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Genetics of Addiction

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ABSTRACT

Addictions are chronic relapsing psychiatric disorders characterized by the compulsive and dyscontrolled use of a drug or activity, with maladaptive and destructive outcomes. Addictions, including substance use disorders (SUDs), are multistep conditions that, by definition, require exposure to an addictive agent - including both licit (alcohol, nicotine) and illicit (cannabis, cocaine, opiates) drug addictions and the behavioral addiction of disordered gambling. Differentiating habit and addiction. We will discuss about developed KARG database, the first molecular database for addiction-related genes with extensive annotations and a friendly Web interface. More information about pathways for addiction; protein which express from addiction gene with 3D structure and detail about inhibitor genes which stop the expression to cure addiction. The moderation of genetic influences like gene–environment (G × E) interactions. Understanding this balance may hold the key to understanding the individual differences in substance use, abuse, and addictive behavior.

Keywords: *Addiction, Pathway, Genes.*

1. INTRODUCTION

Drug addiction, defined as "the loss of control over drug use, or the compulsive seeking and taking of drugs despite adverse consequences," has become one of the most serious problems in the world. It has been estimated that genetic factors contribute to 40%–60% of the vulnerability to drug addiction, and environmental factors provide the remainder(C. Y. Li, Mao, & Wei, 2008; Palmer et al., 2015).Addictions are chronic relapsing psychiatric disorders characterized by the compulsive and dyscontrolled use of a drug or activity, with maladaptive and destructive outcomes.

The World Health Organization estimates that there are 2 billion alcohol users, 1.3 billion tobacco users, and 185 million illicit-drug users worldwide. In recent years, significant progress has been made in identifying susceptibility genes for addictions. Regions on human chromosomes 4, 5, 9–11, and 17 are more likely to harbor susceptibility genes for multiple substances. the susceptibility genes for addiction identified from candidate gene-based or GWAS approaches, we limit our focus

to representative genes that encode aldehyde dehydrogenase (*ADH*), nicotinic acetylcholine receptor (nAChR) subunits, $GABA_A$ (gamma-aminobutyric acid A) receptor subunit 2 (*GABRA2*), ankyrin repeat and kinase domain containing 1 (*ANKK1*), and neurexins, because of their influence on susceptibility to addiction to multiple substances, the strong statistical evidence to support their roles, or the importance of their biological functions in addiction. (M. D. Li & Burmeister, 2009)Addictions are primarily diagnosed using the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).Studies have identified the significant role of heritable influences on individual differences in addiction. Results from twin studies suggest that the variation in liability to nicotine dependence"33-71%" can be attributed to heritable influences;"48–66%"variation in alcohol dependence is heritable, "51–59%" for cannabis addiction. For cocaine use disorders range from 42 to 79%, for female its lower estimated. The magnitude or nature of heritable influences on addiction in men and women is difference. Some genes discussed here are potentially linked to the risk for substance dependence. Thus, this section will serve as a resource for both alcohol and the discussion of genes relevant to illicit drug abuse and dependence. Several studies reported an association of phenotypes of impulsivity, disinhibition and related characteristics with a polymorphism of the GABA A receptor, alpha 2 genes on chromosome 4. On a behavioural level, this gene variation is also related to conduct disorder and the antisocial personality disorder (conditions that incorporate impulsivity and disinhibition) and, not surprisingly, carries an associated predisposition towards dependence on illicit substances as well as on alcohol. Several other polymorphisms potentially associated with disinhibition or related cognitive-based mechanisms include a variation of cholinergic receptor, muscarinic 2 on chromosome 7, and the alcohol dehydrogenase 4 gene on chromosome 4, with the latter potentially carrying its impact via changes in the dopamine reward systems. Another set of genes might operate through polymorphisms in the dopamine receptor D4 gene on chromosome 11 &the dopamine- receptor D2 gene on chromosome 2. (Mayfield, **Figure1**: Criteria for diagnosis for addiction Harris, & Schuckit, 2008)

	DSM-5	DSM-IV
Failure to fulfill major role obligations	√	√ (abuse)
Recurning use in hazardous situations	√	√ (abuse)
Use despite interpersonal problems	√	√ (abuse)
Use despite recurring legal problems	x	√ (abuse)
Tolerance		√ (dependence)
Withdrawal		√ (dependence)
Using more or longer than intended	√	√ (dependence)
Giving up important activities to use	√	√ (dependence)
Spending a lot of time using	√	√ (dependence)
Use despite recurring physical/psychological problems	√	√ (Dependence)
Persistent, failed quit attempts	√	√ (dependence)
Craving-strong urge or dsire to use drug	√	x
Diagnostic and Statistical Manual of Mental Discorders (DSM)-IV:		
Abuse-1 or more of 4 criteria.		
Dependence—3 or more of 7 criteria occuring in the same 12-month period.		
DSM-5 (proposed: dsm5.org)		
Substance use disorder:		
Unaffected—0 or 1 of 11 criteria.		
Moderately affected—2 to 3 of 11 critena occurring in the same 12-month period.		
Severaly affected—4 or more of 11 criteria occuring in the same 12-month period.		

Figure 1: Criteria for Diagnosis for Addiction

Addictive Drugs		Cocaine	Alcohol	Opicids	Nicotine
Neuroactive legand-receptor intenaction	p-Value	539E-05	324E-02	268E-03	7.79E-03
Long-term potcosiation	p-value	321E-08	828E-03	1.05E-02	8.84E-03
	Q-Value	2.8E-07	0.03	0.03	0.04
CoRH signaling pathvay	p-Value	284E-05	3.93E-04	4.67E-03	1.72E-02
	Q-Value	1.2E-or	3.6E-03	0.02	0.05
MAPK signaing pathvay	p-value	128E-04	2.97E-04	7.34E-05	1.00E-02
	Q-Value	3.7E-04	3.6E-03	5.2E-04	0.04
Gap Jactions	p-value	1.93E-08	3.11E-03	3.30E-03	5.85E-03
	Q-Value	2.8E-07	0.01	0.01	0.03

Figure 2: Common Molecular Pathways Identifiedin Different Types of Drug Addiction

ALCOHOL

In addition to widely studied variants in *ADH1B* and *ALDH2*, two functional polymorphisms (rs1693482 and rs698) in *ADH1C* are known to regulate alcohol metabolism and have been found to have a protective influence on alcohol consumption. Unlike rs1229984 in *ADH1B* and rs671 in *ALDH2*, which are uncommon and absent respectively, in non-Asian populations, the *ADH1C* polymorphisms are common. Meta-analysis of the commonly studied serotonin transporter gene (*SLC6A4*) polymorphism found only weak association (odds ratio (OR) =1.2, $P<0.05$) with alcoholism.[4] Several studies in animals and humans support the possible relevance of the l allele of the serotonin transporter on chromosome 17, which produces a transporter with a more rapid reuptake of serotonin. Enhanced transport results in lower levels of this neurotransmitter that might relate to decreased alcohol effects. The mechanism operates through genes that alter enzymes having an important function in the metabolism of alcohol, including mutation in the *ALDH**2 gene on chromosome 12, with a resulting enzyme that is incapable of destroying acetaldehyde at the usual levels found in the blood. About 10% of Asian (Japanese, Chinese and Korean) individuals are *ALDH2**2 homozygotes, with a resulting highly intense aversive response to drinking that contributes to a near-zero rate of alcoholism, but does not appear to affect the risk for dependence on other drugs(Agrawal et al., 2012).

Nicotine

Cigarette smoking is the most common form of tobacco use and is one of the main preventable causes of premature death and disability worldwide. Variants in the chromosome 15 cluster of genes encoding subunits of the nicotinic acetylcholine receptor, including CHRNA5/CHRNA3/ CHRNB4, are among the most robustly replicated association signals for nicotine addiction. In addition, variants in *CHRNA4* (encoding the á4 subunit of the neuronal nicotinic acetylcholine receptor) have also been suggested to influence various aspects of nicotine addiction. Recent meta-analysis of linkage studies identified the *CHRNA4* region on 20q13.2–q13.3 for maximum cigarettes

smoked in a 24-h period. nicotine can also regulate the expression of genes/proteins involved in various functions such as ERK1/2, CREB, and c-FOS(Liu, Li, Fan, Liu, & Wang, 2015).

Cannabis

Inconsistent associations have been reported between variants in the cannabinoid receptor 1 gene (*CNR1*), to which cannabinoids putativelybind, and the fatty acid amide hydrolase gene (*FAAH*) and cannabis dependence symptoms. As with alcoholism, *GABRA2* (encoding theá2 subunit of the GABA (gamma-amino-butyric acid) receptor) has been examined for cannabis dependence but with limited success(Agrawal et al., 2012). These findings are the first to demonstrate that people with this AKT1 genotype are far more likely to experience strong effects from smoking cannabis, even if they are otherwise healthy(Morgan, Freeman, Powell, & Curran, 2016).

Cluster	Cluster function	Score[a]	Nodes	Edges	Gene symbol
I	Apoptotic/macromolecular metabolic process	4.08	25	49	ARRB2, ARRB1, CUL4A, HDAC1, RPS3, ERCC6, GNAS, UBE3A, NBN, CHEK2, BRCA1, ESR1, ARR3, AR, HDAC2, NEDD4, UBB, MSH6, NR3C1, UBC, PDE4D, SUMO1, HIF1A, TUBB2A, ITCH
II	Synaptic transmission/intracellular and second messenger signaling cascade	2.67	13	16	KCNJ9, DRD2, ADRB2, DRD4, NOS3, MAP1A, GCDH, TTN, HTR2A, PSEN1, ACTN1, KCNJ3, GNA11
III	Behavioral response to nicotine	3.00	3	3	UBQLN1, CHRNB4, CHRNA3
IV	Response to abiotic stimulus/cellular metabolic process	3.05	22	32	BRCA2, GAPDH, H2AFX, SPTAN1, PRMT1, PRKG1, MGMT, NCL, HECW2, USP11, ATR, LMNA, GRIN2A, CDK5, TP53, GRIN2B, KPNB1, XRCC6, MRE11A, TCEAL1, PLCG1, PDCD5
V	Cellular response to DNA damage stimulus/DNA metabolic process	3.29	15	23	RPA2, RPA3, CCNH, HSPA4, ERCC3, XRCC1, RPA1, GTF2H1, MLH1, PCNA, MYC, XPC, ATM, CDK2, SUMO2
VI	Synaptic transmission/cell-cell signaling	3.00	3	3	NSF, GABBR1, GABBR2

Figure 3: Gene Clusters Identified in the Nicotine Addiction-Related Network.

Cocaine

Several genes have been implicated in various aspects of cocaine addiction. These include dopaminergic single nucleotide polymorphisms (SNPs) in *DRD2/ANKK1*as well as neighboring *NCAM1* and *TTC12*,

CALCYON, dopamine beta-hydroxylase (*DBH*)and catechol-O-methyltransferase (*COMT*); opioidergic genes such as *POMC*; *CNR1*;orthologs of genes regulating circadian rhythms (*CLOCK*, *PER1*, and *PER2*); tryptophan hydroxylase 2 (*TPH2*) and others gleaned from linkage studies (for example, alpha-endomannosidase (*MANEA*)) - a majority of these await replication. Of particular interest, the functional SNP in the *CHRNA5/A3/B4* cluster on chromosome 15, rs16969968, (extensively discussed in later sections and with reference to nicotine dependence) has been found to be associated with cocaine dependence in two independent studies—paradoxically, the allelic variant of this marker that confers risk for nicotine dependence appears to afford protection from cocaine addiction(Agrawal et al., 2012).A study of 670 cocaine addicts found they were 25 per cent more likely to carry the gene variant than people who did not use the drug. The "cocaine gene" is a variant of the CAMK4 gene and was identified after an initial study on mice. Studies suggest genetic factors account for about 50 per cent of alcoholism while cocaine addiction is about 70 per cent genetic (Bilbao et al., 2008).

Opioids

The gene encoding the mu-opioid receptor (*OPRM1*) to which opioids bind to produce their analgesic and rewarding effects is the most widely studied candidate gene for heroin and other opioid addictions. Functional OPRM1 polymorphisms identified in humans include the extensively-studied rs1799971 (A118G), but a meta-analysis did not support its significant role in opioid addictions. Other aspects of the opioidergic system have also been queried. However, analyses involving prodynorphin (*PDYN*), proenkephalin (*PENK*), and the kappa (*OPRK1*)and delta opioid receptors (*OPRD1*)have not produced consistent result(Agrawal et al., 2012)

2. DIFFERENTIATING HABIT AND ADDICTION

Differentiating a habit from an addiction could be very difficult. First, you must evaluate the outcome of the behavior whether it is positive or negative. You should also know if the effect is balanced or imbalance.

A habit is defined as, "a behavior pattern acquired by frequent repetition or physiologic exposure that shows itself in regularity or increased facility of performance; an acquired mode of behavior that has become nearly or completely involuntary. The act gets imbedded in the brain after continuous repetition that the brain automatically sends signals to the body to perform that act. Habit is a behavior pattern developed by frequent repetition of the act over and over to the point the brain does it automatically. A habit can be controlled or modified. A new study from MIT neuroscientists has found that a small region of the brain's prefrontal cortex, where most thought and planning occurs, is responsible for moment-by-moment control of which habits are switched on at a given time. Neuroscientists have traced our habit-making behaviors to a part of the brain called the basal ganglia, which also plays a key role in the development of emotions, memories and pattern recognition

An addiction is defined as, "compulsive need for and use of a habit-forming substance (as heroin, nicotine, or alcohol) characterized by tolerance and by well-defined physiological symptoms upon withdrawal; persistent compulsive use of a substance known by the user to be harmful". Addiction exerts a long and powerful influence on the brain that manifests in three distinct ways: craving for the object of addiction, loss of control over its use, and continuing involvement with it despite

adverse consequences. researchers first began to investigate what caused addictive behavior, they believed that people who developed addictions were somehow morally flawed or lacking in willpower. For many years, experts believed that only alcohol and powerful drugs could cause addiction. Neuroimaging technologies and more recent research, however, have shown that certain pleasurable activities, such as gambling, shopping, and sex, can also co-opt the brain. An addiction is a compulsive need of a certain thing or substance to the body, which when deprived causes horrible effects. Addiction cannot be controlled and requires professional help for modification. There is a fine line between habit and addiction, and if crossed a habit can easily turn into an addiction. Most addicted people know that they are addicted to certain substances, but they can't turn away from that act or substance even if they want to.(Difference between Habit and Addiction, 2017)

3. KARG: KNOWLEDGEBASE FOR ADDICTION RELATED GENE

Drug Addiction has become one of the most serious problems in the world. We extracted 506 allelic contrasts tests on 286 genetic variants. For all variants with case-control genotype data available in three or more independent samples, we systematically carried out meta-analyses using both the DerSimonian& Laird random-effects model and fixed-effects model. Across 35 candidate gene meta-analyses, a total of 12 genetic variants in 11 different genes (BDNF, CCK, CNR1, COMT, DRD2, DRD4, FAAH, HNMT, OPRK1, OPRM1, SLC4A7) showed nominally significant effects. Six of these variants can be characterized as showing strong epidemiological credibility, as suggested by the criteria of HuGENet Road Map, which is recently proposed for the assessment of cumulative evidence in genetic association studies. identified 10 GWAS studies focused on drug addiction, with 11 independent samples. 5 of them can meet our inclusion criteria, including i) genetic association studies with case-control design, ii) published in a peer-reviewed scientific journals, iii) published in English and iv) original case-control genotype data available. All these five microarray datasets were downloaded from public web sites or provided by the authors upon request. Initial data analyses were performed and Student's t tests were conducted to access the vulnerability of each SNP marker, following the protocols published before. We integrated these 11 GWAS datasets using a meta-signature-based approach. 842 SNPs were identified with at least three items of positive evidence and meta-false discovery rate less than 0.05. Since most of these genetic vulnerable markers are in fact genetic 'tag markers' instead of functional variations, we further expanded this list to 1,907 unique SNPs on the basis of the whole-genome linkage equilibrium data identified by HapMap. Finally, we integrated all available SNP functions to date and performed a comprehensive annotation to facilitate the interpretation of those addiction vulnerable variants identified by association studies. We identified 124 'functional' SNPs dropped into 70 hyplotype blocks. These functional SNPs include nonsynonymous/synonymous SNPs, SNPs putatively modifying transcription factor/microRNA binding or processes of alternative splicing, SNPs under positive or negative selections and SNPs with strong correlations with differentially gene expression. (KARG, 2017)

It is important to recognize that genes alone do not determine addiction phenotypes: Environmental factors also play an important role. Environmental factors that could be considered, based on previous studies, include parental rule setting, major life events, educational attainment, neighborhood characteristics, and peer influence. There are different types of G × E studies. The first group of studies use twin data to estimate differences in heritability across groups (quantitative behavioral genetic studies) without specifying the genetic factors. For example, a Finnish twin study showed

that genetic effects on adolescent smoking decreased and common environmental influences increased at higher levels of parental monitoring, and another study showed that the effect of genetic factors and alcohol use in boys is blunted in rural communities. A second group of studies have investigated specific candidate genes to detect G × E interactions. These studies are reviewed by Milaniak et al. and mainly concern interactions between the serotonin transporter gene, the dopaminergic genes, and alcohol-metabolizing genes with different stages of substance use moderated by factors such as stressful life events, childhood adversity, and educational attainment. The third group of studies investigated the interaction between a genotype based on one specific single-nucleotide polymorphism (SNP) (e.g., rs16969968 on chromosome 15, which is associated with smoking) and environmental factors. For example, both parental monitoring and peer smoking modify the association between nicotine dependence and the SNP rs16969968.

With the availability of large GWA studies for substance use and balanced future data collections including both genetic and environmental information, major breakthroughs are expected for G × E interaction studies. First steps are taken in the pharmacogenetics. For example, an interaction is shown between an SNP in the *CHRNA5* (nicotine acetylcholine subunit A5) gene and the success of nicotine replacement therapy. Individuals with the high-risk genotype were more likely to benefit from the therapy. In contrast, varenicline increased abstinence, but its effect did not vary with *CHRNA5*. This shows that pharmacogenetic evidence can help when health care providers make decisions about medication choice for patients trying to quit smoking. More research is necessary to show whether interactions between genetic factors and environmental factors exist. In my opinion, a wide range of phenotypes should be explored from initiation (e.g., G × Parental Influence for prevention) to dependence (G × Intervention for treatment). These results not only will give insight into the underlying biological mechanism but will also characterize subgroups (based on environmental factors) at high risk for addictive behaviors. With this information, we could bridge the gap between fundamental research and applications for society(Vink, 2016).

4. CONCLUSION

Significant progress has been made in identifying susceptibility loci and genes for addictions. Comparison of linkage peaks for addictions to various substances confirms what we have learned from genetic epidemiological studies, namely that genetic vulnerability to different substances in part overlaps. For most diseases, genetic or genomic assessment of risk or susceptibility is a goal. The history of genetics of complex diseases brings great excitement about new techniques with large increases in genetic power (for example, selected lines, recombinant inbred strains, QTL analysis, gene expression arrays, SNP maps and so on). But application of these new approaches reveals that the complexity of the disease and the genetics of the organism are much greater than we appreciated. This leads to the development of new approaches, which reveal new complexities. The immediate future may bring the realization that we will not be able to define the genetics of dependence until we better understand how genes interact with environmental variables to influence drug responses and related behavior.

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