

Genetic Factors in Addiction

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ABSTRACT

Addiction is receiving any foreign substance (harmful chemicals, etc.), even though the person does not need and becoming dependent on it and could not stop to use it. This topic is a worldwide serious health problem in the interests of the individual, the family and the society. Due to the effects of drugs such as maintaining social relationships, providing temporary happiness and fitness, strengthening the emotion of independence, they are especially widely used by young society.

Many factors play role in the addiction behaviors. Studies that reveal genetic factors in addiction are mostly concentrated on alcohol and nicotine dependence. However, there are several studies showing that genetic variations are present in cocaine, heroin, opiates, and other drug dependences. Some of them are related to dopamine, serotonin, and cannabinoid receptors and cytochrome P450 enzyme system. Addiction is a health problem difficult to explain with a single gene. Both genetic and environmental factors play role in the use of addictive agents and in the transition from use to dependence. Epigenetic factors, single nucleotide polymorphisms are discussed in the text.

Key words: substance abuse, addiction, genetic factors

Introduction

Addiction is a harmful problem for the person, the family and the community. It is a situation where the individual self-enslaves and cannot get rid of despite being aware of the damage. According to the American Psychiatric Association [1] addiction is a substance use disorder causing severe clinical impairments or distress, as defined by three (or more) of the following seven criteria, occurring during one year: 1) Tolerance, 2) Withdrawal, 3) Taking the substance in large quantity or over a long-time than desired, 4) Failed efforts to stop, control or use the substance, 5) Spending much more time to obtain (visiting doctors and travelling) and take the substance or get rid of from its effects, 6) Reduced social and occupational activities due to substance abuse, 7) Continued use of the substance despite being aware of its consistent adverse effects on health and social life.

The use and abuse of addictive agents are a worldwide common health priority. The World Health Organization reported in an 2012 survey that

between 162 million and 324 million people (3.5% and 7.0% of the world's population aged 15-64 years) used an illicit drug (mainly cannabinoids, or the opioid, cocaine or amphetamine-type stimulants) at least once in a year and between 16 million and 39 million people are regular drug user [2].

A lot of addiction based community and health problems occur as a consequence of illegal drug use. There is a relationship between substance use, crime, sexual abuse and interpersonal violence [3]. On average, 13.1% of all people who use drugs intravenously are HIV positive and more than half of them are hepatitis C positive. [2].

Why a person uses these substances and become dependent? Many factors determine the likelihood that someone will become an addict. Several characters and disorders may influence the risk of dependence. Antisocial personality disorder, such as dishonest, manipulative, insensitive and criminal behavior, is the most associated with addiction among all personality disorders. A wide-ranging

epidemiological research revealed that 18% of people with illicit-drug-use problems have antisocial personality disorder, as do 9% of people with alcohol-use problems (more than the 4% found in the general population) [4,3].

Genetic predisposition may be significantly effective in the etiology of substance dependence. Bevilacqua and Goldman showed that heritability of substance use disorders range from 0.39 for hallucinogens to 0.72 for cocaine [6]. But there is a paradox in the heritability of addiction. First of all, addiction depends on the presence of the substance and then the person's choice to take and use it. The availability of addictive substances is determined by economic status, culture, religion, social policy, and narco-trafficking, and it varies along the time and place. This is why twin studies on addiction do not disclose the full reaction range of genotype but demonstrate that under particular social conditions, genotype plays a considerable role in vulnerability [7]. While addictions can not be clarified by Mendelian inheritance and their complexity is less understood, it is obvious that they are highly affected by heritable variations, and identification of genes related with substance abuse, such as alcohol, cigarette and drugs, can reveal to understand basic mechanisms of causality.

The other important factor in addiction is the epigenetic mechanism, which manage the genes by turning them on and off. It is found that addiction can epigenetically 'rewire' the brain by stimulating the genes that are generally activated only during brain growth [8]. Addiction reactivates brain-improvement genes, which involves more common variants. Childhood trauma affects both epigenetics and addiction risk. According to a study from Sweden, people who experienced their parent's death or diagnosis of cancer or witnessed violence especially in their family are at twice the risk of addiction to any substance later in life than those who have not experienced them [8]. Both addiction and chronic stress can stimulate some of the same epigenetic variations in stress systems and in those involved with enjoyment, which may in part explain why addiction and trauma are so firmly linked [8].

Methods

Article searches were conducted with terms involved substance abuse, addiction, genetic factors and genetic etiology of substance addiction mainly by using PubMed. Full text articles or resulting abstracts

with relevant specific topics of genetic etiology for substance addiction were reviewed.

Genetic Risk Factors For Alcohol Dependence

Studies performed by The Collaborative Study on the Genetics of Alcoholism (COGA) and the National Institute on Alcohol Abuse and Alcoholism investigators showed that there is a loci on chromosome 4 which enhances the risk for alcohol dependence [10,11]. Another report suggested a link between alcohol addiction and signs on chromosome 10 in African Americans (12). Studies on a society-based sample of Australian adults defined a suggestive link on human chromosome 5p [13]. Works on Family Alcoholism revealed some suggestive regions related to DSM-IV alcohol dependence (chromosomes 1, 2, 8, 9, 18, and 22) [14].

There is no consensus among these studies because of basic epigenetic variability in the risk for alcohol abuse.

Genetic metabolic factors such as enzymes, which convert alcohols to aldehydes, play a great role in the etiology of alcoholism [15]. Ethanol is oxidized to acetaldehyde and then to acetate by the enzymes alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) respectively.

ADH catalyzes the rate-limiting step in the metabolism of ethanol. There are seven ADH-encoding genes (*ADH1A*, *ADH1B*, *ADH1C*, *ADH4*, *ADH5*, *ADH6*, and *ADH7*) found as a group on chromosome 4q22–23 [15]. Enzymes encoded by *ADH1A*, *ADH1B*, and *ADH1C* include the most important ADH isoforms in the oxidation process of ethanol [15]. *ADH7* acts in stomach mucosa where alcohol is in high concentration. *ADH7* forms with the effect of *ADH1A*, *ADH1B*, and *ADH4* are related with the first steps of alcohol elimination in European people. Variants in the *ADH7* -*ADH1C* -*ADH1B* gene cluster affect post-absorptive alcohol metabolism [16]. There is a relationship between *ADH1B**2 allele (amino-acid changes at positions 48) and decreased alcohol use or risk for alcohol abuse in general population, although the allele frequencies vary among different ethnicities. [17,18]. African American families and southwest California Native Americans are protected on risk for alcoholism due to *ADH1B**3 allele [19,20]. Studies demonstrated that Asian and African people are resistant to alcoholism because of *ADH1C**1 allele [15,21]. The higher presence of *ADH1C**2 allele is found to be related with alcohol

abuse whereas *ADH1B* and *ADH1C* genotypes are found not to be related with the individual risk of alcoholism in Turkish population [22,23]. Both the genomic region and the frequencies of functional variants vary among populations according to ethnicity [24]. Therefore it is possible to say that the effects of functional variants are specific for ethnicity.

Another polymorphism is in the *ALDH2* gene. The *ALDH2*2 (Glu504Lys)* allele is relatively common in Asians and is powerfully related with a reduced risk for alcohol addiction [25]. *ALDH1A1* and *ALDH1B1* alleles found in Finn and Danish society are observed to have a link with alcohol consumption [26, 27].

Multiple single-nucleotide polymorphisms (SNP) in *GABRA2*, which encodes the GABAA (Gamma amino butyric acid-A) receptor $\alpha 2$ subunit, is related to high risk for alcohol addiction [28]. Beside *GABRA2*, the *GABRG1* gene, which encodes the GABAA receptor γ 1 subunit, also reported to have a link with the risk for alcohol abuse and drinking behaviors [29].

According to a recent study, synuclein alpha (SNCA), which is known as non A-beta component of amyloid precursor significantly distinguished alcoholics from controls and the alcohol misuse cohort. Low levels of SNCA that causes high neurobiological activity can make vulnerable for alcohol and resultant alcoholism; excessive alcohol drinking then raises SNCA expression beyond that seen in non-alcohol-using controls [30].

Although candidate gene researches succeeded to identify functional types in alcohol metabolism genes such as *ADH1B*, *ADH1C*, and *ALDH2*, several genome-wide association studies of alcoholism have shown no exact proof for special genetic risk factors [31]. To find out the genetic metabolic factors suspected in the etiology of alcoholism, more studies should be performed on larger populations.

Genetic Risk Factors For Smoking

Nicotine is the primary harmful agent found in tobacco that causes dependence in smokers. After smoking, about 80% of nicotine is converted to ineffective metabolite cotinine; nearly 90% of this reaction is catalyzed by CYP2A6 (cytochrome P450 2A6) enzyme [32]. Cotinine is further oxidized to trans -3' -hydroxycotinine with the reaction mediated also by extremely polymorphic enzyme CYP2A6 [31]. The frequency of *CYP2A6* alleles differs within ethnic populations [34]. Decreased activity or lack

of CYP2A6 enzyme is associated with little risk of smoking, as well as reduced cigarette using, smoking intensity, and withdrawal symptoms; shorter smoking period; and increased cessation. There are also studies that couldn't show any linkage between CYP2A6 alterations and smoking behaviour [35].

Genome-wide association studies put forward that variations among the nicotinic acetylcholine receptor (nAChR) subunit genes on the long arm of chromosomes 15 (*CHRNA5 -CHRNA3 -CHRNB4*) and 8 (*CHRNA6 -CHRNB3*) affect risk for nicotine addiction [36].

It is reported that the nonsynonymous SNP *rs16969968* in exon 5 of *CHRNA5* had coherent influences on the risk for nicotine addiction in both European and African populations. A second locus marked by *rs578776* in *CHRNA3* is in close relationship with nicotine dependence in European Americans but not in African Americans. Another location marked by an intronic SNP in *CHRNA5*, *rs588765*, presents a protective role in nicotine dependence in European populations [37, 38]. It is shown that both the locations labeled by *rs578776* and *rs588765*, which are overlapped, have role in the initiation, cessation, and quantity of smoking [39]. The low-frequency coding modifications *R37H* in *CHRNA3* and *T375I* and *T91I* in *CHRNB4* are reported to lower the risk for nicotine dependence in regular smokers [41].

Risk factors for nicotine dependence have been successfully detected by genetic researches [31,37]. But, these factors clarify the genetic etiology partially in nicotine dependence. Advanced researches are necessary to identify the genetic factors affecting smoking status further.

Genetic Risk Factors For Drug Dependence

Loci on human chromosomes 3 (3q21) and 9 (9q34) are suggested to influence cannabis-dependence symptoms in adolescents [41]. An American community study reported a considerable correlation between heavy cannabis use and antisocial subtype on human chromosomes 16 and 19 [42].

Important link points have been detected on human chromosomes 9 (near the region related with cannabis use) and 12 for cocaine abuse, on chromosome 17 at 103.5 cM for a severe opioid-use group-defined feature, and on 14q for opioid abuse [43- 45]. A significant relation between alcohol-use disorders and illicit drug dependence on human chromosome 2 has been reported after analysis in families

[46]. A wide population study showed a suggestive relation between cannabis abuse and variants in the *ANKFN1* (*Ankyrin-Repeat And Fibronectin Type III Domain Containing 1*) gene on human chromosome 17 [47].

Metabolic pathways of dopamine play a major role in illicit drug use such as amphetamine and cocaine [48]. *DRD2 Taq1 A1* allele (11q23) may influence heroin addiction and polymorphism in dopamine transporter gene 1 (DAT) may be associated with alcoholism and cigarette consumption in young ages [49-51].

OPRM1, encoding the G protein-coupled mu opioid receptor, is the primary site of opioid activity. A nonsynonymous SNP in exon 1 of *OPRM1*, *A118G*, is the common form for opioid addiction, but its relation is arguable [52-56].

Two well-characterized cannabinoid receptors, CB1 (*CNR1*) and CB2 (*CNR2*), have been noticed to have a linkage with psychiatric problems, like substance misuse [57]. Intravenous application of addictive agents has been related with the genetic variant (*AAT*)*n* trinucleotide short tandem repeat in *CNR1* [58]. Beside cannabis dependence, cocaine and other substance dependences were also found to be related with *CNR1* variants [59-62].

Polymorphisms in the COMT (Catechol-O-methyltransferase) gene may be the reason for some psychiatric disorders and substance abuse [63, 64]. An interesting point is the rs16969968 nonsynonymous variant in the $\alpha 5$ nicotinic acetylcholine receptor is also related to cocaine dependence, however the minor allele decreases the risk for cocaine dependence [65]. Serotonin metabolism is also investigated in the genetic etiology of drug addiction. Receptor gene polymorphisms for 5HT may influence addictive tendency, side effects or treatment success [66]. Glutamate decarboxylase (GAD, catalyzes the rate limiting step in GABA synthesis) coding genes are of potential concern in drug and alcohol dependence. The isoforms GAD1 and GAD2 are reported to have a linkage with alcohol dependence in males of Han Taiwanese (GAD1) and Russian (GAD2) descent [67, 68].

Circadian clock genes (*Per*, *Clock*, *Bmal1* and *Cry*) may influence starting and further using of drugs and alcohol. In the last decade, clock genes

have been disclosed to have a major role in revealing acute and chronic alcohol or drug use symptoms. Researches demonstrated both their direct or indirect association with the stress hypothalamo-pituitary-adrenal axis and/or reward system [69].

Brain-derived neurotrophic factor (BDNF) is known as a different marker of stress adaptation and has long been investigated in the field of addiction and its significance in controlling drug addiction-related behavior. In a recent study *BDNF rs6265* and *DRD2 rs1799978* variations were found unrelated with chronic illegal opioid use in methadone treated patients. [70].

Conclusion

Substance addiction varies considerably among individuals due to their society or ancestry. It is a polygenic condition and is difficult to explain with a single gene. Both genetic and environmental factors influence dependence. Genomic approaches yield signals to the underlying genetic etiology of addiction by genome wide procedures and by candidate gene researches. Studies center on drug-induced modifications in the expression and structure of chromatin, lead to improve our knowledge of the ways in which genetic/epigenetic variations and environmental attacks together cause neuronal molecular changes essential to the tendency to dependencies and to the course of dependence and treatment.

In summary, studies and science of genetic etiology for substance related health problems are still in its infancy. For smoking, which is the most cause of diseases and deaths worldwide, several favorable loci found in repeated studies have possibility for clinical translation. For alcohol, epigenetic signs found in several studies are subtler, but there is potency for translation if the last findings are repeated. For other illicit substances, even with active studies for candidate genes, there is no evidence with prompt potential for clinical translation. Studies and replication of any findings before translation are required in this area.

As a consequence, further investigations of epigenetic variations along whole-genome are needed for detecting novel biomarkers for substance misuse or addiction.

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