioid	Case-control	222	Bengali-Hindu Indians	Deb, *et al.*, 2010
CHRM2	Receptor	Cholinergic	Family based association	2282	European and African Americans	Dick, *et al.*, 2007
HTR3A *HTR3B* *SLC 6A4*	Receptor Receptor Transporter	Serotogenic Serotogenic Serotogenic	Case-control	547	African American males	Enoch, *et al.*, 2011
GABRA2	Receptor	GABA-ergic	Retrospective case-control	832	African American males	Enoch, *et al.*, 2011
OPRM1	Receptor	Opioid	Case-control, family control	873 (186)	Germans	Franke, *et al.*, 2001
OPRD1	Receptor	Opioid	Case-control, family based association	668 (162)	Germans	Franke, *et al.*, 1999
OPRK1 *OPRM1*	Receptor Receptor	Opioid Opioid	Case-control	440	Bengali-Hindu Indians	Kumar, *et al.*, 2012
IL-1B	Cytokine	Inflamatory	Case-control	219	European Australians	Liu, *et al.*, 2009
OPRM1	Receptor	Opioid	Case-control	676	European and African Americans	Luo, *et al.*, 2003

ADH4	Metabolism	Alcohol metabolism	Case-control	926	European and African Americans	Luo, *et al.*, 2006
ADH1A *ADH1B* *ADH1C* *ADH4* *ADH5* *ADH6* *ADH7*	Metabolism Metabolism Metabolism Metabolism Metabolism Metabolism Metabolism	Alcohol metabolism Alcohol metabolism Alcohol metabolism Alcohol metabolism Alcohol metabolism Alcohol metabolism Alcohol metabolism	Case-control	718	European and African Americans	Luo, *et al.*, 2007
HTR2A *SLC6A4*	Receptor Transporter	Serotonergic Serotonergic	Case-control	698	Spanish	Saiz, *et al.*, 2009
CHRNA5 *CHRNA3* *CHRNB4*	Receptor Receptor Receptor	Cholinergic Cholinergic Cholinergic	Case-control, family based association	3388, 1858	European and African Americans	Sherva, *et al.*, 2010
OPRL1 *PNOC*	Receptor Ligand	Nociception Nociception	Family based association	1923	European Americans	Xuei, *et al.*, 2008
OPRM1 *OPRD1* *PENK* *POMC*	Receptor Receptor Ligand Ligand	Opioid Opioid Opioid Opioid	Family based association	1923	European Americans	Xuei, *et al.*, 2007
GABRA4 *GABRB1* *CLOCK*	Receptor Receptor Transcription factor	GABA-ergic Gaba-ergic Generation of circadian rhythm	Fuzzy clustering analysis	1758	European and African Americans	Yang, *et al.*, 2012

NCAM1 *TTC12* *ANKK1* *DRD2*	Cell adhesion Tumour suppressor Signal transduction Receptor	Dopaminergic Dopaminergic Dopaminergic Dopaminergic	Case-control, family based association	302, 1090	European Americans	Yang, *et al.*, 2008
OPRD1 *OPRK1*	Receptor Receptor	Opioid Opioid	Case-control	1063	European Americans	Zhang, *et al.*, 2008
CNR1	Receptor	Canabinoidergic	Case-control	1001	European and African Americans	Zuo, *et al.*, 2007