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Review Article

The Influences of Genetic Factors in the Addiction, A Concise Review

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Abstract: The Addictions become the most health and social problems in Iraq, wide spectrum of addiction prevalence were recorded in last years, the current review was proposed to focused on the factors that influenced and lead to addiction in population, the Heritability showed an importance of genetic influences in the progression of addictions such as Substance Use Disorders (SUDs) and gambling that establishment by family, adoption and twins researches. Factors represented by environment and gentic factors that change over time influence substance use disorders also discussed in current review,the Monoamines like norepinephrine (NE), dopamine (DA) and serotonin (5-hydroxytryptamine, 5-HT) influence emotionality, cognition and reward. The rare genetic loci that contributed in addiction incidence also discussed. Conclusion: the current review concluded that there was more than factor involved in the addiction incidence and it may modulate through lifespan, the environment-gene interaction have a major role in addiction.

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INTRODUCTION

Addictions represented as broad category of prevalent, complex illnesses that are related to some extent by environmental etiological and genetic factors. They're frequently chronic and relapsing/remitting. Genetic information's and other studies that provide insight on the roots of addiction help to de-stigmatize the disease and make treatment more successful[1]. Individualization of treatment and prevention, as well as the discovery of new therapeutic targets, perhaps possible with a better understanding of genetic determinants in etiology and treatment response[2].

Addictions are chronic relapsing psychiatric diseases marked by compulsive and dys-regulated use of a drug or activity, as well as maladaptive and catastrophic effects. Addiction results from loosed of volitional control, despite the fact that utilizing addictive substances is voluntary. Misuse of legal and illegal

psychoactive drugs is a severe public health issue that affects individuals, families, communities and societies all over the world. (http://www.unodc.org/unodc/en/data-and-analysis/WDR.html).

Addiction is defined as a strong desire to consume a substance, as well as goal-directed behavior toward high level consumption and a uncontrolled over use. Addictive Disorders have recently been supplemented not only by synthetic substances of use/abuse, but also by behaviors capable of promoting debilitating and dangerous psychopathological states. In fact, in addition to alcohol, cigarettes, cocaine, heroin, cannabis and other drugs, researches has discovered new addictions such as eating disorders, Gambling Addiction, Internet Addiction and Sex Addiction. Some individuals become addicted to one or more substances while others do not. According to twin studies, hereditary variables account for more than half of the blame[3]. The genetic influence on addictions is not owing to a single gene's responsible, but rather to the interaction of multiple genes that, in combination with environmental circumstances, generate a state of "susceptibility" to the disorder[4].

The genetic factors that are generally present among persons and are designated as polymorphisms have been considered when studying the genetics of addiction. When these variables are combined with environmental factors (culture, geographic location, substance availability) and other biological susceptibility factors, they form risk factors[5]. The main studies have focused on alcohol addiction or dependence, but the genetic influence on susceptibility to tobacco addiction, cannabis, opiates and other psychoactive substances has also been investigated[6] The goal of this review is to summarize the existing information on common and rare genetic aspects in addictions.

HERITABILITY OF ADDICTIONS

The importance of genetic influences in the progression of addictions such as substance use disorders (SUDs) and gambling is supported by investigation from family, adoption and twins researches[7-10]. Weighted mean heritability's for addictions derived from various large cohorts of twin's studies[11], Hallucinogens have the lowest heritability (0.39), while cocaine has the greatest (0.72). In spite of heritability assess for addiction are usually more than for substance use, "no pathologic drug uptake" and "beginning of use" are both heritable, indicating that genetic factors have a role in both starting and maintenance[12,9,10].

IMPACT OF GENE ALTERATION DURING LIFESPAN

Environmental with Genetic factors that change over time influence substance use disorders (SUDs). Kendler and colleagues[13]. Gene impacts in alcohol, cannabis and nicotine addictions were discovered to be small in early adolescence but to become more substantial as adults. However, the influence of the family environment faded as one grew older. One idea is that as people get older, they have more freedom to change their lifestyles and social environments, making genotype more powerful[15,14].

THE INHERITANCE IN ADDICTION

Many addiction illnesses are more likely to co-occur in the same person, By analyzing the incidence of cross-transmission in genetically informative cases (e.g., twin studies or adoptive), researchers can determine the associate contribution of genes and environment to this comorbidity[16,17]. Alcoholism and illicit substance use disorders, as well as alcoholism and smoking, have been linked in twin studies[18-20].

Kendler *et al*.[21] looked studied the influence of relate genetic effects on addiction to alcohol, nicotine, caffeine, cocaine and cannabis, in a subset of the Virginia twin case comprising 5000 participants. In this study, one factor acting across all substances was unable to explain genetic risk. Instead, researchers observed two similar characteristics: an illicit agent component that mainly described susceptibility to cannabis and cocaine addiction and a licit agent factor that mainly clarified vulnerability to caffeine, alcohol and nicotine addiction. Internalizing disorders, such as antisocial personality (ASPD), conduct (CD), borderline personality (BPD) and attention deficit hyperactivity (ADHD), are typically comorbid with SUDs (ADHD)[16,17,22]. Anxiety and anxiety-related personality traits in adolescents and young adults, as well as panic disorder, social phobia and heightened harm avoidance, have been found to predict future drinking troubles in longitudinal studies[23].

Genes associated in SUD vulnerability, according to twin research; Genes that function on known methods implicated in drug addiction and the risk of developing other psychiatric diseases are included. Genes that code for metabolic enzymes (ALDH2, ADH1B), for instance genes that code for gatekeeper molecules as well as drug receptors, is one of the substance-specific genes (eg, nicotinic receptors, OPRM1)[24]. the regulators of anxiety, impulsivity and reward, monoamine oxidase A (MAOA), serotonin transporter (SLC6A4) and catechol-O-methyl

transferase (COMT), have all related to the same genetic liability among addictions and other mental illnesses.

THE INTERACTION THE GENETIC AND ENVIRONMENTAL FACTORS

Gene×Environment incompatibility can be separated into two categories despite the fact that genetic and environmental factors interact in a variety of ways[25].

- Gene×Environment correlation (rGE) When a genotype (r) corresponds with the likelihood of being exposed to an environmental factor, this is called a correlation. The impact of CHRNA5 Asn398 on lung cancer risk is a gene-based example of rGE. 38 This functional allele is linked to excessive smoking, resulting in higher carcinogen exposure.
- Gene×environment interaction (G×E): When genotype[26]. influences the environmental exposure impact on a result, Childhood trauma and other early-life stressors are established as risk factors for addiction and associated illnesses, such as some disorders include antisocial personality (ASPD), CD, borderline personality and anxiety. the SLC6A4 gene, The MAOA gene[27,28] COMT[29], the corticotrophin-releasing hormone receptor 1 gene, FKBP5[30], the Glucocorticoid Receptor (GR) gene (NR3C1)[31] and neuropeptide Y the adenylate cyclase activating polypeptide 1 (pituitary) receptor type gene all play a role (ADCYAP1R1)[32].

INTERMEDIATE PHENOTYPES

Deconstructing phenotypes into etiologically less complicated pieces is one technique for discovering gene influences in etiologically complex disorders like addiction. Genetic and environmental mediating mechanisms are available to intermediate phenotypes. Endophenotypes are disease-related heritable intermediate phenotypes[33].

Alleles controlling heterogeneity in alcohol metabolism influence alcohol-stimulated flushing, a protective alcohol-related endophenotype. A little response to alcohol is an endophenotype that predicts the likelihood of developing alcoholism[34-36]. The degree of reaction in humans is determined by pharmacologic alteration in response 51 rather than metabolic variance. A weak sensitivity to alcohol has been linked to variations in the SLC6A4 and the gene encoding the -aminobutyric acid receptor A subunit a6 (GABRA6)[37]. Electrophysiologic, neuropsychological, neuroendocrinology, recently, neuroimaging tests are among the other addiction-relevant intermediate phenotypes. By getting access to the neuronal systems underlying emotion, reward and wanting, neuroimaging has made it easier to link genes to brain networks relevant to addiction. Because the ventral striatum and other brain areas are active during positive reinforcement, reward circuits may be investigated[38], allowing researchers to uncover that the OPRM1 Asn398Asp mutation linked to naltrexone medication response also influences reward processes in the ventral striatum[39].

Genetic variants appear to have a large impact on intermediate phenotypes than on difficult illness phenotypes, which could be owing to their proximity to specificity gene activity and measurement features[40].

SOME GENES DETERMINATION

To find genetic variants influencing addiction, candidate gene and genome-wide investigations are development being combined. In the first, genes that have been linked to the pathophysiology or treatment of addictions are chosen.

MODIFY GENES BY MONOAMINES MOLECULES

Monoamines such as norepinephrine (NE), serotonin (5-hydroxytryptamine, 5-HT) and dopamine (DA) influence emotionality, cognition and reward. As a result, monoamine-regulating genes such as COMT and the SLC6A4) that related to a wide range of psychiatric illnesses, as well as addiction. COMT is an enzyme that breaks down catecholamines like dopamine and norepinephrine. In the prefrontal cortex, where the dopamine transporter is smaller expressed, COMT is critical for dopamine modulation[41,42]. The COMT gene in humans has two promoters transcript to two separate mRNAs that encode two different proteins: a soluble, cytoplasmic protein (S-COMT) and a membrane-bound version (MB-COMT) with 50 extra amino acid residues at the N-terminus[43].

Serotonin levels in synapses are controlled by the SLC6A4, a neurotransmitter involved in mood, appetite and impulse control. Because of their effects, serotonin-specific reuptake inhibitors are the most prescribed class of medicines for mental illnesses. There is a common variable number tandem repeat (VNTR) in the promoter region (HTTLPR) of the serotonin transporter gene SLC6A4[44].

The major alleles in this VNTR have a numbers of copies of a (20- 23) bp defective repetitive region. The L allele consists of 16 copies, whereas the S allele consist of 14 copies, resulting in more efficient transcription[45]. In addition, the L allele has a functional A>G single-

ucleotide polymorphism (SNP)[46], with the LG allele being transcriptionally equivalent to the S allele. 86 in sometimes low-transcribing HTTLPR genes have been associated to anxiety, depression and alcoholism. After stressful life experiences, S allele carriers showed higher sadness and suicidality than L allele carriers with two copies of the allele[47].

The amygdala activity, a brain region that regulates emotional responses to environmental alteration and has been linked to the pathophysiology of depression and anxiety, is implicated in the pathophysiology of sadness and anxiety , has been demonstrated to be influenced by HTTLPR. HTTLPR also appears to be a predictor of stress-induced cortisol release. In animal models, interactions between the HTT[48]. Gene and its environment have also been reported. In the promoter region of the serotonin transporter gene, the rhesus macaque has an orthologous polymorphism (rh-5HTTLPR). Early stress exposure in these animals resulted in dys-regulated behavior and an increased stress response later in life[49]. Based on rearing circumstances, rh-5HTTLPR influenced alcohol uptake and response to stress, which is congruent with human studies. The low level of serotonin transporter in children that taken from their mothers have heightened stress reactivity and a propensity for alcohol in their young stage[50]. The hypothalamic-pituitary-adrenal (HPA) axis, as it does in humans, appeared to mediate the combined impact of rh-HTTLPR and environment on stress reactivity[48].

RARE AND COMMON VARIANTS

Prevalent genetic variations with MAF more than 1% and frequently greater than 5%, have been the subject of genetic investigations of addiction and other common illnesses. These studies are based on the CD/CV theory, which claims that common alleles of ancient origin with a low to moderate effect contribute to susceptibility to common diseases. Recent research proposed, that uncommon variations with a larger effect may play a significant role in the genetic predisposition to prevalent diseases. For schizophrenia and autism, many risks rare variants with moderate to large impact sizes have already been discovered[22,51]. Some of these variations are assumed to be of recent origin or de novo in sporadic situations and are associated with severe kinds of disease. Rare variations' contribution to addiction is mainly unknown. Recent developments in sequencing technologies, on the other hand, have made it possible to conduct broad searches for uncommon variants. Several functioning CYP26 alleles, as well as rare genetic variants linked to addiction, have been discovered in the serotonin receptor 2B gene (HTR2B) and MAOA[34].

Heterozygous women were unaffected, which is consistent with an X-linked recessive form of transmission. Other populations have not been found with this stop codon variation. A frequent MAOA polymorphism that influences MAOA transcription was recently discovered, The MAOA-linked polymorphic region (MAOA-LPR) is a VNTR situated approximately 1.2 kb upstream from the MAOA start codon and inside the transcriptional regulatory region of the gene[53].

Alleles containing variable numbers of tandem copies of a 30 bp region are more common at this VNTR, with three- and four-repeat alleles being substantially more common. Alleles with four repeats transcribe more efficiently than those with three copies, resulting in higher MAOA enzyme activity[53]. There has also been a link between MAOA and the risk of antisocial conduct and impulsivity in the context of testosterone128 and alcohol intake[54,55].

HTR2B

The effect of an HTR2B stop codon on severe impulsive aggression, ASPD and alcoholism appeared to be altered by stress, alcohol consumption and hormones. The HTR2B stop codon, unlike the MAOA stop codon, is recurrent, occurring in at least 100,000 people, but only a tiny percentage of people have it[34]. The HTR2B gene on chromosome 2 encodes the serotonin 2B receptor, which is a G protein-coupled receptor (2q36.3-q37.1).In the human brain, serotonin 2B receptors are found in abundance. Individuals with highly severe impulsive and violent behavior were sequenced to find the mutation. The sequencing sample included population-matched controls and violent offenders who had their crimes psychiatry according to the severity of their acts (homicides, assaults, arsons). Individuals with a history of spontaneous, non-premeditated aggression had a higher level of the variation. Carriers of the stop codon who committed violent crimes did so while inebriated, showing that an HTR2B stop codon by alcohol interaction may result in impulsive violence.

CONCLUSION

The addiction etiology is a complex, its resulted from more complex interaction between genetic, environmental factors and heritability, also these interaction can be modulated according

todevelopmentally changes during lifespan. The genes contributed in the addiction include some genes encoded to proteins involved in the different pathways of addiction, metabolic enzymes, and gatekeeper molecules such as drug receptors, also the genes responsible on the addiction neurobiology disorders like anxiety, impulsivity and reward like SLC6A4 and COMT, however studies referred to that numerous genetic risk factors of addiction didn't discover to yet, on the other hand the genetic predisposition of addiction is an important to improve predict risk capability, predict medication response, new treatments developing and understand better the effects of the environment.

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