•Review•

Advances in genetic studies of substance abuse in China

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Summary: The importance of genetic factors in substance addiction has long been established. The rationale for this work is that understanding of the function of addiction genes and delineation of the key molecular pathways of these genes would enhance the development of novel therapeutic targets and biomarkers that could be used in the prevention and management of substance abuse. Over the past few years, there has been a substantial increase in the number of genetic studies conducted on addiction in China; these studies have primarily focused on heroin, alcohol, and nicotine dependence. Most studies of candidate genes have concentrated on the dopamine, opioid, and serotonin systems. A number of genes associated with substance abuse in Caucasians are also risk factors in Chinese, but several novel genes and genetic risk factors associated with substance abuse in Chinese subjects have also been identified. This paper reviews the genetic studies of substance abuse performed by Chinese researchers. Genotypes and alleles related to addictive behavior in Chinese individuals are discussed and the contributions of Chinese researchers to the international corpus of knowledge about the genetic understanding of substance abuse are described.

1. Introduction

Drug addiction is a chronic relapsing disorder, characterized by a compulsion to use drugs and the emergence of a negative emotional state after withdrawal.[1] The number of people with drug addiction in China has been increasing annually making it a serious public health problem.[2,3]

The brain reward system plays a key role in the development of drug addiction.[4] The common genetic influences underlying addiction are shared by different drugs. Compelling evidence indicates the critical role of the dopamine system, which is directly or indirectly activated by all abused drugs, in drug addiction.[5] In addition to dopamine, multiple neurotransmitter and enzyme systems have been shown to play a role in the reinforcing effects of drugs of abuse, including opioid peptides, γ-aminobutyric acid (GABA), glutamate, endocannabinoids, serotonin and metabolic enzymes.[6,7]

Genetic influences account for 30 to 70% of addiction vulnerability. These genetic influences are induced by multiple genes, each of which may make only a minor contribution to the variance of addiction risk.[8] Addiction is a complex condition that results from the combined interaction of several factors including environmental influences, drug-induced neurobiological changes, and personality traits. Genetic variations that affect these factors may work in concert to affect the vulnerability to addiction and the severity of addiction. Genetic factors influence different stages in the initiation and progression of substance addiction, including dependence, withdrawal and relapse.[9,10] Two main strategies have been used to identify genetic variations that influence addiction vulnerability and other addiction-related phenomena: the candidate gene approach and the genome-wide linkage approach.[11] Coupled with genetic epidemiological analyses, these studies have provided solid evidence about the importance of genetic factors in addiction.

Genetic research on addiction in China has mainly focused on opiates, alcohol, nicotine and some of the newer drugs of abuse, which together make up the majority of substance abuse disorders in China. Opiates, especially heroin, are widely and traditionally abused in China.[12,13] According to the China 2013 Narcotics Report, there are 1.27 million persons with opium addiction in the country, accounting for 60.6% of all drug addicts nationally.[2] The use of the newer drugs of abuse – mainly methamphetamine (METH), 3,4-methylenedioxymethamphetamine (MDMA), and ketamine – has spread in China since 1997.[14] These more recent drugs of abuse are becoming popular recreational drugs;[15] they already account for 38% of all drug addicts (about 800,000 individuals) in the country[2] and, more concerning, for the majority of individuals who are starting to abuse drugs.[16] Additionally, alcohol consumption has increased considerably in China in the past three decades,[17,18] an increase that is occurring

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across all age groups, especially among young people in urban areas.[19] The social burden caused by diseases related to alcohol abuse is considerable in China.[20] Also, chronic smoking problems are particularly serious in China: the Chinese Center for Disease Control and Prevention reports that China has the largest population of smokers in the world (over 350 million) and that many non-smokers experience health problems caused by exposure to second hand smoke.[21,22]

This review focuses on genetic advances in substance abuse research conducted by Chinese researchers, summarizing their contributions to the understanding of drug dependence and to the evidence base that is required to improve the prevention and management of substance addiction in China. We identified potential studies for inclusion in this review by searching the Pubmed database using the terms "genetic" or "polymorphism" or "gene" with "addiction" or "dependence". Identified articles were included in the review if they were conducted at Chinese institutions and if they were considered potentially important by the authors. We also identified additional studies by checking the reference lists of the identified articles and by consulting experts.

2. Candidate gene studies

2.1 Dopamine system

Dopamine is an important neurotransmitter in the brain that controls various functions. The dopamine system plays a key role in reward mechanisms. The variety of genes that encode dopamine receptors, dopamine transporters, and dopamine metabolic enzymes affect the heritability of drug addiction.[23] In the central nervous system, dopamine receptors are widely expressed and involved in the control of locomotion, cognition, emotion and the neuroendocrine system.[24]

The important effects of genetic polymorphisms of dopamine receptors and of the dopamine transporter on substance abuse have long been established.[23,25] Some studies supported the hypothesis that genetic variants in dopamine systems increase the risk of addiction disorders by affecting different aspects of impulsivity or the capacity to inhibit the choice of a less rewarding signal.[23] Using Chinese samples, a number of Chinese studies have verified the results of studies conducted in other contries. The dopamine D_2 receptor (*DRD2*) mRNA was found to be abundantly expressed in all dopaminergic terminal-enriched areas.[26] *DRD2* TaqI A1 allele carriers were shown to be prone to heroin abuse.[27] Li and her team found that individuals who carry the *DRD2* TaqI RFLP A1 allele showed significantly stronger cue-elicited craving.[28] Du and colleagues performed a meta-analysis and suggested a possible association between the dopamine transporter gene 1 (*DAT)* gene polymorphisms and alcoholism.[29] Ling and colleagues reported that polymorphisms of the *DAT* gene may play an important role in smoking onset and that there is a possible interactive effect between *DAT* and early smoking onset that contributes to the susceptibility to nicotine dependence.[30] Dopamine D_4 receptor (*DRD4*) polymorphisms were shown to be related to heroin dependence,[31,32] and *DRD4* exon III variable number of tandem repeat (VNTR) polymorphisms may play important roles in the development of opiate abuse.[33] Heroin addicts who carried the *DRD4* VNTR long-type allele had stronger cue-elicited craving.[34] Catechol-*O*-methyltransferase (*COMT*) played an essential role in dopamine inactivation. The rs4860 (Val158Met) functional single-nucleotide polymorphism (SNP) on the *COMT* gene resulting in a three- to four-fold increase in enzyme activity [35] has been extensively studied in psychiatric disorders, including drug dependence.[36] Chinese heroin addicts with the TT genotype of *COMT* rs737866 variants had higher novelty-seeking scores and an earlier age of onset of heroin use than addicts with the CT or CC genotype.[37] However, findings about the association between this SNP and the age of onset of heroin use remain controversial.[38-42]

Similar to the findings of genetic studies conducted in other countries, studies about the association between genetic variants of the dopamine system and substance abuse in Han Chinese populations with addiction have also been inconclusive. Some studies reported that neither the *DRD2* nor *DAT* gene plays a significant role in alcoholism in Taiwanese populations.[43,44] Even after stratification by the relevant genotypes of alcohol dehydrogenase 2 (*ADH2*) and aldehyde dehydrogenase 2 (*ALDH2*), no significant association was found between the genetic variants of *DRD2* and alcoholism in a Han Chinese population.[45] Tsai and colleagues investigated the associations between *DRD2* TaqI and *DRD4* exon III VNTR polymorphisms and METH dependence in a male Han Chinese sample, but they did not find any significant results.[46] Similarly, no significant difference was found in the VNTR distribution of *DAT1* between heroin abusers and healthy individuals in China.[27] The DAT was the main modulator of MAP/amphetamine-induced dopamine release and dopamine neurotoxicity, but when Liu and colleagues tested the association between a *DAT* gene polymorphism and clinical variations in METH abusers, no significant association was found.[47]

Genetic variants can also affect the treatment outcome for nicotine dependence. Recently, Sun and colleagues found that Chinese smokers with the *COMT* Val/Val genotype had greater abstinence rates when treated with nicotine replacement therapy.[48] Furthermore, *DRD2* variants have been found to be associated with the dose of methadone required in the treatment of Chinese individuals with heroin addiction.[49]

2.2 Endogenous opioid and cannabinoid systems

Opioid peptides activate G-protein-coupled μ-, δ- and κ-opioid receptors, which differ in affinities and response profiles. Opioid receptors are physiologically activated by the endogenous neuropeptides β-endorphin, leu-enkephalin, met-enkephalin and dynorphin. These peptides are not limited to binding with a certain type of opioid receptor. Individuals with a genetic predisposition

to substance abuse may have defects in opioid peptide and receptor genes.[50] Opioid receptors not only mediate the pharmacological actions of opioids, but they also modulate the *in vivo* effects of other drugs of abuse.[51] The human mu-opioid receptor (*MOR*) represents the most important target of morphine, and the genetic variants of the *MOR* gene (*OPRM1*) have been extensively studied with regard to addiction.[52]

Genetic polymorphisms in *OPRM1* have been associated with heroin dependence in Chinese samples;[53] however, several studies with negative results have also been reported.[54,55] Addiction-related subjective responses at the time of first drug use and during drug-seeking behavior may be modulated by *OPRM1* polymorphisms.[56-58] Although many studies have investigated the association between the *OPRM1* A118G polymorphism and alcohol dependence, no consensus has been reached.[59,60] Wang and colleagues performed an ethnicity-specific meta-analysis, which reported that the A118G polymorphism was significantly associated with the risk of alcohol dependence risk in Asians but not in Caucasians.[61]

Preprodynorphin is naturally derived from prodynorphin and is the primary endogenous ligand of the κ-opioid receptor. Variants of the preprodynorphin gene have been studied with regard to opiate, cocaine, and alcohol addiction.[62] Three variants of the Preprodynorphin (*PDYN*) gene were found to be associated with heroin dependence in Chinese subjects.[63] Additionally, *PDYN* was significantly related to the risk of developing opioid dependence, however, this effect has only been found in females.[64]

Endogenous cannabinoid functionally interacts with opioid systems. The cannabinoid brain receptor type 1 (CB1) and mu-opioid receptor type 1 (MOR1) co-localize in the same presynaptic nerve terminals and signal through a common receptor-mediated G-protein pathway.[65] The cannabinoid receptor 1 (*CNR1*) gene is primarily expressed in the central nervous system.[66] The endocannabinoid system has been repeatedly found to be associated with drug addiction. However, no association was found between repeat variations of the *CNR1* gene and heroin abuse in a Chinese sample.[67]

2.3 Serotonin system

Many studies have shown that the brain neurotransmitter serotonin (5-hydroxytryptamine [5-HT]) plays an important role in the regulation of reward-related processing.[68,69] Growing evidence also indicates deregulation of the serotonin system after long-term exposure to abused drugs.[70] Altered 5-HT transmission has been thought to increase susceptibility to a wide range of substance abuse disorders.[71] Genetic polymorphisms of 5-HT system genes collectively give rise to a unique genetic architecture that may contribute to individual risk of addiction, development of addiction, treatment effectiveness and potential for full recovery.[72]

In a recent study, Gao confirmed the significant association between heroin dependence and four SNPs of the 5-HT receptor (*HTR*) genes in a cohort of Han Chinese.[73] The serotonin transporter protein regulates serotonin concentrations in the synaptic cleft. Tan and colleagues provided evidence of an association between heroin dependence and a VNTR polymorphism at the serotonin transporter *(5-HTT)* gene.[57] Upstream of the *5-HTT* gene is a 5-HT transporter gene-linked polymorphic region (*5-HTTLPR*). Compared to the L allele, the S allele is associated with decreased transcription efficiency of the *5-HTT* gene. Wang and colleagues verified that the *5-HTTLPR* polymorphism may be associated with alcohol dependence in a Chinese population, and that the L/L or L/S genotype may be a genetic factor responsible for decreased susceptibility to alcohol abuse.[74] The 5-HT system is also implicated in the pathogenesis of smoking behaviors.[75] Chu and colleagues validated such an effect of the *5-HTTLPR* polymorphism on smoking behavior in Chinese males.[76]

2.4 Alcohol metabolic enzymes

Enzymes involved in ethanol metabolism have been considered major biological factors that influence drinking behavior and the development of alcohol dependence.[77] The genes with the most convincing evidence about their relationships to alcoholism are *ADH* and *ALDH2*, which encode two enzymes that catalyze consecutive steps in alcohol degradation. The human *ADH* genes, *ADH1B* and *ADH1C* were found to have alleles that produce enzymes that catalyze the oxidation of ethanol to acetaldehyde. Alcohol dehydrogenases that perform most of the alcohol metabolism are homodimeric enzymes, which contain α, β, and γ subunits, being encoded by *ADH1*, *ADH2*, and *ADH3* respectively.[78] The genetic variants of these genes, which have different ethnic distributions, encode enzymes with different characteristics. The polymorphic distributions of the *ADH* and *ALDH* genes are quite different in the Han Chinese population compared to other populations.[79] Thus, studies of the Chinese population can provide a unique opportunity to clarify the influence of these genotypic differences on the phenotypic differences and underlying mechanisms of alcoholism.

Genetic differences in the enzymes that metabolize alcohol can substantially affect the risk of alcoholism. Enzymatic studies have shown that *ADH1B**2/*2-encoded enzymes exhibit a 30- to 40-fold greater Vmax for ethanol oxidation than the *ADH1B**1/*1-encoded enzymes.[80,81] The *ADH1B**2 allele, which is common in East Asians, is protective against alcoholism.[82,83] In Chinese patients being treated for alcoholism, the *ADH*2*2 and *ADH*3*1 alleles also showed a protective role.[84] The *ALDH2* gene has two variant alleles: *ALDH*2*1 and *ALDH*2*2. The *ALDH*2*2 allele is associated with a deficiency in *ALDH2* activity, which decreases the risk of alcoholism.[85] However, *ALDH*2*2 and *ADH1B**2 did not decrease the risk of high alcohol consumption in Han Chinese males with stroke.[86] Thomasson and colleagues found that Han Chinese males in Taiwan with alcoholism had significantly lower frequencies of the *ADH1B**2, *ADH1C**1 and *ALDH*2*2 alleles than non-alcoholics.[87]

Nonetheless, there are also studies in Chinese samples that do not confirm these findings.[88] And different minority groups within the Chinese population may have different genetic risk factors for alcoholism; for example, individuals in the Elunchun minority have much lower frequencies of *ADH*2*2 and *ALDH*2*2 alleles than other Chinese minorities.[89]

Alcohol metabolic enzymes may interact with other risk factors for alcoholism (e.g. other genes, gender and environment).[90] Chinese studies found a possible interaction between the *ADH1B*, *ALDH2*, and *DRD2* genes in alcoholics with anxious-depressive symptoms.[91] The *ALDH*2*2 and *ADH1B**2 alleles have cumulative dosage effects on alcoholism, and alcohol metabolism can be influenced by gender and alcohol-related-trait scores in different ways.[92,93] On the other hand, the protective effect of the *ADH*2*2 allele may occur independently of the *ALDH*2*2 allele.[94]

2.5 Monoamine oxidase gene

Monoamine oxidase (*MAO*) has been known to catalyze the oxidative deamination of numerous biogenic amines, including the key neurotransmitters-dopamine, norepinephrine and serotonin. Two forms of MAO have been identified: monoamine oxidase A (*MAOA*) and B (*MAOB*).[95] An estimated 70% of neuronal MAOs are type A, which is expressed at the highest level in catecholaminergic neurons.[96,97] *MAOA* is localized in brain regions that have been implicated in addiction and in the behavioral response to novel stimuli.[98,99] Two *MAOA* polymorphisms, the EcoRV polymorphism at position 1460[100] and the VNTR polymorphism in the promoter region,[101] are particularly important because they affect enzyme activity and transcriptional activity, respectively. A modest increase in dopamine and a dramatic increase in aggressive traits were observed in *MAOA* knockout mice.[102,103]

Genetic variants in the *MAO* gene have been reported to be associated with the risk for substance abuse.[104,105] Chen and colleagues assessed the role of *MAO* gene polymorphisms in alcoholism in five ethnic groups in Taiwan. Significant associations between alcohol abuse and *MAOA* alleles were found among the Han Chinese, but not among the aboriginal groups.[106] Correlation studies suggested that the mitochondrial MAO/ALDH pathway may be the site of action of daidzin, which was shown to suppress alcohol intake in alcohol-preferring laboratory animals.[107] Lee and colleagues hypothesized that the *ALDH2* gene might interact with the *MAOA* gene in subjects with alcoholism. In a study of Han Chinese persons in Taiwan with alcohol dependence and either comorbid antisocial personality disorder or comorbid anxiety-depressive symptoms, they found that the VNTRs of *MAOA* may have modified the protective effect of the *ALDH2* gene.[108,109] Jin and colleagues demonstrated the *MAOA* gene polymorphisms could affect the initiation of smoking in a Chinese sample; individuals with the 1460T/O and three-repeat VNTR genotypes had a significantly increased risk for nicotine dependence.[110] However, no significant relationship was found between the long repeat alleles of the *MAOA* promoter VNTR polymorphism and heroin addiction in Chinese males.[111]

2.6 Cytochrome P450 enzymes

Cytochrome P450 (CYP) comprises a superfamily of enzymes that play an important role in metabolizing clinical medications, abused drugs, toxins and endogenous molecules. Drug metabolism by genetically polymorphic enzymes can have significant clinical implications for therapeutic failure, disease susceptibility and abuse liability.[112] Many of the drug-metabolizing CYP enzymes belong to the CYP2 family, which is highly polymorphic. The *CYP2* family may play a role in modulating central functional pathways that are involved in drug-reinforced behavior and neurotoxicity.[113]

The *CYP450* enzyme gene is a nicotine-metabolizing enzyme involved in neurotransmitter synthesis that plays an important role in nicotine dependence.[114] There is a review available on studies about the influence of CYP2A6 genetic polymorphisms on nicotine kinetics, smoking behaviors, and its differential effects on smoking initiation, conversion to dependence, the amount smoked during dependence, and cessation.[115] Liu and colleagues found reduced metabolic function of *CYP2A6* in Chinese smokers that was associated with fewer cigarettes smoked, a later initiation of smoking regularly, a shorter duration of smoking, and a lower likelihood of smoking cessation.[116] Tang and colleagues reported on the interaction between *CYP2A6* polymorphism and *MAOA* in risk modulation of smoking behavior (i.e., smoking initiation and smoking persistence) in a Chinese male population.[117] Chinese scientists have also identified important associations between genetic polymorphism of the *CYP450* enzyme gene with the concomitant diseases of substance abuse disorders and with the dosage and side effects of pharmacological treatments for substance abuse disorders.[49,118,119]

2.7 Noradrenergic system

The importance of catecholamines in the mediation of substance addiction was first recognized in the 1970s.[120] Norepinephrine mediates morphine's behavioral effects;[121] and noradrenergic pathways play a crucial role in the pathogenesis of a motivation-reward system in heroin addiction.[122,123] The norepinephrine transporter (*NET*) is responsible for the reuptake of norepinephrine into presynaptic neurons, and it is an important factor in the regulation of the noradrenergic system. *NET* gene expression can modulate timing and intensity of the analgesic effect of opiates.[124,125]. Yeh and colleagues confirmed the role of *NET* genetic variants in the development of heroin dependence among Han Chinese.[126] Studies from other countries have also reported that norepinephrine neurotransmission plays a critical role in the pathological processes associated with alcoholism;[127-129] but these findings were not confirmed

in a study in China by Huang and colleagues who found no association between polymorphisms of the *NET* gene and alcohol dependence or its clinical subtypes.[130]

2.8 Glutamatergic and GABAergic systems

Glutamate is one of the most abundant excitatory neurotransmitters in the brain.[131] Glutamate receptors, which are expressed in several regions of the brain including the mesocorticolimbic dopamine regions, play a key role in addiction.[132] Glutamic acid decarboxylase (GAD) is the rate-limiting enzyme in the conversion of glutamate to GABA.[133] A significant association of GAD1 with heroin dependence has been reported.[134] Li and colleagues examined the association between heroin dependence among Han Chinese and 15 SNPs of the *GAD1* gene using the MassARRAY system; they found significant associations of some novel SNP and haplotypes with heroin dependence that had not previously been identified in non-Chinese subjects.[135]

Opiate reinforcement is mediated by the inhibition of GABA release, thus disinhibiting dopamine neurotransmission. Individuals with a dysfunctional GABAergic system may release higher amounts of dopamine.[136] GABA receptors play an important role in the actions of benzodiazepines, barbiturates, alcohol and morphine dependence.[137,138] In 2003, Lin and colleagues reported a female-specific contribution of the GABA(A) receptor subunit genes to non-psychotic methamphetamine use disorder.[139] Then Loh and colleagues reported that the prevalence of the rs211014 SNP of the GABAAγ2 receptor subunit gene was significantly different between heroin-dependent and healthy Han Chinese.[140] Thus Chinese scientists have helped to delineate the functioning of this gene in addiction.

2.9 Circadian clock genes

Circadian clock genes are composed of a group of genes such as Per, Clock, Bmal1 and Cry.[141] Recently, many studies have shown that circadian clock genes are implicated in the origin or development of many diseases. Drug addiction has frequently been coupled with disruptions in diurnal rhythms.[142,143] Some studies have shown that circadian clock genes are implicated in the initiation or development of drug dependence.[144,145] Chinese researchers have also attempted to assess the effects of circadian clock genes on substance abuse. Wang and colleagues[146] and Liu and colleagues[147] found that drug dependence is influenced by inhibition of the expression of mPer1 in mice. Furthermore, Zou and colleagues were the first to report that a 54-nucleotide repeat polymorphism of *hPer3* is significantly associated with heroin dependence.[148]

2.10 Brain-derived neurotrophic factor

Brain-derived neurotrophic factor (BDNF) plays an important role in the growth, survival and differentiation of developing neurons. It is a neurotrophic peptide that mediates synaptic plasticity, including drug-induced neuroadaptations.[149-151] Addictive drugs influence endogenous *BDNF* mRNA/protein expression in the mesocorticolimbic system.[152-154] Genetic polymorphisms in *BDNF* are associated with addiction, including opiate addiction – a finding that has been supported by a number of studies,[155-157] including studies among Chinese heroin addicts.[158] The rs6265 SNP results in a valine-to-methionine substitution in the *BDNF* pre-domain coding region that has been reported to be associated with different psychiatric disorders, including substance abuse.[159] Chinese studies showed AA carriers of *BDNF* rs6265 had an earlier onset of heroin dependence and a clearer tendency toward a family history of heroin dependence than GG carriers.[160,161] Moreover, this SNP was significantly related to alcohol dependence-related depression and to the effectiveness of sertraline treatment for alcohol dependence-related depression.[162]

2.11 Other candidate genes

Chinese studies have also identified other novel genetic variants for substance abuse. Dopamine β-hydroxylase (*DBH)*−1021TT carriers among Chinese heroin abusers were shown to have a longer addiction time and higher dosage of injected heroin.[163] Two novel copy number variants (CNVs) located downstream of the transforming growth factor β-1 binding protein 1 (*LTBP1*) gene and actin-filament binding protein frabin (*FGD4*) gene were associated with alcohol consumption.[164] Wei and collegues found that polymorphisms in the regulatory region of nuclear-related receptor 1 (*Nurr1*) gene were involved in the pathogenesis of alcohol dependence.[165] Their team also genotyped 384 SNPs within 45 candidate genes related to nicotine dependence in a Han Chinese sample by employing the Golden Gate genotyping assay, and confirmed the previous findings that *DRD2, DRD3, DDC, CHRNB3, GABBR2* and *CHRNA4* genetic variants were associated with nicotine dependence. Furthermore, their team was the first to report a significant association between nicotine dependence and genetic variants in *DRD5, MAP3K4 and NPY1R*.[166]

Genetic variants can also affect other aspects of substance addiction, including the development of related diseases, the prevalence of specific behavioral defects, the risk of poly-substance addiction, and the changes in brain function and structure that occur with substance addiction.[167-170] Genetic studies about these relationships have focused on several specific areas:

(a) Addiction related diseases. Amyloid precursor protein-binding protein, family B, member 1 (*APBB1*) is involved in the modulation of β-amyloid secretion and associated with Alzheimer's disease pathogenesis.[171,172] *APBB1* is also associated with nicotine dependence, a finding that was confirmed by a family-based genetic study in a sample of 2037 participants by Chen and colleagues.[173] This relationship between nicotine addiction and

neurocognitive conditions has also been supported by studies which show that tobacco smoking is inversely correlated with Alzheimer's disease and Parkinson's disease.[174,175] The majority of heroin abusers use injection as the primary route of administration[176] and injection drug users comprise the largest risk group for the transmission of hepatitis C virus (HCV)[177] (a condition that is highly prevalent in China). Peng and colleagues assessed genetic variations of HCV infection and found a higher prevalence of the 6a and 3b genotypes of HCV among heroin users than among individuals with HCV infection who do not abuse substances.[178]

(b) Addiction behaviors. It is known that subjective craving contributes to the continuation of drug use in active abusers and to the occurrence of relapse in detoxified abusers.[179] Jin and colleagues found the *DRD2* TaqI RFLP A1 allele and the *DRD4* VNTR polymorphism long type allele are associated with significantly stronger cue-elicited heroin craving in heroin dependence.[28,34]

(c) Poly-substance addiction. Alcohol and tobacco use are linked because they share several genetic risk factors.[180] Zhang and colleagues performed a bivariate genetic analysis of current tobacco smoking and alcohol drinking in China and confirmed common genetic vulnerability to tobacco and alcohol use in male twins.[181]

(d) Addiction-related changes in the brain. Unpublished work from our own lab has found that individuals with heroin addiction who have the *ZNF804A* rs1344706 genetic polymorphism (which has been linked to psychiatric disorders) are more likely to show changes in behavior and in gray matter volume, suggesting that this polymorphism can exacerbate the effects of heroin.

3. Genome-wide association studies

In this exciting era of gene discovery, a revolution of genetic technology has caused a shift from single-locus studies to genome-wide searches. The completion of the Human Genome Project in 2003 made it possible to conduct genome-wide association studies (GWASs).[182] The GWAS approach uses highly dense SNP markers to explore disease-linked genes by comparing patient samples with healthy controls. The GWAS approach is a powerful tool for identifying susceptibility alleles of complex diseases.[183]

The majority of the GWAS of addiction performed to date have focused on alcohol dependence or smoking behavior.[184-186] Deng and colleagues utilized the GWAS method and found that the ankyrin repeat domain 7 gene (*ANKRD7*) has the strongest statistical association with alcohol use disorder in an initial sample of unrelated Caucasian subjects. They then replicated these results in an independent Caucasian sample and another unrelated Chinese Han sample.[187] Li has done the first genome wide linkage scan of nicotine dependence in an African American sample, and found a major susceptibility loci for nicotine dependence on chromosome 10.[188]

4. Animal studies

Experimental genetic techniques, primarily conducted in genetically modified animals, are an important source of new knowledge about the interrelationship of genetic factors and behavioral outcomes in substance abuse. The molecular genetic technique of gene targeting to create mice with specific gene knockout mutations in the central nervous system has been employed to gain insight into the molecular and cellular basis of substance abuse.[189] For example, the differential expression of specific subunits of nicotinic AChR (obtained from knockout studies) has provided an explanation for their differential nicotine effects.[190] In China, Li and colleagues[191] reported that dopamine D3 receptor knockout mice had pronounced hypoalgesia, decreased morphine-induced tolerance, and attenuated withdrawal symptoms; this helped to clarify the interaction between morphine-induced antinociceptive tolerance and D3 receptors.

Irrespective of the presence or absence of genes that may increase or decrease vulnerability to addiction, studies have shown that altering the expression of numerous genes can also affect substance abuse.[192] MicroRNAs (miRNAs) are small, noncoding RNA molecules that regulate gene expression by binding to complementary sequences in the 3' untranslated regions of target mRNA transcripts which usually results in translation inhibition and/or mRNA cleavage.[193] Recent studies have suggested that alterations in miRNA levels are linked to the mechanisms of substance abuse. For example, Huang and Li demonstrated that miRNAs mediated the effects of nicotine on gene expression.[194] Prolonged exposure to morphine causes an increase in miR-23b levels in striatal neuronal cells, which are involved in the regulation of vulnerability to cocaine addiction.[195,196] And Guo and colleagues found that differential expression of miRNA is related to the behavioral phenotype that is expressed when ethanol is withdrawn after chronic use.[197]

5. Summary and future directions

Ethnic differences can affect both the distribution of genotypes related to addiction and the behavioral responses to addiction.[198,199] Therefore, studies performed in the Chinese population provide a unique opportunity to look at the influence of these genotypic differences on phenotypic differences and, thus, to develop a more comprehensive understanding of the underlying mechanisms related to substance abuse. We have reviewed studies in China – primarily those using classic case-control designs – that examined the genetic basis of substance abuse, including studies about opiates, alcohol, nicotine and some more recently adopted drugs of abuse. The genetic research done by Chinese scientists has involved nearly every aspect of addiction, and some

novel gene loci have been identified in Chinese addicts. Nevertheless, studies from China have not, as yet, fully employed the newer genetic techniques that are being used in cutting-edge research in high-income countries.

Future genetic research needs to stratify results for Chinese subjects by minority, gender, place of birth and so forth. Longitudinal studies tracking the influences of parental psychopathology and other early childhood adverse events on substance abuse and the interaction between these exposures and genetic risk factors are required. The potential value of genetic polymorphisms as biomarkers to help in the individualization of pharmacological treatments for drug addiction and in the monitoring of the effectiveness of these treatments needs to be assessed further. Subsequent studies should also assess the utility of these biomarkers for identifying individuals at high risk of substance abuse, individuals who could then become the targets for intensified prevention efforts.

The inter-individual variability of substance addiction is polygenetic; it cannot be explained by the effect of a single gene or by the effect of a small number of genes. Addiction vulnerability and development is the end product of a complex interaction between gene and environment. Thus future efforts to decrease the rapidly increasing health burden associated with substance abuse in China and elsewhere must creatively integrate genetic and behavioral findings to generate a comprehensive understanding of these disorders, which can then be translated into feasible interventions that can be rigorously tested in the real world.

Conflict of interest

The authors report no conflict of interest related to this review.

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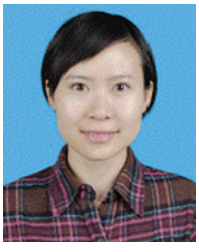

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