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ALLELIC VARIATION IN THE GENES FOR DRUG ABUSE AND ADDICTION: AN OVERVIEW

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ABSTRACT

Drug addiction is a devastating disease characterized by obsessive drug seeking and uncontrolled consumption of addictive elements. A person may become an addict due to high influence of environmental factors such as stress, anxiety, depression, illness, leading to behavioral disturbances and ultimately to drug addiction, often called as drug dependence. However, genetic factors contribute more to the susceptibility to drug addiction, as mutation or single nucleotide polymorphism (SNP), that is, change in a single nucleotide base of a gene, altering the metabolism, can be responsible for addictive behaviors. In the present overview, we have tried to encompass all the significant studies related to genetic polymorphisms and susceptibility factors related to drug abuse and addiction. It would be a swift guide for scientists working in the field of behavioral genetics of drug addictions at molecular level.

KEYWORDS: Addiction, Genetic polymorphism, Opiates, Heroin, Caffeine, Cocaine, Nicotine, Dopamine.

INTRODUCTION

Drug addiction is often called a behavioral disorder. It is a multifactorial disease affected by psychological, physiological, pharmacological, genetic and environmental factors (Isaza *et al*., 2013). The genetic susceptibility to addiction embodies a combination of 100s or 1000s of genes of modest effect. The genetic basis of addiction comprehends the identification of genetic variations vulnerable to addiction (Eric, 2000). Genetic mutations and polymorphisms can be considered as one reason for variations in human regulatory systems like brain functioning leading to drug addiction. Other than genetic factors there can be some environmental factors such as stress, anxiety and depression, which may lead to drug abuse or addiction. Genetic variants can be completely explained through addictive behaviors, or if biologic mechanisms act in the brain to increase the risk of addiction (Laura, 2011).

Genetic factors increase risk of drug dependence and development of disorders like antisocial personality disorder due to excessive usage of drugs (Danielle & Arpana, 2008). Identification of genetic variants and genes associated with addictive behavior can be completely explained through disturbance in brain functions to increase the risk of addiction (Laura, 2011).

Heritability for addictive disorders varies among substances, populations, ages, and gender (Alexis *et al*., 2009). A heritable association characterizes not only an association with tested genetic variants, but also an association with untested, highly correlated SNPs,which when confirmed, support to understand which of the genetic variants take part in the biological mechanism fundamental in correspondence with the disorder (Laura, 2011).

Genetic studies to date have been most successful at identifying genetic factors that influence the transition from regular use to dependence. The current review focuses primarily on the genes and genetic variants responsible for high or low levels of addiction or addictive behaviors towards psychostimulants such as heroin, nicotine, cocaine, caffeine and dopamine etc.

Addiction to heroin

Opioid receptors and drug dependence: Opioids are a large family of biologically active peptides that bind to and activate receptors in humans and can reduce pain and induce euphoria (Roger and Mary, 2012). The term *opiate* is often used as a substitute for opioid. Opioids include alkaloids like morphine which is an active metabolite of heroin, semi-synthetic opioids such as oxycodone, oxymorphone, hydrocodone, hydromorphoneand the synthetic opioid narcotics.These opioids produce effects on neurons by acting on receptors [majorly mu (μ), delta (d) and kappa (k)] located on neuronal cell membranes (Loris, 1996). The opioid receptors and many other membrane receptors are coupled to guanine nucleotide binding proteins known as G-proteins. The G protein-coupled mu opioid receptor (encoded by OPRM1) is the main target of morphine, heroin, and methadone, and it plays an important role in opioid tolerance and dependence. Individual differences in response to opiate drugs may be attributed in part to genetic variations in the OPRM1 gene (Yuferov *et al*., 2010). The human μ-opioid receptor is a primary candidate for the pharmacogenetic variability of the clinical effects of opioid analgesics because it is the major site of action for most opioids (Uhl *et al*., 1994). Mutations or polymorphisms in OPRM1 gene have been investigated for association with substance abuse or addiction and for association with neurological or psychiatric disorders like, 118A>G polymorphism in exon 1 has been reported to cause an amino acid exchange from asparagine to aspartate at receptor protein position 40 of the extracellular receptor terminal (Jorn and Gerd 2005) and the 31G>A polymorphism located in intron 2 involving an A/TGGG motif (Wendel & Hoehe, 1998).

The rewarding effects of drug use are mediated by MOR (μ opioid receptor) and DOR (δ opioid receptor) activation (Di Chiara & Imperato, 1988 and Herz, 1998). DOR is thought to be involved in analgesia, morphine tolerance and mood regulation such as anxiety and depression (Filliol *et al*., 2000, Perrine *et al*., 2006 and Zhu *et al*., 1999). The delta opioid receptor gene OPRD1 was the first human opioid receptor gene to be cloned (Uhl *et al*., 1994) and is with relatively conserved sequence. Studies have associated twocoding variantsof OPRD1 withalcohol anddrug addiction: silent T921Cin exon 3 and non-synonymous transversionG80T in exon 1 (Zhanq *et al*., 2008). T921C polymorphism that has been of more focus is said to be linked with heroin addiction in German Population (Mayer *et al*., 1997) but has also been reported to have no association with heroin abuse and dependence in large relatively homogeneous Han Chinese population (Xu *et al*., 2002).

Genetic polymorphisms in kappa opioid receptors exhibit a significant association with addictive disease (Yuferov *et al*., 2004). In humans, the 36G>T single nucleotide polymorphism (SNP) in exon 2 of KOR (Kappa Opioid Receptor) gene has been found highly associated with heroin dependence (Gerra *et al*., 2007). KOR contains mainly silent polymorphisms, with apparently no consequences on mRNA transcription and receptor structure, but previous studies have reported positive associations of silent mutations in the three opioid receptors with drug addiction (Mayer and Hollt, 2006).

Serotonin receptor and heroin dependence: The serotoninergic (5-HT, 5-hydroxytryptamine) system is responsible for regulation of neuronal activity in broad brain regions. It is particularly important for modulating behavioral and physiological functions such as mood, sentiments, sleep and appetite (Gao *et al*., 2011). Serotonin exerts its effect through binding to its receptors, after activation 5-HT receptors can stimulate either excitatory or inhibitory neurotransmission (Saiz *et al*., 2009 and Drago *et al*., 2010). Studies suggest that genetic polymorphism in serotonin receptors 1B or 2A (HTR1B, HTR2A, hydroxytryptamine receptor 1B, 2A) may alter the brain expression and lead to drug addiction, mainly heroin addiction (Polina *et al*., 2009 and Drago *et al*., 2010). The G861C polymorphism in HTR1B has been identified to be associated with heroin addicton. This polymorphism has been found in a significantly higher frequency in general population and has been known to alter the expression of HTR1B (Sanders *et al*., 2002; Sun *et al*., 2002 and Huang *et al*., 2003). Studies about the Han Chinese population indicate that the G allele especially might be associated with heroin dependence (Gao *et al*., 2011). The G allele has also been shown to be over present in smokers (Lerer *et al*., 2006), alcoholics (Fehr *et al*., 2000) and people with obsessive compulsive disorder (Camarena *et al*., 2004 and Levitan *et al*., 2006). On the other hand, SNP A-1438G is said to alter the promoter activity and the expression of HTR2A in the brain (Parsons *et al*., 2004; Myers *et al*., 2007), whereas the T allele of T102C influences the HTR2A expression in the prefrontal cortex (Underwood *et al*., 2008 and Turecki *et al*., 1999).

PDYN and heroin dependence: Prodynorphin, abbreviated as PDYN, is an opioid peptide precursor protein, products of which inhibit neurotransmission by acting through kappa opioid receptors and are involved in reward, mood regulation, stress comebacks, and motor functions and addicton (Drolet *et al*., 2001; Kelly *et al*., 2002 and Hauser *et al*., 2005). Prodynorphin (PDYN)and k-opioid receptors makes dopaminergic system important for the reinforcing and rewarding effects of drugs of abuse such as heroin (Shippenberg *et al*., 2007). PDYN genes with three or four copies of 68 bp VNTR promoter polymorphism have been found in African American heroin dependents (Ray *et al*., 2005).

Addiction to nicotine: Nicotine dependence endures to be a major public health problem worldwide, which is a component in cigarettes that is responsible for the upkeep of habitual smoking. As a matter of fact the neuronal nicotinic acetylcholine receptors (nAChRs) are mainly the mediators for physiological effects of this drug (Benowitz, 1996). Strong association of nicotine dependence with genetic polymorphisms has been found in the nicotinic receptor gene cluster, α5-α3-β4, on chromosome 15q25 (Laura *et al*., 2008). Several SNPs in this gene cluster have been found to be associated with lung cancer in the genome-wide scan in African-Americans and European populations (Broderick *et al*., 2009 and Hansen *et al*., 2009). Studies have discovered strong association of nicotine dependence with SNP in CHRNB3, the b3 nicotinic receptor subunit gene (Scott *et al*., 2007). Most convincing evidence of nicotine dependence, as reported, iswith the non-synonymous SNP A/G in exon 5 of CHRNA5 gene, changing the amino acid 398 from aspartic acid (encoded by the G allele) to asparagine (encoded by A, the risk allele) (Laura *et al*., 2008).

Addiction to caffeine: Caffeine is one of the most extensively consumed stimulants in the world. It is often used for a variety of medical purposes. Roughly, about 80-90% of the adults consume caffeinated beverages and food (Fredholm *et al*., 1999). In some people, caffeine provokes pleasurable and reinforcing effects that may lead to dependence, while others may experience anxiety, tachycardia, nervousness or other adverse effects with low-to-moderate intakes of caffeine and they are unlikely to develop dependence (Smith, 2002). Some association has been noticed between different anxiety levels after caffeine administration and polymorphisms on the adenosine receptor genes (Alsene *et al*., 2003). The adenosine receptor system mediates the psychoactive effects of caffeine and is thought to play significant role in anxiety (Karen *et al*., 2003). Genome-wide association studies (GWASs) have identified single nucleotide polymorphisms (SNPs) in aryl-hydrocarbon receptor (AHR) and cytochrome P450 1A1 and 1A2 (CYP1A1-CYP1A2) genes to be associated with habitual caffeine and coffee consumption in European decent and in Costa Rican population (Andrea *et al*., 2012). Both CYP1A2 and AHR affect caffeine metabolism, and their link to caffeine consumption shows

additional genetic regulation of intake behavior (Andrea *et al*., 2012).Research also tells that people with ADORA2A 1083TT (adenosine receptor A2A) genotype (ADORA2A 1083 C→T polymorphism) are more likely to limit their caffeine intake (Marilyn *et al*., 2007).

Addiction to cocaine: Cocaine addiction is yet another major health and social problem. Pleasant and addictive effects of cocaine are facilitated by the blockage of DAT (Dopamine transporter or dopamine active receptor), encoded by SLC6A3 gene and its mutant alleles (Madsen *et al*., 2012). DAT in an integral membrane protein which is responsible for the removal of dopamine from the synaptic cleft and its release in the surrounding cells, terminating the signal of the neurotransmitter (Schultz, 1998). This transporter, DAT has been associated with cocaine dependence (Guindalini *et al*., 2008). According to the reported research, allelic variation in the VNTR region (VNTR-6R) of the gene SLC6A3 and the genotype 3435CC in the ABCB1 gene, are both said to be linked with addictive behavior to heroin or cocaine (Isaza *et al*., 2013).

Prodynorphin, abbreviated as PDYN, is an opioid peptide precursor protein, products of which inhibit neurotransmission by acting through kappa opioid receptors and are involved in reward, mood regulations, motor functions and addicton (Drolet *et al*., 2001, Kelly *et al*., 2002 and Hauser *et al*., 2005). The promoter region of this gene has 1-4 repeats of 68 bp (68 bp VNTR/68 bp VNTR promoter polymorphosm) element which contains a single binding site for transcription factor AP-1 (Zimprich *et al*., 2000). This increase in the number of 68 bp repeats in PDYN gene has been shown to be associated with cocaine dependence in European, African, and Hispanic descendant (Zhang *et al*., 2004, Chen *et al*., 2002). Dahl *et al*., (2005) indicated that persons with three or four copies of this polymorphism are more likely to become cocaine dependent.

Addiction to dopamine: Dopamine increases the motivation for food intake (Volkow *et al*., 2002). A polymorphism of the D2 dopamine receptor which renders it less sensitive to dopamine stimulation has been proposed to promote self-stimulatory behavior such as consuming alcohol, abusing drugs, or binging on foods (David and Catherine, 2011). Drugs of abuse induce repeated profound dopamine stimulation, which, with chronic use, may induce changes in neuronal plasticity resulting in increased emotional reactions to drugs, and reduced ability to inhibit drug consumption leading to compulsive chronic drug abuse (Volkow and Li, 2004). The repeated stimulation of DA (dopamine) reward pathways has been proposed by Volkow to trigger adaptations in other neurotransmitters and in brain reward circuitry that may lead to increases in compulsive behaviors affecting both food and drug intake (Volkow and Li, 2004). The dopamine receptor D2 (DRD2) gene has been associated with addictive behaviors like smoking, illegal drug use, gambling and overeating. The Taq1A polymorphism, within the coding region of the gene ANKK1,(the most repeatedly studied polymorphism) is located more than 10 kilobase-pairs downstream from the coding region of the DRD2 gene at chromosome 11q23 (Neville *et al*., 2004).

DISCUSSION

Addiction or illicit use of psychostimulants is an enduring, relapsing brain disease that, if left untreated, can be the major cause of medical, social, and economic problems (Yuferov *et al*., 2010).The development of addiction requires the use of a substance and a subsequent chain of behavioral events that leads to addiction (Laura, 2011). Substances that are addictive induce pleasing effects and relief in stress conditions; continued use of such elements encourages adaptive deviations in the central nervous system resulting in physical dependency, sensitization, tolerance, reversion and desire (Jordi and Magi, 2003). Exposure to drugs that elicit dependence alters gene expression profiles throughout the reward circuitry of the brain (Maze and Nestler, 2011). These altered brain circuits can change the responsiveness of the individual to initial drug exposure or the adaptations that occur in the brain after repeated drug exposure. Substance dependence can be thought of as a pharmacogenetic illness, but it would require a number of studies on genetic variations to fully explain the genetic input to this disease (Laura, 2011).

There are certain specified genes responsible for maintenance of specific brain circuit functions and alterations in these genes might indirectly contribute to addictive responses in many ways. Normal structure and function of specific brain circuits during development or in adulthood can get changed due to a mutant protein or deviation in the levels of a normal functional protein (Eric, 2000). Several of the confirmed genetic findings support the fact that specific allelic variants contribute to the risk of specific substance dependence. According to scientists, this can be elaborated as: the addictive behaviors are complex genetic traits that are both phenotypically and genetically heterogeneous. It is anticipated that there are multiple genetic loci that influence manifestation and variation in such addictive behaviors, and that these loci vary in the direction and magnitude of their effects (Alexis *et al*., 2009).

It is not necessary that everyone who consumes addictive substances becomes an addict, but the chances for a person of becoming an addict vary from person to person or male to female, according to the usage of materials causing addiction. Heritabilities in the range of 0.30–0.60 have been observed for illicit drug dependences that can change with the age and development (Kendler and Prescott, 1998 and Tsuang *et al*., 1998).

Drug abuse and addiction has become a grave worldwide issue with strong genetic and environmental influences. The contribution of genetic factors to individual vulnerability to drug addiction, however, is moderate to large (as much

as 40%-60%) (Tsuang *et al*., 1996; Merikangas *et al*., 1998; Kendler *et al*., 1999). It is believed that by identifying genes involved in the physiologic response to drugs of abuse and addiction, more effective pharmacotherapy can be established (Laura, 2011).

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